SECOND PERIODIC SAFETY UPDATE REPORT

for

ACTIVE SUBSTANCE: SPIKEVAX (COVID-19 Vaccine mRNA-1273)

ATC CODE(S): J07BX03

MEDICINAL PRODUCTS COVERED:

Invented Name of the Medicinal Product(s)	Marketing Authorization Number(s)	Date(s) of Authorization (*Underline Harmonized EU Birth Date)*	Marketing Authorization Holder
SPIKEVAX (COVID-19 mRNA Vaccine [nucleoside modified])	EU/1/20/1507/001	06 Jan 2021	Moderna Biotech Spain, S.L.

AUTHORISATION PROCEDURE in the EU: Centralized

INTERNATIONAL BIRTH DATE (IBD): 18 Dec 2020

EUROPEAN UNION REFERENCE DATE (EURD): 18 Dec 2020

INTERVAL COVERED BY THIS REPORT:

from 01 Jul 2021 to 31 Dec 2021

DATE OF THIS REPORT:
09 Mar 2022

OTHER INFORMATION: SPIKEVAX (Previously COVID-19 Vaccine Moderna)

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DISTRIBUTION LIST

European Medicines Agency (EMA)	1
US Food Drug Administration (FDA)	1
Medicines and Healthcare products Regulatory Agency (MHRA)	1
Health Canada	1

EXECUTIVE SUMMARY

This second Periodic Safety Update Report (PSUR) on SPIKEVAX (mRNA-1273) was compiled for regulatory authorities in the Periodic Benefit-Risk Evaluation Report (PBRER) format detailed in the European Union (EU) and the International Council on Harmonization (ICH)-E2C guidelines (Good Pharmacovigilance Practice guideline Module VII Periodic Safety Update Reports, 2012 and ICH-E2C(R2) and Consideration on core requirements for PSURs of COVID19 vaccines (corePSUR19 guidance [EMA/362988/2021 08 Jul 2021]). This PBRER provides a comprehensive and critical evaluation of the benefit-risk profile of SPIKEVAX based on review of cumulative safety information, and with a focus on new safety information from available worldwide data sources received during the reporting period. The reporting period for this PBRER No. 2 is from 01 Jul 2021, to 31 Dec 2021. Currently, the SPIKEVAX PBRER is on a 6-monthly submission schedule based on the EU reference dates: the European Reference Date List - List of Union reference dates and frequency of submission of PSURs. It summarizes the safety data received and processed by ModernaTX, Inc from worldwide sources for the period covering 01 Jul 2021 to 31 Dec 2021.

During this reporting period, ModernaTX was in pharmacovigilance agreement with co-sponsors: Glaxo SmithKline (GSK), Sanofi, and the Division of Microbiology and Infectious Diseases (DMID)/National Institute of Allergy and Infectious Diseases (NIAID). The agreements began on 16 Dec 2021 (GSK) and 21 Feb 2020 (Sanofi and DMID/NIAID). The entities agreed to share all the relevant safety data from trials mRNA-1273-P101, mRNA-1273-P102, Protocol 21-0012 (DMID/NIAID sponsored), 217670-ZOSTER-091 (GSK sponsored) and QHD00028 (Sanofi sponsored).

During the reporting period, SPIKEVAX was investigated in clinical development Phases 1 to 3 for active immunization to prevent COVID-19 caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).

SPIKEVAX belongs to pharmacotherapeutic group of vaccines, COVID-19 Vaccines and has ATC code: J07BX03. SPIKEVAX is a lipid nanoparticle (LNP)-encapsulated messenger Ribonucleic acid-based vaccine against the 2019 novel coronavirus (CoV) (CoV; SARS-CoV-2). As per Company Core Data Sheet (CCDS) (Version 9, dated 7 Nov 2021), SPIKEVAX is authorized as a suspension for injection for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 years of age and older.

SPIKEVAX is administered intramuscularly (IM) as two 0.5 mL doses, 28 days apart, and is supplied as a multidose-vial (10 doses) at the concentration of 0.20 mg/mL. One dose of the vaccine (0.5 mL) contains 0.10 mg mRNA, encoding the full-length Spike protein of SARS-CoV-

2, modified to introduce 2 proline residues to stabilize the S-protein into a prefusion conformation (S-2P).

During the reporting period, a total of 13 clinical trials with mRNA-1273 were ongoing, and none of the clinical trials came to completion. This PBRER includes information describing several dosing regimens that are being evaluated in eight ongoing clinical trials sponsored by ModernaTX, Inc., three ongoing trials sponsored by DMID of the NIAID, one ongoing trial sponsored by GSK and lastly one ongoing clinical trial sponsored by Sanofi.

Cumulatively, 48,823 subjects have been exposed to either mRNA-1273, mRNA-1273.351, mRNA-1273.211, mRNA-1273.213, mRNA-1273.617.2, and/or placebo in the mRNA clinical development program sponsored by ModernaTX, Inc (the 48,823 does not represent unique subjects).

Of the 48,823 subjects, 36,181 subjects were exposed to mRNA-1273 and the remaining 12,642 subjects were exposed to mRNA-1273 and/or mRNA-1273.351, mRNA-1273.211, mRNA-1273.213, mRNA-1273.617.2, or placebo. Cumulatively 645 subjects were exposed to mRNA-1273 in clinical trials sponsored by DMID, 1,533 subjects were exposed to mRNA-1273 in a clinical trial sponsored by GSK and 104 subjects were exposed to mRNA-1273 in a clinical trial sponsored by Sanofi. The exposure data from Investigator sponsored studies is unavailable.

Cumulatively, as of the end of the reporting period, a total of 827,274,740 doses of SPIKEVAX had been delivered to 77 countries, and an estimated total of 466,804,529 doses of SPIKEVAX had been administered.

The drug is authorised for active immunization to prevent COVID-19 caused by SARS-CoV-2 in 43 countries.

Based on the data presented in this PBRER#2, SPIKEVAX administered as two 100 µg doses given 28 days apart or as a third 100 µg dose for immunocompromised individuals, including a 50 µg booster dose at least 6 months after primary vaccination against SARS-COV-2 is a highly effective vaccine and capable of restoring neutralizing antibodies, particularly against emerging variants of concern (VOCs) in order to help contain the pandemic with an acceptable safety profile for the prevention of COVID-19 in individuals 6 years of age and older. Considering the ongoing public health emergency due to SARS-CoV-2, the available safety and efficacy data from the 8 clinical studies presented herein, and the ongoing post-authorization surveillance, ModernaTX, Inc. considers that the known and potential benefits outweigh the known and potential risks for SPIKEVAX.

During the reporting period, requests related to the topics “Dizziness”, “Neuralgic amyotrophy”, “Erythema Multiforme”, “Glomerulonephritis and nephrotic syndrome”, “Serious Hypertension”,

"Multisystem Inflammatory syndrome", "Capillary Leak Syndrome" and "Cerebral Venous Sinus Thrombosis" were received from Health Authorities (HAs) or regulatory bodies and these were all considered as validated signals. In addition to these signals, "Myelitis Transverse" was triggered following review of a literature article. Of these 9 signals, 1 signal "Dizziness" was closed and categorized as an identified risk (not important). The remaining 8 signals were closed and refuted during the reporting period. Finally, a new signal for myocarditis and pericarditis was opened to further characterize the risks' frequency from "Unknown" to "Very rare" for both myocarditis and pericarditis.

The signal of "Autoimmune Hepatitis" was validated during the review period as a result of a regulatory authority request, however it was refuted following assessment after DLP of this report (closed on 19 Jan 2022).

During the reporting period, SPIKEVAX risk management plan (RMP) was updated to RMP v2.1 to include myocarditis and pericarditis as new important identified risks and was submitted to European Medicines Agency (EMA) on 19 Jul 2021. Consequently, the IB and Informed Consent Forms (ICFs) for all ongoing studies have also been updated to include the information on myocarditis and pericarditis after receipt of SPIKEVAX. Additionally, a joint Direct Healthcare Professional Communication related to the risks of myocarditis and pericarditis was disseminated on 19 July 2021 by ModernaTX, Inc. and Pfizer/BioNtech to general practitioners, cardiologists, specialists in emergency medicine, and vaccination centres in all European Economic Area (EEA) countries. A similar joint direct healthcare professional communication agreed with Swissmedic was disseminated in Switzerland on 12 Aug 2021.

In addition, there have been updates to the RMP versions (v2.2 dated 16 Aug 2021 through v2.3 dated 28 Oct 2021) with no additional changes to the list of safety concerns.

At the time of the DLP of this PBRER, the following important identified and important potential risks are being closely monitored as per SPIKEVAX RMP v2.3 dated 28 October 2021

Important identified risks

- Anaphylaxis
- Myocarditis
- Pericarditis

Important potential risks

- Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)

Missing information

- Use in pregnancy and while breastfeeding
- Long-term safety
- Use in immunocompromised subjects
- Interaction with other vaccines
- Use in frail subjects with unstable health conditions and co-morbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)
- Use in subjects with autoimmune or inflammatory disorders

On 23 Jul 2021, as per Type II Variation EMEA/H/C/005791/II/0021, Committee for Medicinal Products for Human Use (CHMP) granted positive opinion on the SPIKEVAX indication extension in adolescent (age ≥12 years to <18 years) patients age group.

On 31 Jul 2021, as per category 2 RMP commitment, the interim clinical study report for protocol mRNA 1273 P301 (Part A) was finalized and signed. An acceptable safety profile was demonstrated in the participant population enrolled in this study. No unexpected findings were identified in this final assessment of the randomized, blinded phase of the study. On 16 December 2021, outcome of this special obligation (SOB 010) with the final conclusions for the above-mentioned post authorization measure were adopted by the CHMP.

On 12 Aug 2021, the US Food and Drug Administration (FDA) amended the EUA for the Moderna COVID-19 Vaccine to allow for the use of an additional dose in certain immunocompromised individuals, specifically, solid organ transplant recipients or those who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

On 29 Oct 2021, following Pharmacovigilance Risk Assessment Committee (PRAC) discussion on the signal of multisystem inflammatory syndrome (MIS) (EPITT 19732) and as per the assessment reports, PRAC recommended that a follow-up questionnaire should be implemented for all MIS cases. The MAH for all authorized COVID-19 vaccines were requested to prepare and implement a targeted questionnaire in order to follow up cases of MIS.

On 17 Dec 2021, the CHMP requested to the MAH a review of all available evidence on vaccination in pregnant women and breastfeeding that must be provided as a Late Enhanced Gadolinium (LEG) (EMEA/H/C/005791/LEG/055) in order to critically discuss the need to update SPIKEVAX product information. As a result, after the DLP of this report section 4.6 of the SmPC has been updated accordingly.

Analysis of the data contained within this report supports the adequacy of the current RSI (v11.0 dated 10 Dec 2021) for SPIKEVAX. Examination of the data contained within this report supports the conclusion that the overall benefit-risk balance for SPIKEVAX continues to be positive.

The data included in this PBRER does not indicate any unfavorable change in the benefit-risk profile of SPIKEVAX.

The safety profile of SPIKEVAX is closely monitored on a continuous basis. Based on the cumulative evidence, the benefit-risk profile of SPIKEVAX remains positive.

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LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS

Acronym	Definition
ACE	Angiotensin-Converting Enzyme
ACE2	Angiotensin Converting Enzyme 2
ACIP	Advisory Committee on Immunization Practices
AD	Alternate Day
ADEM	Acute Disseminated Encephalomyelitis
ADR	Adverse Drug Reaction
AE	Adverse Event
AERS	FDA Adverse Event Reporting System
AESI	Adverse Events of Special Interest
AI/ID	Autoimmune and Inflammatory Disorders
AIIRD	Autoimmune Inflammatory Rheumatic Diseases
ALT	Alanine Transaminase
ANCA	Anti-Neutrophil Cytoplasmic Autoantibody
AR	Adverse Reaction
AST	Aspartate aminotransferase
ATM	Acute Transverse Myelitis
AUC	Area Under the Curve
AZ	AstraZeneca
BC	Brighton Collaboration
CCDS	Company Core Data Sheet
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CHMP	Committee for Medicinal Products for Human Use
CK	Creatine Kinase

Acronym	Definition
CLS	Capillary Leak Syndrome
CMQ	Customized MedDRA query
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease of 2019
CoV	Coronavirus
CRP	C-reactive protein
CSF	Cerebrospinal Fluid
CSU	Chronic Spontaneous Urticaria
CU	Chronic urticaria
CVST	Central Venous Sinus Thrombosis
DHPC	Direct Healthcare Professional Communication
DLP	Data Lock Point
DMARDs	Disease-Modifying Antirheumatic Drugs
DMID	Division of Microbiology and Infectious Diseases
EBGM	Empirical Baysian Geometrical Mean
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EEG	Electroencephalogram
ELS	Extensive Swelling of Vaccinated Limb
EM	Erythema Multiforme
EMA	European Medicines Agency
EMEA	European Medicines Evaluation Agency

Acronym	Definition
EPITT	European Pharmacovigilance Issues Tracking Tool
ER	Emergency Room
ESR	Erythrocyte Sedimentation Rate
EU	European Union
EUA	Emergency Use Authorization
EVDAS	EudraVigilance data analysis system
FDA	Food and Drug Administration
GBS	Guillain-Barre Syndrome
GBM	Glioblastoma Multiforme
GCA	Giant Cell Arteritis
GMFR	Geometric Mean Fold Rise
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
GSDB	Global Safety Database
GSK	Glaxo SmithKline
GVP	Good Pharmacovigilance Practices
HAs	Health Authorities
HBV	Hepatitis B Virus
HCP	Healthcare Care Professional
HIV	Human Immunodeficiency Virus
HSV	Herpes Simplex Virus
IB	Investigator's Brochure
IBD	International Birth Date
ICH	International Council on Harmonization
ICF	Informed Consent Form

Acronym	Definition
ICSR	Individual Case Safety Report
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IM	Intramuscular
IMID	Immune-Mediated Inflammatory Diseases
IRR	Incidence Rate Ratio
ITP	Immune Thrombocytopenia
HIV	Human Immunodeficiency Virus
HLGT	High Level Group Term
HLT	High Level Term
LEG	Late Enhanced Gadolinium
LNP	Lipid Nanoparticle
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MFS	Miller Fisher Syndrome
MG	Myasthenia gravis
MHRA	Medicines and Healthcare products Regulatory Agency
MIS	Multisystem Inflammatory Syndrome
MIS-A	Multisystem Inflammatory Syndrome in Adults
MIS-C	Multisystem Inflammatory Syndrome in Children
MRI	Magnetic Resonance Imaging
mRNA	messenger Ribonucleic Acid
MS	Multiple Sclerosis

Acronym	Definition
MSSR	Monthly Safety Summary Report
NA	Neuralgic Amyotrophy
NIAID	National Institute of Allergy and Infectious Diseases
NID	Neuroinflammatory Diseases
NIS	Non-Interventional Study
NSAID	Nonsteroidal Anti-Inflammatory Drugs
O/E	Observed-Expected
OR	Odds Ratio
PBO	Placebo
PBRER	Periodic Benefit-Risk Evaluation Report
PMR	Polymyalgia Rheumatica
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred Term
RA	Rheumatoid Arthritis
RMP	Risk Management Plan
ROR	Rate of Return
RSI	Reference Safety Information
RTX	Rituximab
RWE	Real World Evidence
SAARD	Systemic Autoimmune and Autoinflammatory Rheumatic Disease
SAE	Serious Adverse Event
SARs-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SCLS	Systemic Capillary Leak Syndrome
SD	Standard Deviation

Acronym	Definition
SLE	Systemic Lupus Erythematosus
SmPC	Summary of Product Characteristics
SMQ	Standard MedDRA Query
SOC	System Organ Class
SOCV	Single Organ Cutaneous Vasculitis
TEAE	Treatment Emergent Adverse Events
TM	Transverse Myelitis
TSH	Thyroid Stimulating Hormone
TTO	Time-to-Onset
TTS	Thrombosis with Thrombocytopenia Syndrome
UC	Ulcerative Colitis
VAED	Vaccine-Associated Enhanced Disease
VAERS	Vaccine Adverse Event Reporting System
VIIT	Vaccine Induced Immune Thrombotic Thrombocytopenia
VOC	Variants of Concern
VOI	Variant of Interest
VSD	Vaccine Safety Datalink
VTE	Venous Thromboembolic
WAO	World Allergy Organization
WHO	World Health Organization

1. INTRODUCTION

This second Periodic Safety Update Report (PSUR) on SPIKEVAX (COVID-19 mRNA Vaccine [nucleoside modified]) was compiled for regulatory authorities in the Periodic Benefit-Risk Evaluation Report (PBRER) format detailed in the European Union (EU) and the International Council on Harmonization (ICH)-E2C guidelines (Good Pharmacovigilance Practice guideline Module VII Periodic Safety Update Reports, 2012 and ICH-E2C(R2) and Consideration on core requirements for PSURs of COVID19 vaccines (core PSUR19 guidance [EMA/362988/2021 08 Jul 2021]). This PBRER provides a comprehensive and critical evaluation of the benefit-risk profile of SPIKEVAX based on review of cumulative safety information, and with a focus on new safety information from available worldwide data sources received during the reporting period. The reporting period for this PBRER No. 2 is from 01 Jul 2021, to the data lock point (DLP) of 31 Dec 2021. Currently, mRNA 1273 PBRER is on a 6-monthly submission schedule based on the EU reference dates: the European Reference Date List - List of Union reference dates and frequency of submission of PSURs. It summarizes the safety data received and processed by ModernaTX, Inc from worldwide sources for the period covering 01 Jul 2021 to 31 Dec 2021.

The international birth date (IBD) of SPIKEVAX is 18 Dec 2020, the date of the first authorization approval in any country in the world.

SPIKEVAX belongs to pharmacotherapeutic group of vaccines, COVID-19 Vaccines and has ATC code: J07BX03.

SPIKEVAX is a lipid nanoparticle (LNP)-encapsulated messenger RNA (mRNA)-based vaccine against the 2019 novel coronavirus (CoV) (Severe Acute Respiratory Syndrome Coronavirus 2 [SARS-CoV-2]). As per the Company Core Data Sheet (CCDS) (Version 9, dated 7 Nov 2021), COVID-19 mRNA vaccine (nucleoside modified) is authorized as a suspension for injection for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 years of age and older. The safety and efficacy of SPIKEVAX in children less than 6 years of age have not yet been established.

SPIKEVAX is administered intramuscularly (IM) as two 0.5 mL doses, 28 days apart, and is supplied as a multidose-vial (10 doses) at the concentration of 0.20 mg/mL. One dose of the vaccine (0.5 mL) contains 0.10 mg mRNA, encoding the full-length Spike protein of SARS-CoV-2, modified to introduce 2 proline residues to stabilize the S-protein into a prefusion conformation (S-2P). The mRNA-1273 consists of an mRNA drug substance that is manufactured with LNPs composed of four lipids: heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino) octanoate (SM-102); cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC); and 1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000 (PEG2000-DMG).

The mRNA drug substance in SPIKEVAX is chemically similar to naturally-occurring mammalian mRNA with the exception that the uridine nucleoside normally present in mammalian mRNA is fully replaced with N-methyl-pseudouridine, a naturally-occurring pyrimidine base present in mammalian transfer RNAs [1,2]. This nucleoside is included in mRNA-1273 drug substance in place of the normal uridine base to minimise the indiscriminate recognition of the mRNA-1273 by pathogen-associated molecular pattern receptors (e.g., toll-like receptors) [3]. The cap structure used in the mRNA is identical to the natural mammalian Cap one structure [4,5] and is presented in Figure 1-1 below.

Figure 1-1 mRNA 1273 COVID-19 Vaccine Cap 1 mRNA structure

Abbreviations: mRNA, messenger RNA; PolyA, polyadenylated; UTR, untranslated region.

The vaccine encodes for the pre-fusion stabilized spike protein of SARS-CoV-2. After intramuscular injection, cells take up the lipid nanoparticle, effectively delivering the mRNA sequence into cells for translation into protein. The mRNA delivery system is based on the principle and observation that cells in vivo can take up mRNA, translate it, and express protein antigen(s) in the desired conformation. The delivered mRNA does not enter the cellular nucleus or interact with the genome, is nonreplicating, and is expressed transiently. The protein undergoes post-translational modification and trafficking resulting in properly folded, fully functional Spike protein that is inserted into the cellular membrane of the expressing cell(s). The Spike protein is membrane bound, mimicking the presentation of natural infection.

The expressed Spike protein of SARS-CoV-2 is then recognized by immune cells as a foreign antigen which elicits both T-cell and B-cell responses. The immune response to the Spike protein results in functional antibody and T-cell responses and in the generation of memory immune cell populations.

Further details on mechanism of action, indications, pharmaceutical forms and instructions for use are presented in the Company Core Data Sheet (CCDS) for SPIKEVAX (current version [v] 11.0 dated 10 Dec 2021). (20.1).

2. WORLDWIDE MARKETING APPROVAL STATUS

The IBD of SPIKEVAX is 18 Dec 2020. The product is currently authorized in 43 unique countries/regions and unions/areas for active immunization to prevent COVID-19 caused by SARS-CoV-2.

Cumulative information on marketing authorizations in all countries and approval dates are presented in Table 20.5 for use in adults aged 18 years and older, Table 20.6 for use in adolescents aged 12 to < 18 years, Table 20.7 for use as a booster, and Table 20.8 for the third dose in immunocompromised patients in Appendix 20.11.1.

3. ACTIONS TAKEN IN THE REPORTING INTERVAL FOR SAFETY REASONS

Actions related to investigational uses:

Following the categorization of myocarditis and pericarditis as important identified risk on 08 July 2021, the Investigator's Brochure (IB) and Informed Consent Forms (ICFs) for all ongoing studies with mRNA-1273 vaccine have been updated to include the information on myocarditis and pericarditis.

The IB has been updated to provide investigators with information on the association of myocarditis and pericarditis with mRNA-1273 vaccination.

The ICF has been updated to advise participants that myocarditis and pericarditis have been observed following vaccinations SPIKEVAX. This revised ICF is being provided to prospective research participants as well as to those currently enrolled in trials, for whom dosing has not been completed.

On 31 Jul 2021, as per category 2 Risk Management Plan (RMP) commitment, the interim clinical study report for protocol mRNA 1273 P301 (Part A) was finalized and signed. An acceptable safety profile was demonstrated in the participant population enrolled in this study. No unexpected findings were identified in this final assessment of the randomized, blinded phase of the study. On 16 December 2021, outcome of this special obligation (SOB 010) with the final conclusions for the above-mentioned post authorization measures were adopted by the Committee for Medicinal Products for Human Use (CHMP).

Actions related to marketing experience:

On 08 Jul 2021, as per Pharmacovigilance Risk Assessment Committee (PRAC) recommendation, the validated signals of myocarditis and pericarditis (EPITT n° 19713) were considered as important identified risks. To address these risks, the PRAC requested:

- A product information update by 12 July 2021 (Summary of Product Characteristics [SmPC] sections 4.4, 4.8 and PIL sections 2 and 4)
- A Direct Healthcare Professional Communication (DHPC): On 16 Jul 2021, BioNTech/Pfizer and Moderna Biotech Spain, S.L. in agreement with the EMA and Health Products Regulatory issued a joint direct healthcare professional communication summarizing the cases of myocarditis and pericarditis following COVID-19 mRNA vaccination (with their respective vaccines) along with background information on Comirnaty® and SPIKEVAX which included information on reporting these events. This letter was disseminated on 19 Jul 2021 to general practitioners, cardiologists, specialists in emergency medicine, and vaccination centers in all European Economic Area (EEA) countries. A similar joint direct healthcare professional communication agreed with Swissmedic was disseminated in Switzerland on 12 Aug 2021.
- A recommendation from the MAH for the administration of the second dose submitted 02 Aug 2021
- A risk management plan update including measures to further characterize the risk: RMP version 2.1 with DLP 31 May◦2021 was updated to include myocarditis and pericarditis as important identified risks and was submitted to the EMA on 19◦Jul◦2021 (EMEA/H/C/005791/II/0028).
    - A targeted follow-up questionnaire for myocarditis and pericarditis has been created
    - Food and Drug Administration (FDA) and PRAC requested post authorization safety study to characterize natural history of and risk factors for myocarditis temporally associated with Moderna COVID-19 vaccination in children and young adults. Initial development for these 2 studies (mRNA-1273-P910 and p911) is ongoing.
    - All interventional and observational studies listed in the SPIKEVAX pharmacovigilance plan were updated to better characterize the risks of myocarditis and pericarditis

Concomitantly other health authorities including FDA, Medicines and Healthcare products Regulatory Agency (MHRA) and Health Canada requested a label update related to myocarditis and pericarditis.

On 23 Jul 2021, as per Type II Variation EMEA/H/C/005791/II/0021, CHMP granted positive opinion on the SPIKEVAX indication extension in adolescent (age ≥12 years to <18 years) patients age group.

On 12 Aug 2021, the US FDA amended the Emergency Use Authorization (EUA) for the Moderna COVID-19 Vaccine to allow for the use of an additional dose in certain immunocompromised individuals, specifically, solid organ transplant recipients or those who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise.

On 01 Oct 2021, as per Type II Variation EMEA/H/C/005791/II/0031, sections 4.2, 4.4, 4.8 and 5.1 of the SmPC were updated in order to introduce a third dose of SPIKEVAX in the primary vaccination schedule for individuals 18 years of age and older who have undergone a solid organ transplantation, or who are diagnosed with conditions that are considered to have an equivalent level of immunocompromise, based on updated clinical literature; the Package Leaflet is updated accordingly.

On 25 Oct 2021, as per type II Variation EMEA/H/C/005791/II/0034, CHMP issued a positive opinion for a booster dose (50 mcg) at least 6 months after the second dose in individuals 18 years of age and older. As a result of this type II variation, section(s) 2, 4.2, 4.8, 5.1, 6.5 and 6.6 of the SmPC are being updated to provide information on a booster dose in individuals aged 18 years and older. The Package Leaflet (PL) is updated accordingly.

On 28 Oct 2021, as per Type II group of variations EMEA/H/C/005791/II/0015/G to address PRAC requests raised in the 3rd SPIKEVAX Monthly Safety Summary Report (MSSR) procedure (EMEA/H/C/005791/MEA/011.2) the following sections of the SmPC were updated:

- section 4.8 of the SmPC to include details regarding time to onset and duration of the delayed injection site reactions. The Package Leaflet is updated accordingly.
- section 4.8 of the SmPC to include “diarrhea” as an adverse reaction, with the frequency ‘Common’. The Package Leaflet is updated accordingly.

On 29 Oct 2021, following PRAC discussion on the signal of multisystem inflammatory syndrome (MIS) (EPITT 19732) and as per the assessment reports, PRAC recommended that a follow-up questionnaire should be implemented for all MIS cases. The MAH for all COVID-19 vaccines were requested to prepare and implement a targeted questionnaire in order to follow up cases of MIS.

On 17 Dec 2021, the CHMP had requested to the MAH a review of all available evidence on vaccination in pregnant women and breastfeeding that must be provided as a Late Enhanced Gadolinium (LEG) (EMEA/H/C/005791/LEG/055) in order to critically discuss the need to update

SPIKEVAX product information. As a result, after the DLP of this report section 4.6 of the SmPC has been updated accordingly.

4. CHANGES TO REFERENCE SAFETY INFORMATION

The Reference Safety Information (RSI) for SPIKEVAX in effect at end of the reporting period (DLP 31 Dec 2021) used for the purpose of this report is the CCDS v11.0 dated 10 Dec 2021 used to assess listedness of adverse reactions (ARs), risks in risk sections, and to support benefit-risk evaluation. The RSI contains a complete review of the safety profile for the product. This document is provided in Appendix 20.1.

During the review period of this report, the RSI (CCDS) was updated from v 6.0 dated 25 Jun 2021 to v11.0 dated 10 Dec 2021. The safety related changes are summarized below in Table 4.1.

Table 4.1. CCDS safety-related changes during the reporting period

CCDS Version	Date	Safety-Related Changes
7.0	13 Aug 2021	Addition of immunocompromised booster data (sections 4.2, 4.4, 4.8, and 5.1).
8.0	30 Aug 2021	Addition of elasomeran INN (section 1); addition of booster data in sections 2, 4.2, 4.8 and 5.2. Clarifications to immunocompromised text in sections 4.4, 4.8 and 5.2. Edits to accommodate booster in sections 6.5 and 6.6.
9.0	03 Nov 2021	Addition of pediatric data (6-11-year-old) and related edits in sections 4.1, 4.2, 4.8 and 5.2. Addition of heterologous boosting data in sections 4.2, 4.8 and 5.2.
10.0	17 Nov 2021	Extension in shelf life to 9 months and deletion of dry ice statements.
11.0	10 Dec 2021	Section 4.4: Myocarditis/pericarditis: redline edits were discussed and agreed upon at SRB on 10 Dec 2021. Section 4.6: Breastfeeding: aligned text with US Fact Sheets. Section 4.8: removed US-based ADR content and re-organized and simplified to establish Table 1 as the most current and cumulative reflection of ADRs. Minor updates to align with the IB: Table 1: addition of paresthesia per PBRER outcome. Myocarditis and pericarditis frequency reclassified from Not Known to Very Rare to reflect latest available data. Section 5.2: Addition of Adults and Peds Delta data.

ADR: Adverse Drug Reaction; IB: Investigator's Brochure; US: United States

5. ESTIMATED EXPOSURE AND USE PATTERNS

5.1. Cumulative Subject Exposure in Clinical Trials

Cumulatively, 48,823 subjects have been exposed to either mRNA-1273, mRNA-1273.351, mRNA-1273.211, mRNA-1273.213, mRNA-1273.617.2, or placebo in the mRNA clinical development program sponsored by ModernaTX, Inc. Out of the 48,823 subjects, 36,181 subjects were exposed to mRNA-1273 and the remaining 12,642 subjects were exposed to either mRNA-1273.351, mRNA-1273.211, mRNA-1273.213, mRNA-1273.617.2, or placebo. The 48,823 does

not represent unique subjects. Clinical protocol, mRNA-1273-P301, was designed as a 2-part Phase 3 study:

- Part A, the blinded Phase was a randomized, stratified, observer-blind, placebo-controlled study to evaluate the efficacy, safety, and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine compared to placebo in adults 18 years of age and older who have no known history of SARS-CoV-2 infection.
- Part B, the open-label observational Phase was designed to offer participants who received placebo in Part A of this study and who met EUA eligibility an option to request 2 doses of mRNA-1273 vaccine and remain on study.

Estimates of cumulative subject exposure, based upon the enrolment/randomization schemes for ongoing trials, see Table 5.1. Further details on cumulative subject exposure categorized by age, sex, and racial group is provided in Table 5.2, Table 5.3, Table 5.4 and Table 5.5, respectively.

Table 5.1 Estimated Cumulative Subject Exposure from Clinical Trials

Study ID	Vaccine Type	Total Subject Exposure by Study and Product
mRNA-1273-P201	Placebo	42[a]
mRNA-1273-P201	mRNA-1273	558[a]
mRNA-1273-P201	mRNA-1273 Booster	344
mRNA-1273-P201	mRNA 1273 + mRNA-1273.351 Booster	20
mRNA-1273-P201	mRNA-1273.351 Booster	40
mRNA-1273-P203	Placebo	1,159[a]
mRNA-1273-P203	mRNA-1273	2,567[a]
Unblinded (Part 1 or Part 2 with Age >=6 Years)		
mRNA-1273-P204	Placebo	346[a]
mRNA-1273-P204	mRNA-1273	4,781[a]
Blinded (Part 2 with Age<=5 Years)		
mRNA-1273-P204	Overall	5,586[a]
mRNA-1273-P205	mRNA-1273 Booster	305[a]
mRNA-1273-P205	mRNA-1273.211 Booster	899[a]
mRNA-1273-P205	mRNA-1273.213 Booster	718[a]
mRNA-1273-P205	mRNA-1273.617.2 Booster	1,150[a]
mRNA-1273-P205	TBD Booster	8[a]
mRNA-1273-P301	Placebo	2,514[a]
mRNA-1273-P301	mRNA-1273	27,832[a]
mRNA-1273-P301	mRNA-1273 Booster	18,394
mRNA-1273-P304	mRNA-1273	138[a]
mRNA-1283-P101	Overall	104

Study ID	Vaccine Type	Total Subject Exposure by Study and Product
mRNA-1283-P201	Overall	116[a]

a. To have the total for each study, these numbers were counted.

Table 5.2 Cumulative Subject Exposure to Investigational Drug from Ongoing Clinical Trials by Age

Age Range	mRNA-1273						mRNA-1283		
	P201[a]	P203[a]	P204[a]	P205[a]	P301[a]	P304[a]	P101[a]	P201[a]	Total
<2 years	0	0	2,121	**0**	**0**	**0**	**0**	**0**	**2,121**
2 to <6 years	0		3,818	0	0	0	0	0	**3,818**
6 to <12 years	0		4,753	0	0	0	0	0	**4,753**
≥12 and <16 years	0	2,767	0	0	0	0	0	0	**2,767**
≥16 and <18 years	0	959	0	0	0	0	0	0	**959**
>=18 and <65 years	463	0	0	2,371	22,826	114	104	104	**25,982**
>=65 and <75 years	115	0	0	575	6,122	22	0	11	**6,845**
>=75 and <85 years	19	0	0	110	1,308	2	0	1	**1,440**
>=85 years	3	0	0	8	90	0	0	0	**101**
Missing	0	0	21	16	0	0	0	0	**37**
Total	**600**	**3,726**	**10,713**	**3,080**	**30,346**	**138**	**104**	**116**	**48,823**

a=Data from ongoing trials till 17 Dec 2021.

Table 5.3 Cumulative Subject Exposure to Investigational Drug from Ongoing Clinical Trials by Sex

Age Range	mRNA-1273						mRNA-1283		
	P201[a]	P203[a]	P204[a]	P205[a]	P301[a]	P304[a]	P101[a]	P201[a]	Total
Male	210	1,915	5,448	1,481	15,974	69	60	40	**25,197**
Female	390	1,811	5,247	1,555	14,372	69	44	76	**23,564**
Missing	0	0	18	44	0	0	0	0	**62**
Total	**600**	**3,726**	**10,713**	**3,080**	**30,346**	**138**	**104**	**116**	**48,823**

a=Data from ongoing trials till 17 Dec 2021

Table 5.4 Cumulative Subject Exposure to Investigational Drug from Ongoing Clinical Trials by Racial Group

Age Range	mRNA-1273						mRNA-1283		
	P201[a]	P203[a]	P204[a]	P205[a]	P301[a]	P304[a]	P101[a]	P201[a]	Total
White	569	3,124	7,751	2,543	24,032	86	73	81	38,259
Black	16	125	697	208	3,098	28	5	14	4,191
Asian	7	222	780	137	1,395	8	5	10	2,564
American Indian or Alaska Native	3	19	39	19	234	2	1	1	318
Native Hawaiian or Other Pacific Islander	1	3	16	5	68	0	1	0	94
Other	2	36	190	45	593	9	0	4	879
Multiple	2	168	1,117	40	638	2	3	3	1,973
Not Reported	0	22	70	16	171	1	16	3	299
Unknown	0	7	20	7	117	1	0	0	152
Missing	0	0	33	60	0	1	0	0	94
Total	**600**	**3,726**	**10,713**	**3,080**	**30,346**	**138**	**104**	**116**	**48,823**

a=Data from ongoing trials till 17 Dec 2021.

Table 5.5 Cumulative Subject Exposure to Investigational Drug from Ongoing Clinical Trials by Ethnicity

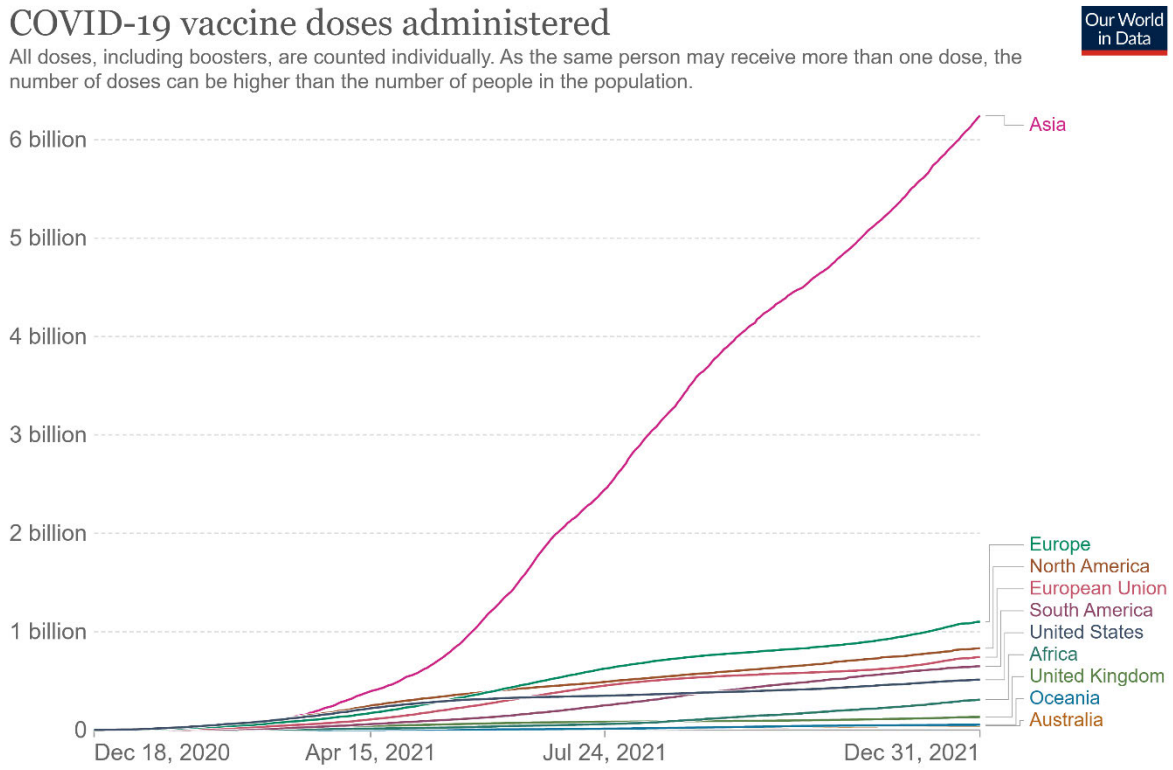
Age Range	mRNA-1273						mRNA-1283		
	P201[a]	P203[a]	P204[a]	P205[a]	P301[a]	P304[a]	P101[a]	P201[a]	Total
Hispanic or Latino	47	432	1,747	439	6,230	11	30	18	**8,954**
Not Hispanic or Latino	552	3,262	8,862	2,569	23,838	127	72	95	**39,377**
Not reported	1	29	61	19	188	0	2	3	**303**
Unknown	0	3	24	9	90	0	0	0	**126**
Missing	0	0	**19**	44	**0**	**0**	**0**	**0**	**63**
Total	**600**	**3,726**	**10,713**	**3,080**	**30,346**	**138**	**104**	**116**	**48,823**

a=Data from ongoing trials till 17 Dec 2021

5.2. Cumulative and Interval Patient Exposure from Marketing Experience

Across manufacturers, administration of COVID-19 Vaccines has progressed as shown in Figure 5-1.

Figure 5-1. Cumulative Uptake of All COVID-19 Vaccines in Countries Where SPIKEVAX was Distributed



Moderna supply chain estimates are used to define the number of doses SPIKEVAX distributed by country; however, administration data are tracked by health officials within some countries receiving the vaccine. Therefore, Moderna estimates administration of SPIKEVAX (i.e., exposure) based on information retrieved through:

- US Centers for Disease Control and Prevention (https://covid.cdc.gov/covid-data-tracker/#vaccinations),
- The European Centers for Disease Control (https://qap.ecdc.europa.eu/public/extensions/COVID-19/vaccinetracker.html#distribution-tab),
- Health Canada (https://health-infobase.canada.ca/covid-19/vaccination-coverage/),
- The Swiss Federal Office of Public Health (https://www.covid19.admin.ch/en/epidemiologic/vacc-doses),

- Our World in Data (https://ourworldindata.org/covid-vaccinations) (data retrieved on 01 Jan 2022).

Cumulatively, as of the end of the reporting period, a total of 827,274,740 doses of SPIKEVAX had been delivered to 77 countries. A proportion of doses distributed have been subsequently donated via either bilateral agreements or collaborative efforts such as COVAX. Some countries rely on the assessment of the World Health Organization (WHO) rather than holding a country level approval. Therefore, the countries that have received SPIKEVAX may exceed the number of countries where SPIKEVAX has been approved), and an estimated total of 466,804,529 doses of SPIKEVAX had been administered. North America, Europe, and Asia accounted for >90% of SPIKEVAX doses distributed and >70% of SPIKEVAX doses administered (Table 5.6). Based on data shared by the Centers for Disease Control and Prevention (CDC) for the US, the Marketing Authorization Holder (MAH) has estimated that approximately 15% of all Moderna doses distributed may be part of such agreements. As tracking data on the administration of doses donated after initial distribution is not available at this time, the MAH has conservatively assumed that only 25% of these doses have been administered globally.

Table 5.6. SPIKEVAX Doses Distributed and Administered through the End of the Review Period

	Doses Distributed		Doses Administered	
	N	%	N	%
Total	**827,274,740**	**100**	466,804,529	**100**
North America	384,938,620	46.5	200,189,117	42.9
United States	350,231,980	42.3	193,650,993	41.5
Europe[c]	211,273,900	25.2	112,474,294	23.5
European Economic Area[d]	181,560,000	21.9	98,068,820	21.0
Asia[b]	176,449,180	21.3	95,811,795	20.5
Middle East[f]	15,553,380	1.9	7,776,690	1.7
Latin America[e]	14,655,580	1.8	7,327,790	1.6
Oceana[g]	10,223,200	1.2	5,111,600	1.1
Africa[a]	14,180,880	1.7	7,090,440	1.5
Governmental donations	--	--	31,022,803	6.6

[a] **Africa:** Angola, Botswana, Burkina Faso, Guinea, Kenya, Nigeria, Zambia

[b] **Asia:** Bangladesh, Bhutan, Brunei, Cambodia, Indonesia, Japan, Kyrgyzstan, Nepal, Pakistan, Philippines, Singapore, South Korea, Taiwan, Tajikistan, Thailand, Vietnam

[c] **Europe:** European Union with Switzerland, United Kingdom, Ukraine, and Moldova

[d] **European Economic Area:** Austria, Belgium, Bulgaria, Croatia, Republic of Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden

[e] **Latin America:** Colombia

[f] **Middle East:** Egypt, Israel, Qatar, Saudi Arabia, United Arab Emirates

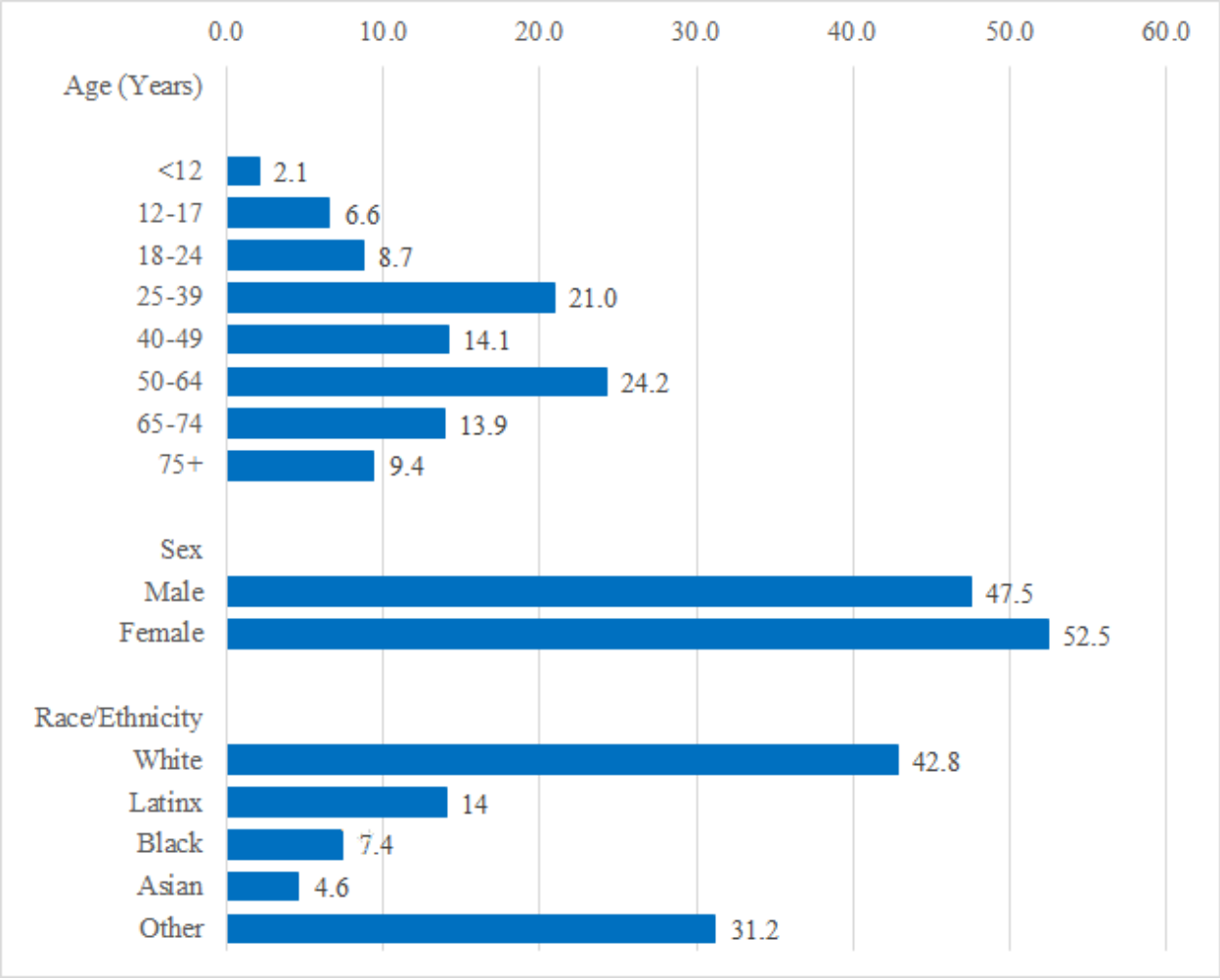
[g] **Oceana:** Australia, Fiji

Extrapolating from the proportion of US vaccine recipients to estimate global use, it is estimated that 216,113,851 individuals received a first dose, 176,800,748 received a second dose, and 73,889,930 received a third dose.

Summaries of Moderna distribution and administered by country and distribution by lots/batches are included in Appendix 20.11.2.

Demographic characteristics of US recipients of all COVID-19 vaccine products are shown in Figure 5-2. Representation was highest among recipients 50-64 years of age, female, and white.

Figure 5-2. Characteristics of US Recipients of All COVID-19 Vaccine Products by Age, Sex, and Race/Ethnicity



Available demographic characteristics of vaccine recipients in the EEA and Canada are shown in Figure 5-3 and Figure 5-4, respectively. In the EEA, representation was highest among recipients

25-49 years of age. In Canada, representation was similar among the age groups and by sex. Information on distribution by gender or receipt of first versus second dose was not identifiable based on information published by European Centre for Disease Prevention and Control (ECDC) at the time that the data were accessed (https://qap.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#distribution-tab, accessed 01 Jan 2022).

Figure 5-3. EEA Recipients of All COVID-19 Vaccine Products by Age

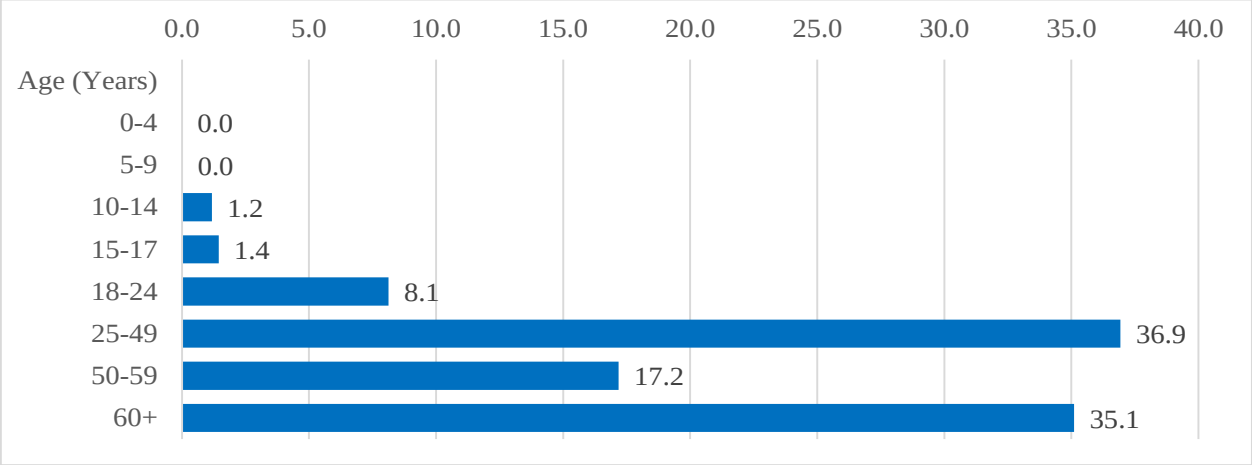
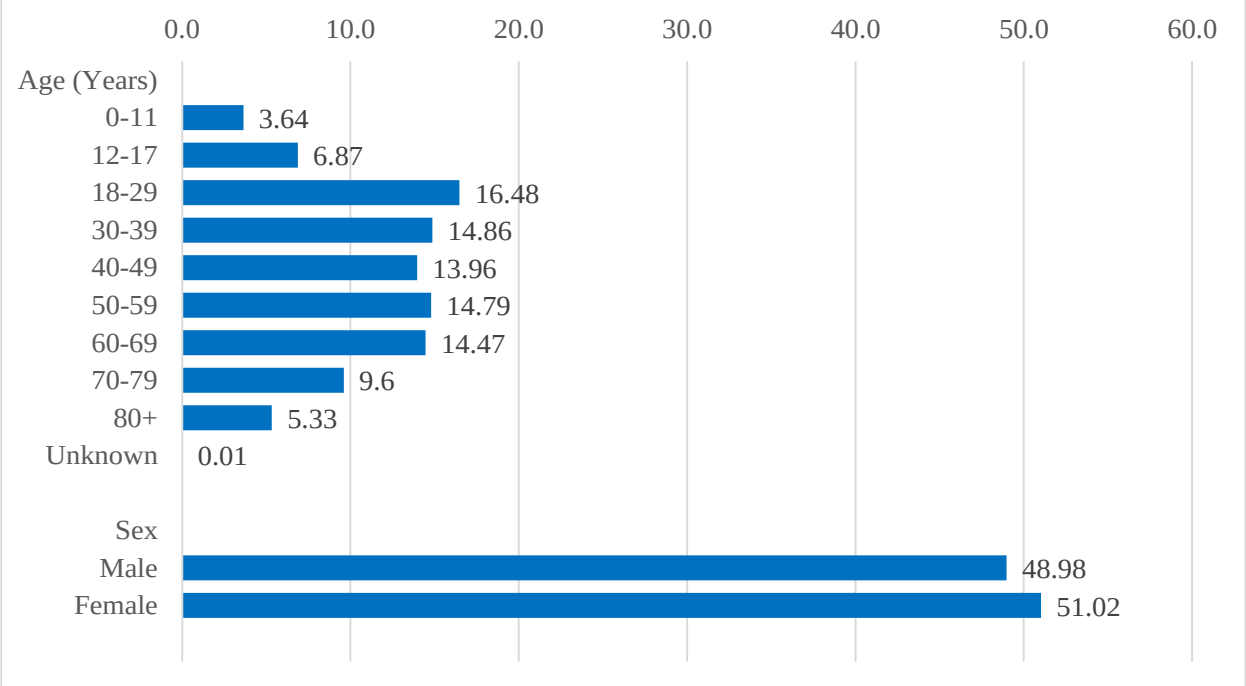


Figure 5-4. Canadian Recipients of All COVID-19 Vaccine Products by Age and Sex



5.2.1. Traceability

Batch monitoring is performed using distribution data derived from Moderna Supply chain and US manufacturing records. Patient-level exposure for the EU is presented below by age; subpopulation data across gender, race and ethnicity are not presently available.

As part of the EU RMP and Summary of Product Characteristics (SmPC), instructions have been provided with our product for healthcare professionals to record the name and batch number of the administered vaccine to improve traceability. Moderna has also developed Traceability and Vaccination Reminder cards.

The card is also accessible electronically and through a QR code, on the applicant's website. The Traceability and Vaccination Reminder cards contain the following elements:

- Placeholder space for name of vaccine;
- Vaccine brand name and manufacturer name;
- Placeholder space for due date and actual date of first and second doses, and associated batch/lot number;
- Reminder to retain the card and bring to the appointment for the second dose of the vaccine;
- QR code that links to a website with additional information on product use; and
- Adverse event reporting information.

The vaccine carton labelling also contains a scannable 2D barcode that provides the batch/lot number and expiry date. In addition, Moderna also provides stickers (two stickers per dose, containing printed batch/lot information, product identification, and 2D bar code) that encodes a unique identifier (serial number) either in cartons or to be shipped along with each shipment, in the countries where this is required.

6. DATA IN SUMMARY TABULATIONS

6.1. Reference Information

The Medical Dictionary for Regulatory Activities (MedDRA) v24.1 is the coding dictionary utilized for the presentation of adverse events (AE)/adverse drug reactions (ADR) in this report. The line listings and summary tabulations are arranged alphabetically by primary MedDRA System Organ Class (SOC) and refer to the Preferred Term (PT) level.

6.2. Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials

A cumulative (18 Dec 2020 to 31 Dec 2021) summary tabulation of serious adverse events (SAEs) from Company-sponsored clinical trials (CTs) is provided in Appendix 20.2. The SAEs presented in this summary tabulation were derived from Company-sponsored interventional clinical trials. Inclusion requirement parameters for the incorporation of data from Company-sponsored CTs are the SAE occurred during active treatment, the SAE originated from a clinical study with SPIKEVAX, event was assessed as serious, and the active treatment was SPIKEVAX or placebo.

6.3. Cumulative and Interval Summary Tabulations from Post-marketing Data Sources

A cumulative (18 Dec 2020 to 31 Dec 2021) and interval (01 Jul 2021 to 31 Dec 2021) summary tabulation of ADRs (serious and non-serious) is provided in 20.3. The ADRs presented in this tabulation were derived from spontaneous sources (healthcare professionals [HCP], consumers, scientific literature, and regulatory authorities [RA]) as well as serious ADRs from non-interventional studies.

7. SUMMARIES OF SIGNIFICANT FINDINGS FROM CLINICAL TRIALS IN THE REPORTING INTERVAL

7.1. Completed Clinical Trials

No clinical trials were completed during the reporting period.

7.2. Ongoing Clinical Trials

There were 8 clinical trials ongoing (mRNA-1273-P201, mRNA-1273-P203, mRNA-1273-P204, mRNA-1273-P205, mRNA-1273-P301, mRNA-1273-P304, mRNA-1283-P101 and mRNA-1283-P201) during the current reporting period. There was no clinically important information that arose from ongoing clinical trials during the reporting period.

Refer to Appendix 20.5 for further details of all the ongoing and planned studies.

7.3. Long-term Follow-up

Patients who have completed mRNA-1273 clinical trials are not subject to long-term follow-up.

7.4. Other Therapeutic Use of Medicinal Product

SPIKEVAX has not been investigated for any other therapeutic use during the reporting period.

7.5. New Safety Data Related to Fixed Combination Therapies

This section is not applicable as COVID-19 mRNA Vaccine is a monotherapy and is not marketed as a combination drug.

8. FINDINGS FROM NON-INTERVENTIONAL STUDIES

The following non-interventional studies were ongoing during the reporting period:

Protocol mRNA-1273-901

Real-World Study to Evaluate mRNA-1273 Effectiveness and Long-term Effectiveness in the US.

Summary: No safety findings have been identified in this study.

Protocol mRNA-1273-P902

Moderna mRNA-1273 Observational Pregnancy Outcome Study

Summary: No safety findings have been identified in this study.

mRNA-1273-P903

Post-marketing safety of SARS-CoV-2 SPIKEVAX vaccine in the US: Active surveillance, signal refinement and self-controlled risk interval (SCRI) signal evaluation in HealthVerity.

Summary: Preliminary estimates of incidence for AESI relevant to vaccine safety monitoring showed substantial variation in estimated incidence rates by outcome, age and gender. This was expected based on known epidemiology and published sources and underscores the importance of subgroup analyses as planned in our ongoing assessments. Where estimates are meaningfully different from published rates in comparable settings, additional review of case definitions based on consideration of claims profiles is ongoing and may support refinement of the case definitions applied.

An increased rate of myocarditis and possibly pericarditis was observed in young men, which is consistent with findings from surveillance and other published Real-World Evidence studies.

mRNA-1273-P904

Post-Authorisation Active Surveillance Safety Study Using Secondary Data to Monitor Real-World Safety of SPIKEVAX in Europe.

Summary: No safety findings have been identified in this study.

mRNA-1273-P905

Monitoring safety of SPIKEVAX in pregnancy: an observational study using routinely collected health data in five European countries.

Summary: No safety findings have been identified in this study.

Please, refer to Appendix 20.6 for further details of the ongoing and planned NIS.

9. INFORMATION FROM OTHER CLINICAL TRIALS AND SOURCES

9.1. Other Clinical Trials

Investigator-sponsored studies

The following 4 Investigator-Sponsored Studies by the National Cancer Institute were ongoing during the reporting period:

Title: A prospective study of rheumatoid arthritis disease activity and immunogenicity following COVID-19 vaccination (RADAVA).

Title: Vaccine responsiveness in patients with chronic lymphocytic leukaemia.

Title: A Phase 2 trial of the safety and immunogenicity of the COVID-19 vaccine in participants with hematologic malignancies and various regimens of immunosuppression, and in participants with solid tumours on PD1/PDL1 inhibitor therapy.

Title: Risk factors for infection with SARS-CoV-2 and for life-threatening evolution of COVID-19 in patients with autoimmune diseases in Switzerland.

Summary: No significant safety findings have been identified in any of the above study during the reporting period of this PBRER.

Other trials sponsored by Licensing partners

During the reporting period, the following clinical trials sponsored by DMID of NIAID were ongoing:

Protocol mRNA-1273-P101/20-0003/NCT04283461

A Phase 1, open-label, dose-ranging study to access the safety and immunogenicity of mRNA-1273 in healthy adults aged 18 years and older.

Protocol mRNA-1273-P102/21-0002/NCT04785144

A Phase 1, open-label, randomized study to access the safety and immunogenicity of a SARS-CoV-2 variant vaccine (mRNA-1273.351) in naïve and previously vaccinated adults.

Protocol 21-0012

A Phase 1/2 study of delayed heterologous SARS-CoV-2 vaccine dosing (Boost) after receipt of EUA vaccines.

No significant safety findings have been identified from the above clinical trials during the reporting period.

During the reporting period following study was conducted by **Licensing partner GSK** was ongoing:

217670 (ZOSTER-091)

A Phase 3, randomized, open-label, controlled, multicentre study to evaluate the immune response and safety of both herpes zoster subunit vaccine in healthy adults aged 50 years and older and the influenza virus vaccine in healthy adults aged 18 years and older when administered sequentially or co-administered with mRNA-1273 booster vaccination.

No significant safety findings in this ongoing clinical trial have been identified during the reporting period.

During the reporting period following study was conducted by **Licensing partner Sanofi** was ongoing:

QHD00028

A Phase II, open-label study to assess the safety and immunogenicity of Fluzone® high-dose quadrivalent (Influenza vaccine), 2021-2022 formulation and a third dose of Moderna COVID19 vaccine (mRNA-1273 vaccine) administered either concomitantly or singly in adults 65 years of age and older previously vaccinated with a 2-dose schedule of Moderna COVID-19 vaccine.

Summary: No significant safety findings in these ongoing clinical trials have been identified during the reporting period.

9.2. Medication Errors

Please, refer to Section 16.3.6.8.1 for a cumulative evaluation on vaccination errors.

10. NON-CLINICAL DATA

An 8-week Good laboratory practices toxicity study (Study # 2308-245) of SPIKEVAX following intramuscular injection in rats with a 2-week recovery period was performed. This study indicated a similar toxicity profile to the aggregate toxicology data presented previously. Using the clinical formulation was used to administer at dose of 40 ug intramuscularly. There were no SPIKEVAX related mortalities, ophthalmic effects or changes in body weight, body weight gain, food consumption, or body temperature. SPIKEVAX elicited a robust serologic antibody response prior to termination that was still stable at recovery necropsy.

The primary observations consisted of erythema/oedema at the injection site with consistent microscopic changes including inflammation and hemorrhage at the injection site, increased cellularity/infiltration of immune cells (lymphocytes, neutrophils) in injection site/draining lymph nodes. Increased cellularity in the bone marrow. These changes were consistent with clinical

pathology changes indicative of systemic inflammation (increased total leukocyte, neutrophil, eosinophil, basophil, and large unstained cells counts; increased fibrinogen and globulin and increases in acute phase markers). These changes resolved or were considered resolving following the recovery period.

Conclusion: No new information was identified from non-clinical data.

11. LITERATURE

A literature search was performed in two major literature databases (EMBASE® and MEDLINE®) covering the period from 01 Jul 2021 to 31 Dec 2021. The literature search was completed in three parts.

Part one search related to the product (mRNA-1273 or "mRNA 1273" or mRNA1273 or "Modernatx 1273" or "moderntx 1273" or "Moderna Covid19 Vaccine" or SPIKEVAX or Elasomeran or "CX-024414" or "TAK-919" or "TAK 919" or TAK919) covered the active ingredient (messenger RNA) and included scientific literature available from conferences, non-clinical and clinical studies, and poster sessions. Part two search covered all literature abstracts for the drug class (mRNA vaccine, SARS CoV-2 vaccine). The search covered an elaborate compilation of free text search terms which included numerous synonymous expressions and abbreviations. Part three search covered multiple adverse event and therapeutic use terms.

Part 1, 2, 3 search strings were combined to review for all the terms. The search covered an elaborate compilation of free text search terms which included numerous synonymous expressions and abbreviations.

Relevant literature articles containing new and significant safety findings relevant to SPIKEVAX published during the reporting period were retrieved. There were 3 articles which contained relevant safety information. The findings from these 3 articles have been summarized below. For more detailed information and full text articles please refer to Appendix 20.11.82.

Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 29 Nov-02 Dec 2021 [6]

In a Nordic cohort study including a meta-analysis of the 23 million residents of Denmark, Finland, Norway and Sweden made available to the MAH prior to publication (Karlstad, 2021) [7] during the 28-day risk-periods following vaccination and during unvaccinated periods experienced by the study participants (6.7 million person-years in total), they observed 1,092 incident myocarditis cases and 1,154 incident pericarditis cases. Incidence rates of myocarditis during unvaccinated time was 9.7 per 100,000 person-years for men, and 4.2 for women. Among 16- to 24-year-old, incidence rates were 18.7 for men and 4.4 for women. Incidence rates of pericarditis increased with increasing age.

The results of the study showed:

- Adjusted Rate Ratios (RRs) comparing the 28-day risk periods following first- and second-dose vaccinations to unvaccinated periods were 1.2 (95% Confidence interval [CI], 0.7 to 1.9) and 7.2 (95% CI, 5.3 to 9.8).
- In males, following the first and second dose, adjusted RRs were 1.5 (95%CI, 0.8 to 2.5) and 9.1 (95%CI, 6.9 to 12).
- In males, 16-24 years of age, the adjusted RR was 14.2 (95%CI, 8.4-23.8) for a second dose of SPIKEVAX. For females, the comparative adjusted Incidence Rate Ratio (IRRs) were lower.
- Among all males, the excess number of events per 100,000 vaccinated in the 28-day risk periods were 0.3 (95%CI, -0.1 to 0.8) and 5.4 (95%CI, 4.0 to 6.8) following first and second doses for SPIKEVAX. The excess number of events for females were low.
- Among males 16–24 years, the excess number of events per 100,000 vaccinated in the 28-day risk periods following first and second doses were 1.7 (95%CI, -0.2 to 3.7) and 18.8 (95%CI, 9.6 to 28.0) for SPIKEVAX. The corresponding excess number of events for males 25 to 39 years of age were somewhat lower.
- In a mixed schedule (BNT162b2-mRNA-1273), close to 40 cases (34 males) occurred following the second dose. In males 16-24 years, 17 cases occurred, with an excess number of events of 26.5 (95%CI, 13.9 to 39.1).
- Incidence Rate Ratios of myocarditis or pericarditis combined in males 16–24 years were close to those of myocarditis.
- In males 25–39 years the RRs were generally lower. In females 16–24 years the IRRs were similar to those of males of the same age, however, with wider CIs.
- A 7-day risk period was also evaluated for the 228 myocarditis cases in the 28-day risk-window after a second dose of mRNA:
    1. 145 vaccination, events occurred within the first week, yielding higher IRRs. The excess events, per 100,000 vaccinated, during 7-day risk-window represented the majority of excess events during the 28-day risk-window.
    2. In males 12–39 years, at least 75% of the cases were admitted to hospital within 10 days of vaccination.
    3. Comorbid conditions did not differ markedly between vaccinated and unvaccinated cases.

4. Length of stay did not markedly differ between vaccinated and unvaccinated cases.

The authors concluded that the information collected in this study of 23.1 million individuals shows higher rates of myocarditis and pericarditis within 28 days following vaccination with SARS-CoV-2 mRNA vaccines when compared to unvaccinated. These associations were strongest within the first 7 days, were increased for all combinations of mRNA vaccines and were more pronounced after the second dose. A second dose of SPIKEVAX, either after SPIKEVAX or BNT162b2 as a first dose, had the highest risk. Young males aged 16-24 years had the highest increased risk. They also concluded that there was a higher risk after a second dose and a higher risk in young men, information that has already been documented and communicated to health care provided through appropriate risk communication measures.

The authors also presented excess events within 28 days in young males of 5.7 per 100,000 after a second-dose vaccination with BNT162b2 and 18.8 after a second-dose vaccination with SPIKEVAX which are higher than previously reported.

Relevance: Information presented within this study prompted a safety evaluation which was used to change the reporting frequency of the events of myocarditis and pericarditis from unknown to very rare overall and rare for males younger than 40 years of age.

Association between COVID-19 messenger RNA vaccines and the occurrence of myocarditis and pericarditis in people aged 12 to 50 in France - Study based on data from the National Health Data System SNDS [8]

A population-based matched case-control analysis using French national health data from the National Health Data System (SNDS) linked to data from national information systems on vaccination against COVID-19 (VAC-SI) and on health tests screening for SARS-CoV-2 (SI-DEP). has shown a large increase in the odds of myocarditis within 7 days after vaccination, noting that CIs were wide. All cases of hospitalization for myocarditis or pericarditis occurring between 15 May 2021 and 31 Aug 2021 among all people aged 12 to 50 in France were included. Each case was matched to 10 controls of the same age, sex, and department of residence. The risks of hospitalization for myocarditis or pericarditis were compared between people exposed and not exposed to Pfizer-BioNTech and Moderna vaccines, separately by sex and by age group, by conditional logistic regression models adjusted on history of myocarditis or pericarditis in the previous 5 years, the history of SARS-CoV-2 infection in the previous month and the social deprivation index.

A total of 919 cases of myocarditis (median age 26, 21% female) and 917 cases of pericarditis (median age 34, 38% female) occurred among people aged 12 to 50 in France during the study period. These cases were matched respectively to 9190 controls (for myocarditis) and 9170

controls (for pericarditis). Overall, vaccination with Pfizer BioNTech and Moderna vaccines was associated with an increased risk of hospitalization for myocarditis and pericarditis within 7 days of vaccination. The association with the risk of myocarditis appears particularly pronounced in young men under 30 years of age, particularly after the second dose of Moderna vaccine (adjusted odds ratio (OR) 79.8; 95% CI [29.8-213.4]), leading to an excess of cases reaching 132 per million doses in this population. Although the occurrence of myocarditis is less frequent than in men, this risk is also increased in young women under 30 years old after the second dose (OR 40.6 [9.9-166.4] and 37 cases in excess per million doses for Moderna). The risk of pericarditis also appears to be more marked after the Moderna vaccine in people under 30 years of age, in particular after second dose in men (OR 15.0 [3.3-68.4] and 18 excess cases per million doses) and after the first dose in women (OR 27.9 [2.4-328, 0] and 6 excess cases per million doses).

The clinical course of cases of myocarditis and pericarditis appears generally favorable, with a hospital stay of around 2 to 4 days on average. Over the period studied, no deaths were reported among people hospitalized for myocarditis or pericarditis following vaccination.

In addition, infection with SARS-CoV-2 in the previous month was also associated, in multivariate analyses, with the occurrence of myocarditis (OR 7.9 [5.0-12.3]) and with occurrence of pericarditis (OR 3.9 [2.3-6.6]).

The conclusion of this study is that the number of cases attributable to vaccines appears to be infrequent in relation to the number of doses administered. This study also confirms the favorable clinical course of cases of myocarditis and pericarditis following vaccination. However, the number of cases attributable to vaccines appears to be infrequent in relation to the number of doses administered. This study also confirms the favorable clinical course of cases of myocarditis and pericarditis following vaccination.

Relevance: Information presented within this study prompted a safety evaluation which was used to change the reporting frequency of the events of myocarditis and pericarditis from unknown to very rare overall and rare for males younger than 40 years of age.

Myocarditis Following COVID-19 mRNA Vaccine: A Case Series and Incidence Rate Determination [9]

A retrospective case series was performed utilizing the Mayo Clinic COVID-19 Vaccine Registry (which tracks recipients of COVID-19 vaccines administered at the Mayo Clinic main campus in Rochester, Minnesota, and the Mayo Clinic Health System in the upper Midwest states). The authors measured the IRR for myocarditis temporally related to COVID-19 mRNA vaccination compared to myocarditis in a comparable population from 2016 through 2020. Clinical characteristics and outcomes of the affected patients was collected. A total of 21 individuals were

identified, but ultimately seven patients met the inclusion criteria for vaccine-associated myocarditis. An incidence rate ratio for myocarditis following COVID-19 mRNA vaccination was found to be increased for males at a rate ratio of 6.69 (95% CI 2.35-15.52) with poor precision for females (IRR 1.41, 95% CI 0.03 – 8.45). Limited sample size precluded stratified analyses.

Relevance: Information presented within this study prompted a safety evaluation which was used to change the reporting frequency of the events of myocarditis and pericarditis from unknown to very rare overall and rare for males younger than 40 years of age.

The consequences of COVID-19 pandemic on patients with monoclonal gammopathy–associated systemic capillary leak syndrome (Clarkson disease) [10]

Information presented in this article according to the authors, is in reference to recent reports of episodes and relapses of Clarkson's disease due to infections associated with SARS-CoV-2 as well as after receiving any of the COVID-19 vaccines. The authors, the EurêClark registry is an international study group, which gather observations of Monoclonal Gammopathy associated Systemic Capillary Leak Syndrome (MG-SCLS) and prospectively monitor attacks, preventive treatments, complications and outcome of patients. The MG-SCLS also known as "Clarkson's syndrome" is a rare condition characterized by unexplained recurrent attacks of systemic capillary hyperpermeability in the presence of monoclonal gammopathy (MG).

All patients with a diagnosis of monoclonal gammopathy–associated SCLS included in the EurêClark registry and alive at the start of COVID-19 pandemic (February 1, 2020) were included and evaluated until July 10, 2021. Thirty patients were included, with a female-to-male ratio of 1.3 and a mean ± standard deviation age of 58 ± 14 years. Every patient had an IgG gammopathy with kappa (n = 24) or lambda light chain (n = 7). Most patients were under long-term treatment with IVIg (n = 27, 90%). Five patients (17%) experienced a relapse related to a proven (n = 3) or highly probable severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, with a fatal outcome in 4 patients. None had evidence of COVID-19 pneumonia, and all experienced typical flare of Clarkson's disease with severe hypovolemic shock and refractory multiple-organ failure. Twenty patients underwent COVID-19 vaccination with BNT162b2 (Pfizer-BioNTech, Pfizer Inc, New York City, NY), n = 17; Ad26.COV2.S (Janssen Pharmaceuticals, Beerse, Belgium), n = 1; and mRNA-1273 (Moderna Inc, Cambridge, MA), n = 2. Vaccination was uneventful in 18 patients, including 2 not receiving IVIg. Two patients treated with IVIg had a relapse after a second dose of mRNA vaccine, with a favorable outcome in both cases. During the time of the study, 5 patients had a new diagnosis of Clarkson disease and were reported to the EurêClark registry. All required intensive care unit management, and 1 died during this opening episode. Four had their first flare triggered by a polymerase chain reaction–confirmed COVID-19 infection. The last

patient, previously known to have a monoclonal gammopathy, had a typical opening flare of SCLS 3 days after the first injection of ChAdOx1 (AstraZeneca).

One of the most important points of this article is the burden that the COVID-19 pandemic has brought to patient with Clarkson disease. As the authors mentioned in their article, COVID-19 infection seems to induce very frequently a relapse of Clarkson disease. “Every patient from our cohort with a proven or suspected SARS-CoV-2 infection had a severe flare, fatal in 80% of cases. To the best of our knowledge and in the published literature, there is no report of uneventful SARS-CoV-2 infection in these patients.” Viral infection in general, frequently elicits relapse in patients with Clarkson disease. But it seems that vascular leakage plays a major role in COVID-19 pathophysiology and may explain the high relapse risk during SARS-CoV-2 infection. Another important point noted by the authors was the lack of response to treatment with IVIg to patients infected with COVID-19, including those that may had been asymptomatic, when compared to those that may had experienced a flare temporarily related to the administration to one of the COVID-19 vaccines.

The evidence provided in this article only shows that rare disorders like SCLS during conditions like the one we are living today, in which just with SPIKEVAX, as of 31 Dec 2021, more than 400 million people have been vaccinated, continuous surveillance activities need to maintain evaluating the information to becomes available in order to assess any possible associations.

Relevance: Information provided in this article prompted a safety evaluation requested by a health authority.

12. OTHER PERIODIC REPORTS

No other periodic reports have been written for SPIKEVAX.

13. LACK OF EFFICACY IN CONTROLLED CLINICAL TRIALS

No data regarding lack of efficacy that would constitute a significant risk to the treated population were received during the reporting period.

14. LATE-BREAKING INFORMATION

No late-breaking information has been received after the DLP that impacts the safety profile of SPIKEVAX.

15. OVERVIEW OF SIGNALS: NEW, ONGOING OR CLOSED

15.1. Validated signals during the reporting period

The ModernaTX, Inc has an established signal management process (based on EMA GVP Module IX-Signal Management-Rev 1 and Module IX Addendum I) including signal detection, validation

and evaluation. During weekly signal detection, data sources are electronically screened for new safety information related to SPIKEVAX and any new potential signals are reviewed by a team of physicians and scientists from multiple disciplines, including non-clinical, clinical and Pharmacovigilance (PV) personnel. Observed over expected (O/E) analysis is also used to support initial screening of datasets, to detect statistical trends used to support qualitative medical and scientific review of new safety information, and to provide statistical guidance on significant trends. Following initial review of the available data, a determination is made on the basis of the nature and the quality of the new information whether further investigation is warranted, at which point those topics referred for further investigation are considered "validated signals"; Potential signal detection data sources include: safety data from ModernaTX, Inc-sponsored clinical trials and other studies (e.g. from observational research and investigator initiated studies supported by ModernaTX), spontaneous AE reports, published literature, and communications from external sources, including regulatory agencies, and (if applicable) business partners. The ModernaTX, Inc's PV system relies primarily on AEs contained in its global PV database (Argus) that captures suspected AE reports. Routine PV also includes a periodic review of the literature that involves targeted keyword searches in widely recognized databases (i.e., MEDLINE, EMBASE) as well as abstracts from scientific meetings.

To supplement the results of the routine PV activities, ModernaTX, Inc performs monthly aggregate quantitative signal detection reviews for possible ARs on various data sources, such as 1) their GSDB, using a calculated intra-product disproportionality ratio named product fractional reporting ratio (PFRR). This PFRR compares the reporting percentage of each MedDRA PT in current review period with that of the same PT respectively, in the previous period and cumulatively, which are reviewed for triggering of potential signals using predefined thresholds for PFRR and PT counts; 2) EudraVigilance data analysis system, using EMA's electronic Reaction Monitoring Reports (eRMR); and 3) VAERS, using the lower bound of the 90% confidence interval of the Empirical Baysian Geometrical Mean (EBGM) (EB05).

This routine aggregate review also includes O/E analyses, which are performed as follows. The MAH first estimates the number of doses used globally in the relevant timeframe. Moderna supply chain estimates are used to define the number of doses SPIKEVAX distributed by country; however, administration data are tracked by health officials within countries receiving the vaccine. Therefore, Moderna estimates administration of SPIKEVAX based on information retrieved through the US Centers for Disease Control and Prevention (https://covid.cdc.gov/covid-data-tracker/#vaccinations), the European Centers for Disease Control (https://qap.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#distribution-tab), Health Canada (https://health-infobase.canada.ca/covid-19/vaccination-coverage/), the Swiss Federal Office of Public Health (https://www.covid19.admin.ch/en/epidemiologic/vacc-doses),

and Our World in Data (https://ourworldindata.org/covid-vaccinations) (data retrieved on 01 Jan 2022). For countries that do not publish vaccine administration numbers by brand, it is assumed that half of distributed doses have been administered.

In order to calculate observed reporting rates, a risk window of 21 days was then assigned after each administered vaccine dose unless otherwise specified (e.g., for anaphylaxis, a risk window of 3 days was assigned; for myocarditis, both 21- and 7-day windows were used). This window was selected for consistency with analyses that have been conducted by the US Vaccine Safety Datalink. The sum of all person-time as applicable for the reporting period or cumulative analysis time frame was then used as a denominator to calculate the reporting rate. Population-based expected rates were then multiplied by the same person-time estimate to identify the count of expected cases.

Age, gender, and age by gender stratified assessments of observed to expected rates were additionally performed where feasible. Our knowledge of demographics for administration data is limited to the information tracked and published by health officials within countries receiving the vaccine. Not all health authorities provided the same age strata when sharing this information, and these are not always aligned with age categories presented in literature-based sources of external data on the estimated incidence of conditions of interest. Since a large proportion of SPIKEVAX doses to date have been administered in the US, we applied the US age distribution to the total administered doses of vaccine administered and corresponding person-time accrued. Because the Pfizer-BioNTech vaccine has been authorized for use in adolescents (12-17 years) in the US, it is expected that the large majority of COVID-19 vaccine doses seen in this age group are not Moderna's SPIKEVAX. To account for this, we limited the total assumed accrued exposure in individuals < 18 years to 3% of the total. The estimate of 3% was selected based on the assumption that adolescent use in the US, where approximately half of global administrations have occurred and authorization is limited to age ≥ 18 years, is substantially lower than use in the EEA, where adolescent use is authorized and approximately 6% of COVID-19 vaccinations across all brands have been administered to individuals < 18. Based on the distribution of adverse event reports of all types in safety database, is it estimated that 95% of doses in individuals <18 years of age have been administered to adolescents.

The following ongoing, or closed signals were identified during the reporting period of this PBRER as described in Appendix 20.4.1.

Table 15.1 Status of Validated Signals

Signal	Cross reference to the corresponding procedure for which a safety evaluation or regulatory request has been closed during the reporting period	Status (Ongoing/ Closed)	Outcome (Refuted/ Substantiated)	Assessed in another regulatory procedure (MSSR or a variation)
Dizziness	MSSR procedure No EMEA/H/C/005791/MEA/0011	Closed	Substantiated*	MSSR report # 07 with DLP 31 Jul 2021
Neuralgic Amyotrophy	MSSR procedure No EMEA/H/C/005791/MEA/0011	Closed	Refuted	MSSR report # 07 with DLP 31 Jul 2021
Erythema Multiforme	EMA Signal Assessment report on Erythema Multiforme	Closed	Refuted	MSSR report # 07 with DLP 31 Jul 2021 and MSSR report # 08 with DLP 31 Aug 2021
Glomerulonephritis and nephrotic syndrome	SDA 036; EPITT No 19720	Closed	Refuted	MSSR report # 07 with DLP 31 Jul 2021 and MSSR report # 08 with DLP 31 Aug 2021
Serious Hypertension	(EMA/PRAC/408565/2021)	Closed	Refuted	MSSR report # 08 with DLP 31 Aug 2021 and MSSR report # 09 with DLP 30 Sep 2021
Multisystem Inflammatory Syndrome	Erythema labelling variation based on outcome of Signal Assessment report on Erythema Multiforme	Closed	Refuted	MSSR report # 08 with DLP 31 Aug 2021 and MSSR report # 09 with DLP 30 Sep 2021
Myelitis Transverse	EMEA/H/C/005791/IAIN/0040	Closed	Refuted	MSSR report # 09 with DLP 30 Sep 2021 and MSSR report # 10 with DLP 31 Oct 2021
Capillary Leak Syndrome	Signal Assessment report on glomerulonephritis and nephrotic syndrome	Closed	Refuted	MSSR report # 10 with DLP 31 Oct 2021 and MSSR report # 11

Signal	Cross reference to the corresponding procedure for which a safety evaluation or regulatory request has been closed during the reporting period	Status (Ongoing/ Closed)	Outcome (Refuted/ Substantiated)	Assessed in another regulatory procedure (MSSR or a variation)
				with DLP 30 Nov 2021
Cerebral Venous Sinus Thrombosis	SDA 037. EPITT No 19724	Closed	Refuted	MSSR report # 11 with DLP 30 Nov 2021 and MSSR report # 12 with DLP 31 Dec 2021
Myocarditis and pericarditis (PRAC FU EPITT 19713 - Nordic data)	EMEA/H/C/005791/IAIN/0045	Closed	Substantiated***	MSSR report # 12 with DLP 31 Dec 2021
Autoimmune hepatitis	EMA Signal assessment of Autoimmune hepatitis EPITT ref. No. 19750 / ongoing	Ongoing	Refuted**	MSSR report # 12 with DLP 31 Dec 2021

**Identified Risk (Not Important)*
***Autoimmune hepatitis was closed (refuted), after the DLP i.e., on 19 Jan 2022.*
**** frequency of Myocarditis and pericarditis updated from ""unknown"" to ""Very rare"".*

15.2. Requests from Health Authorities or Regulatory Bodies (e.g., PRAC)

Table 15.2 Topics requested by Health Authority (not considered as validated signal)

Topics	Date Requested by Authority	Requesting Authority	Status	Outcome	Assessed in another Regulatory Procedure
Acute Disseminated Encephalomyelitis (ADEM)	02 Sep 2021 (MSSR #7) 22 Sep 2021 (MSSR #8)	EMA	Open An AESI – routine surveillance ongoing	Not considered a safety issue	MSSR #8 MSSR #9 MSSR #10 PBRER#2
Guillain-Barre Syndrome (GBS)	02 Sep 2021 (MSSR #7) 22 Sep 2021 (MSSR #8) 22 Oct 2021 (MSSR #9)	EMA	Open An AESI – routine surveillance ongoing	Not considered a safety issue	MSSR #8 MSSR #9 MSSR #10 PBRER #2
Thrombosis with Thrombocytopenia (TTS)	02 Sep 2021 (MSSR #7) 22 Oct 2021 (MSSR #9) 30 Nov 2021 (MSSR #10)	EMA	Open An AESI – routine surveillance ongoing	Currently reviewed in Safety Summary Reports	MSSR #8 MSSR #10 MSSR #11 PBRER #2

Topics	Date Requested by Authority	Requesting Authority	Status	Outcome	Assessed in another Regulatory Procedure
Myelitis Transverse	02 Sep 2021 (MSSR #7) 22 Sep 2021 (MSSR #8)	EMA	Open An AESI – routine surveillance ongoing	Not considered a safety issue	MSSR #8 MSSR #9 MSSR #10 PBRER #2
Vaccine failure/lack of efficacy	02 Sep 2021 (MSSR #7)	EMA	Closed	Not considered a safety issue	 Included in SSRs 1 – 12 PBRER #2
Neuralgic amyotrophy	02 Sep 2021 (MSSR #7)	EMA	Closed	Not considered a safety issue	MSSR #8 MSSR #9 PBRER #2
Autoimmune/ Inflammatory Disease Flare-ups of: Rheumatoid arthritis; Multiple Sclerosis; Systemic Lupus Erythematosus; Ulcerative Colitis; Crohn's Disease Myasthenia Gravis	30 Sep 2021 (MSSR #8) 13 Jan 2022 (PBRER #1) 07 Dec 2021 (MSSR #8 & 9)	EMA/ Health Canada	Open An AESI – routine surveillance ongoing	Not considered a safety issue	MSSR #8 MSSR #9 MSSR #10 PBRER #2
Rhabdomyolysis	02 Sep 2021 (MSSR #7) 22 Sep 2021 (MSSR #8)	EMA	Open An AESI – routine surveillance ongoing	Not considered a safety issue	MSSR #8 MSSR #9 PBRER #2
Menstrual disorder or post-menopausal hemorrhage	02 Sep 2021 (MSSR #7)	EMA	Closed	Not considered a safety issue	MSSR #8
Herpes Zoster	02 Sep 2021 (MSSR #7)	EMA	Closed	Not considered a safety issue	MSSR #8 MSSR #9

Topics	Date Requested by Authority	Requesting Authority	Status	Outcome	Assessed in another Regulatory Procedure
Subgroup analysis for any topic for 12-17 yo	02 Sep 2021 (MSSR #7)	EMA	Subgroup analyses for 12-17 yo ongoing in SSRs	Ongoing	Included in all SSRs 7 - 12
Deaths Deaths in all subjects	22 Sep 2021 (MSSR #8) 22 Oct 2021 (MSSR #9)	EMA	Closed Sub-population deaths are included under the relevant topic	Not considered a safety issue	Included in SSRs 1-12 MSSR #10
Vasculitis	22 Sep 2021 (MSSR #8)	EMA	Open An AESI - ongoing routine surveillance	Not considered a safety issue	MSSR #9 MSSR #10 PBRER #2
CVST	22 Sep 2021 (MSSR #8)	EMA	Open An AESI - ongoing routine surveillance	Not considered a safety issue	MSSR #9 MSSR #10 MSSR #11 MSSR #12 PBRER #2
Encephalitis	22 Oct 2021 (MSSR #9)	EMA	Open An AESI - ongoing routine surveillance	Not considered a safety issue	MSSR #10 PBRER #2
Pregnancy (change in case definition and expected stillbirths in the observed/expected rate ratios)	22 Oct 2021 (MSSR #9)	EMA	Closed	Request completed	MSSR #10
Elderly (waning immunity)	22 Oct 2021 (MSSR #9)	EMA	Closed	Not considered a safety issue	MSSR #10
Stroke and Thromboembolism (< 18 yo)	30 Sep 2021 (MSSR #8) 04 Nov 2021 (PBRER #1)	EMA Health Canada	Open An AESI - ongoing routine surveillance	Not considered a safety issue	MSSR #9 MSSR #11

Topics	Date Requested by Authority	Requesting Authority	Status	Outcome	Assessed in another Regulatory Procedure
Corneal Graft Rejection	07 Dec 2021 (MSSR #8 & 9)	Health Canada	Closed	Not considered a safety issue	Submitted to HC
Immune Thrombocytopenia flare-ups (ITP))	13 Jan 2022 (PBRER #1)	EMA	Open An AESI - ongoing routine surveillance	Not considered a safety issue	PBRER #2
Glomerulonephritis and nephrotic syndrome	30 Sep 2021 (MSSR #8) 04 Nov 2021 (PBRER #1)	EMA Health Canada	Closed	Not considered a safety issue	MSSR #7 MSSR #8 PBRER #2
Generalized Convulsions	30 Sep 2021 (MSSR #8)	EMA	Open An AESI - ongoing routine surveillance	Not considered a safety issue	MSSR #7 MSSR #8 MSSR #9
Thyroiditis Subacute	13 Jan 2022 (PBRER #1)	EMA	Closed	Not considered a safety issue	PBRER #2
Polymyalgia Rheumatica	13 Jan 2022 (PBRER #1)	EMA	Closed	Not considered a safety issue	PBRER #2

16. SIGNAL AND RISK EVALUATION

16.1. Summaries of Safety Concerns

Table 16-1 provides the Summary of Safety Concerns as per RMP v2.0 with effective date 11 Jun 2021 in place at the beginning of the reporting period.

Table 16-1 Summary of Safety Concerns (As per RMP v2.0 dated 11 Jun 2021)

Important identified risks	• Anaphylaxis
Important potential risks	• Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)
Missing information	• Use in pregnancy and while breastfeeding • Long-term safety

	• Use in immunocompromised subjects • Interaction with other vaccines • Use in frail subjects with unstable health conditions and co-morbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders) • Use in subjects with autoimmune or inflammatory disorders

During the reporting period, RMP v2.1 was updated to include myocarditis and pericarditis as important identified risks and was submitted to EMA on 19 Jul 2021. In addition, there have been updates to the RMP versions (v2.2 dated 16 Aug 2021 through v2.3 dated 28 Oct 2021) with no changes to the list of safety concerns.

16.2. Signal Evaluation

A summary of the results of evaluations of validated signals that were evaluated/re-evaluated and closed (rejected/refuted or considered to be potential or identified risks following evaluation) during the reporting interval is provided below.

Ten (10) signals were closed, nine (9) during the reporting period and one (1) after the reporting period. Based on a scientific evaluation of the available information, eight were refuted one signal ("Dizziness") was categorised as an identified risk (not important), and one signal ("Myocarditis and pericarditis (PRAC FU EPITT 19713 - Nordic data") previously categorized as an important identified risk, remained as such, and was closed following further characterization of the risk frequency.

16.2.1. Dizziness

Table 16-2 Dizziness

Signal evaluation criteria	Summary
Source	The signal evaluation was requested by the Medicines and Healthcare products Regulatory Agency (MHRA). During the review, MHRA identified that dizziness was not currently listed in the UK SmPC for COVID-19 Vaccine. This signal arose from signal detection of UK adverse drug reaction (ADR) reports.
Background	The MAH has developed mRNA-1273, a novel lipid nanoparticle (LNP)-encapsulated messenger RNA (mRNA)-based vaccine against the 2019 novel coronavirus (CoV; SARS-CoV-2). mRNA-1273, the prototype COVID-19 vaccine, encodes for the full-length spike (S) glycoprotein of the Wuhan-Hu-1 strain of SARS-CoV-2, modified to introduce 2 proline residues to stabilize the S glycoprotein into a prefusion conformation (S-2P). mRNA-1273 consists of an mRNA that is manufactured with LNPs composed of 4 lipids: SM-102, cholesterol, DSPC, and PEG2000-DMG. Dizziness is a term used to describe a range of sensations, such as feeling faint, woozy, lightheaded or unsteady. Dizziness that creates the false sense that you or your surroundings are spinning or moving is called vertigo. Dizziness has many causes, including: Overheating and dehydration, Poor blood oxygenation, poor circulation or low blood pressure, Anxiety, Neurological conditions, Low blood

Signal evaluation criteria	Summary
	sugar, Medications and Motion sickness. In general, Dizziness impacts ~15 to 20% of adults annually.
Methodology	The analysis of Dizziness was performed to determine Dizziness customized MedDRA query (CMQ) association with the use of mRNA-1273 treatment and Dizziness secondary to Tinnitus (Vestibular Disorders) was performed using several data sources. • Clinical Trial Data: The Dizziness CMQ PTs were cumulatively reviewed in the MAH safety database with a data lock point (DLP) of 25 Nov 2020, in P301 study. Solicited adverse reactions were also reviewed. • Review of the Pharmacovigilance Database: Post marketing data for validated signal of Dizziness were cumulatively reviewed in the MAH GSDB with a DLP of 30 Jun 2020. The term Dizziness was analyzed by using a cluster of MedDRA PTs dizziness, dizziness exertional, dizziness postural, persistent postural-perceptual dizziness, procedural dizziness, vertigo, vertigo CNS origin, vertigo positional. • Clinical literature search review: A literature search was performed 15 Jul 2021 using PubMed, with the following criteria (Dizziness OR Vertigo OR Tinnitus) AND (mRNA-1273 OR Moderna COVID vaccine OR COVID vaccine OR COVID-19 vaccine OR COVID OR SARS-CoV-2).
Results	Clinical Trial Data: No reports of Severe Medically Attended TEAEs within 28-Days of Any Injection were observed for Dizziness. From the Dizziness CMQ query, only PT of Dizziness was observed during first and second injection, of this one report of Dizziness was serious. No Serious or severe reports of Tinnitus were reported. Tinnitus 28-day counts identical to overall, with overall reports of 20 (<0.1) (PBO 11[<0.1] vs mRNA-1273, 9 [<0.1]). Observed to Expected Analysis Dizziness was observed in 20,080 cases cumulatively in the GSDB (reporting rate 191.14 per 100,000 person-years). This was below population-based estimates suggesting an annual incidence of approximately 3% per year (315,158 cases expected rate ratio 0.06, 95% CI 0.06 – 0.06). Stratified analyses showed higher rates in women than men, however this was consistent with expectation. Sensitivity analyses assuming capture of 50% or 25% of cases in estimation of the reporting rate did not change the interpretation of findings. Tinnitus (defined based on the PT of tinnitus alone) was observed in 2,316 cases cumulatively (reporting rate 22.05 per 100,000 person-years). This was below population-based estimates suggesting an incidence of approximately 54 per 100,000 person-years (5,672.8 cases expected rate ratio 0.41, 95% CI 0.39 – 0.43). Stratified analyses showed higher rates in men and older individuals; however, this was consistent with expectation. Sensitivity analyses assuming capture of 50% cases in estimation of the reporting rate suggest a potential increase in the rate of tinnitus for younger women. Review of the Pharmacovigilance Database Cumulatively, there were 20,080 cases (21,265 events) that involved 4,185 serious cases (1,429 events). There were 24 cases with fatal outcome. A breakdown of the cases reported by gender was 4,722 males, 15,034 females, and

Signal evaluation criteria	Summary
	81 unknown, with a mean age of 51.3 years (SD: 17.9) and a median age of 51 years. This review has been segmented to focus on Dizziness in conjunction with HLT Inner Ear (which includes the PT tinnitus), HLT Non-Site Injuries, or vaccine reactogenicity. Review of post marketing data showed no significant excess in serious, severe or medically attended events. Dizziness is commonly reported after SPIKEVAX administration with typical reactogenicity adverse events. Tinnitus data are inconclusive. SPIKEVAX Tinnitus reports had similar age distribution to background rates. Few unresolved long duration cases were reported. Co-reported adverse events were typical of reactogenicity and usual tinnitus comorbidity. MedDRA HLT of Inner Ear events primarily involved vertigo. There were no unresolved long duration cases reported. Road Traffic Accidents and Falls with fractures or intracranial hemorrhage were not clearly linked to SPIKEVAX. Machinery operation accidents were not reported. **Clinical literature search review:** • **Results:** The search returned no case reports, case series or studies. • **Summary:** No published reports were found that reported cases, case series or studies focusing on dizziness or vertigo or tinnitus in conjunction with mRNA-1273 or another mRNA vaccine against COVID. • **Conclusion:** Although dizziness has been reported in listings of common adverse events that are considered typical reactogenicity of mRNA vaccines against COVID, neither dizziness, vertigo nor tinnitus has been the focus of reporting or study in relation to these vaccines. With regard to COVID-19 disease, neither tinnitus, vertigo nor dizziness has been clearly shown to be a direct result of SARS-COVID-2 infection.
Discussion	Dizziness is uncommon and associated with symptoms of reactogenicity. Clinical trial and post marketing data showed a minimal imbalance between placebo and mRNA-1273 P301 study cohorts. TEAEs showed more in vaccinees arm, as noted above; this is suggestive of early reactogenicity. No imbalance in serious events or medically attended events were observed. Only increase in 7day after 2nd dose suggesting reactogenicity-related events. There were no literature reports of Dizziness following SPIKEVAX/mRNA-1273 retrieved from the literature search. No significant imbalances were observed with Dizziness associated with Tinnitus (Vestibular Disorders) or Vertigo as data are inconclusive with limited information. The reports of tinnitus mostly occurred in the week following vaccination and thus are frequently accompanied by some of the common signs and symptoms of reactogenicity that can lead to further discomfort, anxiety and seeking of medical attention. Observed to expected analyses showed reporting rates below the background. Fatality associated events were not linked causally to vaccine (e.g., cases of suicide and serious chronic diseases such as Guillain-Barre syndrome and alcoholism). Increased incidence of dizziness was statistically significant in 7 days after dose 2, and therefore dizziness has been added to the product information.
Conclusion	Based on this cumulative review, there is evidence to suggest a causal association between mRNA-1273 and Dizziness (Day 1 – 7 after the second dose). Dizziness was considered a identified risk (not important) and being added to mRNA-1273 label with uncommon frequency. Dizziness associated Vestibular Disorders or

Signal evaluation criteria	Summary
	Vertigo had an insufficient evidence at this time and a causal association between mRNA-1273 cannot be established.

16.2.2. Neuralgic Amyotrophy

Table 16-3 Neuralgic Amyotrophy

Signal evaluation criteria	Summary
Source	As per Swissmedic Request for Safety Assessment of Neuralgic amyotrophy, 15 Jun 2021, Swissmedic received one (1) ADR report with PT 'Neuralgic amyotrophy' (4.1(b)) and one (1) ADR report with PT 'Brachial plexus neuritis' () in a timely relation to the administration of COVID-19 Vaccine Moderna dispersion for injection. Furthermore, one (1) report with PT 'Neuralgic amyotrophy' 4.1(b)) was reported following 'COVID-19 vaccine' (not further specified), which is currently being assessed by the respective PV center and asked the MAH for their position on 'Neuralgic amyotrophy' in connection with the administration of COVID-19 Vaccine Moderna dispersion for injection. Cumulative review of this topic covers the period from 18 Dec 2020 to 31 Dec 2021 and is presented in Section 16.3.6.4.5.
Background	As noted in the MAH OE analysis, there is a background rate of neuralgic amyotrophy in the general population. Thus, at least some of the cases of neuralgic amyotrophy following vaccination would have occurred in the absence of vaccination.
Methodology	The company's GSDB was queried for valid, clinical and spontaneous case reports received from Health Care Providers, Health Authorities, consumers and literature, cumulative from 18 Dec 2020 to 31 May 2021, worldwide, and for Switzerland, reported for the mRNA-1273 vaccine (Moderna COVID-19 vaccine Moderna) using the following Preferred Terms (PTs): "Neuralgic amyotrophy, Radiculitis brachial, and Brachial plexus injury".
Results	There were 28 case reports identified worldwide in the MAH GSDB with the PTs of Neuralgic amyotrophy, Radiculitis brachial, and Brachial plexus injury. Six out of the 28 cases (21.4%) were considered serious reports, and 22 (78.6%) were considered non-serious reports. Most of the reports (57.1%) involved persons >50 years old, and females (75%); 39.2% had onset of the events within seven days following last vaccination, and 10 reports were after 1st dose, 12 after the 2nd dose and 6 unknown dose number. There was only one report of neuralgic amyotrophy reported in Switzerland; this report is heavily confounded by the patient's medical history of nocturnal shoulder pain with no other information describing how long the patient has suffered from nocturnal shoulder pain. Sometimes this is the only sign of an attack, i.e., with annoying pain in the upper arm lasting a few hours associated with a subsequent loss of pinch grip for a few months. In reports of neuralgic amyotrophy the patient may have suffered from severe pain in both shoulders and arms for weeks on end and may have a serious orthopnea requiring nocturnal positive pressure. Patients usually suffer only one attack in their life, but up to 25% may go on to suffer a recurrence. Neuralgic amyotrophy is more common in men (male to female ratio 3: 2), with an age of onset usually in the second or third decade but ranging from the neonatal age to the seventh decade.

Signal evaluation criteria	Summary
	Based on the WHO-UMC causality assessment there were 14 reports considered conditional (event or laboratory test abnormality/ more data needed for proper assessment); 13 reports were considered possible (event or laboratory test abnormality, with reasonable time relationship to drug intake; could also be explained by disease or other drugs), and 1 was unlikely (event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable but not impossible); Disease or other drugs provide plausible explanations). As of 31 May 2021, there have been 250,275,820 doses of the mRNA-1273 vaccine distributed worldwide, and 3,980,200 doses of the mRNA-1273 vaccine distributed in Switzerland. Reporting rate for neuralgic amyotrophy worldwide is 0.1 case per 1 million doses of the mRNA-1273 vaccine distributed; reporting rate of neuralgic amyotrophy for Switzerland is 0.2 cases per 1 million doses of the mRNA-1273 vaccine distributed.
Discussion	See Results above.
Conclusion	Based on the analysis of all the safety data available as of 31 May 2021, the MAH considers that Neuralgic amyotrophy, Radiculitis brachial, and Brachial plexus injury are not presently a safety issue of concern. The MAH will continue to closely evaluate events of "Neuralgic amyotrophy, Radiculitis brachial, and Brachial plexus injury" using routine surveillance.

16.2.3. Erythema Multiforme

Table 16-4 Erythema Multiforme (EPITT 19720)

Signal evaluation criteria	Summary
Source	On 23 Jul 2021, Moderna received a PRAC request to evaluate a signal of erythema multiforme (EM). Events of erythema multiforme have been intensively monitored by EMA for COVID-19 vaccines as this is considered an AESI. Supportive cases were picked up during monitoring of these events in EudraVigilance. As of 21 Jun 2021, there were 90 cases of EM reported for SPIKEVAX. Out of the 90 cases, 67 cases were from the United States, 18 from the European Union, 3 from the United Kingdom, and 2 from Singapore. Taking into consideration the above initial evidence of EM, with cases revealing a plausible temporal association to SPIKEVAX, it is considered that the signal deserves further assessment. It was suggested that the MAH for SPIKEVAX (Moderna Biotech Spain, S.L.) should perform a cumulative review of cases reported for erythema multiforme. The MAH should discuss the need to update the product information and risk management plan and submit proposals as appropriate
Background	Erythema multiforme is immune-mediated, multiple rings or target-like lesions (usually less than 3cm per lesion, and multiple), often starting on hands and feet and moving to the trunk, with three concentric color zones (center is dusk/dark with blister or crust, next ring is paler pink, the outer ring is bright red. and can be accompanied by mucosal lesions). The lesions usually develop over 3-5 days and resolve in 1-2 weeks, and in some individuals, it may become a recurrent condition. Current theories suggest a vaccine-induced delayed hypersensitivity reaction when the antigens are presented on keratinocytes, prompting a CD8+ T cell response (Type IV hypersensitivity). EM is often associated with viral infections, including the herpes simplex virus (HSV), and bacterial infections like mycoplasma pneumoniae. EM is also associated with some medications including NSAIDs, statins, sulfonamides, antiepileptics, and antibiotics. Most

Signal evaluation criteria	Summary
	EM usually resolves within several weeks without sequelae, but some patients have recurring episodes for years. EM usually occurs between the ages of 20-40 years, with a slightly higher incidence in males.
Methodology	The assessment of EM in association with the signal evaluation included a cumulative review of clinical trial data for any terms including "Erythema multiforme" from mRNA-1273 P301 as a 25 Nov 2020 and review of Erythema multiforme in the MAH safety database with a data lock point (DLP) of 31 Jul 2021.
Results	There were no reports of EM in clinical trial database. Post marketing data reported 141 cases with 142 events, of which 29 cases met the case definition for EM. Review of these 29 cases did not show any prominent clinical pattern of occurrence of EM. The observed reporting rates of EM are well below background incidence rates. The reported cases require further follow-up to confirm the final diagnosis/etiology. The available data was limited by frequent missing data elements (medical history, concomitant medication, diagnostic biopsy, infectious disease panels) that challenged a comprehensive medical review, and the absence of clear dechallenge/rechallenge information that is common with vaccine products. There were no significant trends regarding age and gender. The event outcomes were unavailable for the majority of cases, so it's unknown if a final etiology was identified for some of the reported cases. There was no clear temporal association with mRNA-1273 administration and the events reports of EM. There was insufficient evidence to demonstrate a causal relationship between SPIKEVAX administration and EM.
Discussion	See Results above.
Conclusion	Overall, there was no imbalance in clinical trial data. There were no literature reports of EM following SPIKEVAX/mRNA-1273 retrieved from the literature search. Observed reporting rate for post-marketing data shows no increase in the observed vs. the expected rate. Based on this cumulative review, there is insufficient evidence at this time of a causal association between mRNA-1273 and EM. The evidence does not show a causal association between SPIKEVAX/mRNA-1273 and EM. Based on all data reviewed, the signal of EM is refuted. The recommendations are no changes to current weekly signal detection process for SPIKEVAX/mRNA-1273 for events of EM, and no changes to clinical trial conduct, labelling, other reference safety information or the risk management plan. The topic of EM will be monitored through routine PV activities.

16.2.4. Glomerulonephritis and nephrotic syndrome

Table 16-5 Glomerulonephritis and nephrotic syndrome (EPITT 19724)

Signal evaluation criteria	Summary
Source	Signal assessment report (EPITT 19724) on glomerulonephritis and nephrotic syndrome was received from PRAC on 23 Jul 2021 requesting the MAH to provide a cumulative review of glomerulonephritis and nephrotic syndrome from all available sources using HLT Glomerulonephritis and nephrotic syndrome to include cases of IgA nephropathy (glomerulonephritis) and minimal change disease (nephrotic syndrome) and related terms. This was triggered by several literature alerts and EudraVigilance data analysis system (EVDAS) data reviews by PRAC.

Signal evaluation criteria	Summary
	Cumulatively, the data reviewed covers the period from 18 Dec 2020 to 31 Dec 2021 and is presented in Section 16.3.6.7.4.
Background	Glomerulonephritis is damage to the tiny filters inside the kidneys (the glomeruli). It is often caused by the immune system attacking healthy body tissue. Glomerulonephritis does not usually cause any noticeable symptoms. It is more likely to be diagnosed when blood or urine tests are carried out for another reason. A normal capillary in a glomerulus keeps red blood cells, white blood cells and most proteins in the blood and only lets watery fluid into the urine. A capillary in a diseased glomerulus lets protein into urine (proteinuria) and red blood cells into the urine (hematuria). Causes of Glomerulonephritis: **Infectious:** • Post-streptococcal glomerulonephritis. May develop a week or two after recovery from a strep throat infection or, rarely, a skin infection (impetigo) and Bacterial endocarditis. **Autoimmune Diseases:** • Systemic Lupus Erythematosus (lupus): A chronic inflammatory disease, lupus can affect many parts of your body, including your skin, joints, kidneys, blood cells, heart, and lungs. • Goodpasture's syndrome. A rare immunological lung disorder that can mimic pneumonia, Goodpasture's syndrome causes bleeding in your lungs as well as glomerulonephritis. • IgA nephropathy. Recurrent episodes of blood in the urine, this primary glomerular disease results from deposits of immunoglobulin A (IgA) in the glomeruli. • IgA nephropathy can progress for years with no noticeable symptoms. **Vasculitis**: • Polyarteritis nodosa. This form of vasculitis affects small and medium blood vessels in many parts of your body, such as your heart, kidneys, and intestines. • Granulomatosis with polyangiitis. Wegener's granulomatosis affects small and medium blood vessels in your lungs, upper airways, and kidneys. **Other**: High blood pressure, Diabetic kidney disease (diabetic nephropathy), Focal segmental glomerulosclerosis.
Methodology	The signal evaluation included a cumulative review of clinical trial data for any terms from HLT of Glomerulonephritis and nephrotic syndrome from mRNA-1273 P301 as a 25 Nov2020 and review in the MAH safety database with a DLP of 31 Jul 2021.
Results	There were no reports from clinical trials between the placebo and mRNA-1273 arms for events within the terms including MedDRA HLT of Glomerulonephritis and nephrotic syndrome. Post marketing data reported 33 cases with 38 events, review of these cases did not show any prominent clinical pattern of occurrence of Glomerulonephritis and nephrotic syndrome outside of what would be expected in a large, vaccinated population. Of 33 cases, 28 cases (84.8%) were medically confirmed. There were no reports of fatal cases. The observed reporting rates of

Signal evaluation criteria	Summary
	Glomerulonephritis and nephrotic syndrome are well below background incidence rates and the reported cases require further follow-up to confirm the final diagnosis/etiology. The available data was limited by frequent missing data elements to facilitate full medical review, and absence of clear dechallenge/rechallenge information that is common with vaccine products. There were no trends regarding age and other factors. There was no clear temporal association with mRNA-1273 administration and the events reports of Glomerulonephritis and nephrotic syndrome.
Discussion	See Results above.
Conclusion	Overall, the findings reviewed with respect to SPIKEVAX do not show convincing evidence of a link to glomerulonephritis, the MAH does not plan to update the product information and/or risk management plan, including relevant risk minimization measures. Similarly, the MAH does not see a need to issue recommendations for patients who experience these events after the first dose and what action should be taken regarding administration of a second dose. There is virtually no evidence to support such a recommendation. Such a decision about revaccination is best handled by the patient and their physician, taking into account the specific clinical situation and patient preferences. Based on this cumulative review, there is insufficient evidence at this time of a causal association between mRNA-1273 and Glomerulonephritis and nephrotic syndrome.

16.2.5. Serious Hypertension

Table 16-6 Serious Hypertension

Signal evaluation criteria	Summary
Source	The MAH received a request from a health authority to provide the cumulative review of serious hypertension that was initiated on the previous PBRER for which a signal evaluation was conducted and refuted during this reporting period. This updated reporting interval review on the topic of serious hypertension provides the new information collected during the reporting interval of this PBRER. Cumulatively, the data reviewed covers the period from 18 Dec 2020 to 31 Dec 2021 and is presented in Section 16.3.6.1.1. In the cumulative review, ModernaTX, Inc should provide at least but not limited to the following: • A tabulated overview of all serious cases, stratified by 1) Age; 2) Gender; 3) Time-to onset; 4) Severity; and 5) Duration • A summary overview of the serious cases 1) for which the causality (as per WHO-UMC causality assessment system) is considered at least possible or probable; and 2) for which the role of the vaccine cannot be excluded. In addition, on 06 May 2021 routine safety surveillance team meeting, a signal of disproportionate reporting (SDR) for PT Hypertensive crisis was flagged for further medical review by the MAH. Disproportionality was noted for events of PT Hypertensive crisis, an IME, with ROR (-) ≥2 for North America only (ROR – 2.06). No disproportionality was noted for other events within Narrow Hypertension SMQ.

Signal evaluation criteria	Summary
	Based on both triggers, the MAH considered the concept of serious hypertension (including hypertensive crisis) as a potential signal with a detection date of 06 May 2021. An analysis of serious hypertension was submitted in the first 6-month PBRER. Signal validation and evaluation occurred at a 10 Sep 2021 safety and risk management team meeting.

Background	Hypertension is a common health issue among adults worldwide. In 2019, the global prevalence of hypertension in adults aged 30-79 years was 32% in women and 34% in men, with just 47% of women and 38% of men receiving treatment for their hypertension. Additionally, of those receiving treatment, less than half (23% of women and 18% of men) had well-controlled hypertension (Zhou 2021).
	It is important to consider the impact of the COVID-19 pandemic on lifestyle, such as diet and exercise routines, and on regular medical care, which, in turn, is likely to have a noticeable impact on the detection, treatment, and control of a highly prevalent condition like hypertension. A longitudinal study of the impact of the COVID-19 pandemic on changes in blood pressure was conducted by Laffin, et al. (2022) [11] and included 464,585 participants in an employer-sponsored wellness program in the United States for which it was a requirement to have their blood pressure measured by trained personnel in each of the years from 2018 to 2020. The findings revealed that there were no differences between the 2019 and 2020 blood pressure for those participants who had their measurements taken through March 2020; however, there was a significant increase in the annual blood pressure for participants whose blood pressure was measured from April to December 2020, blood pressure was significantly higher than it was in 2019. Weight gain during the pandemic period was investigated as a potential contributor, but this was ruled out, as there was a decrease in weight for men, overall, and the increase in weight for women was the same as during the pre-pandemic period. Both systolic and diastolic blood pressure increases were seen in men and women and across age groups, with larger increases in both measurements for women, in systolic blood pressure for older participants, and in diastolic blood pressure for younger participants.
	The mRNA-1273 RSI was reviewed to identify any information relevant to the signal of serious hypertension.
	• IB (v7.0 dated 18 Aug 2021): Hypertension discussed in Section 5.5.1 “Safety” as a commonly reported unsolicited treatment emergent adverse events (TEAE) in Study P301 Part A as of 04 May 2021 and in Section 6.1.2 “Possible Risks and Adverse Reactions”
	  • “TEAEs that were reported for ≥ 1% of participants in the mRNA-1273 group and did not show higher incidence compared with the placebo group were arthralgia, myalgia, nasal congestion, and **hypertension**”
	• Hypertension is **not listed** in RMP (v2.0 dated 08 Jun 2021) as an important risk though use in patients with unstable health conditions and comorbidities, including cardiovascular disease, listed as missing information
	• Hypertension is **not listed** in in labelling documents including:
	  • CCDS (v8.0 dated 30 Aug 2021)
	  • SmPC (dated 17 Aug 2021)

Signal evaluation criteria	Summary
	• US EUA Fact Sheets (dated 27 Aug 2021)
Methodology	The ModernaTX, Inc global safety database was queried for valid case reports of serious hypertension received from HCP, HA, consumers, and literature for the mRNA-1273 vaccine (COVID-19 vaccine Moderna) SPIKEVAX, using the Standard MedDRA Query (SMQ) of Hypertension (narrow). The output was further refined by filtering for serious events, henceforth referred to as "serious hypertension". Identified events of serious hypertension were evaluated utilizing the European Society of Cardiology and European Society of Hypertension (ESC/ESH) 2018 guidelines (Williams 2018) which classify blood pressure according to seated clinic blood pressure measurements and by the highest level of blood pressure, whether systolic or diastolic; and were categorized, accordingly Clinical trial data from the Phase 3 interventional mRNA-1273 P301 study Part A as of the data cutoff of 04 May 2021 was reviewed using the Narrow Hypertension Standardized MedDRA Query (SMQ, MedDRA version 23.0) on unsolicited TEAE data to identify reports of hypertension. All unsolicited TEAEs and serious TEAEs were reviewed. Post-marketing data: ModernaTX, Inc's GSDB was queried for spontaneous, valid case reports received from healthcare providers, health authorities, literature, and consumers, from 18 Dec 2020 to 30 Jun 2021, worldwide, using the narrow Hypertension SMQ (MedDRA version 24.0) and filtering for events of hypertension that were assessed as serious. This analysis includes all serious reports of PT Hypertensive crisis. Literature Search Criteria**:** Combinations of "Hypertension" AND at least one of mRNA-1273 OR Moderna COVID vaccine OR COVID vaccine OR COVID-19 vaccine OR COVID OR SARS-CoV-2. Databases Used: PubMed search performed on 20 Aug 2021
Results	Clinical trial data: Based on the review of the mRNA-1273 P301 Study Part A as of 04 May 2021, there was no imbalance noted in the incidence of all unsolicited TEAEs or in serious TEAEs within the Narrow Hypertension SMQ between the placebo and mRNA-1273 arms. The serious cases of hypertension reported in mRNA-1273 recipients were reported in elderly subjects with multiple cardiovascular risk factors and did not have a strong temporal association with vaccine administration. Post-marketing data: Upon review of serious post-marketing reports within the Narrow Hypertension SMQ, while there is a temporal association of these events with vaccine administration, the majority of events occurred in the population typically at risk for hypertension or occurred concurrently with events that could directly or indirectly contribute to the elevation of blood pressure (stress, anxiety, pain, other cardiovascular events, reactogenicity, etc.,). The one notable difference from the background population at higher risk of hypertension was that the majority of reports were in females. Cumulatively, 534 serious cases of hypertension were identified including a total of 543 serious events of hypertension. Of these, 19 cases had a fatal outcome, including 20 fatal events, and 421 cases (78.8%) of serious hypertension were medically confirmed. Following review of the safety information included in this analysis, there was insufficient evidence at this time to support a causal association between serious hypertension and SPIKEVAX. There was no non-clinical

Signal evaluation criteria	Summary
	data to support a direct effect of mRNA-1273 or SM-102, the small molecule lipid used in the LNP formulation of mRNA-1273, on blood pressure. While there has been proposed a theoretical mechanistic link between systemic spike protein and renin-angiotensin system which could lead to increases in BP, this causal association in non-clinical studies has not been demonstrated. There was a temporal association with SPIKEVAX administration in post-marketing reports of serious hypertension, particularly for the first few days after the first dose of SPIKEVAX. The occurrence of hypertension after SPIKEVAX administration could also potentially be due to a component of the acute stress/anxiety/pain response or as a secondary symptom from reactogenicity symptoms or the inflammatory response associated with vaccination (Immunization stress-related responses: A manual for program managers and health professionals to prevent, identify and respond to stress-related responses following immunization (Pan Y et al, 2015 [12]; Sacco M et al, 2013 [13]; Pickering TG et al, 2003 [14]). In addition, there was a female predominance for the post-marketing reports of serious hypertension which differed from the baseline tendency for a higher risk of hypertension in males. However, white coat hypertension has been reported to have a stronger association with female gender (Gualdiero P et al, 2000 [15], Streitel KL et al, 2011 [16]; Thomas O et al. 2016 [17]). However, the post-marketing reports of serious hypertension primarily occurred in older patients, many of whom had multiple cardiovascular risk factors or concurrent events that could directly or indirectly contribute to elevated blood pressure. The observed report rate for post-marketing reports of serious hypertension were well below background incidence rates. There was limited evidence in the literature supporting a potential causal association between hypertension and mRNA COVID-19 vaccination.
Discussion	See Results above. Additionally, there were no reports of serious hypertension events in children 0-17 years during the reporting period (01 Jul 2021 to 31 Dec2021). Please see results in Section 16.3.6.1.1.
Conclusion	Based on review of the clinical safety data, non-clinical safety information, scientific literature and medical plausibility, the cumulative evidence is insufficient to support a causal association between serious hypertension and SPIKEVAX. ModernaTX, Inc considers that cases included in the review of serious hypertension temporally associated with the administration of SPIKEVAX, did not raise any safety concerns. ModernaTX, Inc will continue to monitor events of serious hypertension using routine surveillance. The benefit-risk evaluation remains positive.

16.2.6. Multisystem Inflammatory Syndrome

Table 16-7 Multisystem Inflammatory Syndrome (EPITT 19732)

Signal evaluation criteria	Summary
Source	The signal of Multisystem Inflammatory Syndrome (MIS) was triggered based on a PRAC recommendation dated 03 Sep 2021 within a signal procedure (EPITT ref. No. 19732). Cumulative review of this topic covers the period from 18 Dec 2020 to 31 Dec 2021 and is presented in Section 16.3.6.5.1.

Signal evaluation criteria	Summary
Background	In the initial months of the COVID-19 pandemic, it was observed that a fraction of children was developing a life-threatening, hyperinflammatory state, later named Multisystem Inflammatory Syndrome in Children (MIS-C). There have been similar reports of this condition following COVID-19 infection in adults (MIS-A). MIS is a rare complication, and the prevalence is still unclear; however, the rate of occurrence seems to be lower in adults than in children. By mid-May 2020, the CDC and WHO had recognized MIS-C with published case definitions, with the CDC later publishing a case definition specifically for MIS-A. The immunopathology of MIS is not clearly understood, and it can mimic severe, hyperinflammatory COVID-19 disease, making diagnosis difficult. Clinical presentations have similarities with other recognized disease states, such as Kawasaki Disease (KD), toxic shock syndrome (TSS), and macrophage activation syndrome (MAS)/secondary hemophagocytic lymphohistiocytosis (HLH). MIS-C typically has an onset within 4-6 weeks of primary COVID-19 infection; however, this time frame is extended to 12 weeks for MIS-A. Signs and symptoms of MIS include fever, abdominal pain, vomiting, diarrhea, altered mental status, rash, shock/hypotension, and chest pain. Clinical findings include cardiac dysfunction, myocarditis, pericardial effusion, acute kidney injury, pneumonia, elevated inflammatory markers. Steroids and IVIG have been used to successfully treat MIS, in addition to supportive care, including intravenous fluids, vasopressors, and mechanical ventilation. Children who develop MIS-C are generally previously healthy and the overwhelming majority appear to return to their pre-morbid baseline with respect to cardiac status. Patients with MIS-A have been reported up to age 50 years and, compared to MIS-C, are more likely to have underlying health conditions and experience an identifiable antecedent respiratory illness. Although it is a rare illness, there is an estimated 1 in 125,000-250,000 individuals affected by MIS each year, worldwide. Most cases occur in children (majority younger than age ten, and the remainder between the ages 10 to 20), but MIS has been documented in adults ranging from ages 18-82, as well. The disease occurs more commonly in males than in females (male to female ratio 1.3:1), and more often seasonally in the winter and spring (historically, the colder months of the year). As of 27 Aug 2021, total number of cases with MIS-C were 4,661. There is limited information available regarding MIS in adults. Davogustto et al [18], found that among 7196 patients with evidence of SARS-CoV-2 infection by RT-PCR, 15 patients met the risk of MIS-A. The median age of these 15 patients was 45.1 (21.3-84.0) years and similar to MIS-C, the disease occurs more commonly in males than in females.
Methodology	A search of the clinical trial database was performed to identify MIS reported with mRNA-1273 as a suspect drug in the pivotal phase three protocol, mRNA-1273-P301 Part A through 04 May 2021. A search from the GSDB from IBD of 18 Dec 2020 to 02 Sep 2021 was performed to identify possible cases of MIS in children and adults. The search included terms from the MedDRA version 24.0, coded to the following PTs multisystem inflammatory syndrome in children, systemic inflammatory response syndrome, multiple organ dysfunction syndrome, Kawasaki's disease, toxic shock syndrome, distributive shock, hypotensive crisis, vaccine associated enhanced disease, vaccine associated enhanced respiratory disease, cytokine release syndrome, cytokine storm,

Signal evaluation criteria	Summary
	hemophagocytic lymphohistiocytosis, macrophage activation, macrophages increased, septic shock, autoinflammatory disease. The epidemiology data analysis was performed using the MSSR 8 DLP of 31 Aug 2021. Due to a minimal data difference of 7 cases, this analysis was not repeated but leveraged previous observed vs expected data analysis.
Results	Clinical trial data: There were thirteen events following administration of placebo to 14,073 study subjects (one report of MIS in an adult after primary COVID-19 infection) and four events following administration of mRNA-1273 to 14,134 study subjects. The four events reported in the mRNA-1273 group included two events of septic shock, one event of toxic shock syndrome, and one event of multiple organ dysfunction syndrome. All events were assessed as not related to mRNA-1273. There was no identified pattern or risk for MIS in study subjects administered mRNA-1273. Post-marketing data: Cumulative there were 197 reports (3 for MIS-C and 194 for MIS-A). No differences noted between males and females. Most of the cases were reported in individuals >50 years of age. This age group may have multiple co-morbidities and may be more susceptible to immune mediated disorders. There were 3 reports in individuals <21 years of age and all three are confounded and important information is missing. Out of the 194 reports identified under the MIS-A related terms search, there were 3 reports classified as Level 2b of diagnostic certainty with 2 conditionals and 1 possible. Very little information provided in these reports. Confounded by severe respiratory conditions in one report as well as associated comorbidities like diabetes, Chronic obstructive pulmonary disease (COPD), Cardiovascular conditions, and associated myopericarditis in an individual within the population at risk for myocarditis and pericarditis. The rest of the reports are heavily confounded due to the reported events including septic shock, sepsis, acute respiratory distress, associated COVID-19 pneumonia, Haemophagocytic lymphohistiocytosis (19 cases), cytokine storm related events right after vaccination. All these events are considered differential diagnosis conditions providing important confounders in the evaluation of these reports.
Discussion	See Results above.
Conclusion	Based on review of the safety data, the cumulative evidence is insufficient to support a causal association between MIS-C/A and SPIKEVAX that will require updating the reference safety information for SPIKEVAX, including no new changes to the RMP. The signal was refuted. The MAH will continue to review cases of MIS-C/A using routine surveillance. The PRAC also recommended that a follow-up questionnaire should be implemented for all MIS cases. The MAH for SPIKEVAX and Comirnaty® were requested to prepare and implement a targeted questionnaire in order to follow up cases of MIS.

16.2.7. Myelitis Transverse

Table 16-8 Myelitis Transverse

Signal evaluation criteria	Summary
Source	The signal of Myelitis Transverse was triggered during the routine literature search by MAH and simultaneously from a PRAC request. Cumulative review of this topic covers the period from 18 Dec 2020 to 31 Dec 2021 and is presented in Section 16.3.6.4.2.
Background	Acute transverse myelitis (ATM) is a rare acquired neurological spinal cord disorder (1.34-4.6 cases per million/year), that can present with the rapid onset of weakness, sensory alterations, and bowel or bladder dysfunction [19]. Acute transverse myelitis can occur as an independent entity, usually as a postinfectious complication, but TM also exists on a continuum of neuroinflammatory disorders that include acute disseminated encephalomyelitis, multiple sclerosis, myelin oligodendrocyte glycoprotein (MOG) antibody disease, neuromyelitis Optica spectrum disorder (NMOSD), and acute flaccid myelitis (AFM). ATM has also been identified as a neurological complication of COVID-19 infection [20] [21]. More than one-third of COVID-19 patients report neurological symptoms. COVID-19 related myelopathy has been described in the literature starting within the first month after COVID-19 infection onset, either concomitantly with COVID-19 symptoms or within 10 days after their remission [22]. Immune disorders, as well as viral, bacterial, and fungal infections affecting the spinal cord, may also cause transverse myelitis. Viruses associated with transverse myelitis include herpes viruses, including varicella zoster virus (responsible for shingles and chickenpox). Research has shown ATM patients had lower levels of thyroid stimulating hormone (TSH) and FT3 and higher levels of FT4 and FT4/FT3 compared with healthy controls, whether male or female [23]. Moreover, levels of TSH and FT3 in patients with ATM were inversely correlated with disease severity. Most patients with acute transverse myelitis associated with SARS-CoV2 infection partially recover within three months to two years after initial diagnosis. Some degree of disability may remain, but physical therapy has been shown to improve outcomes [24]. A review of the literature and the MAH's GSDB spontaneous reports post authorization did not provide sufficient evidence of a causal association between exposure to SPIKEVAX and transverse myelitis. The MAH was requested by a regulatory authority to conduct a cumulative review of reports of transverse myelitis including Brighton collaboration case definition classification and WHO causality assessment of all cumulative cases, and to present cases of special interest with further details.
Methodology	The signal evaluation included a cumulative review of clinical trial data for MedDRA PT of Myelitis Transverse from mRNA-1273 P301 as a 04 May 2021 and review in the MAH safety database with a DLP of 30 Sep 2021.
Results	There were no reports from clinical trials in reporting between the placebo and mRNA-1273 arms for the topic of Myelitis Transverse. Post marketing data reported 76 cases with 76 events. Of which 33 cases met the case definitions for acute transverse myelitis (ATM) using the Brighton Collaboration case definition. A review of the cumulative cases did not show any prominent clinical pattern of occurrence of Myelitis Transverse. Many of the reports were medically confirmed. Of the 33 cases that met Brighton levels 2 and 3 of diagnostic certainty for ATM, 25 had MRI reports that were diagnostic of ATM. Further analysis of the 33 cases which met Brighton case definitions for acute myelitis, showed various confounding

Signal evaluation criteria	Summary
	factors, comorbidities, and concomitant medications, including cases of pre-existing transverse myelitis, a flare of Guillain Barre Syndrome (GBS), and intervertebral disc disorder. According to the WHO-UMC causality assessment, most of the 33 cases that met Brighton's case definition for acute transverse myelitis were considered "Possible", based on temporal association and the presence of alternate associations, including risk factors, comorbidities, and medications, that provide a more plausible explanation for the occurrence of the events. The observed reporting rates of Myelitis Transverse are well below background incidence rates though numerical increases are observed in older males (65 and older). Point estimates based on observed are not statistically significantly elevated but are elevated in sensitivity analyses based on assumed poor case capture with no false-positive errors. Risk factors for transverse myelitis that were reported included comorbidities, such as hypertension, diabetes mellitus, gastroesophageal reflux disease, hyperlipidemia, tobacco use, connective tissue / autoimmune diseases, mixed connective tissue disease, systemic sclerosis, urticarial vasculitis, thyroid disease, nutritional deficiency (vitamin B12, vitamin E; copper) and recently COVID-19 infection [24]. These disease conditions may present with myelitis and are confounders in causality assessment. It is also important to note that of the 33 cases that met the Brighton's Collaboration case definition for Transverse myelitis, seven reported concomitant use of aspirin and statins due to hypercholesterolemia. Statins have been implicated in causing transverse myelitis. Overall, there were insufficient data (frequent missing data elements) to facilitate a comprehensive medical review. There were no trends regarding age and other factors. There was no clear temporal association with mRNA-1273 administration and the events reports of Myelitis Transverse.
Discussion	See Results above.
Conclusion	Overall, the findings reviewed with respect to SPIKEVAX do not show convincing evidence of a link to Myelitis Transverse. Based on the analysis of all the safety data available as of 30 Sep 2021, the MAH considers that cases included under acute transverse myelitis do not provide sufficient information to establish a causal relationship to the administration of SPIKEVAX and the signal is refuted. No new safety issue of concern was identified. The MAH will continue to monitor events for acute transverse myelitis using routine pharmacovigilance surveillance.

16.2.8. Capillary Leak Syndrome (EPITT 19743)

Table 16-9 Capillary Leak Syndrome

Signal evaluation criteria	Summary
Source	Prior to considering Capillary Leak Syndrome (CLS) as a signal, CLS was analyzed in several MSSRs. **Initial Request from PRAC** PRAC AR MSSR#6 (dated 05 Aug 2021): The MAH was asked to present a cumulative of reports of capillary leak syndrome (CLS) following vaccination with SPIKEVAX in the next MSSR. Analyses should consider age, gender, dose, time to onset, course of the event, treatment and risk factors."

Signal evaluation criteria	Summary
	Follow-up Request from PRAC "PRAC AR MSSR#7 (dated 02 Sep 2021): " Request 12 - Capillary leak syndrome The MAH was requested, in the next MSSR, to present any new cases and any new information from published literature concerning cases of CLS and exacerbations in pre-existing CLS following the COVID-19 vaccinations, including any information on possible mechanism of action. Furthermore, if new information to already presented cases is identified, it is also expected that the MAH presents this new information, with adjusted causality assessments. The MAH was requested to broaden the search strategy to include the cases with PT "Capillary permeability increased", in addition to the cases with PT Capillary leak syndrome. **Follow-up Request from PRAC** PRAC AR MSSR#8 (dated 30 Sep 2021): "The MAH should continue to present any new cases and any new information from published literature concerning cases of CLS and exacerbations in pre-existing CLS following the COVID-19 vaccinations, including any information on possible mechanism of action. Furthermore, if new information to already presented cases is identified, it is also expected that the MAH presents this new information, with adjusted causality assessments. For the future MSSR, the MAH is expected to make an extra effort to retrieve additional information for the above-mentioned 3 cases with limited information and of 'possible' WHO-UMC causality (Request for the next MSSR (Req 7))"" **Final Request from PRAC** PRAC AR MSSR#9 (dated 04 Nov 2021): "Req 7 MSSR#8 addressed. Further evaluation of CLS has not been undertaken by the PRAC Rapporteur as part of this MSSR. A signal has been raised (EPITT 19743) and a cumulative review will be requested to the MAH. Further analysis of capillary leak syndrome will be performed in the signal procedure.
Background	Having considered the available evidence from the ongoing monitoring of this safety topic in the MSSRs and the new case reports from a national database in Italy, the PRAC has recommended that the MAH of SPIKEVAX (Moderna Biotech Spain, S.L) should provide an updated analysis of the association between SPIKEVAX and CLS from all available sources. Based on the review, the MAH should consider whether any precautionary measures are considered warranted including an update of the product information and/or the RMP. If warranted, relevant changes to the product information and/or the RMP wording should be submitted. Capillary Leak Syndrome also named Systemic Capillary Leak Syndrome and Clarkson disease is very rare and serious (potentially lethal). It was first described in 1960 by Dr. Bayard Clarkson and characterized by transient and severe hemoconcentration and hypoalbuminemia caused by leakage of fluids and macromolecules from the capillaries to the surroundings tissues/extra vascular space. Although often reversible and episodic, complications related to hemoconcentration and hypoperfusion can occur, and may include acute renal failure, thrombosis and pulmonary embolism. Massive peripheral oedema can lead to compartment syndromes and rhabdomyolysis and death especially in the post leak phase when fluids are mobilized from peripheral tissues into the intravascular space [25]. A typical presentation begins with fatigue, dizziness and flu-like symptoms followed by the rapid onset of shock, systemic pitting oedema, sudden

Signal evaluation criteria	Summary
	weight gain, hemoconcentration and hypoalbuminemia. Other common disease manifestations include acute renal failure, pleural and pericardial effusions, rhabdomyolysis, and sometimes compartment syndrome of the extremities. After a variable number of days, the vascular permeability spontaneously improves, and the blood pressure stabilizes. During this recovery phase, life-threatening pulmonary oedema can develop [26]. The frequency of episodes can vary widely between patients, with intervals ranging from days to years [25]. The majority of patients have a detectable monoclonal protein in the serum, although the importance of the monoclonal protein in the disease pathogenesis is unclear [25]. SCLS is a diagnosis of exclusion and is often confused with sepsis, angioedema, or anaphylactic shock. CLSs are mostly due to viral infections, malignant hematological diseases, inflammatory diseases, treatments such as chemotherapies/anti-tumoral therapies and therapeutic growth factors. [26], [27], [28]. For example, infection-related symptoms precede 44% to 64% of all acute flares [28], [25], and flares have been reported with SARS-CoV-2 infection [28]. The pathophysiology is not fully known, especially on the transient aspect, and it involves a multifactorial endothelial disruption for which mechanisms are still unclear. Damage to endothelial cells causes extravasation of plasma and proteins from the capillaries to the interstitial space, resulting in diffuse oedema (mainly in the arms and legs), hypotension, hypoalbuminemia and hemoconcentration [29], [28]. Treatment is empirical and involves fluid management (which is most critical). Symptomatic care during the acute phase -vasopressor therapy, drugs amplifying cAMP levels in the severest cases, and treatment of complications i.e., pulmonary, renal. Prophylactic use of monthly polyvalent immunoglobulins to prevent relapses seems recommended [25] Prognosis remains poor, also because of misdiagnosis and complications i.e. sepsis-like with pitting oedema, non-cardiogenic pulmonary oedema, hypovolemic shock with multi-organ failure. Since its characterization in 1960 by Clarkson, there have been fewer than <500 cases described in the medical literature [30], [31]. However, this diagnosis is underreported, often unrecognized and/or mislabeled as hypoalbuminemia, culture-negative sepsis or oedema. There is an increasing awareness on CLS and acknowledgement of a multifaceted potentially lethal disease [32].
Methodology	**Clinical trial data:** The topic of CLS was cumulatively reviewed in the MAH clinical database with a DLP of 04 May 2021, searched for any PTs Capillary Leak Syndrome and Capillary permeability increased in P301 study. Review of the Pharmacovigilance Database Post marketing data for potential signal of CLS events were retrieved from the Company safety database using the following MedDRA preferred terms: "Capillary Leak Syndrome and Capillary Permeability Increase" with a DLP of 31 Oct 2021. The term Capillary Leak Syndrome and Capillary Permeability Increase was searched using MedDRA version 24.0. Cases from all sources and relevant literature were reviewed.
Results	**Clinical trial data:** There were zero cases observed. **Review of the Pharmacovigilance Database**

Signal evaluation criteria	Summary
	A cumulative search of GSDB as of 31 Oct 2021, was performed for individuals with medical history of CLS. The search retrieved 8 individuals, after reviewing these 8 cases, 6 were considered CLS. In summary, out of the 8 identified cases, there were 5 cases that were considered as CLS cases; an additional case ([redacted]), although not presenting the hallmarks of CLS, is combined with this CLS cases to a conservative approach because of its fatal outcome. Out of the 6 cases mentioned above with the diagnosis of CLS following SPIKEVAX, 2 did not have a history of CLS and 4 had a history of CLS including the case where the first episode occurred after receiving Vaxzevria; for this case and based on the reported information it seems the denovo CLS episode is mentioned after Vaxzevria and a flare-up after SPIKEVAX, may be indicating this particular patient's susceptibility to develop CLS. This is more in keeping with the episodic nature of CLS than an event induced by the two different vaccines. There is no element in these cases explaining denovo CLS vs. flare-up, except that based on the knowledge of this disease, it is more likely to have recurrent episodes after the initial event.
Discussion	See Results above.
Conclusion	Overall, the findings reviewed with respect to SPIKEVAX do not show convincing evidence of a link to Capillary Leak Syndrome, based on the analysis of all the data available regarding the topic of CLS as of 31 Oct 2021, the MAH considers that Capillary Leak Syndrome related events are not presently a safety issue of concern that would justify inclusion of any of these terms in the product information and/or the RMP. The MAH will continue to closely evaluate events of "Capillary Leak Syndrome-related events" using routine surveillance

16.2.9. Cerebral Venous Sinus Thrombosis

Table 16-10 Cerebral Venous Sinus Thrombosis

Signal evaluation criteria	Summary
Source	The signal of Central venous sinus thrombosis (CVST) was triggered from a signal assessment request from Swissmedic (letter dated 26 Nov 2021).
Background	CVST and other thrombotic events in COVID-19 patients (even under anti-thrombotic treatment) have been reported to occur between 3–30 days after onset of infection (Carli 2021). It was reported that Venous thromboembolic (VTE) complications have been consistently reported to be increased in SARS-CoV-2 infection, most probably as the results of a thrombophilic state secondary to inflammation and immune-thrombosis [33]. Aside from the thromboembolic complications due to COVID-19 disease, thromboembolic conditions are frequently observed in the general population receiving the vaccine (i.e., independent of COVID-19 and vaccination), particularly in subjects higher than 65 years [34]. Thromboembolic events may occur in the absence of reported risk factors. As such it is not surprising that some thromboembolic events for which a causal association is difficult to ascertain have been reported closely following vaccination. Several cases of unusual thrombotic events that have developed after vaccination with the recombinant adenoviral vector vaccines encoding the

Signal evaluation criteria	Summary
	spike protein antigen of SARS-CoV-2 have been reported. Post COVID-19 vaccination, stroke had been reported with all vaccine types, but no causal relationship has been established [35]. Markus and colleagues reported that thrombotic complications occurring as part of COVID-19 related vaccine induced immune thrombotic thrombocytopenia (VITT) can include ischemic stroke as well as cerebral venous thrombosis. VITT has been associated with ChADOX1 CoV-19 Vaccine and Ad 26. CoV2. S vaccine both of which are manufactured using an adenovirus vector. VITT is caused by antibodies that recognize platelet factor 4 (PF4, also called CXCL4) bound to platelets. These antibodies are immunoglobulin G (IgG) molecules that activate platelets via low affinity platelet FcγIIa receptors (receptors on the platelet surface that bind the Fc portion of IgG). (See Up to Date "The adaptive humoral immune response") Ultimately, platelet activation (and possibly activation of other cells such as neutrophils) results in marked stimulation of the coagulation system and clinically significant thromboembolic complications. No such immunopathogenesis mechanism has been described for mRNA vaccines.
Methodology	Clinical Trial Data The topic of CVST was cumulatively reviewed in the MAH clinical database with a DLP of 04 May 2021, searched using the following MedDRA v 24.0 preferred term "Cerebral venous sinus thrombosis, Transverse sinus thrombosis, Superior sagittal sinus thrombosis, and Cavernous sinus thrombosis" was performed in P301. Review of the Pharmacovigilance Database Post marketing data for potential signal of CVST events were retrieved from the Company safety database using the following MedDRA preferred terms: “Cerebral venous sinus thrombosis, Transverse sinus thrombosis, Superior sagittal sinus thrombosis, and Cavernous sinus thrombosis” with a DLP of 30 Nov 2021, using MedDRA version 24.0. Cases from all sources and relevant literature were reviewed. Of note, throughout the document for simplicity CVST is used in text or tables to describe the entire topic; it is inclusive of all the PTs from the search strategy i.e., Cerebral venous sinus thrombosis, Transverse sinus thrombosis, Superior sagittal sinus thrombosis, and Cavernous sinus thrombosis. Clinical literature search review: A cumulative literature search in PubMed as of 30 Nov 2021 was performed using the following search criteria, (Cerebral venous sinus thrombosis) OR (Superior sagittal sinus thrombosis)) OR (Transverse sinus thrombosis)) OR (Cavernous sinus thrombosis)) OR (CVST)) AND (SPIKEVAX)) OR (mRNA-1273)) OR (mRNA 1273)) OR (mRNA1273)) OR (Moderna Covid19 Vaccine)). Additional cumulative focused (plausible mechanism) search was performed in PubMed with the following search criteria, ((Cerebral venous sinus thrombosis) OR (CVST)) AND (Covid 19 vaccine)) OR (Moderna Covid19 Vaccine)) AND (mechanism) OR (mechanism of action) which has resulted 19 articles.
Results	**Clinical trial data:** There were zero cases observed. **Review of the Pharmacovigilance Database**

Signal evaluation criteria	Summary
	A cumulative search of GSDB as of 30 Nov 2021, was performed and the search retrieved 122 cases (139 events). In summary, out of the 122 identified cases, there were 72 cases meeting the BCC case level definitions, causality assessment did not identify any certain or probable/likely cases causally associated with SPIKEVAX administration. 62% of cases were considered possible because of the temporal association or insufficient information to rule out a causal association but alternative explanations existed with co-existing diseases, medical history or other concomitant drugs more likely causality. A range of risk factors was identified for the events of CVST, Transverse sinus thrombosis, Superior sagittal sinus thrombosis, and Cavernous sinus thrombosis. When stratified by age and gender, women of child-bearing potential had an increased risk for CVST- this increased risk in women is accordance with population studies. Use of oral contraceptives, drug hypersensitivity, previous history of thrombotic events, hypertension, diabetes, hyperlipidaemia was the commonest and potentially treatable. A biological basis for VITT, including CVST, has been postulated for the adenovirus-vectored COVID-19 vaccines. This proposed mechanism would not be applicable to non-adenovirus vectored COVID-19 vaccines, including SPIKEVAX. No unique or novel risk factors were identified from this small aggregate sample. Insufficient information was present in the literature to suggest a hypothesis for a causal association rather than a chance occurrence between SPIKEVAX administration and the event of CVST. Furthermore, the Observed to expected ratio confirms that the event is very rare and significant disproportionality was not identified in EVDAS. Based on the body of evidence, the signal is refuted and no change to the reference safety information is required. **Clinical literature search review:** Review of these retrieved literature articles suggest few articles [36], [37], [38] with a speculative hypothesis between mechanistic possibility of Covod-19 and CVST but there are no articles which described a direct casual mechanism between the COVID-19 mRNA and CVST. Overall, there was a small number of articles describing Cerebral venous sinus thrombosis and mRNA vaccine and none of these shown any direct temporal association with mRNA vaccines against COVID-19 disease. There are no pathognomonic findings to link vaccine to these adverse events. Conclusion: Literature search results did not provide evidence of causal association between mRNA vaccines or mRNA-1273 and Cerebral venous sinus thrombosis.
Discussion	See Results above.
Conclusion	Overall, based on the analysis of all the safety data available as of 30 Nov 2021, the MAH considers that cases included under CVST and considering the patients' risk factors (including patients' age older than 65 years of age), use of contraceptives, familial and personal history of deep vein thrombosis, as well as other comorbidities, including obesity, hypertension, Type 2 diabetes mellitus) these reports are heavily confounded, and do not provide sufficient information to establish a causal relationship to the administration of SPIKEVAX. No new safety issue of concern was identified. The available data does not warrant an update change to the label/SmPC and/or

Signal evaluation criteria	Summary
	the RMPs. The MAH will continue to monitor events for CVST using routine pharmacovigilance surveillance.

16.2.10. Myocarditis and pericarditis (EPITT 19713)

Table 16-11 Myocarditis and pericarditis

Signal evaluation criteria	Summary
Source	On 14 Oct 2021, the PRAC requested ModernaTX, Inc to provide by 28 Oct 2021 responses to a list of questions including a risk estimation of myocarditis and pericarditis overall and per age groups, gender, vaccine dose(s). It also included to provide characterization of myocarditis and pericarditis, with focus on estimation of the incidence of myocarditis and pericarditis, with the view to better characterize the current 'unknown' frequency in the product labelling; discuss any plausible pathophysiological mechanisms of myocarditis and pericarditis observed after COVID-19 vaccine SPIKEVAX; data on the characteristics, severity, duration and outcome of myocarditis and pericarditis after vaccination with COVID-19 mRNA vaccine SPIKEVAX.
Background	Since July 2021, myocarditis and pericarditis have been considered as undesirable effects that may occur following vaccination against COVID-19 with a messenger RNA vaccine, especially in young men. Available data suggest that the course of myocarditis and pericarditis following vaccination is typically milder than viral myocarditis or pericarditis and is self-limited. The clinical course of cases of myocarditis and pericarditis appears generally favorable; those individuals who are hospitalized have lengths of stay of around 2 to 4 days on average. Analysis of post-authorization safety data has shown that this identified risk of myocarditis and pericarditis is generally within 7 days following vaccination against COVID-19 with an mRNA vaccine in people aged 12 to 40 years, particularly young people under 30 years old. However, the number of cases attributable to vaccines appears to be very rare in relation to the number of doses administered. Myocarditis and pericarditis are included within the warnings and precautions section of the MAH's CCDS. Based on the analysis of all the safety data available as of 31 Dec 2021, the MAH considers cases included under the AESI of myocarditis and pericarditis to be consistent with the known safety profile of SPIKEVAX.
Methodology	Multiple studies have recently estimated the risk of myocarditis following receipt of mRNA vaccines targeting SARS CoV-2. Both literature and surveillance sources consistently describe an increase in the incidence of myocarditis, predominantly within several days following receipt of a second dose of vaccine, that appears largely isolated to younger men (<30 years of age). Some variation has been observed in the magnitude of the association, which may be partially attributable to factors such as random variation (given the very low incidence of the outcomes) and stimulated reporting/differential ascertainment (given increased awareness and monitoring following identification of the risk and appropriate public health measures to ensure appropriate treatment of potential cases).
Results	***Moderna US PASS (mRNA-1273-P903)*** In the third interim report of the US PASS study (31 October 2021), a retrospective observational cohort study used secondary, de-identified individual-level medical and pharmacy claims data provided by HealthVerify were used to assess risk of AESI including myocarditis and pericarditis. This data source includes more than 140 million patients insured under commercial, Medicare or Medicaid plans, and/or served by providers participating in several large US medical and pharmacy insurance claims submission systems. Myocarditis was observed in 2,186 patients in a historical comparison cohort (IR 9.98 cases per 100,000 person-years 95% CI 9.47 – 10.30) and in 253 patients following vaccination (IR 9.94 cases per 100,000 person-years, 95% CI 8.72 – 11.17), producing an incidence rate ratio of 1.01 (95% CI 0.88 – 1.14). An increased risk was observed in young men, where the incidence following vaccination was 34.71 cases per 100,000 person-years (IRR 3.30, 95% CI 2.29 – 4.65). Although there were small numerical increases in men ages 30-39 and young women, these estimates are based on small numbers and lack precision. Observed vs expected analyses

Signal evaluation criteria	Summary

considering a 7-day risk window following vaccination produced findings with similar interpretation with an increase was observed in all individuals 18 to 29 years of age, where 9 events were observed and 2 expected (O/E ratio 4.93, 95% CI 2.25 – 9.36).

A smaller, numerical increase for men ages 18 to 29 was also observed for pericarditis. This outcome was observed in 5,418 patients in the historical cohort (IR 24.51, cases per 100,000 person-years 95% CI 23.86-25.16) and in 533 patients following vaccination (age and sex standardized IR 20.95 cases per 100,000 person-years, 95% CI 19.17 – 22.73), producing an incidence rate ratio of 0.85 (95% CI 0.78 – 0.93). In young males, 32 cases after vaccination produced an IR of 30.85 per 100,000 person-years (95% CI 20.16 – 41.54), corresponding to an IRR of 1.41 (95% CI 0.97 – 1.99). Overall observed to expected analyses and most age and sex specific analyses did not show an increase for the 7-day risk window, however an increase was observed in the 18 to 29-year age group (4 cases expected, 14 observed, OE ratio 3.31, 95% CI 1.81 – 5.56). This was again driven by young males, where 2 cases were expected and 10 observed (OE ratio 4.19, 95% CI 2.01 – 7.71).

Moderna Global Safety Database (Data Through 31 October 2021)

As recently described in the 10th Monthly Summary Safety Report, myocarditis (with or without pericarditis) was reported in 1,807 cases cumulatively (reporting rate 9.89 per 100,000 person-years) and in 353 cases during this review period (reporting rate 14.47 per 100,000 person-years).

Considering the rate of myocarditis occurrence as a proportion of vaccine recipients rather than as a function of estimated person-years, the cumulative reported cases correspond to an overall reporting rate of 1.02 cases of myocarditis per 100,000 vaccine recipients. Data from the US military suggest an expected incidence of 2.12 cases per 100,000 vaccine recipients [39]. Compared to this background rate an increase in the reporting rate is apparent for males ages 18-24 years, with a reporting rate of 7.79 cases per 100,000 person-years (O/E rate ratio 3.68, 95% CI 3.09 – 4.38). Sensitivity analyses assuming that the reported cases correspond to 50% or 25% of total exposed cases suggest that the increased risk could plausibly extend to men under 50 years of age and potentially include young women.

Table 1. Observed/Expected Analyses Stratified by Age, Myocarditis, Expected Rate Based on US Military Data, Cases per 100,000 Vaccine Recipients – Cumulative to 31 Oct 2021

	Vaccine recipients*	Observed		Expected		As observed: RR (95% CI)	Assuming 50% of cases were reported: RR (95% CI)	Assuming 25% of cases were reported: RR (95% CI)
		Cases	Rate	Cases	Rate			
All	177,096,375	1,807	1.02	3754	2.12	0.48 (0.46, 0.51)	*0.96 (0.92, 1.01)*	*1.93 (1.85, 2)*
By age								
<18	5,312,891	51	0.96	89	1.67	0.57 (0.41, 0.81)	*1.15 (0.86, 1.53)*	*2.3 (1.79, 2.94)*
18-24	15,938,674	664	4.17	267	1.67	2.49 (2.16, 2.87)	*4.98 (4.37, 5.68)*	*9.96 (8.78, 11.3)*
25-39	38,961,202	628	1.61	652	1.67	0.96 (0.86, 1.08)	*1.93 (1.75, 2.12)*	*3.85 (3.54, 4.2)*
40-49	26,564,456	179	0.67	563	2.12	0.32	*0.64*	*1.27*

Signal evaluation criteria	Summary								
							(0.27, 0.38)	*(0.56, 0.73)*	*(1.14, 1.42)*
	50-64	46,045,057	136	0.30	976	2.12	0.14 (0.12, 0.17)	*0.28 (0.24, 0.32)*	*0.56 (0.5, 0.62)*
	65-74	26,564,456	64	0.24	563	2.12	0.11 (0.09, 0.15)	*0.23 (0.19, 0.28)*	*0.45 (0.39, 0.53)*
	75+	17,709,637	31	0.18	375	2.12	0.08 (0.06, 0.12)	*0.17 (0.13, 0.22)*	*0.33 (0.27, 0.4)*
	By gender								
	Male	84,120,778	1,424	1.69	1783	2.12	0.8 (0.74, 0.86)	*1.6 (1.51, 1.69)*	*3.19 (3.03, 3.37)*
	Femal e	92,975,597	355	0.38	1615	1.74	0.22 (0.2, 0.25)	*0.44 (0.4, 0.48)*	*0.88 (0.82, 0.94)*
	By age and gender								
	Male								
	<18	2,523,623	48	1.90	54	2.12	0.9 (0.61, 1.32)	*1.79 (1.28, 2.51)*	*3.59 (2.65, 4.86)*
	18-24	7,570,870	590	7.79	161	2.12	3.68 (3.09, 4.38)	*7.35 (6.23, 8.67)*	*14.7 (12.53, 17.25)*
	25-39	18,506,571	517	2.79	392	2.12	1.32 (1.16, 1.5)	*2.64 (2.35, 2.96)*	*5.27 (4.73, 5.87)*
	40-49	12,618,117	118	0.94	268	2.12	0.44 (0.36, 0.55)	*0.88 (0.74, 1.05)*	*1.76 (1.52, 2.05)*
	50-64	21,871,402	75	0.34	464	2.12	0.16 (0.13, 0.21)	*0.32 (0.27, 0.39)*	*0.65 (0.56, 0.75)*
	65-74	12,618,117	34	0.27	268	2.12	0.13 (0.09, 0.18)	*0.25 (0.19, 0.33)*	*0.51 (0.41, 0.62)*
	75+	8,412,078	14	0.17	178	2.12	0.08 (0.05, 0.14)	*0.16 (0.11, 0.23)*	*0.31 (0.23, 0.42)*
	Femal e								
	<18	2,789,268	3	0.11	34	1.23	0.09 (0.03, 0.29)	*0.18 (0.07, 0.42)*	*0.35 (0.18, 0.68)*
	18-24	8,367,804	74	0.88	103	1.23	0.72 (0.54, 0.97)	*1.44 (1.12, 1.86)*	*2.89 (2.31, 3.61)*
	25-39	20,454,631	107	0.52	251	1.23	0.43 (0.34, 0.54)	*0.85 (0.71, 1.02)*	*1.71 (1.46, 2)*
	40-49	13,946,340	60	0.43	296	2.12	0.2 (0.15, 0.27)	*0.41 (0.33, 0.5)*	*0.81 (0.68,*

Signal evaluation criteria	Summary

								0.96)
50-64	24,173,655	59	0.24	512	2.12	0.12 (0.09, 0.15)	*0.23 (0.19, 0.28)*	*0.46 (0.39, 0.54)*
65-74	13,946,340	30	0.22	296	2.12	0.1 (0.07, 0.15)	*0.2 (0.15, 0.27)*	*0.41 (0.33, 0.5)*
75+	9,297,560	17	0.18	197	2.12	0.09 (0.05, 0.14)	*0.17 (0.12, 0.25)*	*0.34 (0.26, 0.45)*

*Rates presented per 100,000 person-years; vaccine recipients extrapolated based on the proportion of vaccine administrations given as first vs. second doses in the US (Gubernot 2021 [39]) Expected rate of 2.12 cases per 100,000 vaccine recipients has been adjusted for lower prevalence among females 12 to 39 years of age relative to males by factor of 1.73 as presented by the Centers for Disease Control and Prevention.

The reporting rate was comparable to population-based estimates from the US not limited to the armed forces (10 per 100,000 person-years, 1,807 cases expected rate ratio 0.99, 95% CI 0.93 – 1.06) when considering a 21-day risk window following vaccination. It should be noted that background estimates of the incidence of myocarditis vary widely, with some sources citing a range of 1-10 cases per 100,000 person-years [39] and others citing a range of 10-20 per 100,000 person-years (Kang 2021). A recent publication from the OHDSI project saw higher estimates, noting that algorithms used have not yet been validated (e.g., Li 2021: average incidence of 29.79 per 100,000 person-years with an estimate of 37 cases per 100,000 person-years in young males (Li 2021)).

Further stratification suggests that the rate is higher after the second dose, however not all reports could be classified by dose based on limitations of spontaneous adverse event reporting (e.g., missing data). Considering cases with known onset and dose number that occur within the 7 days following vaccination, the same pattern of increased reporting in younger men is present. No similar increase has yet been observed following a third dose, however, use of third doses had been more common in older an immunocompromised individual as of the end of the relevant data availability period (Table 2).

Table 2. Reporting Rate of Myocarditis within 7 Days of Vaccination by Age and Dose per 100,000 Doses Administered of SPIKEVAX, Cumulative Through 31 Oct 2021

	All			Males			Females		
	Dose 1	Dose 2	Dose 3	Dose 1	Dose 2	Dose 3	Dose 1	Dose 2	Dose 3
Age (years)									
<18	0.5	0.7	0.0	1.1	1.3	0.0	0.0	0.0	0.0
18-24	2.3	3.1	0.0	4.4	5.9	0.0	0.3	0.6	0.0
25-39	0.7	1.0	0.1	1.3	1.9	0.2	0.2	0.3	0.0
40-49	0.3	0.5	0.1	0.4	0.6	0.3	0.1	0.3	0.0
50-64	0.1	0.2	0.1	0.1	0.2	0.0	0.0	0.1	0.1
65-74	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.1	0.0
75+	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.1	0.0

Includes cases with known dose and time to onset. Number of SPIKEVAX recipients by dose recipients extrapolated based on the proportion of vaccine administrations given as first vs. second doses in the US.

Comparison to data from ACCESS sites shows a similar pattern, with the magnitude of the increase in young men variable based on the participating data center and year for which the

Signal evaluation criteria	Summary

estimate was produced. ACCESS rates span a broad range, and not all settings included within the project provide suitable reference rates. For example, conditions captured primarily in hospital settings will be poorly identified in general practice databases and vice versa. Further, differences in underlying disease incidence may be present comparing different countries, and studies drawn from smaller populations may be poorly precise for stratified analysis of rare outcomes. For these reasons as well as the observation that the majority of doses administered to data have occurred in the US, we consider the US estimates a preferable comparator group. Sensitivity analyses were, however, performed within ACCESS settings likely to capture both inpatient and outpatient care. The cumulative reporting rate (9.09 per 100,000 person-years) was between ACCESS estimates from Spain (FISABIO 2019, 3.36 per 100,000 person-years, 614 cases expected rate ratio 2.94, 95% CI 2.69 – 3.23) and the Netherlands (PHARMO 2019: 23.68 per 100,000 person-years, rate ratio 0.42, 95% CI 0.40 – 0.44).

Observed vs Expected, Pericarditis

Pericarditis (with or without myocarditis) was reported in 974 cases cumulatively (reporting rate 5.33 per 100,000 person-years) and in 172 cases during this reporting period (reporting rate 7.05 per 100,000 person-years). Pericarditis without myocarditis was reported in 823 cases cumulatively (reporting rate 4.51 per 100,000 person-years) and in 147 cases during this reporting period (reporting rate 6.03 per 100,000 person-years).

The cumulative rate for pericarditis was below the US-based incidence estimates, including an estimate of 5.7 hospitalizations per 100,000 person-years has been identified in data from the Nationwide Inpatient Sample (1,041 cases expected rate ratio 0.94, 95% CI 0.86 – 1.02) and an estimate of 7.4 cases per 100,000 that has been observed in US armed service members deployed in the Middle East (1,352 cases expected, rate ratio 0.72, 95% CI 0.66 – 0.78).

Considering European background estimates, the cumulative reporting rate (5.33 per 100,000 person-years) was above published estimates from Finland [40]: 3.30 per 100,000 person-years, 603 cases expected rate ratio 1.62, 95% CI 1.46 – 1.79) and below estimates from Italy (27.70 per 100,000 person-years, 5,059 cases expected rate ratio 0.19, 95% CI 0.18 – 0.21). Findings were similar when considering pericarditis without myocarditis reported within the case and consistent with the last monthly report.

Stratification of observed to expected analyses based on data from the US Nationwide Inpatient sample suggest an increased reporting rate for pericarditis in those ages 18-50 years of age, with larger increases occurring in men ages 18-24. Interpretation is similar in sensitivity analyses where it is assumed that 50% or 25% of cases are captured with no false positive errors, noting that risk becomes larger, and potential increases in young women more plausible (Table 3).

Table 3. Observed/Expected Analyses Stratified by Age, Pericarditis (Without Myocarditis) Expected Rates from the United States Nationwide Inpatient Sample Cases per 100,000 person years – Cumulative to 31 Oct 2021

	Person-years	Observed		Expected		As observed: RR (95% CI)	Assuming 50% of cases were reported: RR (95% CI)	Assuming 25% of cases were reported: RR (95% CI)
		Cases	Rate	Cases	Rate			
All	18,264,867	974	5.33	986	5.40	0.99 (0.9, 1.08)	1.98 (1.83, 2.13)	3.95 (3.68, 4.24)
By age								

	<18 years	547,946	7	1.28	20	3.70	0.35 (0.15, 0.82)	0.69 (0.35, 1.37)	1.38 (0.78, 2.45)
	18-24 years	1,643,838	199	12.11	61	3.70	3.27 (2.46, 4.36)	6.54 (5, 8.57)	13.09 (10.09, 16.98)
	25-39 years	4,018,271	277	6.89	149	3.70	1.86 (1.53, 2.27)	3.73 (3.11, 4.47)	7.45 (6.28, 8.84)
	40-49 years	2,739,730	135	4.93	101	3.70	1.33 (1.03, 1.72)	2.66 (2.12, 3.35)	5.33 (4.31, 6.59)
	50-64 years	4,748,865	187	3.94	323	6.80	0.58 (0.48, 0.69)	1.16 (1, 1.34)	2.32 (2.03, 2.64)
	65-74 years	2,739,730	99	3.61	233	8.50	0.43 (0.34, 0.54)	0.85 (0.7, 1.03)	1.7 (1.45, 2)
	75+ years	1,826,487	42	2.30	159	8.70	0.26 (0.19, 0.37)	0.53 (0.41, 0.69)	1.06 (0.85, 1.31)
	By gender								
	Male	8,675,812	587	6.77	581	6.70	1.01 (0.9, 1.13)	2.02 (1.83, 2.23)	4.04 (3.69, 4.42)
	Female	9,589,055	369	3.85	393	4.10	0.94 (0.81, 1.08)	1.88 (1.66, 2.12)	3.75 (3.36, 4.2)
	By age and gender								
	Male								
	<18 years	260,274	6	2.31	12	4.59	0.5 (0.19, 1.34)	1 (0.45, 2.24)	2.01 (1, 4.02)
	18-24 years	780,823	154	19.72	36	4.59	4.3 (2.99, 6.18)	8.59 (6.08, 12.14)	17.18 (12.28, 24.05)
	25-39 years	1,908,679	172	9.01	88	4.59	1.96 (1.52, 2.54)	3.93 (3.11, 4.96)	7.85 (6.29, 9.8)
	40-49 years	1,301,372	74	5.69	60	4.59	1.24 (0.88, 1.74)	2.48 (1.84, 3.34)	4.95 (3.75, 6.54)
	50-64 years	2,255,711	99	4.39	190	8.44	0.52 (0.41, 0.66)	1.04 (0.85, 1.27)	2.08 (1.75, 2.47)
	65-74 years	1,301,372	51	3.92	137	10.55	0.37 (0.27, 0.51)	0.74 (0.58, 0.96)	1.49 (1.2, 1.85)
	75+ years	867,581	20	2.31	94	10.79	0.21 (0.13, 0.35)	0.43 (0.3, 0.62)	0.85 (0.63, 1.15)
	Female								
	<18 years	287,672	1	0.35	8	2.81	0.12 (0.02, 0.99)	0.25 (0.05, 1.17)	0.49 (0.15, 1.64)
	18-24 years	863,015	44	5.10	24	2.81	1.81 (1.1, 2.98)	3.63 (2.31, 5.7)	7.26 (4.74, 11.12)

Signal evaluation criteria	Summary

25-39 years	2,109,592	102	4.84	59	2.81	1.72 (1.25, 2.37)	3.44 (2.58, 4.6)	6.88 (5.24, 9.05)
40-49 years	1,438,358	61	4.24	40	2.81	1.51 (1.01, 2.25)	3.02 (2.11, 4.32)	6.04 (4.32, 8.44)
50-64 years	2,493,154	85	3.41	129	5.16	0.66 (0.5, 0.87)	1.32 (1.05, 1.66)	2.64 (2.16, 3.23)
65-74 years	1,438,358	47	3.27	93	6.45	0.51 (0.36, 0.72)	1.01 (0.76, 1.35)	2.03 (1.58, 2.6)
75+ years	958,905	22	2.29	63	6.61	0.35 (0.21, 0.56)	0.69 (0.47, 1.02)	1.39 (1.01, 1.92)

Abbreviations: CI = confidence interval; NA = not applicable; RR = rate ratio.

*Rates presented per 100,000 person-years; Kumar 2016 [41]. Age by sex stratified estimates were estimated by multiplying the overall age stratified estimates by the ratio of the applicable gender-specific estimate to the overall estimate. Data from the 2012 calendar year were used.

It should be noted that these analyses are performed based on all reported cases without adjudication and may include both confirmed and not confirmed myocarditis cases as well as miss other cases that could had not being reported to the MAH. Given the high level of international attention that myocarditis has received, and regulatory actions taken to enhance awareness of this important identified risk, we expect that sensitivity is likely high, but the challenge with specificity remains.

In summary, observed vs. expected analyses show an increase in the reporting rate of myocarditis (with or without pericarditis) and pericarditis that is strongest for young men within a few days after the second dose. Although there is a possibility that the risk extends to young women, similar increases are not observed in older vaccine recipients. This is consistent with observations from the literature and observed vs. expected analyses performed in recent monthly reports.

Other Sources of Surveillance Data

Surveillance data from the Paul Ehrlich Institute in Germany suggested qualitatively similar but somewhat higher reporting rates for myocarditis, especially for men 18 – 29 years of age (11.71 cases per 100,000 vaccine recipients in German data, 7.79 in the Moderna Global Safety Database). Observed vs. expected analyses were similar, however, with German data showing an SMR of 4.44 (95% CI 3.57 – 5.46) for this group. In Canada, published surveillance data from Ontario have followed the same demographic trend, with clustering of cases in young men after the second dose of vaccine. Observed reporting rates in the province were higher at 17.1 doses per 100,000 vaccine recipients among men ages 18-24 overall and 28.3 per 100,000 vaccine recipients following dose 2.

Literature Assessing the Risk of Myocarditis and Pericarditis

SARS-CoV-2 Vaccination and Myocarditis in a Nordic Cohort Study of 23 Million Residents

In a Nordic cohort study including a meta-analysis of the 23 million residents of Denmark, Finland, Norway and Sweden made available to the MAH prior to publication (Karlstad, 2021), during the 28-day risk-periods following vaccination and during unvaccinated periods experienced by the study participants (6.7 million person-years in total), they observed 1092 incident myocarditis cases and 1154 incident pericarditis cases. Incidence rates of myocarditis during unvaccinated time was 9.7 per 100,000 person-years for men, and 4.2 for women. Among 16- to 24-year-old, incidence rates were 18.7 for men and 4.4 for women. Incidence rates of pericarditis increased with increasing age. The registry cohort study followed

Signal evaluation criteria	Summary
	individuals from the start of the vaccination campaign in Nordic countries (Denmark, Finland, Norway and Sweden) until first outcome event, a positive SARS-CoV-2 test, a third vaccination, emigration, death, or end of follow-up. All Nordic national registries allow analyses on the entire population and individual level through linkage to other registries such as health care utilization. In the main analysis, the IRRs and risk differences of myo- and pericarditis were estimated based on comparison of vaccinated with unvaccinated follow-up time (considering a 28-day risk window following vaccination). During the 28-day risk period, they observed 106 and 123 myocarditis cases following first- and second-dose vaccinations with BNT162b2, respectively, and 15 and 67 following mRNA-1273, respectively. The estimates were adjusted for sex, age, vaccine priority groups, comorbidities and prior SARS-CoV-2 infection (before start of follow up, 27 Dec 2020; infection after this date was a censoring event). Country-specific estimates were pooled via meta-analysis, considering heterogeneity between the databases. The results of the study showed: Adjusted RRs comparing the 28-day risk periods following first- and second-dose vaccinations to unvaccinated periods were 1.2 (95%CI, 0.7 to 1.9) and 7.2 (95%CI, 5.3 to 9.8) In males, following the first and second dose, adjusted RRs were 1.5 (95%CI, 0.8 to 2.5) and 9.1 (95%CI, 6.9 to 12). In males, 16-24 years of age, the adjusted RR was 14.2 (95%CI, 8.4—23.8) for a second dose of mRNA-1273. For females, the comparative adjusted IRRs were lower Among all males, the excess number of events per 100,000 vaccinated in the 28-day risk periods were 0.3 (95%CI, -0.1 to 0.8) and 5.4 (95%CI, 4.0 to 6.8) following first and second doses for mRNA-1273. The excess number of events for females were low. Among males 16–24 years, the excess number of events per 100,000 vaccinated in the 28-day risk periods following first and second doses were 1.7 (95%CI, -0.2 to 3.7) and 18.8 (95%CI, 9.6 to 28.0) for mRNA-1273.The corresponding excess number of events for males 25 to 39 years of age were somewhat lower. In a mixed schedule (BNT162b2—mRNA-1273), close to 40 cases (34 males) occurred following the second dose. In males 16-24 years, 17 cases occurred, with an excess number of events of 26.5 (95%CI, 13.9 to 39.1). IRRs of myocarditis or pericarditis combined in males 16–24 years were close to those of myocarditis. In males 25–39 years the RRs were generally lower. In females 16–24 years the IRRs were similar to those of males of the same age, however, with wider confidence intervals. A 7-day risk period was also evaluated for the 228 myocarditis cases in the 28-day risk-window after a second dose of mRNA 145 vaccination, events occurred within the first week, yielding higher IRRs. The excess events, per 100,000 vaccinated, during 7-day risk-window represented the majority of excess events during the 28-day risk-window. In males 12–39 years, at least 75% of the cases were admitted to hospital within 10 days of vaccination Comorbid conditions did not differ markedly between vaccinated and unvaccinated cases Length of stay did not markedly differ between vaccinated and unvaccinated cases The authors concluded that the information collected in this study of 23.1 million individuals shows higher rates of myocarditis and pericarditis within 28 days following vaccination with SARS-CoV-2 mRNA vaccines when compared to unvaccinated. These associations were strongest within the first 7 days, were increased for all combinations of mRNA vaccines and were more pronounced after the second dose. A second dose of mRNA-1273, either after

Signal evaluation criteria	Summary
	mRNA-1273 or BNT162b2 as a first dose, had the highest risk. Young males aged 16-24 years had the highest increased risk. They also concluded that there was a higher risk after a second dose and a higher risk in young men, information that has already been documented and communicated to health care provided through appropriate risk communication measures. The authors also presented excess events within 28 days in young males of 5.7 per 100,000 after a second-dose vaccination with BNT162b2 and 18.8 after a second-dose vaccination with mRNA-1273 which are higher than previously reported. ***Association between COVID-19 messenger RNA vaccines and the occurrence of myocarditis and pericarditis in people aged 12 to 50 in France - Study based on data from the National Health Data System (SNDS)*** Similarly, a population-based case-control analysis using French national health data has shown a large increase in the odds of myocarditis within 7 days after vaccination, noting that confidence intervals were wide. The association with the risk of myocarditis appears particularly pronounced in young men under 30 years of age, particularly after the second dose of Moderna vaccine (adjusted odds ratio (OR) 79.8; 95% confidence interval [29.8-213.4]), leading to an excess of cases reaching 132 per million doses in this population. Although the occurrence of myocarditis is less frequent than in men, this risk is also increased in young women under 30 years old after the second dose (OR 40.6 [9.9-166.4] and 37 cases in excess per million doses for Moderna). The risk of pericarditis also appears to be more marked after the Moderna vaccine in people under 30 years of age, in particular after second dose in men (OR 15.0 [3.3-68.4] and 18 excess cases per million doses) and after the first dose in women (OR 27.9 [2.4-328, 0] and 6 excess cases per million doses). The conclusion of this study is that the number of cases attributable to vaccines appears to be infrequent in relation to the number of doses administered. This study also confirms the favorable clinical course of cases of myocarditis and pericarditis following vaccination ***Myocarditis Following COVID-19 mRNA Vaccine: A Case Series and Incidence Rate Determination*** A retrospective case-series was performed utilizing the Mayo Clinic COVID-19 Vaccine Registry. The authors measured the incidence rate ratio for myocarditis temporally related to COVID-19 mRNA vaccination compared to myocarditis in a comparable population from 2016 through 2020. Clinical characteristics and outcomes of the affected patients was collected. A total of 21 individuals were identified, but ultimately 7 patients met the inclusion criteria for vaccine-associated myocarditis. An incidence rate ratio for myocarditis following COVID-19 mRNA vaccination was found to be increased for males at a rate ratio of 6.69 (95% CI 2.35 – 15.52) with poor precision for females (IRR 1.41, 95% CI 0.03 – 8.45). Limited sample size precluded stratified analyses [9]. In a US a population-based cohort study of approximately 2.4 million patients aged ≥18 years observed 15 cases of confirmed myocarditis after any dose of a mRNA COVID-19 vaccine (2 cases after dose 1; 13 cases after dose 2), for an incidence of 0.08 per 100,000 first doses and 0.58 per 100,000 second doses; acute myocarditis was described as a rare event. All reported cases occurred in younger males (median age, 25 years) who were hospitalized and had symptoms resolve with conservative management. The US FDA recently presented an assessment of myocarditis/pericarditis rates using the FDA Biologics and Effectiveness Safety (BEST) active surveillance system, which consists of 4 health claims data sources with a total 76.5–89.5 million annual enrollees. Within the first 7 days after administration of any mRNA COVID-19 vaccine dose (e.g., mRNA-1273 or BNT162b2), the incidence rate of myocarditis/pericarditis per 1 million person-days was generally low for all age groups; rates were highest for males aged 18–25 years after dose 2. At the October 21, 2021 CDC ACIP meeting, the COVID-19 Vaccine Safety Technical (VaST) Work Group summarized the available data to date on myocarditis rates after mRNA COVID-19 vaccination from multiple

Signal evaluation criteria	Summary
	worldwide safety monitoring systems, which indicated myocarditis was associated with both mRNA-1273 and BNT162b2 among adolescents and young adults, more frequently among males. The COVID-19 subcommittee of the WHO Global Advisory Committee on Vaccine Safety (GACVS) also recently reviewed available evidence from multiple countries and noted that while some data suggest increased myocarditis incidence in young males after dose 2 of mRNA-1273 versus BNT162b2, other data do not support this finding, and the overall risk is low. Several large US surveillance systems have shown comparable risk of myocarditis between mRNA-1273 and BNT162b2 (e.g., Vaccine Adverse Event Reporting System [VAERS], FDA BEST System, and Department of Veterans Affairs active surveillance Rapid Cycle Analysis for COVID-19 vaccines).5 For example, the CDC COVID-19 Vaccine Task Force provided the reporting rate of myocarditis among males aged 18–24 years after mRNA-1273 and BNT162b2 as 3.68 and 3.85 per 100,000 second doses administered, respectively, based on data from the VAERS safety passive monitoring system. However, a recent analysis from the Vaccine Safety Datalink (VSD) estimated that there were an excess 9.7 myocarditis/myopericarditis cases per million doses of mRNA-1273 versus BNT162b2 among 18–39-year-olds (adjusted rate ratio [95% CI]: 2.28 [1.00–5.22]; 2-sided p-value: 0.049). Of note, the VSD analysis was based on small case numbers within 7 days after dose 2 (mRNA-1273: 14 cases [810,839 total second doses]; BNT162b2: 12 cases [1,256,525 total second doses]). **Provide an estimation of the incidence of myocarditis and pericarditis, with the view to better characterize the current 'unknown' frequency in the product labeling.** Data on the incidence of myocarditis and pericarditis following vaccination from VAERS that were presented to the US ACIP in October 2021 appear consistent with other sources reporting rates including the MAH Global Safety Database. For men, incidence peaks in adolescents (noting that these data are available for Pfizer only in the United States), with the highest observed rate falling at 38.5 cases per 1,000,000 doses administered. In women, a similar age distribution in the reporting rate is observed, however the overall magnitude is substantially lower. Based on the mentioned estimations from VAERS, myocarditis can then be considered a very rare event (Very rare (<1/10,000)) = ~ 0.385 cases per 10,000 in the subgroup at highest risk). **Discuss any plausible pathophysiological mechanisms of myocarditis and pericarditis observed after COVID-19 vaccine SPIKEVAX.** Several hypotheses have been proposed in the literature to explain the pathophysiology of the mechanisms involved in the occurrence of myocarditis and pericarditis observed after vaccination with any of the two mRNA COVID-19 vaccines. Some of those articles are included below, but still the mechanisms for development of myocarditis or pericarditis are not understood. **Data on the characteristics, severity, duration and outcome of myocarditis and pericarditis after vaccination with COVID-19 mRNA vaccine SPIKEVAX.** Although most cases of vaccine-associated myocarditis have been described as mild and self-limiting, additional data are needed to characterize the natural history and long-term outcomes of these events. In a study by Klein et al [42] using the VSD, 34 confirmed cases of myocarditis/pericarditis had elevated troponin levels, and many had electrocardiographic changes, cardiac MRI changes, or both. However, 2 individuals (6%) required intensive care unit care, and consistent with previously described cases, all patients survived to hospital discharge. In a hospital-based study describing 20 cases of myocarditis and 37 cases of pericarditis without myocarditis (Diaz 2021), all were discharged after a median of two days, and no readmission or death events occurred. For two patients who received a second vaccination after onset of myocarditis, symptoms did not worsen. In the most recent MSSR, cases of myocarditis and pericarditis continue to primarily occur in young adult males, between

Signal evaluation criteria	Summary
	18 to 29 years of age, shortly after the second dose of the vaccine and within the first 6 days after vaccination. Most events were considered mild to moderate in severity and were reported as either resolved or resolving.
Discussion	Although most cases of vaccine-associated myocarditis have been described as mild and self-limiting, additional data are needed to characterize the natural history and long-term outcomes of these events. In a study by Klein et al [42] using the VSD, 34 confirmed cases of myocarditis/pericarditis had elevated troponin levels, and many had electrocardiographic changes, cardiac MRI changes, or both. However, 2 individuals (6%) required intensive care unit care, and consistent with previously described cases, all patients survived to hospital discharge. In a hospital-based study describing 20 cases of myocarditis and 37 cases of pericarditis without myocarditis (Diaz 2021), all were discharged after a median of two days, and no readmission or death events occurred. For two patients who received a second vaccination after onset of myocarditis, symptoms did not worsen. In the most recent MSSR, cases of myocarditis and pericarditis continue to primarily occur in young adult males, between 18 to 29 years of age, shortly after the second dose of the vaccine and within the first 6 days after vaccination. Most events were considered mild to moderate in severity and were reported as either resolved or resolving.
Conclusion	An increased risk of myo- and pericarditis following SPIKEVAX was observed across different studies. While other sources such as an O/E analysis from the company safety database confirm the association, the assessment focused particularly on the following large comparative studies: interim report of the Moderna US PASS (2,438 myocarditis and 5951 pericarditis events), the Nordic cohort study (1092 myocarditis and 1154 pericarditis events) and the French National Health Data System study (919 myocarditis and 917 pericarditis events). Although most cases of vaccine-associated myocarditis have been described as mild and self-limiting, additional data are needed to characterize the natural history and long-term outcomes of these events. Considering available data on a potential frequency, especially data from the EU, the frequencies of myocarditis and pericarditis could be estimated to be "very rare" overall and the frequency of myocarditis would be "rare" for younger males.

16.3. Evaluation of Risks and New Information

16.3.1. New Information on Important Identified Risks

16.3.1.1. Anaphylaxis

16.3.1.1.1. Source of the New Information

The ModernaTx GSDB was queried for valid, clinical, and spontaneous case reports in people who reported anaphylactic reactions, received from HCP, health authorities (HA), consumers and literature, cumulatively from 18 Dec 2020 to 31 Dec 2021 for the mRNA-1273 vaccine (COVID-19 vaccine Moderna), SPIKEVAX.

16.3.1.1.2. Background Relevant to the Evaluation

Anaphylaxis, a potentially life-threatening hypersensitivity reaction, can occur after any vaccination. Anaphylaxis may be immunologically or non-immunologically mediated. Most

persons recover fully with treatment, but serious complications can occur [43]. Reporting from selected healthcare organizations in the US found an overall rate of anaphylaxis after vaccination of 1.3 cases per million doses of vaccines other than SPIKEVAX, administered to both children and adults [44]. Available data seem to suggest a particular patient profile for persons who experience anaphylaxis after vaccination: the vast majority have a history of atopy (history of atopic disease, such as asthma, allergic rhinitis, atopic dermatitis, or food or drug allergy) but anaphylaxis can occur among persons with no known history of hypersensitivity.

16.3.1.1.3. Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

Moderna applied the MedDRA SMQ 'anaphylactic reaction' (narrow scope) to retrieve all cases of adverse events suggestive of anaphylaxis from the ModernaTX global safety database in individuals who received SPIKEVAX.

16.3.1.1.4. Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Observed vs Expected, Anaphylaxis

See Appendix 20.11.3 for tables showing observed vs. expected analyses. In interpretation of these analyses, it is helpful to consider that anaphylaxis is already an identified risk of SPIKEVAX and that reporting rates are higher for women as has previously been noted (Warren 2021). In addition, there has been considerable attention regarding anaphylaxis, and monitoring at the place of vaccination following administration may increase the likelihood of reporting. Moreover, reports identified using the narrow SMQ for 'anaphylactic reaction' may sometimes instead involve other conditions.

Overview of Cases

Cumulative Review (cumulative to 31 Dec 2021)

Cumulatively, through 31 Dec 2021, a total of 1,949 cases (and 1,992 events) were identified with anaphylaxis related events. There were 1,916 cases assessed as serious and 41 cases had a fatal outcome. Of the 1,949 cases, 1,487 (76.3%) were medically confirmed.

Of the 1,992 events (in 1,949 cases), 1,949 (98.1%) were serious events. The most frequently reported anaphylaxis related events' MedDRA Preferred Terms (PTs) were Anaphylactic reaction (1,470, 73.8%) followed by Anaphylactic shock (177 events, 8.9%) and Circulatory collapse (163 events, 8.2%) (Table 16-12).

Table 16-12 Event Distribution by Preferred Term (PT), Cumulative to 31 Dec 2021

PT	# Events	% of Total Events
Anaphylactic reaction	1,470	73.8%
Anaphylactic shock	177	8.9%
Circulatory collapse	163	8.2%
Shock	84	4.2%
Anaphylactoid reaction	62	3.1%
Type I hypersensitivity	27	1.4%
Shock symptom	8	0.4%
Anaphylactoid shock	1	0.1%
Grand total	1,992	100.0%

The majority of cases were reported in females (1,452, 74.5%) compared to males (459 cases, 23.6%); gender was missing or unknown for 38 cases (1.9%). The mean age was 44.0 years (standard deviation [SD] 16.6) with a median age of 42.0 years (min. 12/max. 98); 86 cases (4.4%) were missing age data. The age group with the highest number of cases was the 30-39 years age group (412 cases; 21.1%), however, cases in the 18-29 years age group, as well as in the 40-49 years and 50-64 years age groups had similar percentages (20.0%, 19.8%, and 20.8%, respectively) (Table 16-13).

Table 16-13 Case Distribution by Gender and Age Group, Cumulative to 31 Dec 2021

Age Group (years)	Female		Male		Unknown		Total of # Cases	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases	# Cases	% of Total Cases		
12-15	4	0.2%	2	0.1%	0	0	6	0.3%
16-17	4	0.2%	6	0.3%	0	0	10	0.5%
18-29	272	14.0%	115	5.9%	2	0.1%	389	20.0%
30-39	306	15.7%	102	5.2%	4	0.2%	412	21.1%
40-49	312	16.0%	70	3.6%	4	0.2%	386	19.8%
50-64	321	16.5%	79	4.1%	6	0.3%	406	20.8%
65-74	119	6.1%	49	2.5%	0	0	168	8.6%
75+	58	3.0%	28	1.4%	0	0	86	4.4%
Missing	56	2.9%	8	0.4%	22	1.1%	86	4.4%
Grand total	1452	74.5%	459	23.6%	38	1.9%	1949	100.0%

Event distribution by dose number and time-to-onset (TTO) are described in Table 16-14. The largest number of events have been reported after Dose 1 (1,185 events, 59.5%). Time to onset (TTO) of anaphylactic events occurred most frequently on the day of vaccination (day 0) after any dose (67.4%). There were 329 events (16.5%) reported with insufficient information to determine

TTO. The mean TTO for all doses was 3.1 days (SD 19.7) with a median TTO for all doses of 0.0-days (min. 0/max. 284).

Table 16-14 Event Distribution by Dose and Time-to-Onset (TTO), Cumulative to 31 Dec 2021

Dose Number	TTO All Doses (Days)	# Events	% Events
Dose 1	**Subtotal**	**1,185**	**59.5%**
	0 days	1,008	50.6%
	01-02	87	4.4%
	03-04	17	0.9%
	05-06	10	0.5%
	07-13	34	1.7%
	14-29	17	0.9%
	30+	12	0.6%
Dose 2	**Subtotal**	**438**	**22.0%**
	0 days	304	15.3%
	01-02	80	4.0%
	03-04	13	0.7%
	05-06	3	0.2%
	07-13	11	0.6%
	14-29	11	0.6%
	30+	16	0.8%
Dose 3	**Subtotal**	**40**	**2.0%**
	0 days	30	1.5%
	01-02	4	0.2%
	03-04	2	0.1%
	07-13	3	0.2%
	14-29	1	0.1%
Unknown	Subtotal	329	16.5%
	Missing	329	16.5%
Grand total	**Grand total**	**1,992**	**100.0%**

Cumulatively, a total of 918 events (46.1%) were considered "recovered/resolved", 240 events (12.0%) were "recovering/resolving", and 183 events (9.2%) were "not recovered/not resolved". Outcome was unknown or not reported for 595 events (29.9%) (Table 16-15). It should be noted that there are limitations in capturing follow-up information with spontaneous reports, such that the category of "not recovered/not resolved" may represent an over-estimate for this category of outcome.

Table 16-15 Event Distribution by Outcome, Cumulative to 31 Dec 2021

Event Outcome	# Events	% of Total Events
Fatal	42	2.1%
Not Recovered/Not Resolved	183	9.2%
Recovered/Resolved	918	46.1%
Recovered/Resolved with Sequelae	14	0.7%
Recovering/Resolving	240	12.0%
Unknown	595	29.9%
Grand total	1,992	100.0%

Fatal Cases

Forty-two events (in 41 cases) were reported as fatal. Review of these cases showed that the vast majority were not associated with anaphylaxis; indeed, they were also associated with neither immediate type hypersensitivity reactions nor allergic reactions to vaccine. An example of such fatal cases is 4.1(b) [redacted], a 71-year-old female patient with no reported relevant medical history, who experienced Asthenia, Bacteraemia, Dyspnoea, Hypoxia and Shock approximately 3 months 26 days after the second dose of Moderna COVID-19 vaccine administration. Another example of a case probably not associated with anaphylaxis is 4.1(b) [redacted], an 88-year-old female patient with Hypertensive heart disease, Aortic valve sclerosis, Osteoporosis and Dementia who on the day after vaccination experienced fever, hypotension, circulatory collapse, hypoxia, and death. A case of interest, 4.1(b) [redacted], involved an 85-year-old woman who had multiple pre-existing significant diagnoses including Hypertension, Type 2 diabetes mellitus, Chronic kidney disease, Atrial fibrillation and Hypertrophic cardiomyopathy that were being treated medically. On the day of vaccination, the patient was reported to have experienced anaphylactic shock, dyspnoea and hypoxia, which were also the reported causes of her death that occurred the following day. Abnormal tryptase levels of 30.8 and 33.5 were also noted. Not reported were acute dermatologic or cardiac diagnoses, nor time to onset. Important confounding concurrent illnesses, elderly status, lack of treatment information and clinical details make assessment of this report challenging.

Subpopulation Analysis

Children ages < 12 years (Cumulative to 31 Dec 2021)

No cases of anaphylaxis have been reported in children (<12 years old).

Adolescents ages 12 to 17 years (Cumulative to 31 Dec 2021)

Cumulatively, a total of 16 cases (16 events) of anaphylaxis related events in patients 12 to 17 years old have been reported. Of the 16 events, 15 were considered serious. Thirteen (13) cases were medically confirmed.

Of the 16 cases, 8 were male (50.0%) and 8 were female (50.0%) and ranged in age from 12 years of age to 17 years of age (mean: 15.2, median: 16.0) (Table 16-16).

Table 16-16 Case Distribution by Gender and Age in Adolescent Subpopulation, Cumulative to 31 Dec 2021

Age Group (Years)	Female		Male		Total # of Cases	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases		
12-15	4	25.0%	2	12.5%	6	37.5%
16-17	4	25.0%	6	37.5%	10	62.5%
Grand total	8	50.0%	8	50.0%	16	100.0%

Anaphylactic reaction accounted for 68.8% % of the events (11 events), followed by Anaphylactic shock (18.8%/3 events), Type I hypersensitivity (7.1%/1 event) and Circulatory collapse (7.1% / 1 event) (Table 16-17).

Table 16-17 Event Distribution by Preferred Term (PT) in Adolescent Subpopulation, Cumulative to 31 Dec 2021

PT	Non-Serious		Serious		Total # Events	% of Total Events
	# Events	% of Total Events	# Events	% of Total Events		
Anaphylactic reaction	1	6.3%	10	62.5%	11	68.8%
Anaphylactic shock	0	0	3	18.8%	3	18.8%
Circulatory collapse	0	0	1	6.3%	1	6.3%
Type I hypersensitivity	0	0	1	6.3%	1	6.3%
Grand total	**1**	**6.3%**	**15**	**93.8%**	**16**	**100.0%**

Event distribution by dose number and latency are described in Table 16-18. Of the 9 events with known dosing and event onset information, 7 events (43.8%), occurred the day of vaccination (5 events occurred the day of Dose 1 administration and 2 events occurred the day of Dose 2 administration). Dosing and/or event onset information was unknown or not provided for 7 events (43.8%).

Table 16-18 Event Distribution by Dose Number and Time-to-Onset (TTO) in Adolescent Subpopulation, Cumulative to 31 Dec 2021

Dose Number	TTO ALL Doses (Days)	# Events	% Events
Dose 1	**Subtotal**	**5**	**31.3%**
	0 days	5	31.3%
Dose 2	**Subtotal**	**4**	**25.0%**
	0 days	2	12.5%
	01-02	2	12.5%
Unknown	**Subtotal**	**7**	**43.8%**
	Missing	7	43.8%
Grand total	**Grand total**	**16**	**100.0%**

Outcome for the 16 events included the following: 6 events (37.5%) were resolved, 5 events (31.3%) were resolving, 3 events (18.8%) were not resolved, and for 2 events (12.5%), outcome was either unknown or not provided. There have been no fatal cases in the adolescent subpopulation (Table 16-19). It should be noted that there are limitations in capturing follow-up information with spontaneous reports, such that the category of "not recovered/not resolved" may represent an over-estimate for this category of outcome.

Table 16-19 Event Distribution by Outcome in Adolescent Subpopulation, Cumulative to 31 Dec 2021

Event Outcome	# of Events	% of Events
Not Recovered/Not Resolved	3	18.8%
Recovered/Resolved	6	37.5%
Recovering/Resolving	5	31.3%
Unknown	2	12.5%
Grand total	16	100.0%

SPIKEVAX Dose 3/Booster (Cumulative to 31 Dec 2021)

Cumulatively, there were 40 cases of anaphylaxis (40 serious / 0 fatal) reported following dose 3 or greater of SPIKEVAX. Within 40 cases, there were 40 events (of which 39 were serious). Twenty-four (24) cases were medically confirmed. A breakdown of the 40 cases by gender was 34 females (85.0%) and 5 males (12.5%); 1 case was missing gender data. The mean age was 46.5-years (SD: 17.4) with a median age of 41.5 years (min. 23.0/ max. 90.0); 4 cases were missing age information.

Table 16-20 presents age group distribution (years) of the cases received cumulatively, that containing anaphylaxis related events that occurred after the SPIKEVAX booster. Anaphylaxis related events occurred most frequently in the age group 30-39 years (12, 30%).

Table 16-20 Case Distribution by Age and Gender, Cumulative to 31 Dec 2021 (SPIKEVAX Dose 3/Booster)

Age Group (Years)	Female		Male		Unknown		Total # of Cases	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases	# Cases	% of Total Cases		
18-29	4	10.0%	0	0	0	0	4	10.0%
30-39	12	30.0%	0	0	0	0	12	30.0%
40-49	6	15.0%	0	0	0	0	6	15.0%
50-64	5	12.5%	1	2.5%	1	2.5%	7	17.5%
65-74	3	7.5%	2	5.0%	0	0	5	12.5%
75+	1	2.5%	1	2.5%	0	0	2	5.0%
Missing	3	7.5%	1	2.5%	0	0	4	10.0%
Grand total	**34**	**85.0%**	**5**	**12.5%**	**1**	**2.5%**	**40**	**100.0%**

In general, the TTO for events after the SPIKEVAX booster occurred most frequently on the day of vaccination (75.0 % of events) (See Table 16-21).

Table 16-21 Event Distribution by Time-to-Onset (TTO), Cumulative to 31 Dec 2021 (SPIKEVAX Dose 3/Booster)

Dose Number	TTO All Doses (Days)	# Events	% Events
Dose 3	Subtotal	40	100.0%
	0 days	30	75.0%
	01-02	4	10.0%
	03-04	2	5.0%
	07-13	3	7.5%
	14-29	1	2.5%
Grand total		40	100.0%

For events occurring after Dose 3 of SPIKEVAX, the greatest proportion of event outcomes were reported as "recovering/resolving," (17, 42.5%) followed by "recovered/resolved" (11, 27.5%) (Table 16-22). There were no fatalities reported following dose 3 SPIKEVAX. It should be noted that there are limitations in capturing follow-up information with spontaneous reports, such that the category of "not recovered/not resolved" may represent an over-estimate for this category of outcome.

Table 16-22 Event Distribution by Outcome, Cumulative to 31 Dec 2021 (SPIKEVAX Dose 3/Booster)

Event Outcome	# of Events	% of Events
Not Recovered/Not Resolved	5	12.5%
Recovered/Resolved	11	27.5%
Recovered/Resolved with Sequelae	1	2.5%
Recovering/Resolving	17	42.5%
Unknown	6	15.0%
Grand total	**40**	**100.0%**

16.3.1.1.5. Discussion

Cumulative data show there was a total of 1,949 cases (1,992 events) identified using the narrow SMQ 'anaphylactic reaction', of which 1,916 cases were serious; 41 cases had reported fatal outcome with the vast majority unrelated to anaphylaxis after vaccination. Overall, the majority of cases were reported in non-elderly, adult females, and TTO of anaphylactic events occurred most frequently on the day of vaccination (day 0) after any dose (67.4%).

Although rigorous studies of gender differences in anaphylaxis are lacking due at least in part to the rarity of the condition, the female predominance in reports of anaphylaxis reported here is consistent with the female predominance in immediate type hypersensitivity reactions to vaccines in general that has been found in the majority of studies [45].

The data are reassuring with regard to the number of reports of anaphylaxis with respect to dose number. Reports following dose 1 (59.5% of total reports), dose 2 (22.0%) and dose 3 or booster (2.0%) show a clear decreasing trend; 16.5% of reports did not describe dose number. The MAH will continue to monitor the number of anaphylactic reactions occurring after each dose. The data with regard to adolescents and to booster doses are similarly reassuring. There were only 16 adolescent cases and 40 dose 3 (or booster) cases reported, with no fatalities in either group; characteristics of the cases do not suggest a pattern different from the other anaphylaxis reports overall.

Review of the data does not suggest any new identifiable pattern or trend in reports of anaphylaxis that may differ from the already known safety profile of SPIKEVAX.

16.3.1.1.6. Conclusion

Based on the analysis of all the safety data received cumulatively, ModernaTX, Inc considers that cases of anaphylaxis reported here in temporal association with the administration of SPIKEVAX

did not raise any new safety issues of concern. Risk management and labelling are already in place to address this important identified risk. ModernaTX, Inc will continue to monitor events for anaphylaxis using routine surveillance. The benefit-risk evaluation remains positive.

16.3.1.2. Myocarditis and Pericarditis

16.3.1.2.1. Source of the New Information

New information presented below includes analysis performed on cases received into the GSDB by ModernaTX, Inc. from 01 Jul 2021 to 31 Dec 2021 for SPIKEVAX. Cumulatively, the data reviewed covers the period from 18 Dec 2020 to 31 Dec 2021.

16.3.1.2.2. Background Relevant to the Evaluation

During this reporting period, myocarditis and pericarditis have been considered as undesirable effects that may occur following vaccination against COVID-19 with a messenger RNA vaccine, especially in young men. Available data suggest that the course of myocarditis and pericarditis following vaccination is typically milder than viral myocarditis or pericarditis and is self-limited. The clinical course of cases of myocarditis and pericarditis appears generally favorable; those individuals who are hospitalized have lengths of stay of around 2 to 4 days on average. Analysis of post-authorization safety data has shown that this important identified risk of myocarditis and pericarditis typically manifests within 7 days following receipt of an mRNA COVID-19 vaccines, with this risk greatest among people aged 12 to 40 years (especially those under 30 years old), and most commonly following the second dose. However, the number of cases attributable to vaccines appears to be very rare in relation to the number of doses administered.

Myocarditis and pericarditis are included within the warnings and precautions section of the MAH's CCDS and it is considered an important identified risk in the risk management plan of SPIKEVAX. Based on the analysis of all the safety data available as of 31 Dec 2021, the MAH considers cases included under the AESI of myocarditis and pericarditis to be consistent with the known safety profile of SPIKEVAX.

Multiple studies have recently estimated the risk of myocarditis following receipt of mRNA vaccines targeting SARS CoV-2. Both literature and surveillance sources consistently describe an increase in the incidence of myocarditis, predominantly within several days following receipt of a second dose of vaccine, that appears largely isolated to younger men (<30 years of age). Some variation has been observed in the magnitude of the association, which may be partially attributable to factors such as random variation (given the very low incidence of the outcomes) and stimulated reporting/differential ascertainment (given increased awareness and monitoring following identification of the risk and appropriate public health measures to ensure appropriate treatment of potential cases).

Myocarditis and pericarditis are typically rare events in children. Studies conducted in the pre-COVID era suggest that the incidence in children between 6 years and <12 years old is lower than that observed in young adolescents or infants [46]. Prior to the emergence of COVID-19, myocarditis, mostly due to other viral infection, was described as the most common cause of heart failure in previously healthy pediatric patients.

Myocarditis leading to hospital admission is relatively uncommon in children. As previously noted, the incidence rises with age. There is no gender difference in risk prior to approximately age 6 years, when a differentially greater risk begins to emerge in males. The incidence and differential risk by gender becomes significantly greater starting at approximately the age of 12-years.

COVID-19 is an independent risk factor for myocarditis. The rates of pediatric (age <16 years) myocarditis requiring hospitalization that are attributable to COVID-19 are greater than 36-fold higher than in age matched controls [47]. The risk for myocarditis among patients with COVID-19 has been identified to be nearly 16 times as high as the risk among patients without COVID-19, with the association between COVID-19 and myocarditis being most pronounced among children and older adults. Myocarditis is occurring in patients with SARS-CoV-2 infection at rates estimated to be as high as 876 cases per million in the 12- to 17-year-old males [48]. Hospitalization in young adults due to COVID-19 have a mean length of stay of 5 days, with approximately 5% of patients requiring mechanical ventilation; fatalities have been reported [49]. In the pre-COVID era the prognosis of childhood myocarditis was variable, ranging from full recovery to death or cardiac transplant. Chronic cardiac dysfunction (ie, dilated cardiomyopathy) was reported in 15% to 60% of cases, with patients requiring intensive care, extracorporeal membrane oxygenation, or ventricular assist devices having poorer outcomes.

In contrast, hospitalization for myocarditis following mRNA COVID-19 vaccination is far less common with a mean length of stay of around 1-2 days with no reported deaths (Rosenblum 2021). VAERS (CDC/Advisory Committee on Immunization Practices (ACIP)) data indicate that following 86 million doses of mRNA COVID-19 vaccines administered to persons under 30 years of age, a total of 3 deaths associated with myocarditis had been reported. All 3 had a potential infectious etiology (rather than being considered attributable to vaccine) [50].

16.3.1.2.3. Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

The ModernaTX, Inc. GSDB was queried for valid case reports of myocarditis and pericarditis received from HCP, HA, consumers, and literature for the mRNA-1273 vaccine (COVID-19 vaccine Moderna) SPIKEVAX using the MedDRA PTs of Eosinophilic myocarditis, Coxsackie myocarditis, Cytomegalovirus myocarditis, Enterovirus myocarditis, Malarial myocarditis,

Myocarditis bacterial, Myocarditis helminthic, Myocarditis infectious, Myocarditis meningococcal, Myocarditis mycotic, Myocarditis septic, Myocarditis syphilitic, Myocarditis toxoplasmal, Viral myocarditis, Autoimmune myocarditis, Giant cell myocarditis, Hypersensitivity myocarditis, Immune-mediated myocarditis, Lupus myocarditis, Myocarditis, Myocarditis post infection, Radiation myocarditis, Atypical mycobacterium pericarditis, Bacterial pericarditis, Coxsackie pericarditis, Cytomegalovirus pericarditis, Pericarditis amoebic, Pericarditis fungal, Pericarditis gonococcal, Pericarditis helminthic, Pericarditis histoplasma, Pericarditis infective, Pericarditis meningococcal, Pericarditis mycoplasmal, Pericarditis rheumatic, Pericarditis syphilitic, Pericarditis tuberculous, Purulent pericarditis, Viral pericarditis, Autoimmune pericarditis, Pericarditis, Pericarditis adhesive, Pericarditis constrictive, Pericarditis lupus, Pericarditis malignant, Pericarditis uraemic, Pleuropericarditis, Radiation pericarditis, and Camptodactyly-arthropathy-coxa vara-pericarditis syndrome.

To characterise the level of diagnostic certainty, identified cases were classified into one of five categories, following the Brighton Collaboration Myocarditis/Pericarditis case definition [51], [52]:

- Level 1 (Definitive case)
- Level 2 (Probable case)
- Level 3 (Possible case)
- Level 4 is a reported event of myocarditis/pericarditis with insufficient evidence to meet level 1, 2 or 3 of the case definitions
- Level 5 (Not a case of Myocarditis/Pericarditis)

The Brighton definitions are used to evaluate the strength of the evidence to determine whether a case fulfils the criteria needed to establish a case (of myocarditis or pericarditis). It is not used to ascertain causality.

The CDC working case definition [53] for Acute Myocarditis and Acute Pericarditis was used for medical review of reports identified during this reporting period (01 Jul 2021 to 31 Dec 2021):

- Acute Myocarditis
- Probable
- Confirmed
- Acute Pericarditis

- Myopericarditis (This term was used for patients meeting criteria for both Myocarditis and Pericarditis)

Similar to the Brighton definition, the CDC definition identifies the strength of the evidence to support a diagnosis of myocarditis and/or pericarditis. It is not intended to be used for causality assessment. It was established for the purpose of identifying cases observed following receipt of a COVID-19 vaccine.

In contrast, causality assessment (i.e., characterising the likelihood that a case of myocarditis/pericarditis was attributable to vaccine exposure) was conducted utilizing the WHO-UMC standardized case causality assessment [54].

Further evaluation was conducted in the segment of the reported cases involving patients that were considered (based on epidemiologic characteristics) to be at potentially higher risk for having events of myocarditis and/or pericarditis. This evaluation was conducted in males and females younger than 40 years of age, after the 2nd of SPIKEVAX, regardless of the TTO of the events from the administration of the vaccine. An additional, focused evaluation was conducted on all reports involving patients <18 years of age, as well as those who received a 3rd dose or a booster dose.

- Appendix 20.11.4 and Appendix 20.11.5: includes the reporting period information for fatal case reports.
- Appendix 20.11.6 and Appendix 20.11.7: includes the reporting period cases of myocarditis and pericarditis for patients of ≤40 years of age and after the 2nd or the 3rd dose of SPIKEVAX.

Appendix 20.11.8 and Appendix 20.11.9, Appendix 20.11.10 and Appendix 20.11.11 and Appendix 20.11.12 and Appendix 20.11.13: includes the reporting period cases assessments for Myocarditis and Pericarditis for reports of patients ≤ 40 years of age according to the Brighton collaboration case definitions for Myocarditis and Pericarditis, the CDC working case definition for acute myocarditis and acute pericarditis and case causality assessments according to the WHO-UMC standardized case causality assessment.

16.3.1.2.4. Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Observed vs Expected

See Appendix 20.11.3.

Overview of Cases

Myocarditis and Pericarditis (Cumulative to 31 Dec 2021)

Cumulatively, through 31 Dec 2021, a total of 3,790 cases (3,680 events) of myocarditis and/or pericarditis have been reported, with 2,835 (74.8%) cases medically confirmed. There were 39 cases (42 events) with fatal outcomes.

The majority of cases reporting myocarditis and/or pericarditis involved male patients (2,645, 69.8%) and 1,087 (28.7%) involved female patients; 58 reports (1.5%) did not include gender information. The mean age of the patients was 36.3 years (SD 16.9), with a median age of 31 years (min 12/max 94); 374 cases were missing age information.

The greatest proportion of cases reporting myocarditis and pericarditis events continued to involve males between the ages of 18 to 39-years-old (1,651, 43.6%). Regardless of gender, more than half (56.2%) of cases were reported in patients in the 18 to 39-year-old age group (Table 16-23).

Table 16-23 Number and Percentage of Cases Reporting Myocarditis and Pericarditis by Age and Gender - Cumulative to 31 Dec 2021

Age Group	Female		Male		Unknown		Total # Cases	% Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
12-15	8	0.2	34	0.9	0	0.0	42	1.1
16-17	5	0.1	69	1.8	0	0.0	74	2.0
18-29	275	7.3	1180	31.1	5	0.1	1460	38.5
30-39	191	5.0	471	12.4	7	0.2	669	17.7
40-49	170	4.5	246	6.5	1	0.0	417	11.0
50-64	203	5.4	233	6.1	5	0.1	441	11.6
65-74	106	2.8	111	2.9	1	0.0	218	5.8
75+	48	1.3	46	1.2	1	0.0	95	2.5
Missing	81	2.1	255	6.7	38	1.0	374	9.9
Grand total	**1087**	**28.7**	**2645**	**69.8**	**58**	**1.5**	**3790**	**100.0**

Myocarditis and pericarditis events occurred most frequently after the 2nd dose (1,669; 41.2%). Regardless of dose number, almost half of the events had an onset less than 7 days from vaccination (1,825, 45.1%), inclusive of 147 events following a 3rd or booster dose. There were 1,356 events (33.5%) reported with insufficient information to determine time to onset.

Myocarditis and Pericarditis (Reporting Period – 01 Jul to 31 Dec 2021)

During the reporting period of this PBRER, a total of 3,168 cases (3,062 events) were reported. There were 2,280 cases medically confirmed. There were 32 cases (34 events) with a fatal outcome. (See Appendix 20.11.4 and Appendix 20.11.5).

There were 911 (28.8%) cases of myocarditis and pericarditis reported for females, and 2,204 (69.6%) that involved males; 53 cases (1.7%) did not include gender information. The mean of the patients' ages was 35.7 years (SD 16.3), with a median age of 31.0 years (min 12/max 89); 363 cases were missing age data.

During the reporting period, the myocarditis and pericarditis cases reported continued to involve males aged 18 to 39-years-old at a greater frequency than any other demographic (1,353, 42.7%) Table 16-24.

Table 16-24 Number and Percentage of Myocarditis and Pericarditis Case Reports by Age and Gender - Reporting Period 01 Jul to 31 Dec 2021

Age Group	Female		Male		Unknown		Total # Cases	% Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
12-15	8	0.3	32	1.0	0	0.0	40	1.3
16-17	5	0.2	68	2.1	0	0.0	73	2.3
18-29	229	7.2	961	30.3	5	0.2	1195	37.7
30-39	169	5.3	392	12.4	6	0.2	567	17.9
40-49	144	4.5	209	6.6	1	0.0	354	11.2
50-64	162	5.1	181	5.7	4	0.1	347	11.0
65-74	80	2.5	83	2.6	1	0.0	164	5.2
75+	34	1.1	30	0.9	1	0.0	65	2.1
Missing	80	2.5	248	7.8	35	1.1	363	11.5
Grand total	**911**	**28.8**	**2204**	**69.6**	**53**	**1.7**	**3168**	**100.0**

Of the 3,375 events reported during this reporting period, 2,279 (67.5%) were myocarditis-related events (including three events of eosinophilic myocarditis, and three events of viral myocarditis) and 1,096 (32.5%) were pericarditis-related events (including eight reports of pleuropericarditis) Table 16-25.

Table 16-25 Number and Percentage of Myocarditis and Pericarditis Events by PT - Reporting Period 01 Jul to 31 Dec 2021

PT	# Events	% Total Events
Myocarditis	2,269	67.2
Pericarditis	1,086	32.2
Pleuropericarditis	8	0.2
Eosinophilic myocarditis	3	0.1
Viral myocarditis	3	0.1
Giant cell myocarditis	1	0.03

PT	# Events	% Total Events
Hypersensitivity myocarditis	1	0.03
Immune-mediated myocarditis	1	0.03
Myocarditis infectious	1	0.03
Pericarditis constrictive	1	0.03
Purulent pericarditis	1	0.03
Grand total	**3,375**	**100.0**

There were 1,323 (39.2%) and 147 (4.4%) events of myocarditis and pericarditis reported following the 2nd and 3rd doses, respectively, versus 668 (19.8%) events following the 1st dose; 1,237 (36.7%) events had insufficient data to determine time to onset. Regardless of dose number, the greatest frequency of the myocarditis and pericarditis events reported had a TTO of less than 7 days from most recent vaccination (1,440; 42,7%) (Table 16-26). The median time to onset was 3 days (min: 0/max: 347).

Table 16-26 Distribution of Reported Events of Myocarditis and Pericarditis by Dose Number and TTO – Reporting Period 01 Jul to 31 Dec 2021

Dose Number	TTO (Days)	# Events	% Events
Dose 1	***Subtotal***	***668***	***19.8***
	0 days	53	1.6
	01-02	152	4.5
	03-04	120	3.6
	05-06	52	1.5
	07-13	102	3.0
	14-29	110	3.3
	30+	79	2.3
Dose 2	***Subtotal***	***1,323***	***39.2***
	0 days	95	2.8
	01-02	451	13.4
	03-04	342	10.1
	05-06	60	1.8
	07-13	77	2.3
	14-29	119	3.5
	30+	179	5.3
Dose 3	***Subtotal***	***147***	***4.4***
	0 days	23	0.7
	01-02	52	1.5
	03-04	27	0.8
	05-06	13	0.4

Dose Number	TTO (Days)	# Events	% Events
	07-13	16	0.5
	14-29	12	0.4
	30+	4	0.1
Unknown	***Subtotal***	***1,237***	***36.7***
	Missing	1,237	36.7
Grand total		**3,375**	**100.0**

Myocarditis (Reporting Period – 01 Jul to 31 Dec 2021)

During this review period, there were 2,259 cases (2,279 events) of myocarditis related events, with or without pericarditis, received; of which 2,210 cases were serious. There were 1,636 cases that were medically confirmed. There were 30 cases with fatal outcomes. (See Appendix 20.11.4 and Appendix 20.11.5).

There were 1,705 (75.5%) cases of myocarditis reported in males and 516 (22.8%) in females, with 38 cases (1.7%) missing gender information. The mean age of the patients was 32.9 years (SD: 15.1) with a median age of 28.0 years (min: 12/max: 89); age data was missing in 294 cases. During the review period, the greatest proportion of the cases with an event of myocarditis continued to be reported in males between the ages of 18 to 39 years of age (87; 31.3%) (Table 16-27).

Table 16-27 Number and Percentage of Myocarditis Cases by Age and Gender - Reporting Period 01 Jul to 31 Dec 2021

Age Group	Female		Male		Unknown		Total # Cases	% Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
12-15	5	0.2	29	1.3	0	0.0	34	1.5
16-17	3	0.1	60	2.7	0	0.0	63	2.8
18-29	139	6.2	815	36.1	3	0.1	957	42.4
30-39	97	4.3	304	13.5	3	0.1	404	17.9
40-49	82	3.6	131	5.8	1	0.0	214	9.5
50-64	73	3.2	102	4.5	2	0.1	177	7.8
65-74	46	2.0	42	1.9	0	0.0	88	3.9
75+	15	0.7	13	0.6	0	0.0	28	1.2
Missing	56	2.5	209	9.3	29	1.3	294	13.0
Grand total	**516**	**22.8**	**1705**	**75.5**	**38**	**1.7**	**2259**	**100.0**

Most of the events of myocarditis continue to occur after the 2nd dose of SPIKEVAX during the reporting period (947; 41.6%) and within the first 4 days after the 2nd dose (712; 75.2%) (Table 16-28).

Table 16-28 Distribution of Reported Events of Myocarditis by Associated Dose Number and TTO - Reporting Period 01 Jul to 31 Dec 2021

Dose Number	TTO (Days)	# Events	% Events
Dose 1	***Subtotal***	***388***	***17.0***
	0 days	33	1.4
	01-02	96	4.2
	03-04	89	3.9
	05-06	29	1.3
	07-13	50	2.2
	14-29	52	2.3
	30+	39	1.7
Dose 2	***Subtotal***	***947***	***41.6***
	0 days	67	2.9
	01-02	347	15.2
	03-04	298	13.1
	05-06	35	1.5
	07-13	47	2.1
	14-29	67	2.9
	30+	86	3.8
Dose 3	***Subtotal***	***81***	***3.6***
	0 days	15	0.7
	01-02	29	1.3
	03-04	18	0.8
	05-06	7	0.3
	07-13	5	0.2
	14-29	6	0.3
	30+	1	0.04
Unknown	***Subtotal***	***863***	***37.9***
	Missing	863	37.9
Grand total		**2,279**	**100.0**

Pericarditis (Reporting Period 01 Jul to 31 Dec 2021)

During this reporting period, there were 1,093 cases (1,096 events) received that reported pericarditis related events, of which, 785 cases were medically confirmed. There were 4 cases with fatal outcomes. (See Appendix 20.11.4 and Appendix 20.11.5).

There were 625 cases (57.2%) reported in males and 449 cases (41.1%) reported in females; 19 cases (1.7%) did not report gender. The mean age of the patients was 40.8 years (SD: 17.3), with a median age of 38 years (min: 12/max: 87). Age information was missing in 91 cases. Cases with pericarditis events were reported most frequently in patients between 18 to 39 years of age (508; 46.5%) (Table 16-29).

Table 16-29 Number and Percentage of Pericarditis Cases by Age and Gender - Reporting Period 01 Jul to 31 Dec 2021

Age Group	Female		Male		Unknown		Total # Cases	% Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
12-15	4	0.4	6	0.5	0	0.0	10	0.9
16-17	2	0.2	10	0.9	0	0.0	12	1.1
18-29	106	9.7	209	19.1	2	0.2	317	29.0
30-39	81	7.4	107	9.8	3	0.3	191	17.5
40-49	71	6.5	88	8.1	0	0.0	159	14.5
50-64	99	9.1	90	8.2	3	0.3	192	17.6
65-74	38	3.5	44	4.0	1	0.1	83	7.6
75+	20	1.8	17	1.6	1	0.1	38	3.5
Missing	28	2.6	54	4.9	9	0.8	91	8.3
Grand total	**449**	**41.1**	**625**	**57.2**	**19**	**1.7**	**1093**	**100.0**

Most of the pericarditis related events reported during the reporting period occurred after the 2nd dose (376; 34.3%), with 25.5% (280) of the pericarditis related events reported after the 1st dose of SPIKEVAX with most of them occurring more than a week after receiving the 1st dose of the vaccine (110 cases; 39.3) (Table 16-30).

Table 16-30 Number and Percentage of Pericarditis Events by Dose and TTO - Reporting Period 01 Jul to 31 Dec 2021

Dose Number	TTO (Days)	# Events	% Events
Dose 1	***Subtotal***	***280***	***25.5***
	0 days	20	1.8
	01-02	56	5.1
	03-04	31	2.8
	05-06	23	2.1
	07-13	52	4.7
	14-29	58	5.3
	30+	40	3.6
Dose 2	***Subtotal***	***376***	***34.3***

Dose Number	TTO (Days)	# Events	% Events
	0 days	28	2.6
	01-02	104	9.5
	03-04	44	4.0
	05-06	25	2.3
	07-13	30	2.7
	14-29	52	4.7
	30+	93	8.5
Dose 3	***Subtotal***	***66***	***6.0***
	0 days	8	0.7
	01-02	23	2.1
	03-04	9	0.8
	05-06	6	0.5
	07-13	11	1.0
	14-29	6	0.5
	30+	3	0.3
Unknown	***Subtotal***	***374***	***34.1***
	Missing	374	34.1
Grand total		**1,096**	**100.0**

Fatal Case Summaries

During this review period there were 30 cases with fatal outcomes for myocarditis. (See Appendix 20.11.4 and Appendix 20.11.5).

Brighton Collaboration Case Classification, CDC Working Case Definition, and WHO-UMC Causality Assessment – Report Period 01 Jul to 31 Dec 2021

Further evaluation was conducted in the segment of the reported cases involving patients that were considered (based on epidemiologic characteristics) to be at potentially higher risk for having events of myocarditis and/or pericarditis. This evaluation was conducted in males and females younger than 40 years of age, after the 2nd dose of SPIKEVAX, regardless of the TTO of the events from the administration of the vaccine. An additional, focused evaluation was conducted on all reports involving patients <18 years of age, as well as those who received a 3rd dose or a booster dose. (See Appendix 20.11.6 and Appendix 20.11.7)

Following that strategy, the MAH conducted an evaluation of all the cases identified as cases of Myocarditis and Pericarditis utilizing the Brighton Collaboration Case Definition for Myocarditis/Pericarditis [51], which allows classification of the cases on whether or not they are true cases of myocarditis or pericarditis.

Cases were also evaluated using the CDC working case definition [53] for Acute myocarditis and Acute pericarditis which allows for classification of the cases on whether or not they are probable or confirmed cases of myocarditis and/or pericarditis based on: 1) characteristic symptoms associated with these events; 2) diagnostic test results (e.g. an elevated troponin level or abnormal findings on electrocardiogram, echocardiogram, or cardiac magnetic resonance imaging) that are associated with these syndromes; and 3) absence of other identifiable cause.

Those cases that were classified as Level 1 to Level 3, and probable or confirmed cases of acute myocarditis or pericarditis were assessed using the WHO-UMC causality assessment (which allow to perform a combined assessment of the reported cases taking into account the clinical-pharmacological aspects of the case history and the quality of the documentation of the observation) [54].

Using the CDC working case definition for myocarditis and/or pericarditis, reported cases of possible acute myocarditis or pericarditis with insufficient evidence or information to meet the case definition were classified as “unassessable.” Reported cases of possible acute myocarditis or pericarditis with evidence of NOT meeting any of the parameters for the case definition were classified as “Not a case.”

Following the search strategy mentioned above, there were a total of 953 cases (30%) reported in patients younger than 40 years of age, identified as occurring in males (783; 82.2%) and females (168; 17.2%), and two that did not provide gender information. There were 893 (93.7%) reports after the 2nd dose, and 60 (6.3%) after the 3rd dose.

According to the Brighton Collaboration case definition for myocarditis and pericarditis from those 953 cases, 99 were classified as Level 1, 189 as Level 2, and 7 as Level 3. The rest of the reports were considered Level 4 or Level 5 based on the lack of information required to make a diagnostic case classification (or there was information available that provided a more plausible explanation for the occurrence of the event like diagnosis of concurrent Epstein - Barr virus (EBV) infection, etc.) (See Appendix 20.11.8 and Appendix 20.11.9).

According to the CDC working definition (used to define myocarditis and pericarditis) [53] there were 220 probable cases of myocarditis, 38 Confirmed, and 14 Acute Pericarditis. (See Appendix 20.11.12 and Appendix 20.11.13).

According to the WHO causality assessment (used to characterise strength of association between event and vaccine exposure) there were 11 Probable, and 401 Possible cases, with most of the reports considered possible based on information provided, including elevated troponin levels, abnormal electrocardiogram (ECG), Echocardiogram, and cardiac Magnetic Resonance Imaging (MRI) results compatible with myocarditis or pericarditis. The rest of the reports were considered

conditional or unassessable due to the lack of required information (including symptoms, TTO, dose information or both, myocardial biomarkers, and imaging studies information), (See Appendix 20.11.10 and Appendix 20.11.11).

Subpopulation Analyses

Myocarditis and Pericarditis in Adolescents (12 to 17 years old) – Cumulative to 31 Dec 2021

Cumulatively, there were 116 cases (122 events) of myocarditis and pericarditis in adolescents 12 to 17 years of age (3.1% of all cases reported), with 99 cases medically confirmed. There were 103 (88.8%) cases reported in males and 13 (11.2%) in females. The mean age of the adolescents was 15.7 years (SD: 1.3) and the median age was 16 years (min: 12/max: 17). The majority of the cases reported in adolescents were in males aged 16 to 17 years (69, 59.5%) (Table 16-31).

Table 16-31 Number and Percentage of Myocarditis and Pericarditis Cases in Adolescents (12 to 17 years old) by Age and Gender - Cumulative to 31 Dec 2021

Age Group	Female		Male		# Total Cases	% Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases		
12-15	8	6.9	34	29.3	42	36.2
16-17	5	4.3	69	59.5	74	63.8
Grand total	**13**	**11.2**	**103**	**88.8**	**116**	**100**

Cumulatively, there were 100 events of myocarditis reported in adolescents (including 1 event of myocarditis infectious), with the greatest proportion of the events (45; 44.5%) occurring after the 2nd dose with 43 out of those 45 events having a TTO of less than 7 days.

Cumulative there were 22 events of pericarditis reported in adolescents with 10 (45.5%) occurring after the 2nd dose with 9 of them occurring less than 7 days after the vaccine. There 3 reports of pericarditis after the 1st dose of SPIKEVAX, and 9 with an unknown dose information. There were 6 reports of myopericarditis in adolescents, 5 were in males, with 4 of them after the 2nd dose of SPIKEVAX and with a TTO of 1 to 4 days.

Myocarditis and Pericarditis in Adolescents (12 to 17 years old) – Reporting Period 01 Jul to 31 Dec 2021

During the reporting period, there were 113 cases (119 events) of myocarditis and pericarditis reported in adolescents 12 to 17 years of age, with 96 cases medically confirmed. There were 100 cases reported in males (88.5%) and 13 in females (11.5%). The mean age of the adolescents was 15.7 years (SD: 1.3 years) and the median age was 16 years (min: 12/max: 17). Myocarditis and pericarditis cases in adolescents were most often reported in males aged 16 to 17 years (68; 60.2%) (Table 16-32).

Table 16-32 Number and Percentage of Myocarditis and Pericarditis Cases by Age and Gender in Adolescents (12 to 17 years old) – Reporting Period 01 Jul to 31 Dec 2021

Age Group	Female		Male		Total # Cases	% Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases		
12-15	8	7.1%	32	28.3%	40	35.4%
16-17	5	4.4%	68	60.2%	73	64.6%
Grand total	**13**	**11.5%**	**100**	**88.5%**	**113**	**100.0%**

During the reporting period, there were 97 events of myocarditis reported in adolescents 12 to 17 years old. There were 18 events (18.6%) reported after the 1st dose, 43 (44.3%) after the 2nd dose, and 36 (37.1%) with unknown dose and TTO information. There were no cases of myocarditis after the 3rd dose of SPIKEVAX.

Table 16-33 Number and Percentage of Events Reporting Myocarditis in Adolescents (12 to 17 years old) by Dose and TTO – Reporting Period 01 Jul to 31 Dec 2021

Dose Number	TTO (Days)	# Events	% Events
Dose 1	***Subtotal***	***18***	***18.6***
	01-02	7	7.2
	03-04	4	4.1
	07-13	2	2.1
	14-29	2	2.1
	30+	3	3.1
Dose 2	***Subtotal***	***43***	***44.3***
	0 days	4	4.1
	01-02	15	15.5
	03-04	18	18.6
	05-06	4	4.1
	14-29	2	2.1
Unknown	***Subtotal***	***36***	***37.1***
	Missing	36	37.1
Grand total		**97**	**100.0**

There were 22 events of pericarditis in adolescents received during the reporting period reported in adolescents 12 to 17 years of age; 10 occurred after the 2nd dose (45.5%); 3 events occurred after the 1st dose (13.6%), and 9 events (40.9%) did not provided dose or TTO information. There were no reports of pericarditis after a 3rd dose of SPIKEVAX in adolescents 12 to 17 years of age.

Table 16-34 Number and Percentage of Events Reporting Pericarditis in Adolescents (12 to 17 years old) by Dose and TTO – Reporting Period 01 Jul to 31 Dec 2021

Dose Number	TTO (Days)	# Events	% Events
Dose 1	***Subtotal***	***3***	***13.6***
	0 days	1	4.5
	01-02	1	4.5
	07-13	1	4.5
Dose 2	***Subtotal***	***10***	***45.5***
	01-02	7	31.8
	03-04	1	4.5
	07-13	1	4.5
	30+	1	4.5
Unknown	***Subtotal***	***9***	***40.9***
	Missing	9	40.9
Grand total		**22**	**100.0**

Brighton Collaboration Case Classification, CDC Working Definition, and WHO-UMC Causality Assessment – Adolescents (12 to 17 years old)

See Appendix 20.11.8, Appendix 20.11.9, Appendix 20.11.10, Appendix 20.11.11, Appendix 20.11.12, and Appendix 20.11.13.

Myocarditis and Pericarditis in Children (<12 years old)

There have been no reports received of myocarditis or pericarditis following the use of SPIKEVAX in children less than 12 years old.

Myocarditis and Pericarditis in Patients Receiving a 3rd or Booster dose of SPIKEVAX

All the cases that have been received for myocarditis and pericarditis after a 3rd or Booster dose of SPIKEVAX have occurred during the reporting period of this PBRER (01 Jul to 31 Dec 2021). There were 140 cases (147 events) of myocarditis and pericarditis following a 3rd or booster dose of SPIKEVAX, of which 113 were considered serious and 95 were medically confirmed. There was 1 case with a fatal outcome. There were 81 events of myocarditis (including one event of hypersensitivity myocarditis) and 66 events of pericarditis. The cases involved 83 males (59.3%) and 57 females (40.7%), with a mean age of 46.5 years (SD: 18.6) and a median age of 43.5 years (min: 18/max: 86). Most of the events had a TTO of less than 7 days after receiving the 3rd dose (115; 78.2%).

There were 64 cases of myocarditis and pericarditis after receiving the 3rd dose that were included in the high-risk group evaluation of individuals younger of 40 years of age. Information for those reports that fulfil the Brighton Collaboration case definition Level 1 to 3, as well as the CDC working case definition probable and confirmed, and were classified as possible or probable as per the WHO causality assessment (See Appendix 20.11.8, Appendix 20.11.9, Appendix 20.11.10,

Appendix 20.11.11, Appendix 20.11.12, and Appendix 20.11.13). It is important to note that in most of these reports it is not known whether the 3rd dose was given due to the patient being an immunocompromised individual or as a true booster dose.

16.3.1.2.5. Discussion

A review of the data received during this reporting period showed that events of myocarditis and pericarditis continue to primarily occur in young adult males shortly after the second dose of the vaccine with a TTO less than 7 days.

Evaluation of the data of those patients receiving a booster continues to be consistent with the known safety profile of SPIKEVAX, as well as for reports of myocarditis and pericarditis in adolescents 12 to 17 years of age. There have not been cases of myocarditis or pericarditis reported for children under the age of 12 years old.

As mentioned before, there have been multiple observational studies that have been conducted in an effort to assess and estimate the risk of myocarditis and pericarditis following receipt of mRNA vaccines targeting SARS CoV-2. One of the first observational studies is an unpublished Nordic cohort study (EMA 2021) that included a meta-analysis of the 23 million residents of Denmark, Finland, Norway and Sweden, that according to information made available to the MAH prior to publication (Karlstad 2021), during the 28-day risk-periods following vaccination and during unvaccinated periods experienced by the study participants (6.7 million person-years in total), the authors observed 1,092 incident myocarditis cases and 1,154 incident pericarditis cases. The authors concluded that the information collected in this study shows higher rates of myocarditis and pericarditis within 28 days following vaccination with SARS-CoV-2 mRNA vaccines when compared to unvaccinated, and these associations were strongest within the first 7-days, were increased for all combinations of mRNA vaccines and were more pronounced after a second dose of either after mRNA-1273 or BNT162b2 and, young males aged 16-24 years had the highest increased risk.

Other relevant published observational studies that showed a similar association, included a population-based case-control analysis using French national health data [55], and a retrospective case series study [9] that was performed utilizing the Mayo Clinic COVID-19 Vaccine Registry in which the authors measured the incidence rate ratio for myocarditis temporally related to COVID-19 mRNA vaccination compared to myocarditis in a comparable population from 2016 through 2020. Another relevant observational study that was conducted with the objective of monitoring 23 serious outcomes reported after vaccination with the COVID mRNA vaccines, was [42] in which the authors assessed the safety of the mRNA COVID-19 vaccines (BNT162b2 by Pfizer-BioNTech and SPIKEVAX) from Dec 2020 through Jun 2021. While mRNA vaccination was not associated with an increased risk of myocarditis/pericarditis overall, mRNA vaccination was

associated with excess risk of myocarditis/pericarditis among those aged 12 to 39 years with an estimated 6.3 (95% CI, 4.9 to 6.8) additional cases per million doses in days 0 through 7 after vaccination.

In US, a population-based cohort study of approximately 2.4 million patients aged ≥18 years observed 15 cases of confirmed myocarditis after any dose of a mRNA COVID-19 vaccine (2 cases after dose 1; 13 cases after dose 2), for an incidence of 0.08 per 100,000 first doses and 0.58 per 100,000 second doses; acute myocarditis was described as a rare event. All reported cases occurred in younger males (median age, 25 years) who were hospitalized and had symptoms resolve with conservative management. The US FDA recently presented an assessment of myocarditis/pericarditis rates using the FDA Biologics and Effectiveness Safety [56] active surveillance system, which consists of 4 health claims data sources with a total 76.5–89.5 million annual enrollees. Within the first 7 days after administration of any mRNA COVID-19 vaccine dose (e.g., mRNA-1273 or BNT162b2), the incidence rate of myocarditis/pericarditis per 1 million person-days was generally low for all age groups; rates were highest for males aged 18–25 years after dose 2. At the 21 Oct 2021, CDC ACIP meeting, the COVID-19 Vaccine Safety Technical [57] VaST) Work Group summarized the available data to date on myocarditis rates after mRNA COVID-19 vaccination from multiple worldwide safety monitoring systems, which indicated myocarditis was associated with both mRNA-1273 and BNT162b2 among adolescents and young adults, more frequently among males. The COVID-19 subcommittee of the WHO Global Advisory Committee on Vaccine Safety [58] also recently reviewed available evidence from multiple countries and noted that while some data suggest increased myocarditis incidence in young males after dose 2 of mRNA-1273 versus BNT162b2, other data do not support this finding, and the overall risk is low.

Several large US surveillance systems have shown comparable risk of myocarditis between mRNA-1273 and BNT162b2 (e.g., Vaccine Adverse Event Reporting System [VAERS], FDA BEST System, and Department of Veterans Affairs active surveillance Rapid Cycle Analysis for COVID-19 vaccines). For example, the CDC COVID-19 Vaccine Task Force provided the reporting rate of myocarditis among males aged 18–24 years after mRNA-1273 and BNT162b2 as 3.68 and 3.85 per 100,000 second doses administered, respectively, based on data from the VAERS safety passive monitoring system [59]. However, a recent analysis from the Vaccine Safety Datalink (VSD) [42] estimated that there was an excess 9.7 myocarditis/myopericarditis cases per million doses of mRNA-1273 versus BNT162b2 among 18–39-year-olds (adjusted rate ratio [95% CI]: 2.28 [1.00–5.22]; 2-sided p-value: 0.049). Of note, the VSD analysis was based on small case numbers within 7 days after dose 2 (mRNA-1273: 14 cases [810,839 total second doses]; BNT162b2: 12 cases [1,256,525 total second doses]).

For those case reports for which diagnostic results information is available, including several literature articles and case reviews that have been published, clinical presentation seems to be consistent with the majority of patients having normal ventricular systolic function on echocardiogram, with many have abnormal findings suggestive of myocarditis on cardiac MRI in the setting of elevated troponin and electrocardiographic changes; the presentation of the myocarditis is usually characterised by a mild illness with rapid resolution of symptoms within few days in most patients.

Based on the analysis of all the safety data available as of 31 Dec 2021, the MAH considers cases included under the AESI of myocarditis and pericarditis to be consistent with the known safety profile of SPIKEVAX.

16.3.1.2.6. Conclusion

A review of the data received cumulatively and during this reporting period showed that events of myocarditis and pericarditis continue to primarily occur in young adult males shortly after the second dose of the vaccine with a TTO less than 7 days.

Review of the data also show no difference in the observed safety profile of SPIKEVAX in the adolescent population, or in those individuals receiving a 3rd dose of SPIKEVAX when compared to >18 years old. Implementation of a new reference rate did not change the interpretation of observed vs. expected analyses.

Based on the information provided by both literature and surveillance sources consistently describing an increase in the incidence of myocarditis, predominantly within the first 7 days following receipt of a second dose of vaccine, that appears largely isolated to younger men (<40 years of age).

Based on the analysis of all the safety data received during the reporting period of this PBRER, ModernaTX, Inc, considers that cases of myocarditis and pericarditis to be consistent with the known safety profile of SPIKEVAX and appropriate risk minimization and risk communications strategies have already been implemented by the MAH. The MAH will continue to monitor the reported events of Myocarditis and Pericarditis using routine and enhanced surveillance activities, including 2 Post-Authorization Safety Studies. The benefit-risk evaluation remains positive.

16.3.2. New Information on Important Potential Risks

16.3.2.1. Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)

16.3.2.1.1. Source of the New Information

The ModernaTx GSDB was queried for valid, clinical and spontaneous case reports received from HCP, HA, consumers and literature, cumulative from 18 Dec 2020 to 31 Dec 2021 for the mRNA-1273 vaccine (COVID-19 vaccine Moderna), SPIKEVAX.

16.3.2.1.2. Background Relevant to the Evaluation

The potential for any SARS-CoV-2 vaccine to potentiate subsequent SARS-CoV-2 viral infection has been hypothesized. This hypothesis is based upon the observation that antibody responses may paradoxically be misdirected to facilitate viral cell entry, thereby resulting in a more severe infection than would have occurred in the absence of vaccine priming. In the case of coronaviruses, it has been observed that in laboratory studies in which cats were exposed to large inocula of wild type feline coronavirus, the experimental animals were at elevated risk for feline peritonitis when subsequently exposed to wild type virus. A commercial feline coronavirus vaccine has been available for some years, with no reported increase in the incidence of feline peritonitis [60]. To the knowledge of the MAH, there have been no cases of Vaccine Associated Enhanced Disease (VAED) in humans who have been repeatedly exposed to any of the 4 common human coronaviruses, or to the viruses causing SARS, Middle East respiratory syndrome (MERS), or SARS-CoV-2.

There is currently no widely accepted case definition for VAED; however, a recent publication by the Brighton Collaboration provides some guidance for assessment of potential VAED in COVID-19 [61]. In this guidance, it is suggested that VAED may be identified first as a vaccine failure (i.e., VAED requires exposure to and infection by SARS-CoV-2 in a person who has been fully immunized). The authors acknowledge that there is presently no pathognomonic set of clinical findings to characterise VAED. Furthermore, case classifications that can be readily applied to individual-level data from spontaneous reporting are not defined. The Brighton Collaboration working group states that a definitive case of VAED cannot be ascertained with current knowledge of the mechanisms of pathogenesis of VAED. Probable cases must show an increase in severity or rates of atypical findings when compared to a non-vaccinated control group, however this criterion must be considered at a population or group level rather than an individual level.

The authors further suggest that the clinical presentation must then be recognized as atypical or severe. It is further suggested that assessment of the type and frequency of clinical presentations

is recommended. Clinical parameters of interest include respiratory, cardiovascular, hematological, inflammatory, renal, gastrointestinal, and central nervous system conditions.

16.3.2.1.3. Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

Following this general approach, the MAH first identified cases of COVID-19 or documented lack of efficacy with non-missing information on latency (to focus on individuals with known intervals between vaccine and event dates) within the review period. For these cases, we then identified and reviewed the presence of other adverse events consistent with the clinical parameters of interest in the Brighton Collaboration definition. It was expected that cases with "vaccine failure" (for the purpose of assessing potential VAED, "vaccine failure" is defined as infection with COVID-19 at least 14 days after the second dose of vaccine, which includes recipients of a third or fourth dose regardless of time to onset) may be considered as possible VAED if the concomitant AE occurs more frequently in the "vaccine failure" population than among the subset of COVID-19 cases where COVID-19 onset occurred too soon after the first dose of vaccine for the vaccine to take, which is required in order for VAED, if it exists, to occur.

16.3.2.1.4. Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Overview of Cases

During the review period, there were 6,765 COVID-19 and/or lack of efficacy cases included in this assessment based on known dose and latency. Of these, a total of 5,203 (76.9%) cases of COVID-19 had a latency of at least 14 days after the second vaccine dose Table 16-35).

The most commonly identified condition potentially consistent with VAED among COVID-19 and/or lack of efficacy cases was death, which occurred in 7.9% of vaccine failure cases and 3.4% in the comparison group, i.e., COVID-19 cases that were not yet eligible to be considered VAED (not being defined as a "vaccine failure" based on latency). Multiple other conditions were also identified in both the subset of cases eligible for consideration as VAED per the Brighton criteria referenced above and the comparator. These conditions may occur in typical presentations of COVID-19. Although a larger proportion of vaccine failure cases had at least one of these concomitant conditions reported (14.9% vs 11.2%), it should be noted that COVID-19 cases in the context of vaccine failure compared with individuals diagnosed with COVID-19 within 7 days of the first vaccine dose more frequently reported comorbidities such as hypertension (18.3% vs. 8.9%), drug hypersensitivity (15.9% vs. 12.0%), and coronary artery disease (5.2% vs 0.3%). As such, differences in patient characteristics placing individuals at higher risk for severe outcomes of COVID-19 between those with vaccine failure and those with COVID-19 before vaccination

would have been expected to take full effect makes attribution of the difference to VAED questionable.

Table 16-35 Frequency by Demographic, Geographic Variables, and Distribution of Conditions Potentially Associated with VAED among COVID-19 Cases Where Latency is Known

	COVID Cases with Non-missing Latency	Latency		
		< 14 Days After First Dose	14 Days After First Dose Through < 14 Days After Last Dose	≥ 14 Days After Second Dose
	N (%)	N (%)	N (%)	N (%)
All	6765 (100)	358 (100)	1204 (100)	5203 (100)
Age group				
< 12	0 (0)	0 (0.6)	0 (0)	0 (0)
12 - 17	2 (0)	2 (0.6)	0 (0)	0 (0)
18 - 24	279 (4.1)	36 (10.1)	34 (2.8)	209 (4)
25 - 39	950 (14)	86 (24)	167 (13.9)	697 (13.4)
40 - 49	713 (10.5)	50 (14)	116 (9.6)	547 (10.5)
50 - 64	1455 (21.5)	82 (22.9)	239 (19.9)	1134 (21.8)
65 - 74	1337 (19.8)	35 (9.8)	251 (20.9)	1051 (20.2)
≥ 75	1913 (28.3)	16 (4.5)	369 (30.7)	1528 (29.4)
Missing	116 (1.7)	51 (14.3)	28 (2.3)	37 (0.7)
Sex				
Male	3140 (46.4)	144 (40.2)	554 (46)	2442 (46.9)
Female	3576 (52.9)	200 (55.9)	638 (53)	2738 (52.6)
Missing	49 (0.7)	14 (3.9)	12 (1)	23 (0.4)
Geographic region (or country)				
Asia	122 (1.8)	83 (23.2)	33 (2.7)	6 (0.1)
Canada	2 (0)	1 (0.3)	0 (0)	1 (0)
European Economic Area	1031 (15.2)	22 (6.2)	53 (4.4)	956 (18.4)
Switzerland	24 (0.4)	1 (0.3)	2 (0.2)	21 (0.4)
United Kingdom	135 (2)	25 (7)	40 (3.3)	70 (1.4)
United States	5451 (80.6)	226 (63.1)	1076 (89.4)	4149 (79.7)
At least one additional event potentially related to VAED	1076 (15.9)	40 (11.2)	259 (21.5)	777 (14.9)
Fatal event	550 (8.1)	12 (3.4)	125 (10.4)	413 (7.9)
Acute respiratory distress	315 (4.7)	7 (2)	80 (6.6)	228 (4.4)
Cardiac event	275 (4.1)	12 (3.4)	74 (6.2)	189 (3.6)
Kidney injury	180 (2.7)	5 (1.4)	47 (3.9)	128 (2.5)
Deep vein thrombosis	56 (0.8)	7 (2)	17 (1.4)	32 (0.6)

	COVID Cases with Non-missing Latency	Latency		
		< 14 Days After First Dose	14 Days After First Dose Through < 14 Days After Last Dose	≥ 14 Days After Second Dose
	N (%)	N (%)	N (%)	N (%)
Stroke	51 (0.8)	2 (0.6)	16 (1.3)	33 (0.6)
Myocardial infarction	37 (0.6)	4 (1.1)	8 (0.7)	25 (0.5)
Pulmonary embolism	34 (0.5)	5 (1.4)	7 (0.6)	22 (0.4)
Thrombocytopenia	28 (0.4)	3 (0.8)	5 (0.4)	20 (0.4)
Convulsions	19 (0.3)	1 (0.3)	6 (0.5)	12 (0.2)
Multisystem inflammatory syndrome	12 (0.2)	1 (0.3)	2 (0.2)	9 (0.2)
Arthritis	11 (0.2)	0 (0)	2 (0.2)	9 (0.2)
Hepatic injury	10 (0.2)	1 (0.3)	2 (0.2)	7 (0.1)
Bell's palsy	7 (0.1)	0 (0)	1 (0.1)	6 (0.1)
Myocarditis or pericarditis	0 (0)	0 (0)	0 (0)	0 (0)
Chronic fatigue syndrome	0 (0)	0 (0)	0 (0)	0 (0)
Documented Medical History				
Drug hypersensitivity	1101 (16.3)	43 (12)	229 (19)	829 (15.9)
Hypertension	1276 (18.9)	32 (8.9)	293 (24.3)	951 (18.3)
COVID 19	145 (2.1)	11 (3.1)	34 (2.8)	100 (1.9)
Diabetes mellitus	473 (7)	21 (5.9)	113 (9.4)	339 (6.5)
Asthma	255 (3.8)	16 (4.5)	48 (4)	191 (3.7)
Hyperlipidemia	498 (7.4)	3 (0.8)	120 (10)	375 (7.2)
Gastroesophageal reflux	368 (5.4)	9 (2.5)	87 (7.2)	272 (5.2)
Hypothyroidism	281 (4.2)	4 (1.1)	64 (5.3)	213 (4.1)
Chronic obstructive pulmonary	394 (5.8)	6 (1.7)	107 (8.9)	281 (5.4)
Type 2 diabetes mellitus	390 (5.8)	7 (2)	83 (6.9)	300 (5.8)
Obesity	343 (5.1)	14 (3.9)	79 (6.6)	250 (4.8)
Depression	235 (3.5)	4 (1.1)	55 (4.6)	176 (3.4)
Chronic kidney disease	318 (4.7)	2 (0.6)	88 (7.3)	228 (4.4)
Atrial fibrillation	330 (4.9)	1 (0.3)	90 (7.5)	239 (4.6)
Coronary artery disease	360 (5.3)	1 (0.3)	89 (7.4)	270 (5.2)

Subpopulation Analyses

VAED in Adolescents (12-17 Years of Age)

There were no potential VAED cases identified in individuals 12-17 years of age during the review period.

VAED in Children (<12 Years of Age)

There were no potential VAED cases identified in individuals <12 years of age identified during the review period.

VAED in Patients Receiving SPIKEVAX Booster

In the subset cases used to assess VAED, there were 273 instances of COVID-19 or lack of efficacy identified with known latency in individuals who had received a third vaccine dose; 162 (58.6%) occurred within 14 days of dose 3.

Comparing vaccine failure cases occurring after the primary series with those occurring at least 14-days after a third dose, there was no evidence of VAED. The proportion of cases with at least one additional event potentially related to VAED was slightly higher for those without a booster dose prior to the event compared with those where vaccine failure occurred at least 14 days after a booster dose (15.0 % vs 9.9%). Cases of vaccine failure at least 14 days after a booster dose were more often elderly (49.7% vs 60.4%), which may reflect the age distribution of early booster dose recipients.

16.3.2.1.5. Discussion

Although VAED was raised as a safety concern for COVID-19 vaccines early in the pandemic, current evidence does not suggest that this hypothetical construct presents a true risk. Motivation to monitor COVID-19 vaccine recipients for possible VAED arose from sources such as animal models in which pathogenesis suggested a common potential mechanism producing VAED related to respiratory syncytial virus (RSV) vaccines in MERS and SARS-CoV-1 [62]. To date, no pathognomic presentation of VAED has been recognized following immunization of >182 million individuals. Further, analysis of the immune profile of SPIKEVAX in a mouse model shows elicitation of a protective immune profile that is not associated with vaccine-enhanced disease upon SARS-CoV-2 challenge [63].

Given the diverse clinical manifestations and sequelae of wild-type COVID-19 disease, however, it is nearly impossible to assert that a given clinical course of disease represents enhancement of what would have been observed in the absence of vaccination. As such, identification of VAED at the individual case level is recognized to be infeasible at this time [61]. At a population level, VAED can only occur as a result of infection with wild-type virus following vaccination, and its incidence (if identifiable) would be challenging to interpret based both upon challenges in diagnosis and in ascertainment through post-authorisation data sources (e.g., limitations in the thoroughness of spontaneous reports). Use of historical incidence data would be unlikely to provide useful context given inextricable linkage to factors such as local incidence of COVID-19 in the source population [39]. Further, severity associated with prevailing variants may change over time, making it difficult to claim that a change in severity is attributable to VAED.

Interpretation of analyses considering the possibility of VAED has not changed based on data accrued during this review period. Although surveillance for signs of VAED has been conducted by ModernaTX, Inc and health authorities since the EUA, currently available post-authorisation data do not provide evidence to support the hypothesis that this phenomenon exists. In the absence of a pathognomic presentation, ModernaTX, Inc will continue to review cases of vaccine failure to determine whether discernable changes in population-level characteristics of disease presentation vary for vaccine failure events.

16.3.2.1.6. Conclusion

After careful review of all new safety data received during the reporting period for the safety topic of VAED, the benefit-risk profile for SPIKEVAX remains favorable. The safety topic of VAED will continue to be monitored using the routine pharmacovigilance measures implemented for SPIKEVAX.

16.3.3. New Information on Other Identified Risks Not Categorised as Important

None.

16.3.4. New Information on Other Potential Risks Not Categorised as Important

None.

16.3.5. Update on Missing Information

16.3.5.1. Use in pregnancy

16.3.5.1.1. Source of the New Information

Information presented below includes analysis performed on pregnancy-related cases received by ModernaTX, Inc. from 01 Jul 2021 to 31 Dec 2021 for the mRNA-1273 vaccine (COVID-19 vaccine Moderna) SPIKEVAX. Cumulative data covers the period from 18 Dec 2020 to 31 Dec 2021.

16.3.5.1.2. Background Relevant to the Evaluation

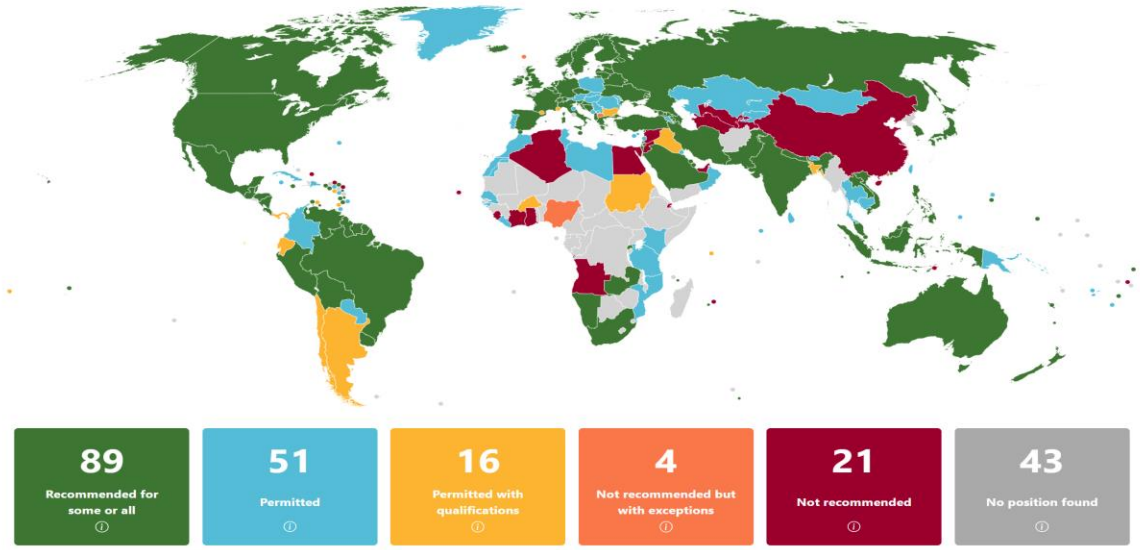
Use of SPIKEVAX in pregnancy is an area of missing information in the EU RMP. No clinical trials were conducted with SPIKEVAX in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition, or postnatal development. Thus far, there have been no specific safety concerns identified for COVID maternal immunization by the MAH, health authorities or public health organizations. There is recognition that in absence of clinical trials, vigilant post-EUA passive report monitoring, real

world evidence, and pregnancy registries are needed to continue monitoring the safety of COVID vaccination in pregnant women. Currently, in general, public health authorities and professional bodies have provided recommendations encouraging COVID maternal immunization, as pregnant women may be at a higher risk of severe COVID-19 disease and death, and there may be a higher risk of pregnancy complications with COVID-19.

WHO recommends the use of the COVID-19 vaccine in pregnant women, "Given the adverse consequences of COVID-19 during pregnancy and the increasing data supporting a favorable safety profile of mRNA1273 in pregnancy, WHO recommends the use of mRNA-1273 in pregnant individuals"[64]. The International Society of Infectious Disease of Obstetrics and Gynecology (ISIDOG) recommend that pregnant women should receive priority vaccination [65].

Countries around the world vary in their policies on COVID-19 maternal vaccination; as of 18 Dec 2021, 89 countries recommend the vaccine for some or all pregnant women (see Figure 16-1). Since the first SPIKEVAX PBRER (DLP 30 Jun 2021), approximately 68 additional countries have recommended COVID-19 vaccination during pregnancy.

Figure 16-1. Global Policies on COVID-19 Vaccination in Pregnancy by Country



Source: Berman Institute 2021
Covid-19 Maternal Immunization Tracker (COMIT): https://www.comitglobal.org/pregnancy, accessed on 04 January 2022, showing the most permissive policy position for each country for any COVID-19 vaccines

16.3.5.1.3. Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

Identification of Case Reports in Moderna GSDB:

The company GSDB was queried for valid SPIKEVAX pregnancy-related case reports received from healthcare providers, health authorities, consumers and literature, cumulatively and for the reporting period.

Reports identified included women vaccinated during pregnancy or around the time of conception, and reports of fetuses/neonates/infants whose mothers were vaccinated during gestation.

The current search strategy to identify "pregnancy-related cases" (Pregnancy [MI-PREG&Pts Preg] is comprised of multiple components:

- Argus field "Patient Pregnant" = YES OR
- MI-PREG SMQ (Pregnancy and neonatal topics SMQ) = YES and Patient Pregnant = NO AND Gender=female and Age Group= (18-49) OR
- MI-PREG =YES AND Patient Pregnant = NO AND Age group <2 y/o OR "Missing" AND PREG-Foetal Outcome <> (Empty) OR
- MI-PREG = YES and Patient pregnant =NO AND Argus field "Child Case Only" = Yes

In addition to the search strategy above, MAH reviewed all cases <2 years of age during this review period to capture additional pregnancy-related cases that have been misclassified, specifically children with prenatal exposure to SPIKEVAX.

Pregnancy-related cases are pulled by case identification numbers and contain "All PTs" which includes both pregnancy-related and non-pregnancy-related events.

"Pregnancy-related events"/ "Pregnancy-related PTs" (such as maternal exposure, pregnancy/labor/delivery/post-partum complications, pregnancy outcomes, foetal and neonatal events) within cases are identified by the MI-PREG SMQ.

Of note, given the search strategy described above, occasionally there are cases of vaccinated non-pregnant woman (often with pre-existing congenital anomalies detected as adults, such as arteriovenous malformations or septal defects detected at the onset of a stroke) or which is flagged by the search strategy and included in the case series.

For Pregnancy Outcomes (included in Appendix 20.11.15) a Pregnancy Outcome (Derived) filter is used with the following criteria:

- If PREG-Foetal Outcome is "Empty" but a PT suggestive of a pregnancy outcome is reported, such as either Abortion-related PT (filter MI-ABORT=YES), Preterm baby related PTs (filter MI-PRETERM=YES), or stillbirth related PTs (filter MI-STILLBIRTH=YES), or full-term baby related PTs (filter MI-FULLTERM=YES) then the PT term is entered as outcome OR
- Use PREG-Foetal Outcome if populated
- Otherwise, classified as "undetermined"

Additionally, a filter (" Gestational Period Group", Applied in Appendix 20.11.15) applied to the safety database identifies exposure as:

- First Trimester
- After first trimester
- Before conception (0-2 weeks)
- Unknown

Appendices for the pregnancy subpopulation analysis are as follows:

- Appendix 20.11.14 Distribution of Case and Event Counts by SOC/HLT/PT Stratified by Event seriousness for Interval and Cumulative.
- Appendix 20.11.15 Summary of pregnancy outcomes by trimester of exposure, and retrospective/prospective case classification, Reporting Period.
- Appendix 20.11.16 Summary of pregnancy outcomes by trimester of exposure, and retrospective/prospective case classification, Cumulative.
- Appendix 20.11.17 Summary of reported congenital anomalies by HLT and PT that occurred in fetuses and neonates, Cumulative

16.3.5.1.4. Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Observed vs. Expected

See Appendix 20.11.3.

Overview of Cases

Cumulative Overview 18 Dec 2020 to 31 Dec 2021

Cumulatively, 4,049 (1,294 serious, 17 fatal) pregnancy-related cases have been reported with a total of 13,063 events, of which 4,026 were serious. 2,035 cases were medically confirmed. A

higher proportion of the cases during the review period were reported as "serious". Serious cases must be interpreted with caution as many are not cases meeting the true definition of "serious" (death, life-threatening, hospitalization, etc.) in part due to a bias from self-reported seriousness classification in some countries, and different regulatory coding practices. The difference observed in this reporting period reflects the changing geographic patterns of reporting as that relates to varying country coding practices. Among the serious cases, there are cases which simply report "maternal exposure during pregnancy" with no reported clinical events and are reported as "serious" cases.

Reporting Period Review 01 Jul 2021 to 31 Dec 2021

During the reporting period, 1,397 (767 serious, and 11 fatal) pregnancy-related cases were reported and included 5,783 events, of which 2,820 were serious. Within the reporting period, 535 cases were medically confirmed. The 11 fatal cases for the reporting period are discussed in the "Serious and fatal cases" section below. Of note, foetal deaths are not usually coded as fatal cases as they are reported in a maternal case where there has not been a maternal mortality. Occasionally, the MAH receives regulatory reports or there are coding discrepancies where foetal deaths are coded or not coded as fatal cases. Summary tables of the cumulative and reporting period pregnancy-related cases by seriousness are presented below (Table 16-36).

Table 16-36 Summary of Interval and Cumulative Pregnancy-related Cases by Case Seriousness and Overall

	Non-serious		Serious		Total # of Cases	% of Total Cases
	# Cases	% of Total Non-serious Cases	# Cases	% of Total Serious Cases		
Prior to Review Period	2,125	77.1%	527	40.7%	2,652	65.5%
Review Period	630	22.9%	767	59.3%	1,397	34.5%
Grand total	**2,755**	**100.0%**	**1,294**	**100.0%**	**4,049**	**100.0%**

Pregnancy-related cases are most commonly reported in 18 to 39-year-olds, which is consistent with child-bearing age (Table 16-37). The age distribution for the reporting period continues to be comparable to what was seen previously. Cases reported of females and males under 2 years of age represent children with exposure during pregnancy. Refer to Adolescent subsection below for a discussion of the cases in 12 to 17-year-olds.

Table 16-37 Distribution by Gender and Age for Pregnancy-related Cases – Reporting Period

Age Group	Female		Male		Unknown		Grand total # Cases	Grand total % of Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases	# Cases	% of Total Cases		
<2*	8	0.6%	13	0.9%	4	0.3%	25	1.8%
12-15	1	0.1%	0	0	0	0	1	0.1%
16-17	6	0.4%	0	0	0	0	6	0.4%
18-29	277	19.8%	0	0	1	0.1%	278	19.9%
30-39	784	56.1%	0	0	0	0	784	56.1%
40-49	114	8.2%	0	0	0	0	114	8.2%
50-64**	12	0.9%	0	0	0	0	12	0.9%
65-74**	2	0.1%	0	0	0	0	2	0.1%
75+**	1	0.1%	0	0	0	0	1	0.1%
Missing	144	10.3%	6	0.4%	24	1.7%	174	12.5%
Grand total	**1349**	**96.6%**	**19**	**1.4%**	**29**	**2.1%**	**1397**	**100.0%**

*Cases under 2 years of age represent foetal cases or newborns/infants born to mothers who received the vaccine during pregnancy.
** Cases in the >50-year-old age group represent either Regulatory Authority cases (that cannot be queried) that report pregnancy in older females, are non-pregnancy related cases, and/or are cases with coding errors.

The most frequently reported pregnancy-related event PTs received during the reporting period are presented below (Table 16-38). These are similar to the previous reporting period; aside from the top two PTs related to maternal immunization and spontaneous abortion (a common outcome of pregnancy), the PTs represent expected reactogenicity seen in the general population. A reporting period review of spontaneous abortion is discussed in a subsection below. Of note, cumulatively there remains a lower percentage of cases with pyrexia in the pregnancy subpopulation (n=386 cases, 9.5%) compared to the SPIKEVAX general population (n=87,450 cases, 20.4%). This observation should be interpreted with caution; however, as fever may be associated with adverse pregnancy outcomes this observation remains of interest for the pregnancy subpopulation.

Table 16-38 Top 10 Most Frequently Reported Event PTs (All PTs*) in Pregnancy-related Cases Stratified by Event Seriousness – Reporting Period (01 Dec 2021 to 31 Dec 2021

PT	Non-Serious		Serious		Total # of Events	% of Total Events
	# Events	% of Total Non-serious Events	# Events	% of Total Serious Events		
Maternal exposure during pregnancy	552	18.6%	231	8.2%	783	13.5%

PT	Non-Serious		Serious		Total # of Events	% of Total Events
	# Events	% of Total Non-serious Events	# Events	% of Total Serious Events		
Exposure during pregnancy	157	5.3%	80	2.8%	237	4.1%
Pyrexia	99	3.3%	108	3.8%	207	3.6%
Headache	116	3.9%	89	3.2%	205	3.5%
Fatigue	114	3.8%	88	3.1%	202	3.5%
Abortion spontaneous	4	0.1%	192	6.8%	196	3.4%
Myalgia	96	3.2%	58	2.1%	154	2.7%
Nausea	63	2.1%	65	2.3%	128	2.2%
Chills	63	2.1%	63	2.2%	126	2.2%
Pain in extremity	56	1.9%	66	2.3%	122	2.1%
Grand total of all events / PTs	**2,963**	**100.0%**	**2,820**	**100.0%**	**5,783**	**100.0%**

*See methodology section which described the difference between "all PTs" and "pregnancy-related PTs." All PTs included pregnancy-related and non-pregnancy-related events.

During the reporting period, myocarditis and pericarditis was added as an Important Identified Risk for SPIKEVAX. Cumulatively, 9 cases of myo- and/or pericarditis have been reported for the pregnancy subpopulation, of which 8 cases were received during the reporting period. Refer to the myocarditis/pericarditis Section 16.3.1.2 of this PBRER.

Pregnancy-related events

During the reporting period, 1,888 pregnancy-related events were reported in 1,274 cases, of which 1,021 events were serious and 9 cases included events with a fatal outcome. Of these, 504 cases were medically confirmed. (*Note: Not all pregnancy-related cases report a pregnancy-related event as identified by the MI-Preg SMQ*).

The top 10 pregnancy related MedDRA PTs for the reporting period are presented below and are similar to the prior cumulative experience (Table 16-39). Only clinical pregnancy-related events are presented in this table (e.g., PTs of "Maternal exposure during pregnancy",

"Exposure during pregnancy", "Maternal exposure before pregnancy" and "Pregnancy" were excluded). When compared to the previous cumulative experience, spontaneous abortion remains the most frequently reported pregnancy-related clinical event. (See section 16.3.5.1 below on spontaneous and missed abortions).

Table 16-39 Top 10 Most Frequently Reported Pregnancy-Related Events by PT and Event Seriousness - Reporting Period

PT	Non-serious		Serious		Total # Events	% of Total Events
	# Events	% of Total Non-serious Events	# Events	% of Total Serious Events		
Abortion spontaneous	4	0.2%	192	10.2%	196	10.4%
Foetal death	0	0	31	1.6%	31	1.6%
Premature labour	1	0.1%	23	1.2%	24	1.3%
Haemorrhage in pregnancy*	0	0	20	1.1%	20	1.1%
Premature delivery	2	0.1%	18	1.0%	20	1.1%
Uterine contractions during pregnancy	5	0.3%	11	0.6%	16	0.8%
Premature baby	2	0.1%	13	0.7%	15	0.8%
Foetal hypokinesia	0	0	14	0.7%	14	0.7%
Pre-eclampsia	0	0	14	0.7%	14	0.7%
Premature rupture of membranes	2	0.1%	12	0.6%	14	0.7%
Total pregnancy-related events	**867**	**45.9%**	**1,021**	**54.1%**	**1,888**	**100.0%**

*Often coded for spontaneous abortion bleeding, and the cases do not describe "hemorrhage" per the clinical definition.
** Table excludes non-clinical PTs (e.g., "Maternal exposure during pregnancy", "Exposure during pregnancy", "Maternal exposure before pregnancy", and "Pregnancy").

Serious and Fatal Cases and Serious Pregnancy-related Events

During the reporting period, of the 767 serious cases, there were 624 cases with serious pregnancy-related events with 1,021 pregnancy-related events. When removing the cases that only had "maternal exposure" or "exposure during pregnancy" without any clinical pregnancy-related adverse events, there were 481 cases with 710 events.

ModernaTX reviews all reports of abortions, fetal deaths and stillbirths, and describes these in subsections of this PBRER (see below). Of note, there is inconsistent coding of spontaneous abortion, fetal death, and stillbirths as "fatal" cases.

Eleven cases were coded as fatal during the reporting period, of which 9 cases concerned fetal deaths or stillbirths; these cases are discussed in the Fetal death/Stillbirth section below. The remaining 2 cases concerned maternal mortality, and are described below:

4.1(b) **:** This is a case of a 30-year-oldfemale diagnosed with a stillbirth at 37+3 weeks gestational age, 30 days after the first and only dose of SPIKEVAX administered at 33+2 weeks gestational age. The patient was a former smoker with a history of renal insufficiency.

Fetal autopsy showed evidence of asphyxia in the heart and lungs and placenta pathology revealed a small placenta with global high grade fetal vascular malperfusion and thrombosis on the fetal side thought to be caused by a non-acute event. The cause/etiology of the placenta thrombi formation is unclear. Additional information regarding maternal reaction, if any, to vaccine, complications during current pregnancy, detailed past obstetrical, medical, social and surgical history, as well as other testing performed for the still birth evaluation (e.g., genetic and infectious evaluation) is not available. Limited data are available, and smoking is a confounder. Given the temporal association, causality is possible.

4.1(b) **:** This is a case of a 40-year-old female, with a history gestational diabetes, died in the hospital after a syncopal event with membrane rupture and vaginal bleeding, at approximately 38-weeks Gestational Age (GA), approximately 13 days after receiving the second dose of SPIKEVAX. Maternal state of health at arrival to the hospital as well as hospital course are unknown. She was induced and the neonate was admitted to the neonatal intensive care unit (ICU) but died due to severe hypoxic-ischemic-encephalopathy and multiple organ failure. Preliminary results from a maternal autopsy showed endometrial bleeding and suspected amniotic fluid embolism. Past medical, surgical, gynecological, obstetrics and social history unknown. Hospital course including labs (platelets [case reports of severe ITP in literature], coags, fibrinogen], and imaging (e.g., brain, lung) and full autopsy results are unknown. Given the temporal association, causality is possible.

Cumulatively, 3 maternal mortality cases have been reported, the first case being described in PBRER#1 (4.1(b)); the MAH assessed this case as unlikely related to SPIKEVAX.

When compared to the previous cumulative experience, no safety concerns were identified following review of serious and fatal cases received during the reporting period for the pregnancy subpopulation.

Spontaneous abortions, Stillbirths and Fetal Deaths

The MAH reviews all cases and performs an O/E analysis of spontaneous abortion, stillbirths and fetal deaths. (See Appendix 20.11.3 for the O/E analysis). Upon medical review, reports coded as "fetal death" and "stillbirth" were classified as spontaneous abortion if they occur before 20-weeks GA, and as stillbirth if they occur after 20 weeks gestational age. The threshold of 20 weeks is per the definitions applied in the United States and aligns with the background rates that are used in the O/E analysis [66] [67].

Spontaneous and Missed Abortions

During the reporting period, 224 cases were identified using the PT terms: Abortion, Abortion early, Abortion induced, Abortion infected, Abortion late, Abortion missed, Abortion of ectopic

pregnancy, Abortion spontaneous, Abortion spontaneous incomplete, Abortion threatened, Anembryonic gestation, Biochemical pregnancy). Of note, some cases have more than one of the aforementioned PTs, as there are 235 events coded with these PTs. Of the 224 cases, 107 were medically confirmed.

With regards to an analysis of latency/TTO, during the reporting period 86 events (36.6%) were missing TTO information; of those with TTO data, there was no clear difference between Dose 1 and Dose 2, and 32.3% of the abortion events occur more than 14 days after vaccination after Dose 1 or 2. Given the small numbers of Dose 3 abortion-related events at this time, a meaningful comparison with the primary series data was not possible. Overall, there was no clear TTO clustering of these abortion-related events. See Table 16-40 below.

Table 16-40 Latency of Abortion-related Events by TTO and Dose - Reporting Period

Dose Number	TTO Doses (Days)	Review Period	
		# Events	% Events
Dose 1	**Subtotal**	72	30.6%
	0 days	5	2.1%
	01-02	6	2.6%
	03-04	3	1.3%
	05-06	5	2.1%
	07-13	12	5.1%
	14-29	17	7.2%
	30+	24	10.2%
Dose 2	**Subtotal**	72	30.6%
	0 days	7	3.0%
	01-02	13	5.5%
	03-04	1	0.4%
	05-06	7	3.0%
	07-13	9	3.8%
	14-29	17	7.2%
	30+	18	7.7%
Dose 3	**Subtotal**	5	2.1%
	0 days	1	0.4%
	01-02	2	0.9%
	07-13	1	0.4%
	14-29	1	0.4%
Unknown	**Subtotal**	86	36.6%
	Missing	86	36.6%
Grand total		**235**	**100.0%**

Fetal Death/Stillbirth

Stillbirth has varying global definitions based on gestational age and fetal weight. For the purposes of this PBRER, and as described above, the MAH applied a definition of a fetal death after 20-weeks gestational age [66] [67]. Congenital anomalies, placental dysfunction associated with fetal growth restriction, and maternal medical diseases and obstetric complications (such as pre-eclampsia, chorioamnionitis, and infections such as group B *Streptococcus* and cytomegalovirus) are common causes of stillbirth. Advanced maternal age (over 40 years) has been associated with an increased risk of stillbirth as well. Evaluation of spontaneous, post-EUA reports is limited due to a lack of complete information, such as medical and obstetric history.

During the reporting period, 42 cases with 45 events were coded as "Fetal death" and/or "Stillbirth". Following medical review, 25 cases occurred after 20 weeks gestational age and were classified as stillbirth and 15 cases occurred before 20 weeks and were classified as spontaneous abortion. One case of "Fetal death" did not have gestational age information and could not be classified, however for the O/E analysis it was considered a spontaneous abortion as the PT was "Fetal death". One duplicate case was identified and, as such, it was not classified. As the MAH classification of these cases is new to the reporting period, a reporting period and cumulative overview is presented in Table 16-41 below for completeness.

Table 16-41 MAH fetal Death and Stillbirth Case Classification – Cumulative and Reporting Period

MAH Medical Review Classification	Reporting Period		Prior to Reporting Period		Cumulative	
	# Cases	% Total Reporting Period Cases	# Cases	% Total Prior Cumulative Cases	#Cases	% Cumulative Cases
Stillbirth	25	59.5%	14	37.8%	39	49.4%
Spontaneous abortion	15	35.7%	22	59.5%	37	46.8%
Unknown	1	2.4%	0	0.0%	1	1.3%
Duplicate (not classified)	1	2.4%	1	2.7%	2	2.5%
Total	**42**	**100.0%**	**37**	**100.0%**	**79**	**100.0%**

Following medical review of the "stillbirth" and fetal death cases >20 weeks gestation age, there was no clear TTO pattern, some cases had clear alternate etiologies, and thus there was insufficient evidence to support causality or demonstrate an increased risk. In addition, it was noted that for many of the pregnancy reports coded as "prospective", there was no evidence in the report to support this classification, thus this classification must be interpreted with caution as there is a high likelihood of coding errors. Overall, cases of stillbirth and spontaneous abortion received

during the reporting period was similar to the prior cumulative experience and no safety concerns were identified.

A summary table of all pregnancy outcomes classified as retrospective and prospective and stratified by timing of exposure, as defined in Annex 3 of the guideline "Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post-Authorisation Data (EMEA/CHMP/313666/2005)", is presented in Appendix 20.11.15. It was noted that for many of the pregnancy reports coded as "prospective", there was no evidence in the report to support that classification, thus this classification must be interpreted with caution as there is a high likelihood of coding errors.

Congenital Anomaly

Cumulatively there have been 83 pregnancy-related reports of congenital anomalies. Upon medical review, only 36 of the cases (some contain parent-child duplicates) occurred in foetuses and neonates. The other 47 reports of congenital anomalies occurred in non-pregnant females and either represented medical history miscoded as an AE, or a pre-existing congenital anomaly detected (such as an arteriovenous malformation or atrial septal defect identified at the time of a cerebrovascular accident). Further review of the congenital anomalies, considering the age at vaccination and foetal development contributed to the assessment of causality. Many cases lacked gestational age at the time of vaccination and thus causality was unassessable. (See Appendix 20.11.16 for case summaries and causality assessments.) There were no patterns and no safety concerns identified. Furthermore, the O/E analysis for congenital anomalies shoes that the reporting/observed rate is below the expected rate. (See Appendix 20.11.3).

Subpopulation Analyses

Pregnancy in Adolescents (12-17 Years of Age)

During the reporting period, 7 pregnancy-related cases were reported in 12-17-year-olds, of which two cases were coded as serious; one case described serious events of chlamydia/gonorrhoea infection (4.1(b)), and the second serious case reported erythema which described red, vesicular lesions on legs with limited information (4.1(b)). There were no cases reported with a fatal outcome. Of the 7 cases, one was in the 12-15-year-old age range (4.1(b) ; the same case mentioned above reporting serious erythema in a 12-year-old female vaccinated at 28 weeks GA), and 6 cases were in the 16-17-year-old age range. Most of the reports were related to maternal exposure or "product administered to patient of inappropriate age" (since approvals did not include this age group until recently in many countries).

When compared to the previous cumulative experience, no unusual patterns or pregnancy-related safety concerns were identified; however, the data are limited with only 15 pregnancy-related cases

reported cumulatively (3 serious, none with a fatal outcome). See Table 16-42 for a cumulative overview of reported cases.

Table 16-42 Summary of Pregnancy-related Events Reported in 12-17-Year-olds - Reporting Period

SOC	HLT	PT	# Events	# Cases
General disorders and administration site conditions	Subtotal	Subtotal	1	1
	Vaccination site reactions	Subtotal	1	1
		Vaccination site pain	1	1
Infections and infestations	Subtotal	Subtotal	2	1
	Chlamydial infections	Subtotal	1	1
		Chlamydial infection	1	1
	Neisseria infections	Subtotal	1	1
		Gonorrhoea	1	1
Injury, poisoning and procedural complications	Subtotal	Subtotal	27	15
	Exposures associated with pregnancy, delivery and lactation	Subtotal	13	13
		Exposure during pregnancy	6	6
		Maternal exposure during pregnancy	7	7
	Product administration errors and issues	Subtotal	14	13
		Accidental overdose	1	1
		Inappropriate schedule of product administration	1	1
		Product administered to patient of inappropriate age	12	12
Metabolism and nutrition disorders	Subtotal	Subtotal	1	1
	Appetite disorders	Subtotal	1	1
		Increased appetite	1	1
Nervous system disorders	Subtotal	Subtotal	2	1
	Disturbances in consciousness NEC	Subtotal	1	1
		Somnolence	1	1
	Dyskinesias and movement disorders NEC	Subtotal	1	1
		Foetal movement disorder	1	1
Pregnancy, puerperium and perinatal	Subtotal	Subtotal	2	2
	Abortions spontaneous	Subtotal	1	1

SOC	HLT	PT	# Events	# Cases
conditions		Abortion spontaneous	1	1
	Normal pregnancy, labour and delivery	Subtotal	1	1
		Pregnancy	1	1
Skin and subcutaneous tissue disorders	Subtotal	Subtotal	1	1
	Erythema	Subtotal	1	1
		Erythema	1	1
Grand total			**36**	**15**

Pregnancy in Children < 12 Years of Age

During the reporting period, and cumulatively, there have been no reports of vaccinated pregnant children less than 12-years of age.

Serious cases of Maternally Exposed Children

The MAH reviewed serious cases from children under 2-years of age who were exposed during gestation. Following review of each case by the MAH, cases were removed from the analysis if they did not represent a maternally exposure child case, for example if the case described lactation exposure or if the incorrect age had been coded. Of the 17 serious cases identified that represented a maternally exposed child, no unusual patterns or safety concerns were identified.

Pregnancy in Patients After a Third Dose or Booster Dose of SPIKEVAX

During the reporting period, 84 pregnancy-related cases were reported in patients receiving a third dose of SPIKEVAX, of which 41 cases were serious, and none were fatal. Of note, case seriousness in some countries is assigned by the reporter, and in regulatory reports by the regulators. Often "serious" is applied to "maternal exposure" alone without serious clinical events, and thus the seriousness criteria applied to these cases must be interpreted with caution. The most frequently reported events in pregnancy-related cases after a SPIKEVAX booster dose are presented below in Table 16-43.

Table 16-43 Top 10 Most Frequently Reported Event PTs (All PTs*) in Pregnancy-related Booster Dose Cases - Reporting Period

PT	Non-Serious		Serious		Total # of Events	% of Total Events
	# Events	% of Total Non-serious Events	# Events	% of Total Serious Events		
Maternal exposure during pregnancy	16	6.8%	3	1.3%	19	8.1%
Pyrexia	3	1.3%	12	5.1%	15	6.4%

PT	Non-Serious		Serious		Total # of Events	% of Total Events
	# Events	% of Total Non-serious Events	# Events	% of Total Serious Events		
Chills	3	1.3%	11	4.7%	14	6.0%
Nausea	5	2.1%	8	3.4%	13	5.5%
Fatigue	2	0.9%	9	3.8%	11	4.7%
Myalgia	2	0.9%	9	3.8%	11	4.7%
Vomiting	3	1.3%	7	3.0%	10	4.3%
Headache	2	0.9%	7	3.0%	9	3.8%
Pain in extremity	1	0.4%	5	2.1%	6	2.6%
Abortion spontaneous	1	0.4%	4	1.7%	5	2.1%
Grand Total	**104**	**44.3%**	**131**	**55.7%**	**235**	**100.0%**

*See methodology section which described the difference between "all PTs" and "pregnancy-related PTs." 'All PTs included pregnancy-related and non-pregnancy-related events.

A number of cases reported represent the use of a heterologous booster dose, or do not report the vaccine type received as the primary series. The most frequently reported booster dose events, regardless of the primary series COVID-19 vaccine, are consistent with expected reactogenicity seen in the primary series SPIKEVAX population. The only non-reactogenicity most frequently reported pregnancy-related clinical PT remains spontaneous abortion and these cases are discussed in the abortion subsection above. Based on the cumulative data to date, no unusual patterns or pregnancy-related safety concerns were identified.

16.3.5.1.5. Discussion

During the reporting period, the pattern of the reports remained generally consistent when compared with the cumulative data, and review of the reporting period serious pregnancy-events and non-pregnancy events did not identify any safety concerns. The O/E analysis, both for the reporting and cumulative periods, has not identified any safety concerns. Overall, cases of pregnancy-related complications are temporally related with the administration of SPIKEVAX; however, the available information is inadequate to provide evidence of increased risk.

Reported cases reflect obstetric events observed in temporal association with SPIKEVAX administration. Many pregnancy-related reports had limited information about past medical and obstetric history, gestational age at time of vaccination, onset of AE, diagnostics, treatment and/or outcome. Where data was available, noted confounding factors for spontaneous abortion/foetal deaths and complications of pregnancy included advanced maternal age, invitro fertilization, intrauterine insemination, concomitant medications, comorbidities (such as hypothyroidism), previous relevant obstetric history, and congenital anomalies which predated the vaccination.

Spontaneous abortion was the most frequently reported pregnancy-related event; however, this is a relatively common occurrence in pregnancy, and the reported(observed) rate is comparable to

the expected background rate in the general population, and no clear time to onset cluster was identified.

During the reporting period, cases of stillbirth and foetal death were medically reviewed and classified as stillbirth if the foetal loss was greater than or equal to 20 weeks gestational age and classified as spontaneous abortion if less than 20 weeks. Cumulatively there are 39 reports classified as stillbirth. Considering that some cases have clear alternate etiologies, there is an absence of a clear time to onset cluster, published articles/studies thus far do not demonstrate evidence of an increased risk of stillbirth after COVID vaccination, and the O/E analysis, there is insufficient evidence to support a causal relationship between SPIKEVAX and stillbirth. The MAH will continue to review cases of spontaneous abortion, foetal death and stillbirth, which will be further evaluated in ongoing real-world data studies (mRNA-1273-P902, mRNA-1273-P903, and mRNA-1273-P905).

Review of the cumulative 36 cases of congenital anomalies and the O/E analysis did not identify any patterns or evidence of increased risk of congenital anomalies associated with maternal immunization with SPIKEVAX.

Review of 17 serious cases received during the reporting period concerning children under 2-years of age who were exposed during gestation did not identify any unusual patterns or safety concerns.

In depth literature reviews performed and reported in the MSSRs (monthly safety reports) have not identified any safety concerns for the use of SPIKEVAX during pregnancy. Thus far, published literature has not identified any evidence of an increased risk of pregnancy, foetal or neonatal complications related to SPIKEVAX maternal immunization. Furthermore, literature demonstrates that there is transfer of maternal antibodies, reduction in COVID-19 in vaccinated pregnant women, recognition that COVID-19 may be more serious and cause complications for both the mother and the foetus; and thus, in sum, published literature supports the favourable benefit/risk profile of maternal SPIKEVAX immunization.

16.3.5.1.6. Conclusion

After review of all new safety data received during the reporting period, the MAH did not identify any safety concerns for maternal immunization and, thus, there is no change to the benefit-risk profile for pregnant woman or their foetuses and neonates. The benefit-risk profile for SPIKEVAX remains favourable for use during pregnancy. The MAH will continue to monitor pregnancy-related reports through routine and additional pharmacovigilance activities according to the RMP.

On 17 Dec 2021, the CHMP has requested to the MAH a review of all available evidence on vaccination in pregnant women and breastfeeding that must be provided as a LEG (EMEA/H/C/005791/LEG/055) in order to critically discuss the need to update SPIKEVAX

product information. As a result, after the DLP of this report section 4.6 of the SmPC has been updated.

16.3.5.2. Use in breastfeeding

16.3.5.2.1. Source of the New Information

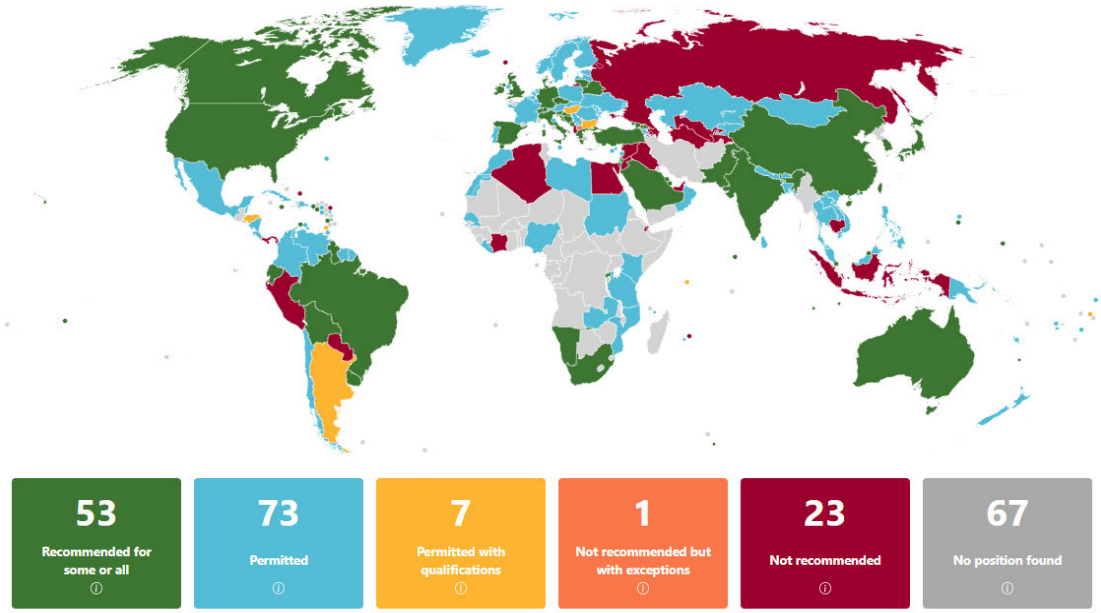
Information presented below includes analyses performed on lactation-related cases received by ModernaTX, Inc. from 01 Jul 2021 to 31 Dec 2021 for the mRNA-1273 vaccine (COVID-19 vaccine Moderna) SPIKEVAX. Cumulative data, also considered in the analyses, cover the period from 18 Dec 2020 to 31 Dec 2021.

The company clinical database and the ModernaTX GSDB was queried for valid clinical and spontaneous case reports reported for SPIKEVAX in lactating women who were vaccinated and their neonates/infants who were exposed via breast milk, received from health care providers, health authorities, consumers, and the literature, for the reporting period and cumulatively.

16.3.5.2.2. Background Relevant to the Evaluation

The use of SPIKEVAX in breastfeeding women is an area of missing information in the RMP. No clinical trials were conducted with SPIKEVAX in lactating women. Thus far, no significant safety concerns have been identified for vaccinated breastfeeding women and/or their breastfed children. No safety concerns have been identified in the literature. The literature describes the potential benefit of antibodies being passed via breast milk, although the effectiveness is not yet established. In many countries where vaccine is available, public health agencies, and professional bodies currently recommend that breastfeeding women get vaccinated and continue to breast-feed, given the potential benefit to the women and their children. During this PBRER#2 reporting period, the number of countries recommending the use of COVID-19 vaccine in lactating women increased (17 countries as of 02 Jul 2021 to 57 countries as of 18 Dec 2021).

Figure 16-2 Global Policies for COVID Vaccine Use in Lactating Women (18 Dec 2021)



Source: (Berman Institute 2022a); the data is as of 18 Dec 2021 and it was accessed on 21 Jan 2022

16.3.5.2.3. Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

Identification of Case Reports in Moderna GSDB:

The MAH queried the GSDB, for the reporting period (01 Jul 2021 to 31 Dec 2021) and cumulatively (18 Dec 2020 to 31 Dec 2021) for valid lactation-related case reports. Lactation-related cases were identified as any case containing at least one lactation-related PT term identified in the SMQ: "Lactation related topics (including neonatal exposure through breast milk)", which includes reports of AEs occurring in both breastfeeding women and breastfed children. Identified lactation-related cases were also pulled by case identification numbers to obtain all PTs reported (lactation-related and non-lactation related events in these cases). Further analysis reviewed the events reported in breastfed children, in lactation-related adolescent reports, and lactation-related reports after Dose 3.

16.3.5.2.4. Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Overview of Cases

Cumulative Overview 18 Dec 2020 to 31 Dec 2021

Cumulatively, 1,497 lactation-related cases (404 serious) have been reported, with a total of 1,589 (331 serious, none were fatal) lactation-related events. Within the 1,497 lactation-related cases, when considering all PTs reported, there were 4,791 events (1,441 serious). Of the 1,497 cases, 304 were medically confirmed.

Reporting Period Review 01 Jul 2021 to 31 Dec 2021

During the reporting period, there were 899 (315 serious, zero fatal) lactation-related cases, with 966 (268 serious) lactation-related events. Within the 899 lactation-related cases, when considering all PTs reported, there were 3,075 events (of which 1,206 were serious).

An increase in the lactation-related cases was observed during the reporting period compared to the period prior to the reporting period. When looking at the cumulative data presented in Table 16-44, 60.1% of the cases were received in the reporting period, and 39.9% prior to the reporting period. This may be explained by the changes in the vaccination recommendations and policies for the use of COVID-19 vaccines lactating women. (See Background section above) Furthermore, there is a notable increase in the proportion of serious cases, of which 78% were reported in the reporting period and 22% prior to the review period. Of note, 72.7% of the serious reports during the review period originated from the United Kingdom (UK). Serious events and cases must be interpreted with caution; many are not events/cases meeting the definition of "serious" (death, life-threatening, hospitalization, etc.) in part due to a bias from self-reported seriousness classification in some countries, and in part due to some regulatory authorities' coding of all events as serious in serious cases. Medical review of these cases find that many do not meet the regulatory definitions of serious adverse events. In addition, note that during the review period, the MAH stopped downloading non-serious VAERS cases, and thus the relative proportion of serious cases increased. Summary tables of the cumulative and reporting period lactation-related cases are presented below. (Table 16-44).

Table 16-44 Summary of Reporting Period and Cumulative Lactation-related Case Counts by Case Seriousness

	Non-Serious		Serious		Total # of Cases	% of Total Case
	# Cases	% of Total Non-serious Cases	# Cases	% of Total Serious Cases		
Prior to Review Period	509	46.6%	89	22.0%	598	39.9%
Review Period	584	53.4%	315	78.0%	899	60.1%
Grand total	**1,093**	**100.0%**	**404**	**100.0%**	**1,497**	**100.0%**

The age and gender distribution of the reports is generally consistent with the expected age and gender of lactating women and their breastfed children (Table 16-45). (Note that some cases either describe mastitis in non-breastfeeding, older women, or reflect age data errors.).

Table 16-45 Age/Gender Distribution for Lactation-related Cases (Including Breastfed Children), Reporting period

Age Group	Female		Male		Unknown		Total # Cases	% of Total Cases
	# Cases	% of Total Female Cases	# Cases	% of Total Male Cases	# Cases	% of Total Unknown Cases		
<2	30	3.3%	27	3.0%	32	3.6%	89	9.9%
02-11	4	0.4%	0	0	2	0.2%	6	0.7%
16-17	1	0.1%	0	0	0	0	1	0.1%
18-29	112	12.5%	0	0	1	0.1%	113	12.6%
30-39	407	45.3%	0	0	2	0.2%	409	45.5%
40-49	68	7.6%	0	0	1	0.1%	69	7.7%
50-64*	7	0.8%	0	0	0	0	7	0.8%
65-74*	1	0.1%	0	0	0	0	1	0.1%
75+*	1	0.1%	0	0	0	0	1	0.1%
Missing	34	3.8%	6	0.7%	163	18.1%	203	22.6%
Grand total	**665**	**74.0%**	**33**	**3.7%**	**201**	**22.4%**	**899**	**100.0%**

*Some of these cases have error in the age coding (regulatory reports included). There is one case of 63 y/o male with nipple inflammation after vaccination, correct age, but not a lactating case. Some mastitis cases are in older non-lactating women.

Lactation-related events reported in the reporting period are presented below by PT term. (Table 16-46) "Suppressed lactation", "mastitis" and "lactation disorder" remain the top 3 lactation-related clinical events reported. There has not been a significant change in the pattern of PTs reported during the reporting period compared to the period prior to the reporting period. Most of the lactation-related events were transient events occurring within days after vaccination.

Table 16-46 Reported Lactation-related Events by PTs and Event Seriousness, Reporting period

Preferred Term	Non-Serious		Serious		Total # of Events	% of Total Events
	# Events	% of Total Events	# Events	% of Total Events		
Maternal exposure during breast feeding	363	37.6%	182	18.8%	545	56.4%
Exposure via breast milk	256	26.5%	40	4.1%	296	30.6%
Suppressed lactation	48	5.0%	7	0.7%	55	5.7%
Mastitis	6	0.6%	33	3.4%	39	4.0%
Lactation disorder	16	1.7%	1	0.1%	17	1.8%
Neonatal insufficient breast milk syndrome	2	0.2%	2	0.2%	4	0.4%
Lactation puerperal increased	2	0.2%	1	0.1%	3	0.3%
Nipple inflammation	3	0.3%	0	0	3	0.3%
Retracted nipple	1	0.1%	1	0.1%	2	0.2%
Galactostasis	0	0	1	0.1%	1	0.1%
Nipple infection	1	0.1%	0	0	1	0.1%
Grand total	**698**	**72.3%**	**268**	**27.7%**	**966**	**100.0%**

In the reporting period, when considering all (not just lactation-related) events, aside from the top two PTs describing lactation exposure events, and the 9th ranked PT "suppressed lactation", the most frequently reported events reflect expected reactogenicity following SPIKEVAX seen in the general population. There has not been a significant change in the pattern of PTs reported during the reporting period compared to the cumulative data. The 10 most frequently reported (all) events within lactation cases for the reporting period are presented in Table 16-47 below.

Table 16-47 Most Frequently Reported PTs (All Events) in Lactation-related Cases, Reporting Period

PT	# Events	% of Total Events
Maternal exposure during breast feeding	545	17.7%
Exposure via breast milk	296	9.6%
Pyrexia	172	5.6%
Headache	143	4.7%
Fatigue	89	2.9%
Chills	84	2.7%
Myalgia	79	2.6%
Nausea	57	1.9%

PT	# Events	% of Total Events
Suppressed lactation	55	1.8%
Arthralgia	54	1.8%
Total Events reported in lactation-related cases*	**3075**	**100%**

*To clarify, cumulatively there were 1,589 lactation-related events and 4,791 total events in lactation-related cases

Medical review of the HLT "Lactation Disorders" was performed for the reporting period and the data was consistent with the previous cumulative experience; no concerning patterns or notable trends were identified.

Subpopulation Analyses

Lactation-related Cases in Children (under 5 years of age) Exposed via Breastmilk

During the reporting period, there were 95 (19 serious, zero fatal) lactation-related cases containing 204 (56 serious) events reported in children with exposure via breastmilk. When compared to the 172 cumulative cases, no change in the reporting pattern for children exposed via breastmilk was observed.

The top PTs (with event counts of 4 or more) in breastfed child cases during this reporting period are presented in Table 16-48, and most were mild/moderate and transient where data were provided. There were 15 cases of pyrexia reported during the reporting period as compared to 32 cumulatively, of which 14 occurred within 4 days after maternal vaccination, one occurred 13 days and another 26 days after vaccination (the only case co-reported with a seizure, unlikely related to vaccination), and 15 are missing time to onset information. There is limited information provided in these cases, including signs/symptoms/diagnosis of infection/alternate etiology. Diarrhea was reported in 7 cases during the reporting period (compared to the 16 cumulatively, 12 of which occurred within two days after vaccination), and transient gastrointestinal signs/symptoms were reported in some cases. Given the temporal association of some of the cases, causality cannot be excluded; however, there is insufficient evidence to identify an increased risk or assess vaccine causality with regards to pyrexia and infant/child gastrointestinal events after exposure via breastfeeding.

Table 16-48 Most Frequently Reported PTs pulled by cases (n≥4) in Lactation-related/Breastfed Child Cases, Reporting Period

PT	# cases with PT	% of Cases*
Exposure via breast milk	88	92.6%
Pyrexia	15	15.8%
Diarrhoea	7	7.4%
Maternal exposure during breast feeding	7	7.4%
Malaise	6	6.3%
Vomiting	6	6.3%

PT	# cases with PT	% of Cases*
Cough	4	4.2%
Crying	4	4.2%

*Percentage of the total number (n=95) of Lactation-related/Breastfed Child cases

The cumulative serious pediatric lactation-related cases were medically reviewed. Many cases are lacking information on clinical course, outcome, pediatric medical history, alternate etiologies/concurrent clinical events. No clinically significant patterns or safety concerns were identified. During the reporting period, one pediatric case of seizure was reported. This case (4.1(b)) was reported by the mother of a 3-month-old female with no reported medical history who experienced seizures and was hospitalized within 24 hours after the mother's vaccination with the first dose of SPIKEVAX. MRI/CT scans, lumbar puncture, bacterial/viral tests, and glucose were normal. Of the three pediatric cases received prior to this reporting period, two cases (4.1(b) and 4.1(b)) are linked (parent-child case, note the parent case of a 30-year-old woman, is under correction of an age coding error) and the seizure occurred on the day of first dose vaccination; the other event of seizure (4.1(b)) reported along with pyrexia occurred 26 days after the mother received the first vaccination, and given the latency is unlikely related to vaccination. There is limited information in the reports. Thus far there is insufficient evidence to demonstrate an increased risk with regards to seizures in neonates whose breastfeeding mothers were vaccinated. The MAH will continue to monitor the reports of seizures in breastfeeding neonates.

While vaccination can induce cytokines, which can be passed via breast milk, vaccination while breast feeding has not been linked to significant adverse events in infants. In fact, women with fever and illness are encouraged to continue breast feeding given the positive impact of the transfer of antibodies, which has also been reported for COVID vaccines, as well as to support infant nutritional needs.

Lactation-related reports in Adolescents (12-17 Years of Age)

During the reporting period, one non-serious lactation-related case in the adolescent subpopulation was reported and this reflects the cumulative data to date. There were no clinical AEs reported and the case has two events: “Maternal exposure during breast feeding”, and “Product administration to patient of inappropriate age”.

Lactation-related Cases in Women Receiving a 3rd Dose of SPIKEVAX, or Their Children Exposed Via Breast Milk

During the reporting period, 18 (5 serious) lactation-related cases were reported in women who received Dose 3 of SPIKEVAX, and this reflects the cumulative data to date. Out of 18 cases, 16 cases were reported for lactating women, one case was reported in a non-lactating 61-year-old

female who had mastitis (4.1(b)), and one serious case was reported in an 8-month-old female (4.1(b)). This child case was reported/coded as "Exposure via breastmilk" and was considered serious (medically significant) by the reporting Regulatory Authority. No associated clinical events were coded with PT terms; however, it was reported that the baby was noted to be irritable during the night and subsequently improved.

There are no lactation-related cases reported after Dose 4 of SPIKEVAX.

Seven cases reported the use of a heterologous SPIKEVAX booster dose, and others do not mention the vaccine type received as the primary series.

The majority of events reported, regardless of the vaccine regimen originally received, are consistent with expected reactogenicity seen in the SPIKEVAX population. No concerning patterns or notable trends were identified. The MAH will continue to monitor these lactation-related reports after booster doses through routine pharmacovigilance.

16.3.5.2.5. Discussion

During the reporting period, the pattern of reports remained generally consistent when compared with the cumulative data. No new safety concerns were identified.

Many of the reports lack time to onset, medical and pregnancy/lactation history, concomitant medications, the age of the breastfed child, and full clinical descriptions of the events and their course/outcome/duration. Where duration and outcome are available, many of the events (such as decreased lactation) occur within a day after vaccination, and most narratives describe mild/moderate, transient events where information is available. Both in the GSDB and in the literature, there are reports of changes in milk production, infant irritability, decreased feeding, sleepiness/sleep disturbance, vomiting, diarrhea, and pyrexia; however, there is insufficient data to establish a causal relationship or increased risk, although given the temporal association causality cannot be excluded. Furthermore, the reviewed literature to date has not identified any significant safety concerns.

16.3.5.2.6. Conclusion

Based on the review of all new safety data received during the reporting period, compared to the cumulative data, for the cases of adverse events in breastfeeding women and their children, the benefit-risk profile for SPIKEVAX remains favorable. The safety of the use of SPIKEVAX in lactating women and events occurring in their breastfed children will continue to be monitored using the routine pharmacovigilance measures.

16.3.5.3. Long-Term Safety

16.3.5.3.1. Source of the New Information

As of the DLP of this PBRER, 8 ongoing clinical trials sponsored by ModernaTX, Inc were ongoing, and no study has been completed. Cumulatively, 48,823 subjects have been exposed to either mRNA-1273, mRNA-1273.351, mRNA-1273.211, mRNA-1273.213, mRNA-1273.617.2, or placebo in the mRNA clinical development program sponsored by ModernaTX, Inc. Out of the 48,823 subjects, 36,181 subjects were exposed to mRNA-1273 and the remaining 12,642 subjects were exposed to either mRNA-1273.351, mRNA-1273.211, mRNA-1273.213, mRNA-1273.617.2, or placebo. The 48,823 does not represent unique subjects.

16.3.5.3.2. Background Relevant to the Evaluation

Per protocols, the clinical development program has a safety follow up period of 12 months in the ongoing Phase 1 study 20-0003, Phase 2a Study mRNA-1273-P201 and, 24 months in the Phase 3 study mRNA-1273-P301. In the Phase 3mRNA-1273-P301 the safety follow-up is based on a median duration of follow-up after the second injection to the data cut-off for database lock (including Part A and Part B) was 183◦days (range: 1 to 218 days), or approximately 6 months. The follow up time is through Day 209 for the Phase 1 study DMID 20-0003 and through at least 180 days (6 months) after the most recent injection (Day 209) for the 555/600 (92.5%) participants who had not discontinued from the study before Day 209 in the Phase 2a Study mRNA-1273-P201.

16.3.5.3.3. Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

The long-term safety profile remains to be characterized through continued trial follow-up, active surveillance for safety, a European post-authorization safety study, and routine pharmacovigilance.

16.3.5.3.4. Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

The long-term safety profile remains to be characterized through continued trial follow-up, active surveillance for safety, a European post-authorization safety study, and routine pharmacovigilance.

16.3.5.3.5. Discussion

The long-term safety profile remains to be characterized.

16.3.5.3.6. Conclusion

See above Section 16.3.5.3.5 Discussion.

16.3.5.4. Use in immunocompromised subjects

16.3.5.4.1. Source of the New Information

The ModernaTx GSDB was queried for valid, clinical and spontaneous case reports representing immunocompromised individuals per medical history or immunosuppression per concomitant medications. The worldwide reports for SPIKEVAX were received from health care providers, health authorities, consumers and literature, cumulatively (18 Dec 2020 – 31 Dec 2021) and for the PBRER #2 reporting period (01 Jul 2021 – 31 Dec 2021).

16.3.5.4.2. Background Relevant to the Evaluation

As immunocompromised and/or immunosuppressed people were excluded from clinical trials, thus constitutes missing information in the RMP. The MAH is monitoring the safety profile in this population through routine pharmacovigilance. Review of literature finds that most articles discuss the potential decreased immunogenicity/effectiveness of the vaccine in immunocompromised population. (Of note, there is a notable overlap with the autoimmune disease and inflammatory disorder population as they are often on immunosuppressive therapies.) No significant safety concerns have been identified in the literature to date.

Several countries and regions (including Israel, France, the United States, Belgium, Ireland, EEA), have amended/approved or are considering authorization/approval of EUAs/sBLAs to allow for an additional primary series dose (3rd Dose/Dose 3) in immunocompromised patients to achieve an adequate, more robust immune response. Furthermore, many are recommending a booster dose (Dose 4) after the three dose priming series in immunocompromised individuals. The third dose of SPIKEVAX recommended for immunocompromised patients is 100 microgram dose, whereas the booster (either 4th dose for immunocompromised, or 3rd dose for the general population) is a 50 microgram dose. The MAH presents AE reports after Dose 3 and Dose 4 of SPIKEVAX in the immunocompromised subpopulation in this PBRER#2. As there are currently limited data available on the third and fourth doses in immunocompromised individuals, the MAH is monitoring the safety through routine pharmacovigilance and literature review.

Furthermore, there have been country-specific authorizations, approvals or pending requests for authorization/approval of SPIKEVAX use in immunocompromised adolescents and in the general adolescent population. The MAH is monitoring and presents cumulative and reporting period data currently available in the ModernaTx GSDB for the 12-17-year-old (adolescent), and under 12-year-old immunocompromised subpopulation in this PBRER. Although SPIKEVAX is not yet

approved in under 12 years of age, ModernaTx continues to monitor the pediatric population as well, as administration errors or unauthorized use may have occurred.

Thus far, the review of post-EUA data has not identified any patterns or specific safety concerns in the immunocompromised population. Many of the serious events and fatalities that were temporally associated with vaccination were confounded or caused by underlying serious medical conditions. In addition, there have been non-serious, serious and fatal reports of COVID-19 in this subpopulation, perhaps reflective of reduced immunogenicity/effectiveness of the vaccine in this population, the surge of the Delta and Omicron variants, waning immunity, and policy and behavior changes. Otherwise, the general pattern of commonly reported adverse events in those with a medical history of immunosuppression/immune compromise or taking immunosuppressive concomitant medications (hereafter referred to as "the immunocompromised subpopulation") is comparable to the general population.

Given that this population may be at increased risk for severe COVID infections, the potential benefit/risk profile remains favorable, despite the possibility that vaccine effectiveness may be reduced in some people in this population.

16.3.5.4.3. Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

For this PBRER#2, ModernaTx identified reports from immunocompromised (which includes immunosuppressed) individuals in the Moderna GSDB cumulatively (18 Dec 2020 – 31 Dec 2021) and for the reporting period of 01 Jul 2021 to 31 Dec 2021.

Methodology:

For the purposes of this PBRER#2, the following operational definitions were applied in the analysis of the immunocompromised/immunosuppressed subpopulation:

The "Immunocompromised Subpopulation": Specifically, cases were identified in the MAH GSDB for immunocompromised and immunosuppressed individuals using a past medical history of hematological malignant tumors SMQ, transplantation, primary/innate and acquired immunodeficiency syndromes (including Human Immunodeficiency Virus [HIV]) and other relevant immunodeficiency PT terms, as well as Anatomical Therapeutic Chemical drug codes for immunosuppressive drugs.

The "General Population" (all SPIKEVAX data in the ModernaTx GSDB: This refers to safety data for all medical topics/areas captured in all safety case reports (all cases and events from all individuals) within the ModernaTx SPIKEVAX GSDB. This data is used to compare the AEs and safety profile in the immunocompromised population to the general population.

16.3.5.4.4. Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Overview of Cases

Cumulatively, there were 5,084 cases (of which 1,913 were serious, and 156 were fatal) with 22,527 events (of which 7,821 were serious) in the immunocompromised subpopulation. Of the 5,084 cases, 2,943 cases were medically confirmed. Cumulatively, 3,285 (64.6%) cases were in females, 1,705 (33.5%) cases were in males, and 94 (1.8%) had missing sex information. The mean age was 57.8 (SD 16.6), and the median was 60.0 years. Two hundred and seventy (270) cases had missing age information. The distribution of cases by age group (cumulative) is presented in Table 16-51 below.

During this interval/reporting period, there were 2,298 cases (of which 1,166 were serious, and 89 were fatal) with 10,208 events (of which 5,426 were serious) in the immunocompromised subpopulation. Of the 2,298 cases, 973 were medically confirmed. For the review period, there were 1,430 (62.9%) cases in females, 801 (34.9%) cases in males, and 67 (2.9%) were missing sex information. The reporting period has fewer cases compared to the previous period (Table 16-49); however, there is a higher percentage of cases that are coded are serious. This may be in part due to the higher number of COVID-19 reports, as well as the shifting geographic distribution of cases. In addition, during this reporting period the MAH stopped downloading non-serious VAERS cases, and only downloaded serious VAERS cases. Serious events must be interpreted with caution, and many are not events meeting the true definition of "serious" (death, life-threatening, hospitalization, etc.) in part due to a bias from self-reported seriousness classification in some countries, and in part due to some regulatory authorities' coding of all events as serious in serious cases.

Table 16-49 Reporting Period vs. Cumulative Immunocompromised Cases, by Seriousness

	Non-Serious		Serious		Total # of Cases	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases		
Prior to Review Period	2,039	64.3%	747	39.0%	2,786	54.8%
Review Period	1,132	35.7%	1,166	61.0%	2,298	45.2%
Grand total	**3,171**	**100.0%**	**1,913**	**100.0%**	**5,084**	**100.0%**

Note that cumulatively, a total of 1,421 (including 548 serious and 32 fatal cases) overlap between the subpopulation of those with a medical history of autoimmune/inflammatory diseases (MedHx autoimmune or inflammatory disorders (AI)/ID) and immunocompromised/immunosuppressed subpopulations, as many people with AI/ID are on immunosuppressive therapies. During the

reporting period, 559 cases (including 304 serious and 16 fatal) overlap. (Please also refer to the Section 16.3.5.7 on Use in Autoimmune Disease and Inflammatory Disorders.)]

During the reporting period, the distribution of cases by age showed that most events reported in the immunocompromised subpopulation were in the 50-74-year-old age group (Table 16-50). Distribution of cases by age group in the reporting period when compared to cumulative data demonstrates a higher proportion of reports from people age 18-49 years of age (31.6% vs. 27.9%), and lower proportion in reports from people above 65 years of age (31.3% vs. 38.3%). More reports are from females, which is consistent with the general trend in the safety database for the general population, as well as consistent with the autoimmune/inflammatory disease population some of whom are on immunosuppressant therapy. Some common autoimmune diseases are more frequent in females.

Table 16-50 Distribution of Cases by Age Group for Immunocompromised Subpopulation (Reporting Period)

Age Group	Female		Male		Unknown		# Cases	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases	# Cases	% of Total Cases		
<2	0	0.0%	0	0.0%	0	0.0%	0	0.0%
12-15	0	0.0%	1	0.0%	0	0.0%	1	0.0%
16-17	2	0.1%	0	0.0%	0	0.0%	2	0.1%
18-29	128	5.6%	60	2.6%	0	0.0%	188	8.2%
30-39	188	8.2%	62	2.7%	0	0.0%	250	10.9%
40-49	206	9.0%	79	3.4%	3	0.1%	288	12.5%
50-64	389	16.9%	239	10.4%	7	0.3%	635	27.6%
65-74	248	10.8%	187	8.1%	7	0.3%	442	19.2%
75+	138	6.0%	136	5.9%	3	0.1%	277	12.1%
Missing	131	5.7%	37	1.6%	47	2.0%	215	9.4%
Grand total	**1430**	**62.2%**	**801**	**34.9%**	**67**	**2.9%**	**2,298**	**100.0%**

Table 16-51 Distribution of Cases by Age Group for Immunocompromised Subpopulation (Cumulative)

Age Group	Female		Male		Unknown		# Cases	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases	# Cases	% of Total Cases		
<2	0	0.0%	0	0.0%	1	0.0%	1	0.0%
12-15	0	0.0%	1	0.0%	0	0.0%	1	0.0%
16-17	5	0.1%	2	0.0%	1	0.0%	8	0.2%
18-29	218	4.3%	91	1.8%	3	0.1%	312	6.1%
30-39	370	7.3%	116	2.3%	1	0.0%	487	9.6%

Age Group	Female		Male		Unknown		# Cases	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases	# Cases	% of Total Cases		
40-49	441	8.7%	174	3.4%	3	0.1%	618	12.2%
50-64	925	18.2%	502	9.9%	13	0.3%	1440	28.3%
65-74	759	14.9%	444	8.7%	9	0.2%	1212	23.8%
75+	409	8.0%	323	6.4%	3	0.1%	735	14.5%
Missing	158	3.1%	52	1.0%	60	1.2%	270	5.3%
Grand total	**3285**	**64.6%**	**1705**	**33.5%**	**94**	**1.8%**	**5084**	**100.0%**

Cumulatively as well during the reporting period, the most frequently reported PTs in the immunocompromised subpopulation (pyrexia, fatigue, headache, chills, myalgia, and nausea) are comparable to the general population and reflect expected reactogenicity (Table 16-52). The reports of dyspnea and arthralgia have been reviewed and no pattern indicating a safety concern was identified. During the reporting period, COVID-19 ranked #10 in the immunocompromised subpopulation and #15 in the general population; while cumulatively, COVID-19 ranked #14 in the immunocompromised subpopulation and #30 in the general population, demonstrating the increased reporting of COVID-19 during this reporting period. This may reflect the decreased immunogenicity of vaccination and/or the susceptibility to more severe disease seen in the immunocompromised subpopulation, as well as waning immunity and changes in disease epidemiology, public health policies, and individual behavior.

Table 16-52 Top10 Events by Preferred Term (PT) During Reporting Period vs. Cumulative, Comparing Immunocompromised Subpopulation to the General Population

Reporting Period						Cumulative					
Immunocompromised Subpopulation			General Population			Immunocompromised Subpopulation			General Population		
PT	#	%	PT	#	%	PT	#	%	PT	#	%
Pyrexia	472	4.6%	Pyrexia	44,460	6.2%	Fatigue	1,047	4.6%	Headache	89,454	5.4%
Fatigue	460	4.5%	Headache	40,502	5.7%	Pyrexia	1,032	4.6%	Pyrexia	89,235	5.4%
Headache	422	4.1%	Fatigue	35,142	4.9%	Headache	1,007	4.5%	Fatigue	76,889	4.7%
Chills	277	2.7%	Myalgia	26,841	3.7%	Chills	731	3.2%	Chills	62,451	3.8%
Myalgia	270	2.6%	Chills	24,215	3.4%	Nausea	619	2.7%	Myalgia	54,167	3.3%
Nausea	264	2.6%	Malaise	21,513	3.0%	Myalgia	612	2.7%	Nausea	45,937	2.8%
Pain in	22	2.2	Nausea	19,18	2.7	Pain in	504	2.2	Pain in	39,36	2.4

Reporting Period						Cumulative					
Immunocompromised Subpopulation			General Population			Immunocompromised Subpopulation			General Population		
PT	#	%	PT	#	%	PT	#	%	PT	#	%
extremity	4	%		7	%	extremity		%	extremity	5	%
Arthralgia	217	2.1 %	Injection site pain	17,623	2.5 %	Arthralgia	476	2.1 %	Injection site pain	38,764	2.3 %
Dyspnoea	209	2.0 %	Vaccination site pain	16,031	2.2 %	Malaise	416	1.8 %	Malaise	36,335	2.2 %
COVID-19	207	2.0 %	Arthralgia	15,564	2.2 %	Pain	414	1.8 %	Pain	34,007	2.1 %

% = % of events.
*Arthralgia ranks #11 (2.0% of events) cumulatively for the general population.
**Dyspnoea ranks #13 (1.2% of events) in the reporting period for the general population.

Serious Cases and Events

Cumulatively, there were 1,913 serious cases, with 10,070 events of which 7,820 were serious. With regards to demographics, 775 (40.5%) reports were in males, 1,112 (58.1%) in females, and 26 (1.4%) were missing sex data. The mean age was 57.70 years (SD 17.3), the median age was 59.0 years (range: 14-98 years), and 96 cases were missing age information.

During the reporting period there were 1,166 serious cases with 6,316 events of which 5,425 were serious. Of the 1,166 serious cases reported, 438 (37.6%) were in males, 709 (60.8%) were in females, and 19 (1.6%) were missing gender information. The mean age was 55.4 years (SD 17.4), and the median age 56.0 years (range 14-98 years) and 83 were missing age information.

During the reporting period as well as cumulatively, the top three serious events were pyrexia, headache and fatigue for the immunocompromised subpopulation and the general population and reflect expected reactogenicity (Table 16-53).

In the reporting period, COVID-19 ranked #4 in the immunocompromised subpopulation and #6 in the general population within the serious reported events. During the reporting period 165 out of the cumulative 209 serious events of COVID-19 were reported, demonstrating an increase in the serious COVID-19 reports in the immunocompromised population during this reporting period; this is similar to the pattern seen in the general population, suggesting that waning immunity and new variants may be the predominant explanation. The immunocompromised subpopulation may be at risk for COVID-19 and more severe COVID-19 disease, as aforementioned. Cumulatively, COVID-19 is the fifth most frequently reported serious PT in the immunocompromised subpopulation and eighth in the top 10 serious PTs for the general population, and as discussed previously, the immunocompromised subpopulation is at risk of a suboptimal immune response to vaccination which makes this group more vulnerable to COVID-

19 in general, and this subpopulation may also be at higher risk for more serious complications and outcomes of COVID-19.

(Serious events must be interpreted with caution, and many are not events meeting the true definition of "serious" (death, life-threatening, hospitalization, etc.) in part due to a bias from self-reported seriousness classification in some countries, and in part due to some regulatory authorities' coding of all events as serious in serious cases).

Table 16-53 Top 10 Preferred Terms (PT) for Serious Events During Reporting Period vs. Cumulative Comparing Immunocompromised Subpopulation to the General Population

Reporting Period - Serious						Cumulative - Serious					
Immunocompromised Subpopulation			General Population			Immunocompromised Subpopulation			General Population		
PT	#	%	PT	#	%	PT	#	%	PT	#	%
Pyrexia	226	4.2%	Pyrexia	9,110	1.3%	Pyrexia	313	4.0%	Pyrexia	11,519	0.7%
Fatigue	196	3.6%	Headache	8,311	1.2%	Fatigue	241	3.1%	Headache	10,334	0.6%
Headache	191	3.5%	Fatigue	6,922	1.0%	Headache	240	3.1%	Fatigue	8,783	0.5%
COVID-19	165	3.0%	Nausea	4,881	0.7%	Dyspnoea	212	2.7%	Dyspnoea	6,374	0.4%
Dyspnoea	148	2.7%	Chills	4,727	0.7%	COVID-19	209	2.7%	Nausea	6,371	0.4%
Nausea	140	2.6%	COVID-19	4,279	0.6%	Nausea	185	2.4%	Chills	5,985	0.4%
Chills	116	2.1%	Dyspnoea	4,246	0.6%	Chills	155	2.0%	Syncope	5,617	0.3%
Dizziness	92	1.7%	Myalgia	3,820	0.5%	Dizziness	126	1.6%	COVID-19	4,992	0.3%
Pain in extremity	89	1.6%	Dizziness	3,441	0.5%	Asthenia	114	1.5%	Myalgia	4,866	0.3%
Arthralgia	88	1.6%	Pain in extremity	3,306	0.5%	Pain in extremity	114	1.5%	Dizziness	4,743	0.3%

% = % of total serious events.

Fatal Cases and Events

Cumulatively, of the 156 fatal cases with 573 total events, 66 (42.3%) were in females and 90 (57.7%) were in males; none had missing sex data. One hundred and forty-six (146) cases were medically confirmed. The mean age was 71.0 years (SD: 12.6), and the median age was 72.0 (min 27.0 and max 98.0); 3 had missing age. Of the 156 fatal cases, 90 were classified as "frail" for past medical history and criteria PTs included in "frail"), indicating that most of fatal cases had multiple comorbidities (such as cardiovascular, diabetic, neurological disorders) and older age. Please refer to Fatalities Section 16.3.6.8.2.

During the reporting period, there were 89 fatal cases with 380 serious events, 34 (38.2%) were in females and 55 (61.8%) were in males. The mean age was 71.2 years (SD: 13.0), and the median age was 72.5 (min 27.0 and max 98.0); and 1 missing age data. Of these 89 cases, 68 (76.4%) cases occurred in those greater than 65 years of age. Of the 89 fatal cases, 45 were classified as "frail" for past medical history and criteria PTs included in "frail"), indicating that many of fatal cases had multiple comorbidities (such as cardiovascular, diabetic, or neurological disorders) and older age. Please refer to Fatalities Section 16.3.6.8.2.

During the reporting period, the top PTs reported included COVID-19, COVID-19 pneumonia, dyspnoea, asthenia and condition aggravated. Cumulatively, COVID-19, COVID-19 pneumonia, dyspnoea, asthenia, and hypoxia rank in the top PTs in fatal cases. Overall, the top PTs in fatal cases in the immunocompromised subpopulation during the reporting period were similar to those reported cumulatively (Table 16-54).

Table 16-54 Top Fatal Event Preferred Terms (PT) (≥5 events in Reporting Period) in Fatal Cases in Immunocompromised Subpopulation (Reporting Period vs Cumulative)

Reporting Period			Cumulative		
PT	# Events	% of Total Events	PT	# Events	% of Total Events
COVID-19	36	9.5%	Death	74	12.9%
Death	35	9.2%	COVID-19	41	7.2%
Dyspnoea	12	3.2%	Dyspnoea	17	3.0%
Asthenia	9	2.4%	Asthenia	12	2.1%
Condition aggravated	9	2.4%	COVID-19 pneumonia	11	1.9%
COVID-19 pneumonia	9	2.4%	Hypoxia	11	1.9%
Hypoxia	9	2.4%	Condition aggravated	10	1.7%
Respiratory failure	9	2.4%	General physical health deterioration	10	1.7%
Cough	7	1.8%	Pyrexia	10	1.7%
General physical health deterioration	7	1.8%	Respiratory failure	10	1.7%
Pneumonia	7	1.8%	Pneumonia	9	1.6%
Pyrexia	7	1.8%	Cardiac arrest	8	1.4%
Acute respiratory failure	5	1.3%	Cough	8	1.4%

In the fatal cases, the comorbidities (and potential confounders) seen in the immunocompromised subpopulation include diseases that define the immunocompromised patients such as leukemia and rheumatoid arthritis (on treatment), and other comorbidities such as hypertension, diabetes and COPD are seen in both the immunocompromised population and the general population.

While it is noted that multiple confounding conditions and comorbidities are reported, there is a limitation to the quality of spontaneous reporting (including missing "cause of death", and clinical course of events, diagnostics, and treatment) which may limit the assessment of causality related to vaccination.

Overall, there were no clusters of unexpected causes of deaths identified in the available data in the immunocompromised subpopulation.

Subpopulation Analyses

Use in Immunocompromised Children (<12 years old)

Cumulatively, for SPIKEVAX, in the ModernaTX GSDB, there is one case (4.1(b)) in the age group of 0-11 years-old. This case of 3-month-old infant of unknown sex was reported as "exposure via breast milk" with no clinical adverse events reported. The mother's concurrent medical conditions included Immunodeficiency and Cholangitis. Thus, there are no cases from vaccinated immunocompromised children under the age of 12 years.

Use in Immunocompromised Adolescents (12-17 y/o)

Cumulatively, there are 9 cases (3 serious and 0 fatal) in immunocompromised adolescents. Four (4) of the 9 cases are medically confirmed. Within the 9 cases, there are 25 events (13 events resolved; 3 events resolving, 7 events not resolved, and 2 missing data). Three (3) (33.3%) reports were in males, 5 (55.6%) in females, and 1 (11.1%) with missing gender data. Eight (8) (88.9%) cases were reported in 16-17-year-olds, and 1 case (11.1%) was reported in 12-15-year-olds. Four (4) (44.4%) cases were reported in the United States, 2 (22.2%) cases were from UK, 2 cases (22.2%) from the EEA, and 1 case (11.1%) originated from Canada. Six (6) (66.7%) reports came from a Regulatory Authority and 3 (33.3%) were from spontaneous sources.

During the reporting interval, for SPIKEVAX, in the ModernaTX GSDB, there are 3 cases (1 serious and 0 fatal) in immunocompromised adolescents. None of the 3 cases is medically confirmed. Within the 3 cases, there are 11 events (10 events resolved; 1 event not resolved). Of the 3 cases, 1 (33.3%) was reported in a male and 2 (66.7%) in females. Two (2) cases were reported in 16-17-year-olds, and 1 case was reported in 12-15-year-olds. One (33.3%) case was reported in the United States, 1 (33.3%) case was from UK, and 1 case (33.3%) was from the EEA. Two (66.7%) reports came from a Regulatory Authority and 1 (33.3%) was from spontaneous sources.

Most of the events in this age group represent expected reactogenicity however, there was one notable case of erythema multiforme. The patient also had pneumonia occurring on an unknown date after SPIKEVAX administration.

Data for the use of SPIKEVAX in immunocompromised adolescents are limited. The MAH will continue to monitor these reports via routine pharmacovigilance.

SPIKEVAX Dose 3 or Dose 4 in Immunocompromised Patients

As there are currently limited data available on the third and fourth doses in immunocompromised individuals, the MAH is monitoring the safety through routine pharmacovigilance and literature review. The data presented in this section represent combined data for third and fourth doses of SPIKEVAX in immunocompromised individuals.

All of the cases after Dose 3 and 4 were received in the reporting period; thus, the reporting period data are the same as the cumulative data. Cumulatively, there were 792 cases (of which 429 were serious, and 9 were fatal) reported after Dose 3 and Dose 4 in the immunocompromised subpopulation, with 2,408 events (of which 1,359 were serious). Of 792 cases, 3 cases were reported for Dose 4, all of which were non-serious; thus, the majority of the reports are for Dose 3. Of the 792 cumulative cases, a total of 231 cases were medically confirmed. These data should be interpreted with caution as it is difficult to differentiate if the 3rd dose administered was 100 mcg (3rd dose of the priming series) vs 50 mcg (booster dose) in this population. The distribution by gender of the 792 cases reported was 520 in females (65.7%), 244 in males (30.8%) and 28 (3.5%) with missing gender data. The mean age of 54.0 years (SD: 16.5) and a median age of 54.5 years (min 17.0/ max 92.0), with 74 cases missing age information.

Serious events must be interpreted with caution, and many are not events meeting the true definition of "serious" (death, life-threatening, hospitalization, etc.) in part due to a bias from self-reported seriousness classification in some countries, and in part due to some regulatory authorities' coding of all events as serious in serious cases.

The pattern of age distribution of cases (Dose 3 or Dose 4) for the reporting/cumulative period is described below (see Table 16-55).

Table 16-55 Age/Gender Distribution of the Cases in the Immunocompromised Subpopulation (Reporting Period/Cumulative) (Dose 3 or Dose 4 of SPIKEVAX)

Age Group (years)	Female		Male		Unknown		# Cases	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases	# Cases	% of Total Cases		
16-17	1	0.1%	0	0	0	0	1	0.1%
18-29	43	5.4%	16	2.0%	0	0	59	7.4%
30-39	74	9.3%	21	2.7%	0	0	95	12.0%
40-49	86	10.9%	30	3.8%	3	0.4%	119	15.0%

Age Group (years)	Female		Male		Unknown		# Cases	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases	# Cases	% of Total Cases		
50-64	158	19.9%	71	9.0%	4	0.5%	233	29.4%
65-74	68	8.6%	56	7.1%	6	0.8%	130	16.4%
75+	39	4.9%	39	4.9%	3	0.4%	81	10.2%
Missing	51	6.4%	11	1.4%	12	1.5%	74	9.3%
Grand total	**520**	**65.7%**	**244**	**30.8%**	**28**	**3.5%**	**792**	**100.0%**

The most common events reported after Dose 3 or Dose 4 are reflective of expected reactogenicity as is seen in the general population (Table 16-56).

Table 16-56 Top 10 Most Frequently Reported Preferred Terms (PTs) after Dose 3 or Dose 4 in the Immunocompromised Subpopulation (Reporting Period/Cumulative)

Reporting/Cumulative Period					
Immunocompromised Subpopulation			General Population		
PT	#	%	PT	#	%
Pyrexia	142	5.9%	Headache	3,295	6.1%
Headache	120	5.0%	Pyrexia	2,955	5.5%
Fatigue	96	4.0%	Fatigue	2,284	4.3%
Nausea	76	3.2%	Chills	1,905	3.5%
Chills	73	3.0%	Nausea	1,791	3.3%
Pain in extremity	72	3.0%	Expired product administered	1,789	3.3%
Arthralgia	67	2.8%	Myalgia	1,596	3.0%
Myalgia	65	2.7%	Pain in extremity	1,526	2.8%
Expired product administered	52	2.2%	Arthralgia	1,277	2.4%
Pain	48	2.0%	Dizziness	1,008	1.9%

Serious Events (SPIKEVAX 3rd dose or 4th dose)

Cumulatively (all within the reporting period), 429 serious cases were reported of which 9 were fatal cases. Of these 429 cases (1,358 serious events), 83 cases were medically confirmed. Three hundred and forty-one (341) (79.5%%) were reported from the UK, 68 (15.9%) from the USA, 18 (4.2%) from the EEA, and 2 (0.5%) from Switzerland.

Serious events must be interpreted with caution, and many are not events meeting the true definition of "serious" (death, life-threatening, hospitalization, etc.) in part due to a bias from self-reported seriousness classification in some countries, and in part due to some regulatory authorities' coding of all events as serious in serious cases.

There are 11 serious events of myocarditis and/or pericarditis reported after Dose 3 in the Immunocompromised subpopulation. Please refer to Section 16.3.1.2 on Myocarditis/Pericarditis for further detail.

Table 16-57 presents the top serious PTs reported post Dose 3 in the immunocompromised subpopulation compared to the general population during this reporting/cumulative period.

Table 16-57 Top Ten Serious Preferred Terms (PT) Reported After Dose 3 in the Immunocompromised Subpopulation vs. General Population (Reporting Period)

Reporting/Cumulative Period – Serious Events					
Top Serious PTs in Immunocompromised Subpopulation	**# Events**	**% Events**	**Top Serious PTs in General Population**	**# Events**	**% Events**
Pyrexia	82	6.0%	Headache	2,153	7.1%
Headache	75	5.5%	Pyrexia	1,945	6.5%
Fatigue	65	4.8%	Fatigue	1,494	5.0%
Nausea	50	3.7%	Nausea	1,277	4.2%
Pain in extremity	47	3.5%	Chills	1,175	3.9%
Arthralgia	40	2.9%	Myalgia	938	3.1%
Chills	35	2.6%	Arthralgia	837	2.8%
Myalgia	33	2.4%	Pain in extremity	816	2.7%
Dizziness	32	2.4%	Dizziness	649	2.2%
Vomiting	29	2.1%	Vomiting	571	1.9%

% Events = % of Total Events.

16.3.5.4.5. Discussion

The review of the GSDB and the literature during the reporting period have not identified any new safety concerns. It is noted that there was an increase in COVID-19 related adverse events during the reporting period, as was also seen in the general population. Frequently reported serious events reported in the immunocompromised subpopulation were generally comparable to those of the overall population. During this reporting period, COVID-19 is at #10 on the list of frequently reported events for the immunocompromised subpopulation, #4 on the reported serious events, and #1 most frequently reported fatal event. Given that immunosuppression may inhibit a protective immunogenic response to vaccination (which is included in the label), this subpopulation may not be fully protected, and thus may experience/report more COVID-19 disease after vaccination. Serious and fatal cases are confounded by multiple comorbidities and past medical history. There were no identified concerning or unusual patterns of unexpected deaths. The literature describes decreased immunogenicity of the some of the immunocompromised

subpopulation, and there is recognized waning of protection; thus, this increase in COVID-19 reports can be understood in this subpopulation especially in the context of new variants and changing epidemiology, as well as possibly changes in policies and behaviors.

There are relatively few (n=9) reports in immunocompromised adolescents, and thus analysis of the safety profile in this population is extremely limited. The MAH will continue to monitor these cases through routine pharmacovigilance.

Currently, some countries have approved/authorized/recommend a third dose in the primary series as well as a fourth “booster” dose in severely immunocompromised individuals given potential decreased immune response, as well as a third booster dose in mildly immunosuppressed individuals (and the general population) due to waning of immunity and the emergence of new variants. All of the third and fourth dose cases were received during this reporting period. Of the 792 cases, only 3 cases were after Dose 4 and thus the majority are after Dose 3. Overall, the general trends or pattern of commonly reported adverse events for the immunocompromised subpopulation after the third dose are comparable to those of the general population, and no new safety concerns were identified. The MAH will continue to monitor SPIKEVAX safety in immunocompromised patients after Dose 3 and Dose 4, through routine pharmacovigilance.

16.3.5.4.6. Conclusion

After review of all new safety data received during the reporting period in the immunocompromised subpopulation, the benefit-risk profile for SPIKEVAX remains favorable. The MAH will continue to monitor AEs in immunocompromised subpopulation using the routine pharmacovigilance measures implemented for SPIKEVAX.

16.3.5.5. Interaction with Other COVID-19 vaccines (Heterologous Vaccine Schedule)

16.3.5.5.1. Source of the New Information

The company (herein referred to as ModernaTx) GSDB was queried for valid, clinical, and spontaneous case reports received from HCP, HA, consumers, and literature, reporting period (18 Dec 2020 to 31 Dec 2021), reported for SPIKEVAX. Additional requests from regulators included presentation of the safety profile and interactions of heterologous COVID-19 vaccines schedule.

"In the next PSUR the MAH is requested to present data, including literature, and discuss the safety profile of SPIKEVAX in relation to heterologous COVID-19 vaccines schedule. The data and discussion should be presented in relevant sections e.g., off-label use, or in addition to the already presented PSUR headline “Interaction with other vaccines (Heterologous Vaccine Schedule” [EMA/PRAC].

16.3.5.5.2. Background Relevant to the Evaluation

Several vaccines have demonstrated efficacy against SARS-CoV-2 mediated disease (herein referred to as "COVID-19"), yet there are limited data on the clinical efficacy/safety or immunogenicity of heterologous vaccine regimens (including those employing different vaccine platforms, such as vectored vaccines) [68]. Currently, various heterologous combinations are being tested in clinical trials or post-EUA, or post-market settings, either as heterologous priming (heterologous-prime boost) or heterologous boost. Heterologous priming is also referred to as the "interchangeability" of vaccine products. In a scenario of heterologous priming schedules (commonly referred to as "mix and match" schedules), the second dose uses a different vaccine product than the first dose administered. According to the WHO, reasons for the utility of heterologous priming include "reducing reactogenicity," "increasing immunogenicity," and "enhancing vaccine effectiveness." However, the WHO also notes that "the most common reason for considering a heterologous COVID-19 vaccine as second priming dose is lack of availability of the same vaccine in settings with limited vaccine supply or unpredictable supply" (WHO, 10 Aug 2021). Nevertheless, the WHO advised that heterologous priming should only be implemented if there is documented "supporting evidence." In the case of heterologous boosting, a vaccine from a different vaccine platform is administered other than the vaccine used to complete the primary vaccine series (WHO, 10 Aug 2021).

On 20 Oct 2021, the USA FDA expanded the use of a booster dose for COVID-19 vaccines in eligible populations. In the case of heterologous use, the Agency has authorized the Moderna COVID-19 Vaccine for use in eligible individuals "as a heterologous booster dose following completion of primary vaccination with a different available COVID-19 vaccine. For example, Pfizer-BioNTech COVID-19 Vaccine and Janssen COVID-19 vaccine recipients 18 years of age and older may receive a single booster dose of the Moderna COVID-19 Vaccine."

In support of these authorizations for mix and match, and booster uses, Moderna is committed to reviewing cumulative data for its SPIKEVAX heterologous prime-boost strategy with the different combinations of the three types of leading COVID-19 vaccine candidates. COVID-19 vaccines emerging from different platforms differ in efficacy, duration of protection, and side effects, therefore, understanding these data will continue to support the safety profile despite combination use while also monitoring potential interactions. Limited data are currently available on the interactions of SPIKEVAX with other COVID-19 vaccines, drugs and/or other vaccines. As such, it is unclear whether the performance of heterologous regimens including SPIKEVAX are complementary, synergistic, or exhibit lower effectiveness compared with the two doses SPIKEVAX regimen that is authorized in numerous jurisdictions.

The focus of this cumulative review for "Interaction with Other Vaccines/Heterologous Vaccines" data is on 1) Heterologous vaccine administration (i.e., interchange of vaccines ("Mix and Match") and booster; and 2) Heterologous vaccine interactions (and other reported interactions, if any).

Literature Search and Findings

ModernaTX conducted a targeted literature search covering the period 18 Dec 2020 to 31 Dec 2021. There were 5 relevant peer-reviewed publications identified. Cumulatively, selected articles/abstracts are presented in Appendix 20.11.18. Information on heterologous coadministration with other non-COVID-19 vaccines is presented in Section 16.3.6.8.5.

Summary of literature results:

Of the relevant literature publications, five were highlighted and described below.

"Heterologous prime-boost strategies for COVID-19 vaccines",

Sapkota et. al. [69] reviewed the 'mix and match' approach to test for effectiveness of Oxford (AZD1222), Pfizer (BNT162b2), Moderna (mRNA-1273) and Novavax (NVX-CoV2373) vaccines for COVID in 'Com-Cov2 trial' in UK, and that of Oxford and Pfizer vaccines in 'CombivacS trial' in Spain. They reported that "Heterologous prime-boost trials showed safety, effectiveness, higher systemic reactogenicity, well tolerability with improved immunogenicity, and flexibility profiles for future vaccinations, especially during acute and global shortages, compared to the homologous counterparts." They concluded and recommended "large, controlled trials are warranted to address challenging variants of concerns including Omicron and other, and to generalize the effectiveness of the approach in regular as well as emergency use during vaccine scarcity".

Arabella S V Stuart et al [70], "Immunogenicity, safety, and reactogenicity of heterologous COVID-19 primary vaccination incorporating mRNA, viral-vector, and protein-adjuvant vaccines in the UK (Com-COV2): a single-blind, randomized, phase 2, non-inferiority trial," determined that "Heterologous second dosing with m1273, but not (NVX-CoV2373 [NVX], Novavax), increased transient systemic reactogenicity compared with homologous schedules. Multiple vaccines are appropriate to complete primary immunization following priming with BNT or ChAd, facilitating rapid vaccine deployment globally and supporting recognition of such schedules for vaccine certification."

The Swantje I Hammerschmidt et. al. [71] study, "Robust induction of neutralizing antibodies against the SARS-CoV-2 Delta variant after homologous SPIKEVAX or heterologous Vaxzevria-SPIKEVAX vaccination" determined that, "Homologous prime-boost immunization with Moderna's SPIKEVAX as well as heterologous immunization with AstraZeneca's Vaxzevria

followed by Moderna's SPIKEVAX were identified as highly potent vaccination regimens for the induction of Delta-neutralizing antibodies."

Tina Schmidt et al. [72] study, *"Cellular immunity predominates over humoral immunity after homologous and heterologous mRNA and vector-based COVID-19 vaccine regimens in solid organ transplant recipients"* analyzed "SARS-CoV-2-specific T cells and antibodies in 40 transplant recipients and 70 controls after homologous or heterologous vaccine-regimens. Plasma blasts and SARS-CoV-2-specific CD4 and CD8 T cells were quantified using flow cytometry." Their findings included that "while antibodies were only detected in 35.3% of patients, cellular immunity was more frequently found (64.7%) indicating that assessment of antibodies is insufficient to identify COVID-19-vaccine responders." They concluded that "heterologous vaccination seems promising in transplant recipients, and combined analysis of humoral and cellular immunity improves the identification of responders among immunocompromised individuals."

The Jialu Zhang, et. al. [73] study, *"Boosting with heterologous vaccines effectively improves protective immune responses of the inactivated SARS-CoV-2 vaccine"* showed that "the humoral and cellular immune responses induced by different vaccines when administered individually differ significantly. In particular, inactivated vaccines showed relatively lower level of neutralizing antibody and T cell responses, but a higher IgG2a/IgG1 ratio compared with other vaccines. Boosting with either recombinant subunit, adenovirus vectored or mRNA vaccine after two-doses of inactivated vaccine further improved both neutralizing antibody and Spike-specific Th1-type T cell responses compared to boosting with a third dose of inactivated vaccine." Their results suggest "new ideas for prophylactic inoculation strategy of SARS-CoV-2 vaccines".

16.3.5.5.3. Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

ModernaTx, queried the GSDB cumulatively from 18 Dec 2020 to 31 Dec 2021, for valid case reports of interactions with other vaccines from HCP, HA, consumers, and literature, worldwide, reported for SPIKEVAX using the following criteria: Heterologous interchange of vaccines.

A cumulative review of potential interaction of SPIKEVAX with other COVID-19 vaccines from other manufacturers was performed using the preferred term "Interchange of vaccine products" with SPIKEVAX including 4 criteria:

1. PT='Interchange of vaccine products'
2. Medical history is in any one of this Manufacturer's Vaccine (AstraZeneca, Janssen, Pfizer, Other)

3. Concomitant Medication is in any one of this Manufacturer's Vaccine (AstraZeneca, Janssen, Pfizer, Moderna, Other)
4. Co-Suspect is in any one of this Manufacturer's Vaccine (AstraZeneca, Janssen, Pfizer, Moderna, Other)

The following appendices support this medical topic:

- Appendix 20.11.18: Selected abstracts/articles
- Appendix 20.11.19: Fatalities
- Appendix 20.11.20, Appendix 20.11.21, Appendix 20.11.22 and Appendix 20.11.23: Case narrative listings

16.3.5.5.4. Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Observed versus Expected

Refer to Appendix 20.11.3.

Heterologous Interchange Vaccine Schedule

Cumulatively, there was a total of 6,348 reported cases (26,528 events, 1,949 serious cases, and 38 cases (0.60%) with fatal outcomes). Case reports of interchange were received from Pfizer (2370; 37.3%), AstraZeneca (2045; 32.2%), other manufacturers (1,110; 17.5%) and Janssen (272; 4.3%). The majority of the reported cases were by regulatory authorities (5,156; 81.2%); originated from the EEA (2,549; 40.2%); and in females (3504, 66.04%). The most frequent age group for reported cases was in the 50-64 years (1875; 35.3%); with a female predominance (1043;19.66 %) relative to males (819, 15.44 %) in the same age group (Table 16-58). The median age of reported cases was 52 years. Of the 26,528 events, 34.68% (9,199) had resolved, while 26.3% (6,976) had not resolved. There were 4,809 (18.13%) events with unknown/missing outcome.

During the reporting interval, there were 745 cases (747 events, 214 serious cases, and 1 case with a fatal outcome) with 240 cases (32.2%) in males and 445 (59.7%) in females. The most frequent age group for reported cases was in the 50-64 years (199; 26.7%). The median age of reported cases was 50 years. Of the 747 events, 73.0% (545) had resolved, while 2.4% (18) had not resolved. There were 181 (24.2%) events with unknown/missing outcome.

Table 16-58 Age and Gender Distribution of Cumulative "Interchange of Vaccine Product" Cases (Cumulative till 31 Dec 2021)

Age Group	Cumulative							
	Female		Male		Unknown		Total	
	Cases	% Of Total Cases	Cases	% Of Total Cases	Cases	% Of Total Cases	Cases	% Of Total Cases
<12 years	4	0.08	11	0.21	0	0.00	15	0.28
12-17 years	59	1.11	32	0.60	4	0.08	95	1.79
18-24 years	178	3.35	151	2.85	4	0.08	333	6.28
25-39 years	727	13.70	503	9.48	11	0.21	1241	23.39
40-49 years	613	11.55	418	7.88	8	0.15	1033	19.47
50-64 years	1043	19.66	819	15.44	13	0.25	1875	35.34
65-74 years	455	8.58	373	7.03	5	0.09	833	15.70
75+ years	296	5.58	194	3.66	10	0.19	500	9.42
Missing	129	2.43	165	3.11	129	2.43	423	7.97
Grand Total	**3504**	**66.04**	**2660**	**50.13**	**184**	**3.47**	**6348**	**119.64**

Case distribution by region is presented below in Table 16-59. The EEA reported the highest proportion of cases (2,549; 40.2%).

Table 16-59 Distribution of Interchange Vaccine Product Cases by Region

Region	Cumulative cases	Review period cases
Missing	21	21
Asia	55	55
Canada	200	184
European Economic Area	2549	2339
Switzerland	2	2
United Kingdom	2029	2015
United States	1492	690

Overview of Frequency of Events/Cases by PTs

Cumulatively, the most frequently reported preferred terms for interchange vaccines was headache (6.5%), fatigue (5.8%) and pyrexia (5.4%); all consistent with reactogenicity reactions and general population. The PTs of "Interchange of Vaccines Products" reported 1,378 events in 1,374 cases (4.7%). The top 20 PTs are presented in Table 16-60.

Table 16-60 Top 20 PTs for the Interchange of Vaccines by Events/Cases (Cumulative)

PT	Event Counts	% Events	Case Counts	% Cases
Headache	1928	7.4	1733	6.5
Fatigue	1712	6.1	1435	5.8
Pyrexia	1595	6.3	1491	5.4
Interchange of vaccine products	1378	5.8	1374	4.7
Myalgia	1131	4.4	1023	3.8
Chills	1100	4.4	1042	3.7
Injection site pain	833	2.4	556	2.8
Nausea	829	3.4	789	2.8
Arthralgia	770	3.0	698	2.6
Malaise	753	2.9	679	2.6
Pain in extremity	627	2.4	560	2.1
Dizziness	502	1.9	455	1.7
Inappropriate schedule of product administration	405	1.7	405	1.4
Pain	361	1.5	351	1.2
Vaccination site pain	338	1.4	323	1.1
Dyspnoea	309	1.2	292	1.0
COVID-19 immunization	288	1.2	288	1.0
Chest pain	255	1.0	236	0.9
Injection site swelling	250	0.9	203	0.8
Vomiting	233	0.9	223	0.8
Lymphadenopathy	226	0.9	210	0.8

While a high proportion of reported cases for "Interchange of Vaccines" were after dose 3 (2,174; 34.2%), more than half (3,384; 53.3%) of the reported cases had missing dose numbers. The majority of the events had a time to onset in the first 3 days (51.4%) (Table 16-61 and Table 16-62).

Table 16-61 Distribution of Events and Cases by Time to Onset (TTO) All Doses (18 Dec 2020 to 31 Dec 2021)

Time to onset, most recent dose	Events		Cases	
	N	%	N	%
Mean (standard deviation)	4		4.76	
Median (Min-Max)	-		1	
0 days	7,682	28.96	2,701	42.55
1 - 3 days	5,953	22.44	2,048	32.26
4 -6 days	447	1.69	243	3.83

Time to onset, most recent dose	Events		Cases	
	N	%	N	%
7-13 days	391	1.47	181	2.85
14-29 days	336	1.27	184	2.90
≥30 days	449	1.69	214	3.37
Unknown	11,270	42.48	3,384	53.31

Table 16-62 Most Frequently Reported Events and Cases of PT "Interchange of Vaccine Products" by Dose Number (Cumulative as of 31 Dec 2021)

Number of Events for Interchange by Dose Number	Cumulative			
	Events		Cases	
	N	%	N	%
Total	26,528		6,348	
Dose number prior to onset				
Dose 1	2,915	10.99	891	14.04
Dose 2	5,718	21.55	1,477	23.27
Dose 3+	6,623	24.97	2,174	34.25
Dose 4	2	0.01	2	0.03
Unknown	11,270	42.48	3,384	53.31

The outcomes for most events were recoveries as at the time of reporting (9199;34.7%). Table 16-63.

Table 16-63 Summary of Outcomes

Outcome	Events		Cases	
	N	%	N	%
Fatal	95	0.36	38	0.60
Not Recovered/Not Resolved	6,976	26.3	2,369	37.32
Recovered/Resolved	9,199	34.68	3,598	56.68
Recovered/Resolved with Sequelae	137	0.52	91	1.43
Recovering/Resolving	5,312	20.02	1,769	27.87
Unknown	4,809	18.13	1,687	26.58

Overview of Serious Cases and Events of Interchange Vaccines by Manufacturer

Of the 6,348 cases, 1,949 cases (9,399 events) were assessed as serious and 38 had a fatal outcome. Among the serious cases reported, the highest number of cases were from Pfizer (718; 36.8%), AstraZeneca (575; 29.5%), Janssen (43; 2.2%) and other manufacturers (556; 28.5%). There was a male preponderance in overall reported cases (1097; 56.29%), while 30 (1.54%) reported cases

were missing gender data values with most cases reported in the 50-64 years. Of the 9,399 events, 956 cases (49.05%) were resolved. Most cases (1092; 56.03%) for the interchange of vaccine products were after dose 3.

Age distribution among serious interchange vaccine products presented in Table 16-64; details by MAH further are described in their respective sections below under fatalities by interchange vaccine products (MAH).

Table 16-64 Age Distribution of Serious Cases by Manufacturer (Cumulative as of 31 Dec 2021)

	AZ		Janssen		Pfizer		Other MAH	
	Cases	% Of Total Cases	Cases	% Of Total Cases	Cases	% Of Total Cases	Cases	% Of Total Cases
<12 years	0	0	0	0	*2	0.3%	0	0
12-17 years	1	0.2%	0	0	**4	0.6%	0	0
18-29 years	38	6.6%	7	16.3%	151	21.0%	44	7.9%
30-39 years	59	10.3%	5	11.6%	152	21.2%	47	8.5%
40-49 years	99	17.2%	4	9.3%	108	15.0%	126	22.7%
50-64 years	284	49.4%	14	32.6%	139	19.4%	231	41.5%
65-74 years	65	11.3%	5	11.6%	63	8.8%	49	8.8%
75+ years	11	1.9%	6	14.0%	46	6.4%	20	7.0%
Missing	18	3.1%	2	4.7%	49	6.8%	39	100.0%
Grand Total	**575**	**100.0%**	**43**	**100%**	**718**	**100%**	**556**	**7.9%**

*< 2 years cases (Pfizer only due to its EUA)
*16-17 years cases (Pfizer only due to its EUA)

Table 16-65 presents outcome and dosing/TTO data.

Table 16-65 Overview of Serious Data for Interchange Vaccine Products (Cumulative as of 31 Dec 2021)

	Cumulative			
	Events		Cases	
	N	%	N	%
Total	9,399		1,949	
Dose number prior to onset				
Dose 1	504	5.36	118	6.05
Dose 2	1,214	12.92	319	16.37
Dose 3+	3,714	39.51	1,092	56.03

	Cumulative			
	Events		Cases	
	N	%	N	%
Dose 4	-	0		-
Unknown	3,967	42.21	1,197	61.42
Time to onset, most recent dose				
Mean (standard deviation)	6.57		6.57	
Median (Min-Max)	1		1	
0 days	2,299	24.46	744	38.17
1 - 3 days	2,355	25.06	835	42.84
4 -6 days	219	2.33	120	6.16
7-13 days	205	2.18	88	4.52
14-29 days	129	1.37	65	3.34
≥30 days	225	2.39	94	4.82
Unknown	3,967	42.21	1,197	61.42
Outcome				
Fatal	95	1.01	38	1.95
Not Recovered/Not Resolved	2,554	27.17	921	47.26
Recovered/Resolved	2,708	28.81	956	49.05
Recovered/Resolved with Sequelae	98	1.04	60	3.08
Recovering/Resolving	2,052	21.83	754	38.69
Unknown	1,892	20.13	567	29.09
Duration				
Mean (standard deviation)	4.33		4.33	
Median (Min-Max)	1		1	
0-1 days	1,110	11.81	545	27.96
2-3 days	607	6.46	272	13.96
4-6 days	198	2.11	106	5.44
7-29 days	158	1.68	82	4.21
≥30 days	31	0.33	18	0.92
Unknown	7,295	77.61	1,697	87.07

Overview of Frequency of Serious Adverse Events/Cases for Heterologous Interchange Vaccines

Among the serious cases, the most frequently reported serious PT in the group of Interchange of vaccine products were headache, pyrexia, fatigue, chills, and nausea. Most of the events reflect

common and well-described reactogenicity. The percentage of all events of headache, pyrexia, fatigue, chills, and nausea were comparable or lower than the respective percentage of these events in the general population with SPIKEVAX. Table 16-66 presents top 3 serious PTs, number of events after each dose and number of serious and cumulative cases.

Table 16-66 Top 3 Serious PTs, Number of Serious Cases, # Events by Dose by Co-Suspect Manufacturers of COVID Vaccines Reported (Cumulative as of 31 Dec 2021)

Heterologous Co-Suspect	Top 3 Serious PTs (#; %)	# Events after Dose 1	# Events after Dose 2	# Events after Dose 3	# of Serious Cases	Total Cumulative	
						# Cases	% Total Cases
Pfizer BioNTech COVID-19 vaccine	Pyrexia (209;5.8%) Fatigue (203;5.6%) Headache (199;5.5%)	180	517	1,380	718	2370	37.3
AstraZeneca COVID-19 vaccine	Headache (219;8.1%) Fatigue (158;5.8%) Pyrexia (142;5.2%)	156	392	831	575	2045	32.2
Janssen COVID-19 vaccine	Interchange of vaccine products (10;4.6%) Nausea (7;3.2%) Chills (6;2.7%)	42	102	19	43	272	4.3
Other Manufacturers	Headache (178;7.3%) Pyrexia (177;7.2%) Fatigue (168;6.9%)	46	132	1,337	556	1110	17.5
Unknown MAH	Interchange of vaccines (64;14.1%) Fatigue (15; 3.3%) Headache (13;2.9%)	81	81	156	63	551	8.7
Total		**504**	**1,224**	**3,723**	**1955**	**6348**	**100.0**

Majority of outcomes for serious events included resolved (2,708) and resolving (2,052). Overview of fatalities are described below.

Overview of Fatalities for Interchange Vaccine Products

A total of 38 cases (135 events) had fatal outcomes, of which 26 were medically confirmed, and the highest deaths were associated with Co-suspect manufacturer Pfizer Table 16-67. Males disproportionately had more fatal outcomes (25; 65.8%) compared to females (11; 28.9%). The median age of fatal outcome cases was 62.0 years (Range: 26/98). Fatalities were highest (34.2%)

among the age group 75+ (mainly driven by Pfizer) followed by 50 – 64-year age group (31.6%). Time to onset was highest following dose 3 (25.2%), within the first 3 days (17.8%). The majority of deaths were reported by regulatory authorities (32;84.2%) and about half of the deaths were in the EEA (47.4%) region followed by the US (21.1%) then UK (15.8%).

Pfizer has the highest proportions of fatal cases cumulatively (19). See Appendix 20.11.20 for all fatalities.

Table 16-67 Number of Fatal Cases with Co-Suspect Manufacturers of COVID Vaccines Reported (Cumulative as of 31 Dec 2021)

Heterologous Co-Suspect	Cumulative # of Deaths	Cumulative	
		# Total Cases	% Fatal Total Cases
Pfizer BioNTech COVID-19 vaccine	19 cases (54 events)	2370	0.8%
AstraZeneca COVID-19 vaccine	6 cases (8 events)	2045	0.3%
Janssen COVID-19 vaccine	2 cases	272	0.7%
Other Manufacturers	8 cases	1110	0.7%
Unknown	3 cases	63	4.8%
Total	**38**	**6348**	

Among serious cases with fatal outcomes, the top 10 most frequent MedDRA PTs reported are presented in Table 16-68.

Table 16-68 Top 10 PTs Associated with Fatal Outcomes for Interchange Vaccine Product (Cumulative as of 31 Dec 2021)

PT	# Events	% of Total Events
Death	12	8.9%
Dyspnoea	7	5.2%
Interchange of vaccine products	7	5.2%
Cardiac arrest	5	3.7%
Pyrexia	5	3.7%
Acute myocardial infarction	3	2.2%
Pulmonary embolism	3	2.2%
Sudden death	3	2.2%
Asthenia	2	1.5%
Cerebral thrombosis	2	1.5%

Detailed Fatal Overviews by Manufacturer

AstraZeneca Interchange Vaccine Fatalities

Of the 6 cases of interchange vaccine with AstraZeneca (AZ) and SPIKEVAX, cases were equally distributed among gender (50.0% male/female) with a median age of 58 years. Half (50.0%) of the cases were in the 50-64 years age group, 33.3% 65-74 years with 16.7% were missing. Half of these cases were from Germany (50.0%) followed by UK (33.3%), and Korea (16.7%). Fatalities were equally distributed among dose 1 and 2. However when known, it was highest after booster dose 3 (25.0%) with half of the cases missing (50.0%). PTs for interchange with AZ are presented below in Table 16-69.

Table 16-69 Distribution of PTs for Interchange Vaccine with AZ (Cumulative)

PT	# Events	% of Total Events
Death	3	37.5%
Intracranial mass	1	12.5%
Myocardial infarction	1	12.5%
Pneumonia viral	1	12.5%
Sudden death	1	12.5%
Viral myocarditis	1	12.5%
Grand total	**8**	**100.0%**

AstraZeneca -SPIKEVAX Case narrative listings are provided in Appendix 20.11.21.

Pfizer Interchange Vaccine Fatalities

Of the 19 cases (54 events) of interchange vaccine with Pfizer and SPIKEVAX, cases were disproportionately distributed among males (73.7%) compared to females (21.1%) and 5.3% had missing information. The median age of fatal cases was 67 years, this is higher compared to other products. Pfizer COVID-19 vaccine-related deaths were also disproportionately higher in older, 75+ years cases (47.4%) compared to other COVID vaccines (i.e., AZ) as well as deaths in younger age group 30-39 years (15.8%). Other vaccines did not have fatal cases in younger groups. Similar to AZ, the highest fatalities were from Germany (22.2%) followed by the USA. (16.7%), and France/Italy (11.1%). Pfizer fatalities were also equally distributed among dose 1 and 2 (5.6%). Similarly, when known, TTO for deaths were highest after booster dose 3 (46.3%) with 42.6% of the cases missing. Top 10 PTs for interchange with Pfizer are presented below in Table 16-70.

Table 16-70 Distribution of Top 10 PTs for Interchange Vaccine with Pfizer (Cumulative)

PT	# Events	% of Total Events
Death	4	7.4%
Dyspnoea	4	7.4%

PT	# Events	% of Total Events
Cardiac arrest	3	5.6%
Acute myocardial infarction	2	3.7%
Asthenia	2	3.7%
Oxygen saturation decreased	2	3.7%
Pulmonary embolism	2	3.7%
Pyrexia	2	3.7%
Sepsis	2	3.7%
Sudden death	2	3.7%

Pfizer-SPIKEVAX Case narrative listings are provided in Appendix 20.11.20.

Janssen Interchange Vaccine Fatalities

There were only 2 fatal cases (aortic aneurysm rupture and cardiac arrest) for interchange vaccine with Janssen and SPIKEVAX. Both cases were in males with a median age of 57 years, with both cases occurring within the 50-64 years age group, similar to AZ. The two cases were reported from Germany and Korea (50.0%); consistent with both AZ and Pfizer. Fatalities were equally distributed among doses 2 and 3.

Other MAHs Interchange Vaccine Fatalities

Of the 8 cases (24 events) of interchange vaccine with other MAH including non-mRNA other products and SPIKEVAX, cases included 4 males (50.0%) and 3 females (37.5%) and 1 missing (12.5%) with a median age of 71.5 years. Similar to other covid vaccines, 37.5% cases were in the 50-64: the 75+ years age group was 37.5%, and the 65-74 age group was 25.0%. Half of these cases were from the US (50.0%) followed by UK (37.5%), and Germany (12.5%). Contrary to AZ, Pfizer and Janssen (when known), fatalities were disproportionately distributed among dose 1 (37.5%) and dose 2 (12.5%) with 45.8% unknown. Top 10 PTs for interchange with other COVID vaccines which included all other non-mRNA platform is presented below in Table 16-71.

Table 16-71 Distribution of PTs for Interchange Vaccine with Other MAH (Cumulative)

PT	# Events	% of Total Events
Death	3	12.5%
Acute kidney injury	1	4.2%
Acute myocardial infarction	1	4.2%
Acute respiratory failure	1	4.2%
Candida infection	1	4.2%
Cardiac arrest	1	4.2%

PT	# Events	% of Total Events
Cardiogenic shock	1	4.2%
Cerebrovascular accident	1	4.2%
Coagulopathy	1	4.2%
COVID-19	1	4.2%

Other MAH-SPIKEVAX Case narrative listings are provided in Appendix 20.11.22.

Unknown Product Interchange Vaccine Fatalities

There were only 3 fatal cases (7 events) for interchange vaccines with unknown products and SPIKEVAX. Two cases were in males (66.7%) and 1 female (33.3%) with a median age of 56 years with cases equally distributed (33.3%) across age groups 18-29, 50-64, and 75+ years. The 3 cases were derived from Argentina, Thailand, and USA (33.3% respectively). Most deaths were in dose 2 (71.4%) with 28.6% unknown. PTs included death (28.6%) and 14.3% in cardio-respiratory arrest, chest discomfort, dyspnea, loss of consciousness, and pulmonary embolism.

Overview of Serious Subpopulation Cases for Interchange Vaccine Products

Cumulative review of subpopulation cases (<12 and 12-17) including events after booster dose/3rd reported with co-suspect manufacturers' of COVID vaccines is presented below.

The highest reports after Booster/3rd dose were reported with other MAH (443) followed by Pfizer (341) (Table 16-72).

Table 16-72 Subpopulation Cases and after the 3rd Dose with Co-suspect Manufacturers of COVID Vaccines (Cumulative:18 Dec 2020 – 31 Dec 2021)

Manufacturers	Co-Suspect Subpopulations	Subpopulation Case Counts
Pfizer BioNTech COVID-19 vaccine	0-11	4
	12-17	6
	Booster/3rd Dose	341
AstraZeneca COVID-19 vaccine	0-11	0
	12-17	1
	Booster/3rd Dose	290
Janssen COVID-19 vaccine	0-11	0
	12-17	0
	Booster/3rd Dose	7
Other MAH COVID-19 vaccine	Booster/3rd Dose	443
Unknown Covid vaccine	12-17	1
	Booster/3rd Dose	15

Interchange of Vaccine Products in <12 Years of Age

Cumulatively, there were 15 cases (48 events) of Interchange of vaccine products for under 12 years; of which 4 were serious, 7 were medically confirmed and no fatal outcomes. Gender distribution was 11 males (73.3%) and 4 females (26.7%) with a median age of 0.7 year (Range: 0.1/11). Of the 15 cases, 8 were under 2years (53.3%) and 7 were 2-11 age group (46.7%). A high proportion of reported cases were mainly by a regulatory authority (66.7%), and from the UK (7; 46.7%) followed by USA (4; 26.7%). The top 3 events in this age group were fatigue (6;12.5%), product administered to patient of inappropriate age (5; 10.4%), and pyrexia (4; 8.3%). Dose 3 had the highest events (16.7%) with a time to onset less than 3 days; 68.8% of dosing information was missing. Most events resolved within one day or on the same day.

Interchange of Vaccine Products in Adolescents (12-17 Years of Age)

Cumulatively, 95 cases (266 events, 8 serious cases, 79 medically confirmed, and no fatal outcome) were reported for Interchange of vaccine products for 12-17 years. The majority of the cases reported were by regulatory authorities (57; 60.0%); from the US (67; 70.5%). Reports in females (59; 62.1%) were more common compared to males (32; 33.7%) with a median age of 16.0 years (Range: 12/ 17). The top 3 events in this age group were product administered to patient of inappropriate age (56;21.1%), interchange of vaccine products (55;20.7%), and pyrexia (13;4.9%). Most (143; 53.8%) of 266 reported events had resolved. Distribution of reported events was higher after dose 1 (83; 31.2%) compared to after dose 2 (72; 27.1%), 10.5% of events (28 events) were reported after dose 3 with 31.2% of events (83) were reported with missing dose information. Time to onset after all doses (1-3) was 0 days (same day reactions). Most events resolved on the same day.

Interchange of Vaccine Products for SPIKEVAX as Third Dose

Cumulatively, there were 2174 cases (34.3%) after dose 3 (booster) and 2 cases (0.03%) after dose 4 reported in the group of Interchange of vaccine products. Of these, 1092 (56.03%) were considered serious.

Confounding Factors

The top 20 potential confounders of causality for these events include medical history which is presented in Table 16-73. Use with AZ COVID-19 vaccine had the highest frequency among medical history followed by lisinopril for concomitant medications. Over half of the cases had missing information on confounders.

Table 16-73 Medical History Confounders

Medical History	Cases (N)	Cases (%)
No Med History/Blanks	**2410**	**38.0**
COVID-19 VACCINE ASTRAZENECA	815	12.8
PFIZER BIONTECH COVID-19 VAC	704	11.1
COMIRNATY	345	5.4
COVID-19 VACCINE	297	4.7
Suspected COVID-19	294	4.6
Hypertension	253	4.0
Drug hypersensitivity	184	2.9
Asthma	169	2.7
ASTRAZENECA COVID-19 VACCINE	146	2.3
Disease risk factor	121	1.9
Comirnaty	110	1.7
Immunodeficiency	109	1.7
JANSSEN COVID-19 VACCINE	102	1.6
COVID-19	90	1.4
Diabetes mellitus	87	1.4
Seasonal allergy	85	1.3
Hypersensitivity	69	1.1
Clinical trial participant	65	1.0
Food allergy	63	1.0
COVID-19 VACCINE JANSSEN	62	1.0

16.3.5.5.5. Discussion

Notably, there has been an increasing trend in the use of interchange of vaccine products (Mix &Match and booster) for the global COVID-19 mass vaccination campaign, especially for the booster/more than 2 doses. Hence, a high proportion of reports were noted after dose 3. Overall, the adverse events reported with heterologous vaccine interchange and boosting were in line with those expected from reactogenicity with SPIKEVAX. Frequently reported adverse events raised no notable concerns and did not show any specific new patterns.

The analysis of the cumulative data reported for heterologous vaccines interchange did not find that the safety profile of SPIKEVAX is different when used with other heterologous vaccines.

16.3.5.5.6. Conclusion

The data provided in this PBRER describe sufficiently the cumulative safety profile of SPIKEVAX. The benefit-risk evaluation remains positive. Based on the analysis of the cumulative safety data available as of 31 Dec 2021 for the risk associated with heterologous interchange and

booster, the MAH considers that heterologous priming schedule/Mix & Match and boosting-related events are not presently a safety issue of concern, and the benefit-risk profile for SPIKEVAX remains favorable. The MAH will continue to evaluate heterologous priming schedule/Mix & Match and boosting-related events using routine surveillance.

16.3.5.6. Use in frail subjects with unstable health conditions and co-morbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders)

16.3.5.6.1. Source of the New Information

ModernaTX, Inc queried the GSDB for the reporting period from 01 Jul 2021 through 31 Dec 2021, for valid, spontaneous case reports received from HCP, HA, consumers, and literature, worldwide, reported for SPIKEVAX.

16.3.5.6.2. Background Relevant to the Evaluation

Frail subjects with unstable health conditions and co-morbidities were excluded from initial clinical trials. Therefore, ModernaTX, Inc is characterizing safety through post-marketing routine monitoring of adverse events in this special population. Frail individuals are at a higher risk for serious COVID-19 disease including hospitalizations and deaths [74].

16.3.5.6.3. Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

Reports from frail individuals were identified in the Moderna GSDB using “Frail” custom search, which included subjects of all ages with unstable health conditions and comorbidities (e.g., COPD, diabetes, chronic neurological disease, cardiovascular disorders).

16.3.5.6.4. Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Overview of Cases

Cumulatively as of 31 Dec 2021, a total of 42,652 cases (200,234 events) were reported in frail subjects of which 15,189 cases (35.6%) were assessed as serious, and 2,121 cases (5.0 %) had a fatal outcome. Most of these cases (33,942 cases. Most of these cases; 79.5%) were medically confirmed. The median age of frail subjects was 62 years (min 1.0/max 121.0) and mean 59.3 (SD: 17.9); 234 were missing. There were significantly more cases reported in those of female gender (29,201; 68.5%) than male (13,218; 31.0%) and 233 (0.5%) were missing gender descriptor. Most cases were from the USA (79.2%) followed by the EEA (13.9%).

During the reporting period, there were a total of 12,229 cases (63,373 events), of which 7,294 cases (59.6%) were serious, 822 cases (6.7%) had a fatal outcome, and 7,782 cases were medically

confirmed (63.6%). More cases were reported in females (7,304 cases; 59.7%) than males (4,826 males (39.5%), and gender was unknown in 99 cases (0.8%). The median age was 61.0 years (min -1.0/ max 120) and mean age was 59.0 (SD 18.5). Of the 12,229 frail cases in this interval period, 5191 cases (42.4 %) were in the elderly age group 65 years and older. Most cases in this reporting interval were from the USA (52.4%) followed by EEA 28.3% and UK 9.8%. See Table 16-74 below for age distribution.

Table 16-74 Age Distribution of Reports in the Frail Population this Reporting Period

Age Group	Review Period	
	# Cases	% of Total Cases
<2	9	0.1%
12-15	19	0.2%
16-17	21	0.2%
18-29	880	7.2%
30-39	1,160	9.5%
40-49	1,515	12.4%
50-64	3,081	25.2%
65-74	2,619	21.4%
75+	2,572	21.0%
Missing	353	2.9%
Grand total	12,229	100.0%

The most frequently reported events in frail subjects by PT were pyrexia, fatigue and headache. The most frequently reported PTs are listed below (Table 16-75).

Table 16-75 Most Frequently Reported Events by Preferred Term in Frail Subjects >=2% (Review Period)

PT	# Events	% of Total Events
Pyrexia	2,207	3.5%
Fatigue	1,929	3.0%
Headache	1,841	2.9%
COVID-19	1,810	2.9%
Dyspnoea	1,696	2.7%

During this review period, events were most frequently reported after dose 2 (39.5%) than after dose 1 (22.7%) and after dose 3 (12.2%). There were 6 events reported after 4th dose all occurring on day 0. When latency was known, events were most frequently reported as occurring 14 days or more (23.2%) after 2nd dose. See Table 16-76.

Table 16-76 Time to Onset by Dose Number in the Frail Population Review Period

Dose Number	TTO All Doses (Days)	Review Period	
		# Events	% Events
Dose 1	**Subtotal**	14,370	22.7%
	0 days	3,813	6.0%
	01-02	2,997	4.7%
	03-04	986	1.6%
	05-06	630	1.0%
	07-13	1,427	2.3%
	14-29	1,121	1.8%
	30+	3,396	5.4%
Dose 2	**Subtotal**	25,049	39.5%
	0 days	4,439	7.0%
	01-02	3,718	5.9%
	03-04	834	1.3%
	05-06	423	0.7%
	07-13	935	1.5%
	14-29	1,302	2.1%
	30+	13,398	21.1%
Dose 3	**Subtotal**	7,700	12.2%
	0 days	2,398	3.8%
	01-02	2,789	4.4%
	03-04	605	1.0%
	05-06	373	0.6%
	07-13	556	0.9%
	14-29	452	0.7%
	30+	527	0.8%
Dose 4	**Subtotal**	6	0.0%
	0 days	6	0.0%
Unknown	**Subtotal**	16,248	25.6%
	Missing	16,248	25.6%
Grand total		63,373	100.0%

Outcomes

When reported, the most frequent event outcome was not resolved (32.8%), followed by resolved (26.6%). The category "Not recovered/Not resolved" is an overestimate as it reflects information

submitted at the time of the report (generally without additional follow-up). Fatal cases are reviewed below and in Section 16.3.6.8.2.

Serious Cases in the Frail Population (Review Period)

There were 7,294 serious cases (43,451 events) in the frail population in this reporting period, of which 5,476 (75.1%) were medically confirmed and 822 cases (6.7% of cases in this subpopulation) had a fatal outcome.

Serious frail cases were most frequently seen in age group 65 and over (47.8%), followed by in the 50 – 64-year-old age group (23.2%).

The Age distribution of frail population in serious cases are presented below in Table 16-77.

Table 16-77 Age Distribution of Frail Population in Serious Cases Review Period

Age Group	Review Period	
	# Cases	% of Total Cases
<2	5	0.1%
12-15	10	0.1%
16-17	11	0.2%
18-29	511	7.0%
30-39	593	8.1%
40-49	801	11.0%
50-64	1,691	23.2%
65-74	1,607	22.0%
75+	1,882	25.8%
Missing	183	2.5%
Grand total	**7,294**	**100.0%**

COVID-19 and Dyspnoea were the two most frequently reported events terms in serious cases in the frail population, followed by Pyrexia, fatigue and headache.

More serious events were reported following the 2nd dose (45.2 %) than other doses in this interval.

The most frequently reported outcome of events in serious cases (when known) in this reporting period the frail population was Not recovered (35.6%) followed by recovered (23.6%). Not recovered is an overestimate as it reflects information submitted at the time of the report (generally without additional follow-up).

Following is a brief summary of the serious cases of the 2 most commonly reported event terms (Covid-19 and Dyspnoea) in the Frail Subpopulation

Serious Cases of COVID-19 in the Frail subpopulation.

There were 1,419 serious cases (12,670 events) with Preferred term COVID-19, accounting for 19.5% of serious cases in the frail subpopulation. Majority (77.4%) occurred in those aged 65 years and older. Most of these events (9,449 events ;77.5%) occurred in a time frame (14+ days after 2nd SPIKEVAX dose) suggestive of vaccine failure. There were 260 of these serious cases which had fatal outcomes.

Serious Cases of Dyspnoea in the Frail Subpopulation

There were 1,319 serious cases (13,607 events) with Preferred term Dyspnoea, accounting for 18.1% of serious cases in the frail subpopulation. Majority (53.3%) occurred in those aged 65 years and older and 482 cases (36.5%) were co-reported in those with events of COVID-19. Events in serious cases of dyspnoea were most frequently (41.2%) reported to have occurred 30+ days after second dose. Medical history (see Table 16-78 below) of Asthma (in 32%) and of COPD (in 8%) was reported in patients represented in the frail subpopulation and confound many of these cases of dyspnoea. There were 165 of these serious cases of dyspnea in the frail subpopulation which had a fatal outcome.

Fatal Cases in the Frail Subpopulation: There were 822 fatal cases in the frail subpopulation in this reporting period of which 76.5% were in the elderly 65 years of age or older. Mean age was 73.2 (SD 14.4) and median of 75.0 (min:17.0 /max; 101.0) and 3 (0.4%) m missing. Gender distribution was 57.9% male and 41.7% female with 4 missing gender. The top 3 most frequently reported event terms in the fatal cases in the frail subpopulation was Death, COVID-19 and Dyspnoea.

Frail patients also have comorbidities or unstable health conditions which are subject to worsening and can lead to fatal outcomes. The most frequently reported of those concurrent diseases and concomitant medications in the cumulative period is presented in Table 16-78 and Table 16-79.

Table 16-78 Most Frequent Reported Comorbidities >4% (Cumulative period)

Medical History	Cases (N)	Cases (%)
Total Unique Cases	42,652	100%
Drug hypersensitivity	14,346	34%
Asthma	13,566	32%
Hypertension	11,542	27%
Diabetes mellitus	9,149	21%
Type 2 diabetes mellitus	4,124	10%
Food allergy	3,864	9%
Chronic obstructive pulmonary disease	3,584	8%
Atrial fibrillation	3,391	8%

Medical History	Cases (N)	Cases (%)
Gastrooesophageal reflux dis	2,680	6%
Hypothyroidism	2,630	6%
Hyperlipidaemia	2,605	6%
Hypersensitivity	2,329	5%
Seasonal allergy	2,255	5%
Obesity	2,015	5%
Coronary artery disease	1,970	5%
Depression	1,960	5%
Anxiety	1,607	4%

Table 16-79 Most Frequent Reported Concomitant Medications >=2% (Cumulative period)

Medical History	Cases	Percent
Total Unique Cases	42,652	100%
Non-Documented Cases	34,620	81%
METFORMIN	1,462	3%
ATORVASTATIN	1,344	3%
LISINOPRIL	1,116	3%
METOPROLOL	759	2%
AMLODIPINE	665	2%

Subpopulation Analyses

Frail Population Children < 12 years

During the reporting period, there were 9 cases (20 events) in the frail subpopulation in age group < 12 years, of which 5 cases were serious, none had a fatal outcome and 7 were medically confirmed. Six of the 9 cases were reported in the context of maternal exposure and are discussed in the pregnancy and lactation Section 16.3.5.1 and Section 16.3.5.2. The other 3 cases (4.1(b) , 4.1(b) and 4.1(b)) likely represent an error in age capture based on details in case narrative, medical history or concomitant medications reported.

Frail Population Children 12-17 years

During the reporting interval, there were 40 cases (137 events), of which 21 were serious, 1 had a fatal outcome and 21 were medically confirmed. The most frequently reported medical history in these frail adolescents was asthma in 13 of the 21 serious cases. Of the serious cases in frail adolescents the top PTs were dyspnea, myocarditis, and pyrexia (5 events; 6.0% each), followed by chest pain (4 events; 4.8%).

It is of note that all 5 cases reporting dyspnoea had a medical history of dyspnoea while three of the 5 reporting myocarditis had relevant medical history of myocarditis (in 2 cases) or cardiomyopathy (in 1 case).

The fatal case (4.1(b) [redacted]) described myocarditis in a 17-year-old male with a medical history of cardiomyopathy. Please see Section 16.3.1.2 on Myocarditis for more information.

Frail Patients After a Third Dose or Booster Dose of SPIKEVAX

During this reporting period, there were 1,613 cases (7,706 events), reported after SPIKEVAX booster dose of which 950 cases (58.9%) were serious, 67 cases (4.1%) had a fatal outcome and 744 (46.1%) were medically confirmed. All cases were reported after dose 3 except for one serious case (with 4 events) after dose 4.

Of these, 950 serious cases (5,177 events), gender distribution was 36.8% male and 62.3% female, and 0.8% missing. Distribution by age was highest (38.0%) among the elderly (65 years and older). The median age was 59.0 (min 0.9/ max 101.0) with an average age of 58.8 years (SD:17.8).

The most frequently reported event terms after 3rd SPIKEVAX dose in the frail subpopulation (Table 16-80) were in line with expected reactogenicity with SPIKEVAX and similar to those reported in the immediate period after Dose 1 and 2. Most frequently reported events had a time to onset of less than 3 days (62.0 %) after 3rd dose in the frail population. There were 4 events after the 4th dose occurring on same day as SPIKEVAX dose.

Table 16-80 Most Frequently Reported Event Terms after 3rd SPIKEVAX Dose in the Frail Population >=2%

PT	# Events	% of Total Events
Pyrexia	290	3.8%
Headache	281	3.6%
Fatigue	237	3.1
Chills	179	2.3%
Nausea	175	2.3%
Pain in extremity	167	2.2%
Myalgia	154	2.0%

Of these, 950 serious cases (5,177 events) after 3rd dose in the frail subpopulation, occurring after 3rd SPIKEVAX dose in the frail subpopulation, gender distribution was 36.8% male and 62.3% female, and 0.8% missing. Distribution by age was highest (38.0%) among the elderly (65 years and older). The median age was 59.0 (min 0.9/ max 101.0) with an average age of 58.8 years (SD:17.8). Most events (70.8%) in serious cases after 3rd dose were reported to have occurred less than 5 days post vaccination.

Events outcomes in serious cases in the frail subpopulation were most frequently reported as Not recovered (42.9%) followed by recovered (23.5%) and recovering. There were 4 events reported after dose 4 and they all had an unknown outcome (Table 16-81).

Table 16-81 Most Frequently Reported Event Terms in Serious cases after 3rd SPIKEVAX Dose in the Frail Population >=2% Reporting Period

PT	# Events	% of Total Events
Pyrexia	194	3.7%
Headache	172	3.3%
Fatigue	158	3.1%
Nausea	114	2.2%
Dyspnoea	108	2.1%

Fatal cases after Third Dose or Booster Dose of SPIKEVAX

There were 67 fatal cases reported after the 3rd SPIKEVAX dose with a mean age of 77.4 (SD 12.7) and median of 77.0 (min:39.0/max: 101.Most of the cases (83.6%), occurred in elderly 65 years and older. The most frequently reported event term in these cases were Death (11.4%), Unresponsive to stimuli (2.2%), Dyspnoea (1.9%) and COVID-19 (1.6%). Most of the events in these fatal cases occurred less than 5 day after SPIKEVAX, followed by the 14-29-day period.

16.3.5.6.5. Discussion

The general pattern of commonly reported adverse events in the frail subpopulation is comparable to those in the general population, but especially the elderly. This is to be expected, as the elderly comprise a significant portion of the frail population (42.4% reporting period). These events reflect expected reactogenicity and COVID-19 related terms. Most events, as also seen in the general population, were clustered after each dose in the period less than 5 days after vaccination. The period 30+ days after dose 2 had the most reported events, likely due to the large time span allowing for development of co-incidental events. Similar to observations in the elderly, many (77.4%) of the events in serious COVID-19 cases occurred in a time frame suggestive of vaccine failure (14 days or more after 2nd dose). Patients with comorbidities that qualify as frailty may be more susceptible to serious, including fatal. COVID-19 disease, due to inadequate immune response, waning immunity, or emergence of variant strains.

The increase in booster dose in this population is likely contributory to the decrease in COVID-19 ranking discussed above.

The most frequently reported events terms in serious cases in the frail population closely match that seen in the elderly. Age and frailty are correlated, with percentages rising with age. The

percentage of fatal cases in the frail population (6.7%) is mostly attributable (in 76.5% of cases) to the elderly (65 years and older) with the same top 3 event terms in these cases.

Serious cases in frail adolescents most frequently reported events confounded by their underlying medical conditions (respiratory or cardiac).

Case reports after a third or booster vaccine dose has increased as expected with an uptake in administration in many countries.

The adverse event profile reported after Dose 3 in the frail subpopulation is in line with that seen in the general population and noted to be of similar reactogenicity events and similar time to onset profile as after dose 1 and 2.

16.3.5.6.6. Conclusion

Based on the analysis of all the safety data received during the reporting period of this PBRER, ModernaTX, Inc considers that events in the frail subpopulation reported in temporal association with the administration of SPIKEVAX, did not raise any safety issue of concern. ModernaTX, Inc will continue to monitor events in the frail subpopulation using routine surveillance. The benefit-risk evaluation remains positive.

16.3.5.7. Use in Patients with Autoimmune or Inflammatory Disorders

16.3.5.7.1. Source of the New Information

Information presented below includes analyses performed on cases from the subpopulation with known history of autoimmune and inflammatory disorders (MedHx AI/ID) received by ModernaTX, Inc. from 01 Jul 2021 to 31 Dec 2021 for the mRNA-1273 vaccine (COVID-19 vaccine Moderna) SPIKEVAX. Cumulatively, the data reviewed covers the period from 18 Dec 2020 to 31 Dec 2021.

16.3.5.7.2. Background Relevant to the Evaluation

Use of SPIKEVAX in individuals with autoimmune and inflammatory disorders (AI/ID) is an area of missing information in the Risk Management Plan (RMP). There are limited data from clinical trials on the use of SPIKEVAX in individuals with autoimmune and inflammatory disorders, as those requiring immunosuppressive treatments were excluded. Thus, ModernaTx is closely monitoring the safety profile of SPIKEVAX in this population through routine pharmacovigilance. In general, public health and professional groups recommend COVID vaccination for patients with autoimmune or inflammatory disorders (AI/ID). These recommendations highlight the likely potential benefits of COVID vaccines in this population with the potential risk of more severe COVID infections, sequelae, and impact on underlying immune mediated diseases [75-78].

As noted in the PBRER#1 (covered period: 18 Dec 2020 – 30 Jun 2021; submission date: 26 Aug 2021), exacerbation of autoimmune conditions can be related to inflammation caused by infections. It is theoretically possible that exacerbation could be related to the immune response to many vaccines, including mRNA COVID vaccines [79-81]. For this PBRER#2, ModernaTx conducted an evaluation of potential "conditions aggravated"/flares, a topic that remains under continued monitoring through routine pharmacovigilance.

Of note, those individuals with autoimmune and inflammatory disorders (AI/ID) may be on immunosuppressive medications, which may reduce the immunogenicity and efficacy of the vaccine and may be a risk factor for more severe COVID-19 disease [82,83]. (Note, those AI/ID cases of patients who are on immunosuppressive therapy included in this section, are also included and overlap with the immunocompromised section of this PBRER (See the Section 16.3.5.4 on "Use in Immunocompromised Subjects" and Section 16.3.6.8.6 "Vaccine Failure").

16.3.5.7.3. Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

Identification of Case Reports in Moderna Global Safety Database:

The ModernaTx global safety database (GSDB) was queried for valid, clinical, and spontaneous case reports for SPIKEVAX in people with a medical history of autoimmune and/or inflammatory disease (hereafter referred to as “MedHx AI/ID”), received from health care providers, health authorities, consumers, and literature, for the review period (01 July 2021 – 31 Dec 2021) and cumulatively (18 December 2020 – 31 December 2021).

Reports from individuals with a MedHx AI/ID were identified from ModernaTx global safety database using the Immune-mediated/autoimmune disorders Standard MedDRA Query (SMQ) "Immune-mediated/autoimmune disorders SMQ" Preferred Terms (PTs) identified in past medical history.

Data for this MedHx AI/ID subpopulation was also compared to the general population. The “General Population” (all SPIKEVAX data in the ModernaTx Global Safety Database) refers to safety data for all medical topics/areas captured in all safety case reports (all cases and events from all individuals) within the SPIKEVAX Global Safety Database.

Subsections describe MedHx AI/ID data for all, serious and fatal cases, as well as for adolescent and Dose 3/4.

See: *Methodology for AI/ID Potential Flares* (in the Flares Section below)

Literature Methodology: The MAH has been reviewing literature for the MedHx AI/ID subpopulation and SPIKEVAX in the monthly MSSRs. In general, the articles conclude that the

vaccine is safe, well-tolerated and has a favorable benefit/risk profile. Although flares continue to be reported in articles, there is limitation to interpretation given the natural course of the diseases and the lack of background or controlled unvaccinated flare rates, authors conclude that the benefit of vaccination outweighs the potential risk of flares which are responsive to treatment. To date, literature has not presented sufficient evidence to identify or quantify definitively increased risks, significant safety concerns or changes to the benefit/risk profile. In addition, many of the articles describe research regarding the immunogenicity for AI/ID patients on immunosuppressant therapy. These articles have demonstrated that some treatments (e.g., B-cell depleting Rx, steroids, JAK inhibitors, antimetabolites, and TNF inhibitors; https://rheum-covid.org/covaripad-summary/) may cause reduced immunogenicity, and the clinicians are advised to consider options for possible adjustments of treatments prior to vaccination, or the timing of vaccination (especially related to infusion therapy). In many countries, severely immunosuppressed patients are recommended to receive a third dose in the priming series and a fourth/booster dose. Despite the acknowledged potential for reduced immunogenicity, the literature supports the use of COVID vaccines in the AI/ID immunosuppressed populations.

For the in-depth subsections for possible AI/ID flares below, the following literature search strategy was applied, and articles were reviewed, and selected; relevant articles are summarized and discussed in the respective sections. (Note, previously some articles have been presented and discussed in the 2021 MSSRs.)

Literature Search strategy: A targeted literature search for relevant publications on Rheumatoid arthritis, Multiple sclerosis, Myasthenia gravis, Systemic lupus erythematosus, Ulcerative colitis, Crohn's disease and mRNA COVID vaccines was conducted using PubMed of the National Library of Medicine (PubMed NLM) (covering the period from 01 July 2021 to 31 December 2021) and Google Scholar and applying the following search terms: Rheumatoid Arthritis, Myasthenia gravis, Myasthenia gravis crisis, Myasthenic syndrome, Multiple sclerosis, Multiple sclerosis relapse, Relapsing multiple sclerosis, secondary progressive multiple sclerosis, Lupus nephritis, Lupus pneumonitis, Systemic lupus erythematosus, Systemic lupus erythematosus rash, Colitis ulcerative, Acute hemorrhagic ulcerative colitis, Crohn's disease, Inflammatory bowel disease, mRNA COVID vaccination, mRNA-1273, mRNA 1273, mRNA1273, ModernaTx 1273, ModernaTx 1273, Moderna Covid19 Vaccine, SPIKEVAX.

16.3.5.7.4. Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Overview of Cases (MedHx AI/ID):

Cumulatively, there were 15,229 cases (of which 4,692 were serious, and 241 were fatal) with 74,645 events (of which 17,907 were serious) in people with a history of autoimmune or

inflammatory disorders (MedHx AI/ID). Of the 15,229 cumulative cases, a total of 11,153 cases were medically confirmed. A breakdown of the 15,229 cases reported by sex was 12,475 females (81.9%), 2,624 males (17.2%), and 130 (0.9%) sex unknown (missing information). The number of reports from females is notably higher than from males, which is consistent with the background epidemiology, as many autoimmune or inflammatory diseases are more common in females. The mean age was 53.7 years (SD: 16.1), median age was 54.0 years, and 367 cases were missing age information (Table 16-83).

During this review period, there were 4,728 cases (of which 2,480 were serious, and 113 were fatal) with 24,011 events (of which 11,410 were serious) identified using the search criteria for people with a history of autoimmune or inflammatory disorders (MedHx AI/ID). In the reporting period, 2,351 cases were medically confirmed. Of the total cumulative cases, 31.0% were reported during this PBRER reporting period. The gender breakdown of cases was 3,528 females (75.8%), 1,080 males (22.8%) and 66 (1.4%) were missing gender data. The mean age was 52.0 years (SD 16.5) and the median age was 52.0; Table 16-82 presents age group distribution (years) of the cases during the reporting period.

[Note that cumulatively, a total of 1,421 cases (of which 548 were serious and 32 were fatal) overlap between the MedHx AI/ID and the immunocompromised/immunosuppressed populations, as many people with AI/ID are taking immunosuppressive therapies. During the review period, 559 cases (of which 304 were serious and 16 were fatal) overlapped. (Please also refer to the Section 16.3.5.4 on Use in immunocompromised patients)].

The age distribution of all MedHx AI/ID cases for the review period is generally comparable to the cumulative distribution. More reports are from females, which is consistent with the general trend in the safety database for the general population, as well as consistent with the autoimmune/inflammatory disease population, as some common autoimmune diseases are more frequent in females.

Table 16-82 Case Distribution by Gender and Age Group in the MedHx AI/ID Subpopulation (Reporting Period)

Age Group	Female		Male		Unknown		# Cases	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases	# Cases	% of Total Cases		
<2*	0	0	1	0.0%	0	0	1	0.0%
12-15**	2	0.0%	1	0.0%	0	0	3	0.1%
16-17**	3	0.1%	2	0.0%	0	0	5	0.1%
18-29	297	6.3%	112	2.4%	1	0.0%	410	8.7%
30-39	588	12.4%	149	3.2%	2	0.0%	739	15.6%

Age Group	Female		Male		Unknown		# Cases	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases	# Cases	% of Total Cases		
40-49	730	15.4%	152	3.2%	5	0.1%	887	18.8%
50-64	1031	21.8%	287	6.1%	13	0.3%	1331	28.2%
65-74	532	11.3%	216	4.6%	6	0.1%	754	15.9%
75+	273	5.8%	127	2.7%	3	0.1%	403	8.5%
Missing	126	2.7%	33	0.7%	36	0.8%	195	4.1%
Grand total	**3,582**	**75.8%**	**1,080**	**22.8%**	**66**	**1.4%**	**4,728**	**100.0%**

* This is a case of a neonate born with congenital hydronephrosis, and the mother had rheumatoid arthritis
**Please refer to the Subsection on Adolescents 12-17 years of age.

Table 16-83 Case Distribution by Gender and Age Group in the MedHx AI/ID Subpopulation (Cumulative)

Age Group	Female		Male		Unknown		# Cases	of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases	# Cases	% of Total Cases		
<2*	0	0	1	0.0%	0	0	1	0.0%
12-15**	2	0.0%	4	0.0%	0	0	6	0.0%
16-17**	19	0.1%	7	0.0%	0	0	26	0.2%
18-29	824	5.4%	208	1.4%	3	0.0%	1035	6.8%
30-39	1893	12.4%	311	2.0%	3	0.0%	2207	14.5%
40-49	2452	16.1%	350	2.3%	8	0.1%	2810	18.5%
50-64	3639	23.9%	685	4.5%	24	0.2%	4348	28.6%
65-74	2357	15.5%	616	4.0%	14	0.1%	2987	19.6%
75+	1046	6.9%	391	2.6%	5	0.0%	1442	9.5%
Missing	243	1.6%	51	0.3%	73	0.5%	367	2.4%
Grand total	**12,475**	**81.9%**	**2,624**	**17.2%**	**130**	**0.9%**	**15,229**	**100.0%**

* This is a case of a neonate born with congenital hydronephrosis, and the mother had rheumatoid arthritis
**Please refer to the Subsection on Adolescents 12-17 years of age.

Many of the most frequently reported events (pyrexia, fatigue, headache, chills, myalgia, nausea and arthralgia) in the review period as well as cumulatively, represent expected reactogenicity following SPIKEVAX, and are seen in both the MedHx AI/ID subpopulation and in the general population (Table 16-84). One challenge is to differentiate some of the signs and symptoms of reactogenicity from potential flares, as fatigue, myalgia, arthralgia, and fever are common in both. Here the review of the narrative, additional pathognomonic signs/symptoms, duration, severity, treatment, and diagnostics are considered in case review.

Of note, during the review period, COVID-19 was the 12th most frequently reported event in the MedHx AI/ID subpopulation and the 15th most frequently reported event in the general population; while cumulatively, COVID-19 was the 35th most frequently reported event in the MedHx AI/ID subpopulation and 30th in the general population. This increased relative frequency of COVID-19 adverse event (AE) reports during the reporting period may reflect the decreased immunogenicity of vaccination and/or the susceptibility to more severe disease seen in the MedHx AI/ID subpopulation, as well as waning immunity and changes in the epidemiology (including new variants), policies, and behavior.

Table 16-84 Top Events by Preferred Term (PT) During Reporting Period vs. Cumulative, Comparing MedHx AI/ID Subpopulation to the General Population

Reporting Period						Cumulative					
MedHx AI/ID Subpopulation			General Population			MedHx AI/ID Subpopulation			General Population		
PT	#	%	PT	#	%	PT	#	%	PT	#	%
Pyrexia	960	4.0%	Pyrexia	44,460	6.2%	Headache	3,209	4.3%	Headache	89,454	5.4%
Fatigue	944	3.9%	Headache	40,502	5.7%	Fatigue	3,084	4.1%	Pyrexia	89,235	5.4%
Headache	925	3.9%	Fatigue	35,142	4.9%	Pyrexia	2,931	3.9%	Fatigue	76,889	4.7%
Nausea	576	2.4%	Myalgia	26,841	3.7%	Chills	2,213	3.0%	Chills	62,451	3.8%
Myalgia	559	2.3%	Chills	24,215	3.4%	Nausea	2,000	2.7%	Myalgia	54,167	3.3%
Chills	518	2.2%	Malaise	21,513	3.0%	Pain	1,969	2.6%	Nausea	45,937	2.8%
Arthralgia	469	2.0%	Nausea	19,187	2.7%	Pain in extremity	1,843	2.5%	Pain in extremity	39,365	2.4%
Pain in extremity	450	1.9%	Injection site pain	17,623	2.5%	Myalgia	1,525	2.0%	Injection site pain	38,764	2.3%
Dyspnoea	444	1.8%	Vaccination site pain	16,031	2.2%	Arthralgia	1,471	2.0%	Malaise	36,335	2.2%
Dizziness	373	1.6%	Arthralgia	15,564	2.2%	Dizziness	1,355	1.8%	Pain	34,007	2.1%

Serious Cases and Events

Cumulatively, there are 4,692 cumulative serious cases, 17,905 serious events, and 3,350 cases were medically confirmed. Demographical distribution included 3,399 cases (72.4%) reported for females, 1,238 cases (26.4%) reported for males, and 55 (1.2%) with missing sex data. The mean age was 54.7 years (SD: 16.9) and a median age of 55.0 years. The highest percentages of cases occurred in those 50-64 years (28.5%), followed 65-74 years (18.1%), 40-49 years (16.9%), 30-39 years (13.6%),75 years or older (12.5%), and 18-29 years (7.3%)

During the review period, there are 2,480 serious cases, 11,049 serious events, and 1,508 cases were medically confirmed. Demographical distribution included 1,776 cases (71.6%) reported for females, 671 cases (27.1%) reported for males, and 33 (1.3%) with missing sex data. The mean age was 53.1 years (SD: 17.0) and a median age of 53.0 years. The highest percentages of cases occurred in those 50-64 years (28.1%), followed by 40-49 years (17.7%), 65-74 years (16.6%),

30-39 years (14.7%), 75 years or older (10.2%), and 18-29 years (8.5%).

The most frequently reported serious events in the MedHx AI/ID population during this review period, as well as cumulatively, reflect expected reactogenicity events, such as pyrexia, fatigue, headache, dyspnoea, nausea, and chills. These events were generally comparable to the most frequently reported serious events in the general population both during this review period and cumulatively (Table 16-85). Of note, during this review period, COVID-19 is the 6th most frequently reported serious event in both the MedHx AI/ID subpopulation and in the general population. When looking at the event of COVID-19 cumulatively, it is the 6th most frequently reported serious event in the MedHx AI/ID subpopulation and the 8th most frequently reported serious event in the general population; although here it must be noted that a substantial proportion of the COVID-19 cases are reported during the reporting period (230/271= 84.9% for the AI/ID population and 4,279/4,992= 85.7% for the general population). Thus, COVID-19 adverse event reports were notably higher in this reporting period as described above.

Also, of note, in the MedHx AI/ID subpopulation, the PT, "Condition aggravated", is the 8th most frequently reported serious event both during the review period and cumulatively. (See sections below on AI/ID conditions aggravated/flares.)

Table 16-85 Top 10 Serious Events by Preferred Terms (PT) During Reporting Period vs. Cumulative, Comparing MedHx AI/ID Subpopulation to the General Population

Reporting Period - Serious Events						Cumulative - Serious Events					
MedHx AI/ID Subpopulation			General population			MedHx AI/ID Subpopulation			General Population		
PT	#	%*	PT	#	%*	PT	#	%*	PT	#	%*
Pyrexia	386	3.4%	Pyrexia	9,110	4.6%	Pyrexia	533	3.0%	Pyrexia	11,519	4.0%
Fatigue	346	3.0%	Headache	8,311	4.2%	Fatigue	469	2.6%	Headache	10,334	3.6%
Headache	326	2.9%	Fatigue	6,922	3.5%	Headache	448	2.5%	Fatigue	8,783	3.0%
Dyspnoea	283	2.5%	Nausea	4,881	2.5%	Dyspnoea	440	2.5%	Dyspnoea	6,374	2.2%
Nausea	245	2.1%	Chills	4,727	2.4%	Nausea	337	1.9%	Nausea	6,371	2.2%
COVID-19	230	2.0%	COVID-19	4,279	2.2%	COVID-19	271	1.5%	Chills	5,985	2.1%
Chills	195	1.7%	Dyspnoea	4,246	2.2%	Chills	270	1.5%	Syncope	5,617	1.9%
Condition aggravated	166	1.5%	Myalgia	3,820	1.9%	Condition aggravated	255	1.4%	COVID-19	4,992	1.7%
Dizziness	158	1.4%	Dizziness	3,441	1.7%	Asthenia	246	1.4%	Myalgia	4,866	1.7%
Arthralgia	157	1.4%	Pain in extremity	3,306	1.7%	Dizziness	231	1.3%	Dizziness	4,743	1.6%

* "%" refers to percentage of serious events, not serious cases

Fatal Cases and Events

Out of the 241 cumulative fatal cases containing 922 events, 229 cases were medically confirmed; 130 cases (53.9%) were in females, 110 cases (45.6%) were in males, and 1 case (0.4%) was missing sex data. The mean age of 67.9 years (SD: 15.5), and the median age was 70.0 years (range: 18 to 100 years). Of the 241 fatal cases, 37.8% occurred in those 75 years or older, 28.6% in 65-74-year-olds, and 21.2% in 50-64-year-olds, 5.4% in 40-49-year-olds, 5.4% in 30-39-year-olds, and 1.7% in 18-29-year-olds, and the majority had multiple comorbidities. Of the 241 fatal cases, 171 occurred in "frail" persons defined by comorbidities and age.

During the reporting period, out of the 113 fatal cases containing 558 events, 108 cases were medically confirmed; 57 cases (50.4%) were in females, 55 cases (48.7%) were in males, and 1 case (0.9%) was missing sex data, with a mean age of 65.2 years (SD: 16.2). The median age was 68.0 years (range: 18 to 100 years). Of the 113 fatal cases, 31.9% occurred in those 75 years or older, 27.4% in 65-74-year-olds, and 23.9% in 50-64-year-olds, 8.0% in 30-39-year-olds, 7.1% in 40-49-year-olds, and 1.8% in 18-29-year-olds, and the majority had multiple comorbidities. Of the 113 fatal cases, 76 occurred in "frail" persons defined by comorbidities and age.

Comorbidities reported in fatal cases include AI/ID and non-AI/ID conditions. Rheumatoid arthritis is the second most common past medical history/comorbidity reported in the MedHx AI/ID subpopulation, which reflects that higher background prevalence of RA; while other more common comorbid conditions such as hypertension, Type 2 diabetes mellitus, chronic obstructive pulmonary disease (COPD), hyperlipidemia, and chronic kidney disease are similar to those reported in the general population fatal reports.

In fatal cases, the most frequently reported events/PTs coded as "fatal" in the MedHx AI/ID cases were generally similar to those reported cumulatively, with slight differences in frequencies and rank. In both the MedHx AI/ID subpopulation as well as in the general population, COVID-19 is the 2nd most frequently reported event cumulatively and during this review period, with the majority of cases being reported during the reporting period (Table 16-86). The event of COVID-19 pneumonia is also in the top 10 most frequently reported events reported the during the review period and cumulatively, for both the MedHx AI/ID subpopulation and the general population, again (as mentioned in the serious cases section) most cases are from the reporting period. For the MedHx AI/ID subpopulation, "Condition aggravated" appears as the 5th most frequent PT terms for fatal events during the review period as well as cumulatively.

Note: some events are coded as fatal in the database, although may not be the cause of death, and thus must be interpreted with caution; these may simply represent events that occurred in a fatal case.)

Table 16-86 Most Frequently Reported Fatal Events_by Preferred Term (PT) in Fatal Cases in MedHx AI/ID Subpopulation vs. General Population (Reporting Period and Cumulative)

Reporting Period						Cumulative					
MedHx AI/ID Subpopulation			General Population			MedHx AI/ID Subpopulation			General Population		
PT	#	%	PT	#	%	PT	#	%	PT	#	%
Death	47	8.4%	Death	1,077	12.0%	Death	108	11.7%	Death	2,723	18.0%
COVID-19	38	6.8%	COVID-19	537	6.0%	COVID-19	45	4.9%	COVID-19	651	4.3%
Dyspnoea	22	3.9%	Dyspnoea	296	3.3%	Dyspnoea	31	3.4%	Dyspnoea	476	3.1%
Acute respiratory failure	13	2.3%	Cardiac arrest	172	1.9%	Cardiac arrest	17	1.8%	Cardiac arrest	379	2.5%
Condition aggravated	11	2.0%	Pyrexia	166	1.9%	Condition aggravated	15	1.6%	Pyrexia	264	1.7%
Pyrexia	11	2.0%	SARS-CoV-2 test positive	149	1.7%	Pyrexia	15	1.6%	Asthenia	193	1.3%
Respiratory failure	11	2.0%	COVID-19 pneumonia	138	1.5%	Respiratory failure	15	1.6%	Unresponsive to stimuli	190	1.3%
COVID-19 pneumonia	10	1.8%	Cough	128	1.4%	Acute respiratory failure	14	1.5%	COVID-19 pneumonia	180	1.2%
Fatigue	8	1.4%	Asthenia	116	1.3%	COVID-19 pneumonia	14	1.5%	Myocardial infarction	171	1.1%
SARS-CoV-2 test positive	8	1.4%	Pneumonia	110	1.2%	Hypoxia	11	1.2%	Pneumonia	171	1.1%

While there are confounding factors and comorbidities described in most of the fatal cases, causality cannot always be excluded given the temporal association; however, there were no identified concerning or unusual/unexpected patterns of deaths. There is insufficient evidence to establish an increased risk of death after vaccination in the AI/ID population. Refer to Section 16.3.6.8.7) (Elderly), (Section16.3.5.6) (Frail), and Section 16.3.6.8.2 (Fatalities).

Use in Patients with Autoimmune or Inflammatory Disorders (Children < 12 Years of Age)

Cumulatively, 1 case was reported in the age group of 0-11 years old. This case, 4.1(b) [redacted], describes the occurrence of congenital hydronephrosis in a male fetus exposed via maternal vaccination. The mother's medical history included rheumatoid arthritis. Thus, there are no reports for vaccinated children under 12 with AI/ID medical history.

Use in Patients with Autoimmune or Inflammatory Disorders (Adolescents 12-17 Years of Age)

Currently, there are still limited data for the MedHx AI/ID adolescent population. The MAH continues to monitor adolescent MedHX AI/ID reports through routine pharmacovigilance.

Cumulatively, there are 32 cases (6 serious cases, and 0 fatal cases) in adolescents 12-17 years of age in the MedHx AI/ID subpopulation. Twenty-nine (29) of the 32 cases are medically confirmed. Within the 32 cases, there are 56 events (10 serious events). There were 11 cases (34.4%) in males, and 21 cases (65.6%) in females, and none with missing sex data. The mean age is 16.0 years (SD 1.5), median age of 17.0 (min 12.0, max 17.0) and none with missing age data. Six (6) cases (18.8%) were reported for 12-15-year-olds, and 26 cases (81.3%) were for 16-17-year-olds.

During this review period, there were 8 cases (5 serious) in adolescents 12-17 years of age in the MedHx AI/ID subpopulation. There were no fatal cases. Five (5) cases were medically confirmed. Within the 8 cases, there were 16 events (of which 8 were serious). Five (5) cases were female (62.5%) and 3 cases were male (37.5%). The mean age was 15.4 years (SD 1.7) and the median age was 16.0 years (min 12.0, max 17.0).

The table below (Table 16-87) summarizes the distribution of autoimmune conditions in the past medical history in the adolescent population with autoimmune/inflammatory disorders.

Table 16-87 MedHx AI/ID Adolescent (12-17-year-old) Subpopulation: AI/ID Medical Conditions

Medical History	# Cases	% of Total Cases
"Diabetes mellitus (DM) [Type 1 DM (n=7), and "DM/autoimmune disorder" (n=2)]"	9	28%
Autoimmune disorder	5	16%
Systemic lupus erythematosus	4	13%
Coeliac disease	3	9%
Autoimmune thyroiditis	2	6%
Colitis ulcerative	2	6%
Crohn's disease	2	6%
Antiphospholipid syndrome	1	3%
Juvenile idiopathic arthritis	1	3%
Kawasaki's disease	1	3%
Myasthenia gravis	1	3%
Psoriasis	1	3%
Raynaud's phenomenon	1	3%
Rheumatoid arthritis	1	3%
Vitiligo	1	3%

Cumulatively, 26 (46.4%) of the events reported for 12-17-year-olds were "Product administered to patient of inappropriate age". The majority (19 of the 26) of the cases describe either medication errors or expected reactogenicity. Individual serious cases of interest include, Myocarditis (4.1(b)

4.1(b) and 4.1(b)), Erythema multiforme (4.1(b)), Multisystem inflammatory syndrome in children (4.1(b)), and Myasthenia gravis/Condition aggravated (4.1(b)) and have been described in previous monthly reports. (See section below on MG Flares.)

Use in Patients with Autoimmune or Inflammatory Disorders (Patients Receiving SPIKEVAX Dose 3 or Dose 4)

Currently limited data are available on the third and fourth doses in MedHx AI/ID individuals, and the MAH is monitoring the safety through routine pharmacovigilance and literature review. The data presented in this section represent combined data for third and fourth doses of SPIKEVAX in MedHx AI/ID Subpopulation individuals. These data should be interpreted with caution as it is difficult to determine if the 3rd dose administered was 100 mcg (3rd dose of the priming series, used in AI/ID patients who are on significant immunosuppressive therapy) or a 50 mcg (booster dose) in this population.

Cumulatively, for those receiving Dose 3 or Dose 4 of SPIKEVAX in the MedHx AI/ID subpopulation, there were 789 cases of which 480 were serious, and 12 were fatal. Within the 789 cumulative cases, there were 3,393 events (of which 1,920 were serious). It should be noted that all but 4 cases were received during the review period. Additionally, of the cumulative 789 cases, only one (1) Dose 4 case has been received, thus, in the data presented in this section, all except one case refer to Dose 3. And as noted, per the reports, dosage (50 vs 100 micrograms) is usually not known/reported, and thus there is limited ability to differentiate a third dose of the priming series (100 mcg) versus a third booster dose (50 mcg).

A breakdown of the 789 cases reported by gender was: 166 males (21.0%), 604 females (76.6%), and 19 (2.4%) missing sex data, with a mean age of 54.3 years (SD: 15.8) and a median age of 55.0 years (min 16/ max 100), with 50 cases missing age information. Events were reported most frequently in those aged 50-64 years, both during the review period and cumulatively (Table 16-88).

Table 16-88 Case Distribution by Gender and Age Group in the MedHx AI/ID Subpopulation in Patients Receiving Dose 3 or Dose 4 of SPIKEVAX (Cumulative)

Age Group (Years)	Female		Male		Unknown		Total # of Cases	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases	# Cases	% of Total Cases		
16-17	1	0.1%	0	0	0	0	1	0.1%
18-29	40	5.1%	13	1.6%	0	0	53	6.7%
30-39	78	9.9%	15	1.9%	0	0	93	11.8%

Age Group (Years)	Female		Male		Unknown		Total # of Cases	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases	# Cases	% of Total Cases		
40-49	99	12.5%	24	3.0%	5	0.6%	128	16.2%
50-64	193	24.5%	50	6.3%	2	0.3%	245	31.1%
65-74	111	14.1%	34	4.3%	1	0.1%	146	18.5%
75+	44	5.6%	26	3.3%	3	0.4%	73	9.3%
Missing	38	4.8%	4	0.5%	8	1.0%	50	6.3%
Grand total	**604**	**76.6%**	**166**	**21.0%**	**19**	**2.4%**	**789***	**100.0%**

*With the exception of 4 cases, all cases were received during the review period.

Cumulatively, and during the review period, the most frequently reported MedDRA PTs for Dose 3 events reported for the MedHx AI/ID subpopulation are reflective of expected reactogenicity seen in the primary series of SPIKEVAX and were comparable to the general population (Table 16-89).

Table 16-89 Top 10 Preferred Terms (PT) for MedHx AI-ID Subpopulation vs. General Population (Dose 3 or Dose 4 SPIKEVAX) (Cumulative)

MedHx AI/ID Subpopulation			General Population		
PT	# Events	% of Total Events	PT	# Events	% of Total Events
Pyrexia	160	4.7%	Headache	3,300	6.1%
Headache	136	4.0%	Pyrexia	2,965	5.5%
Fatigue	121	3.6%	Fatigue	2,290	4.2%
Nausea	96	2.8%	Chills	1,911	3.5%
Chills	94	2.8%	Nausea	1,795	3.3%
Pain in extremity	91	2.7%	Expired product administered	1,794	3.3%
Myalgia	86	2.5%	Myalgia	1,599	3.0%
Arthralgia	82	2.4%	Pain in extremity	1,535	2.8%
Dyspnoea	58	1.7%	Arthralgia	1,278	2.4%
Pain	55	1.6%	Dizziness	1,012	1.9%

Serious Events (Patients Receiving SPIKEVAX Dose 3 or Dose 4)

While slightly different frequencies and rank order were noted, serious events reported in the MedHx AI/ID subpopulation that have received Dose 3 of SPIKEVAX were comparable to the general population for the reporting period and cumulatively and are reflective of expected reactogenicity (Table 16-90).

The cumulative top PTs for serious events reported for the MedHx AI/ID subpopulation did not present a medically significant varying pattern from that of the general population.

Table 16-90 Top 10 Serious Preferred Term (PT) for MedHx AI/ID Subpopulation vs. General Population (Dose 3 or Dose 4 SPIKEVAX) (Cumulative)

Cumulative - Serious Events					
MedHx AI/ID Subpopulation			General Population		
PT	#	%*	PT	#	%*
Pyrexia	89	4.6%	Headache	2,154	7.1%
Headache	85	4.4%	Pyrexia	1,947	6.5%
Fatigue	59	3.1%	Fatigue	1,496	5.0%
Nausea	59	3.1%	Nausea	1,278	4.2%
Arthralgia	50	2.6%	Chills	1,176	3.9%
Chills	46	2.4%	Myalgia	939	3.1%
Pain in extremity	44	2.3%	Arthralgia	837	2.8%
Myalgia	42	2.2%	Pain in extremity	819	2.7%
Dyspnoea	38	2.0%	Dizziness	649	2.2%
Vomiting	34	1.8%	Vomiting	571	1.9%

* "%" refers to percentage of serious events, not serious cases

Potential Flares (Patients Receiving Dose 3 or Dose 4 of SPIKEVAX):

Using the search strategies described in the methodology section, there were 59 potential flare cases identified after Dose 3, none were identified after Dose 4. When looking at AI/ID PTs (representing potential flares) reported after Dose 3, the most frequently reported AI/ID events are 7 cases of multiple sclerosis (MS)/MS relapse, there are 5 cases of rheumatoid arthritis, and there are 4 cases of ulcerative colitis. As there are still limited data, and an absence of data on vaccination administration data for specific AI/ID conditions, the interpretation of these reported AI/ID PTs is reasonably precluded. (Sections below and attached appendices for further description of AI/ID flares.)

Autoimmune and Inflammatory Conditions Aggravated/ Potential Flares

Methodology for AI/ID Potential Flares

ModernaTx applies two complementary, overlapping, combined strategies to review cases of potential flares after vaccination, both of which require caution in interpretation and medical review of the narrative to identify reports of flares:

1. Reports in the MedHx AI/ID subpopulation coded with "condition aggravated", "disease progression", or "disease recurrence" (This requires medical review to identify if the AI/ID condition flared or a non-AI/ID condition (such as migraine) aggravated.)

2. Reports of AI/ID Adverse Events (AEs) (identified using the MedDRA Immune-mediated/autoimmune disorders SMQ) reported in the MedHx AI/ID. [Here there are three types of cases – flares of described pre-existing AI/ID conditions, new onset of AI/ID condition in a subject with a different pre-existing AI/ID conditions (as an individual may have several AI/ID conditions), and lastly coding errors where events are miscoded/misclassified as medical history or AEs]. (Note, this includes reports in patients with MedHX AI/ID coded with AEs coded with the following PTs that were applied in PBRER#1: "Rheumatoid arthritis", "Multiple sclerosis", "Multiple sclerosis relapse", "Relapsing multiple sclerosis", "Secondary progressive multiple sclerosis", "Myasthenia gravis", "Myasthenia gravis crisis" "Myasthenic syndrome", "Lupus nephritis", "Lupus pneumonitis", "Systemic lupus erythematosus", "Systemic lupus erythematosus rash", "Acute hemorrhagic ulcerative colitis", "Colitis ulcerative", and "Crohn's disease")

For this report, the two search strategies have been combined into one data filter, and the section of flares now uses the combined data. Preliminary medical review of the cases further classified these cases. Based on frequency and clinical significance, the MAH performed an in-depth review of the cases of potential flares for: rheumatoid arthritis, myasthenia gravis, multiple sclerosis, systemic (and cutaneous) lupus erythematosus, and inflammatory bowel disease (including Crohn's and ulcerative colitis).

One of the well-known challenges of spontaneous, passive reports is the lack of complete, consistent data. Because of the inconsistent and often incomplete quality of the data, it is difficult to apply international standards/definitions for diagnostic certainty, disease stability prior to the vaccine, and flares/exacerbations of autoimmune/inflammatory disorders. Consequently, the MAH ranked the relative diagnostic certainty of the cases of potential flares based on the data provided and medical judgment using the following scale and considerations:

1. High: a or b
    a. (Signs/symptoms pathognomonic for flare) and (placed on steroids/immunosuppressants/disease specific treatment)
    b. [(HCP assessment/physical exam/diagnosis) or (s/s pathognomonic for flare)] and (laboratory data or radiologic/diagnostic results indicative of a flare or therapeutic procedure for a flare)

    Note: The diagnostic certainty classification are relative categories of cases in the GSDB within the limitations of the data; thus, "high certainty" is descriptive of the relative information of the reported case and does not correlate to a clinical standard of high diagnostic certainty.
2. Medium: Signs and symptoms (pathognomonic for flare)

3. Low: “flare” or AI/ID condition aggravated reported
4. Unassessable: ambiguity in the case; for example, information provided/reported cannot differentiate expected reactogenicity from a true flare
5. Not a flare (new onset of another autoimmune disease, AEs not related to AI/ID, etc.)

In addition, the cases do not consistently provide the severity of the flare and rarely describe the impact on activities of daily living, etc. Here, where available, the MAH notes hospitalizations, life-threatening events, fatalities, and any descriptors that indicate the severity. No available clinical scales of disease activity were applied because the data were not sufficient to support meaningful applications of disease severity to the cases. (Note: some of the literature is able to apply more rigorous clinical scales; however, flares and publications describing cohorts of AI/ID vaccinees and rare flares are often insufficient to inform any general/population rates of flares or severity.)

For the cases with “high”, “medium” and “low” diagnostic certainty, the MAH has applied WHO-UMC causality assessments. Note, causality assessment takes into consideration the time to onset and/or (when available) disease state/stability prior to vaccination, confounding factors (e.g., infection) and alternate etiologies. Additionally, the challenge of applying causality assessment arises as the diseases by nature are relapsing and remitting, and thus in and of themselves are risk factors/etiologies for flares. Positive rechallenges are equally as challenging to apply the standard definition which requires full resolution (often not clearly stated in the reports/narratives) and/or absence of treatment for the adverse event; however, cases were noted that described a “worse flare” after a subsequent dose and, there is no established risk window for AI/ID flares after vaccination. Applying the theoretical biologic plausibility that immune response to infections can trigger flares, and considering the immune response to mRNA vaccination, the MAH looked at risk windows of one to three days (biologically consistent with an innate immune response), and one week to one month (consistent with an adaptive immune response). The exact immune pathophysiological pathway has not been identified, and it must be noted that the range of AI/ID conditions and flares each have unique immune mediator considerations. If the time-to-onset of the flare is not reported, causality was considered unassessable.

Appendices for this section include:

- Appendix 20.11.24 Rheumatoid arthritis flares, case summaries
- Appendix 20.11.25 Rheumatoid arthritis flares, narratives
- Appendix 20.11.26 Multiple sclerosis flares, case summaries
- Appendix 20.11.27 Multiple sclerosis flares, narratives

- Appendix 20.11.28 Myasthenia gravis flares, case summaries
- Appendix 20.11.29 Myasthenia gravis flares, narratives
- Appendix 20.11.30 Systemic lupus erythematous, case summaries
- Appendix 20.11.31 Systemic lupus erythematous, narratives
- Appendix 20.11.32 IBD (including Ulcerative Colitis and Crohn's disease), case summaries
- Appendix 20.11.33 IBD, narratives

Routine surveillance in the MSSRs uses the search strategy for SMQ AI/ID PT terms reported in the population that has a MedHx AI/ID which represents a proxy for potential flares. In addition, cases in the MedHx AI/ID coded with "condition aggravated", "disease progression", and "disease recurrence" are reviewed.

Table 16-91 shows the most frequently reported events by PTs relevant to AI/ID flares.

Table 16-91 Selected, Most Frequently Reported Events by Preferred Terms (PTs) Relevant to AI/ID Flares, by Seriousness (Cumulative)

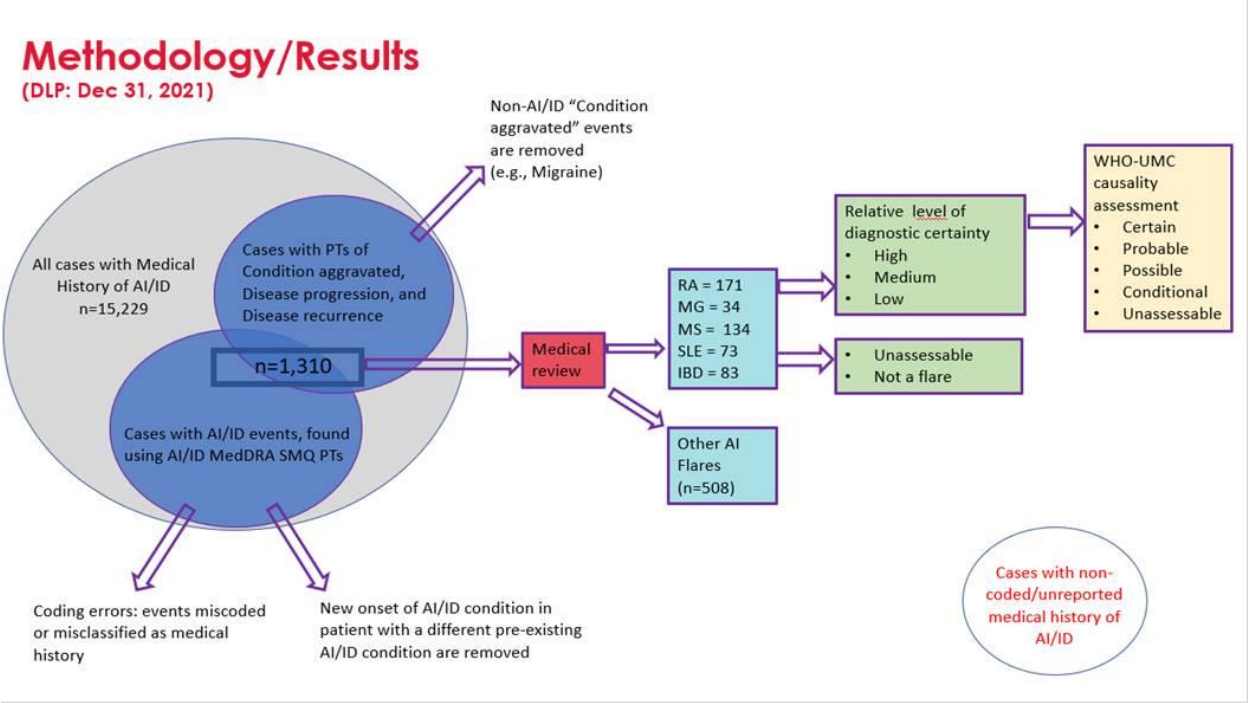
PT	Non-serious		Serious		Total # Events	% of Total Events
	# Events	% of Events	# Events	% of Events		
Condition aggravated	417	4.7%	255	2.8%	672	7.5%
Rheumatoid arthritis	20	0.2%	141	1.6%	161	1.8%
Psoriasis	70	0.8%	17	0.2%	87	1.0%
Colitis ulcerative	7	0.1%	54	0.6%	61	0.7%
Systemic lupus erythematosus	7	0.1%	51	0.6%	58	0.6%
Multiple sclerosis	1	0.0%	56	0.6%	57	0.6%
Multiple sclerosis relapse	0	0	55	0.6%	55	0.6%
Immune thrombocytopenia	3	0.0%	50	0.6%	53	0.6%
Autoimmune disorder	8	0.1%	40	0.4%	48	0.5%
Guillain-Barre syndrome	0	0	38	0.4%	38	0.4%
Myasthenia gravis	3	0.0%	26	0.3%	29	0.3%

Of the 1310 cases of potential flares, 1003 cases were classified as potential AI/ID flares based on preliminary case review, and 307 cases represented non-AI/ID flares (e.g., exacerbations of migraines, hypertension, depression, asthma) or new onset AI/ID.

An in-depth analysis focused on the AI/ID conditions with a higher reporting frequency and/or clinically significant/serious reports includes the events of rheumatoid arthritis (RA) (171 cases), multiple sclerosis (MS) (134 cases), myasthenia gravis (MG) (34 cases), systemic lupus

erythematosus (SLE) (73 cases), and irritable bowel disease (IBD) [83 cases, which includes ulcerative colitis (62 cases), Crohn's disease (14 cases), and unspecified IBD (7 cases)].

As described in "Methods of Evaluation", for the purposes of this PBRER#2, cases of potential flares after vaccination were medically reviewed and classified, with a focus on five groups (RA, MG, MS, SLE, and IBD) selected based on frequency and clinical significance/serious criteria.



Based on a medical review of the narratives, noted aspects included the past medical history (including disease stability prior to vaccination), concomitant medications, signs/symptoms, clinical course/diagnostics, severity, and treatment with steroids and/or immunosuppressant therapy or other interventions, and response/outcome. Post-EUA data including spontaneous and health authority reports are limited in the quality and completeness of the data. Many of these cases are lacking information on disease stability prior to the flare, potential other contributing factors and full clinically relevant information (physical exam, labs, radiology, biopsies, treatment, response, course of flare). These data limitations often preclude robust case and pattern analysis or risk/causality assessment. The diagnostic certainty classification are rather relative categories of cases in the GSDB within the limitations.

Note that the following additional AI/ID medical topics are specifically discussed in the respective sections of this PBRER: Guillain-Barre syndrome (GBS), transverse myelitis, acute disseminated encephalomyelitis (ADEM), subacute thyroiditis, immune thrombocytopenia (ITP), IgA nephropathy, and polymyalgia rheumatica.

Literature:

General review of the literature shows that AI/ID flares have been reported for COVID-19 vaccines. Studies are limited by small, often uncontrolled cohorts (i.e., only reporting flare rates in vaccinated individuals), and data for flares is not always delineated by vaccine type. Articles often conclude with the need for more robust, generalizable studies; and in addition, conclusions emphasize that the benefit of COVID vaccination outweighs the potential risk of flares.

Some selected articles with mRNA 1273 specific data have been presented in the MSSRs, here the MAH presents a high-level summary table of studies with relevant flare data, and as can be seen publications regarding flares range across different types of AI/ID, across various COVID vaccines, and estimate rates from 0-12%:

Author	Vaccines Given	Population (n=mRNA 1273)	Flares (flares for mRNA 1273)
Connolly et al	M, P	325 IMID, survey, one week f/u after dose 1	No flares Local/systemic similar to CTs
Watad et al	M, P, AZ	Case series, 17 flares (n=2 mRNA1273 flares), 10 new onset; 28 day follow-up at 5 large tertiary centers 9USA,UK, Israel)	"flares were temporarily associated with vaccination, but no way to determine causality" Rare, most were moderate, responsive to therapy.
Boekel et al	M, P, AZ	505 patients with IMID; 203 healthy controls	5% of patients reported worsening of their IMID up to 2 months post-vaccination
Geisen et al	M,P	26 with IMID; 42 healthy controls	No severe adverse effects or flares of arthritis observed; no adjustments of treatment in 6 weeks post-vaccination
Tzioufas et al	M, P	605 Systemic Autoimmune and Autoinflammatory rheumatic disease (SAARD) pts.	7.6% came out of remission; 5% increase in low disease activity; 2% moderate disease activity; 0.6% high disease acitvity
Sattui et al	M, P, AZ, J	Online international survey – Global Rheumatology Alliance (42%RA)	Rheumatic disease flares that required medication changes occurred in 4.6%.
Izmirly et al	M, P, J	90 SLE	11.4% post-vaccination flares
Felten et al	M. P. AZ	SLE	3% flares after a median of 3 days; flare pre-vx, predictive of flare after
Weaver et al	M, P, AZ, J	3,316 IBD – PREVENT-COVID	2% IBD flare following vaccination
Botwin et al	M, P	246 IBD	GI symptoms – 6% after D1, 11.5% after D2

Key for COVID Vaccine manufacturers: M=Moderna, P= Pfizer, AZ= AstraZeneca, J=Janssen/J&J

Selected articles are included in each of the subsections. Here, a recently published review article is included; while focused more on dermatologic manifestations of autoimmune and inflammatory disease, summarized and reflects that general key themes of published articles to date; including a discussion on the hypothesis that double-stranded RNA (fragments contained in mRNA vaccines) can trigger an inflammatory response and the generation of type 1 interferons, which are known to flare AI/ID.

COVID-19 vaccine safety and efficacy in patients with immune-mediated inflammatory disease: Review of available evidence [84]

Abstract: Dermatologists diagnose and treat many immune-mediated inflammatory diseases (IMID). Understanding the inherent immune dysregulation of these diseases as well as the additional disruption that comes as a result of IMID treatments has been important during the COVID-19 pandemic. With vaccines becoming widely available, dermatologists need to be

familiar with the risks and benefits of vaccination in these patients, particularly those taking biologics, in order to have informed discussions with their patients. In this review, we present the current evidence related to COVID-19 vaccine safety and efficacy in patients with IMID and review existing recommendations for vaccination against SARS-CoV-2. Given the current evidence, there is minimal concern that these patients are at any greater risk of harm from COVID-19 vaccination compared to healthy controls. For most, the benefit of avoiding severe COVID-19 through vaccination will outweigh the theoretical risk of these vaccines. A question that is still outstanding is whether patients on biologics will generate a sufficient immune response to the vaccine, which may be dependent on the specific biologic therapy and indication being treated. This underscores the importance of following patients with IMID after vaccination to determine the safety, efficacy, and duration of the vaccine in this population.

Summary:

Patients with immune-mediated inflammatory disease (IMID) may experience disease flares or have diminished immune responses after COVID-19 vaccination, particularly those receiving B-cell depleting therapies. More research is necessary to determine how biologic therapies impact vaccine responses in patients with IMID and to develop strategies to optimize responses in this population.

Rheumatoid Arthritis (RA) Flares:

Background:

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune, inflammatory disorder that predominantly involves synovial joints, eventually causing destruction of the joints. The etiology is unclear; however, it is recognized that a combination of genetic predisposition and environmental factors are involved and result in a break of immune tolerance and dysregulation. The strongest genetic risk factor for RA is HLA-DRB1. Other gene variants that include cytokine promoters and T-cell-signaling genes have been identified. RA affects approximately 1% of the population in the US and in Europe and is twice as common in females compared to males. Chronic mucosal inflammation may play a role, and infections and the microbiome may contribute to the development of RA. Autoantibodies to rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA) have the most clinical relevance and are often used in diagnosis (UpToDate: "Epidemiology of, risk factors for, and possible causes of rheumatoid arthritis", "Clinical Manifestations of rheumatoid arthritis", "Pathogenesis of rheumatoid arthritis"). The natural course of RA is characterized by flares and asymptomatic periods. Physical and emotional stress, poor sleep, or infections can trigger flares. Given the inflammatory nature of RA, it is hypothetically possible that innate immune stimulation (infection, vaccination, etc.) may trigger clinical signs and symptoms of RA.

It is unclear whether RA predisposes patients to more severe COVID disease. However, often RA patients have existing comorbidities identified as risk factors that predispose them for severe or fatal COVID. In addition, immune dysfunction and immunosuppressive medications may put RA patients at higher risk for increased COVID severe disease. It has been recognized that some of the treatments for RA may lower the immunogenicity and potential effectiveness of vaccination. Many professional rheumatology organizations are recommending the use of COVID vaccines for autoimmune inflammatory rheumatic disease patients. While disease flares have been reported in the literature and in the MAH's safety database, these are predominantly transient, mild/moderate, and respond to therapy. (UpToDate, "COVID-19: Care of adult patients with systemic rheumatic disease").

Results:

Cumulatively, there were 171 potential cases of rheumatoid arthritis flare, of which, 141 cases were serious and 4 had fatal outcomes. In total, there were 1,094 events/all PTs (415 of which were serious) reported in the 171 cases. One hundred- twenty-eight (128) cases were medically confirmed. The majority of reports were in females (138; 80.7%) compared to males (27; 15.8%) (sex information was missing or unknown for 6 cases) and were most frequently reported in individuals 50 to 74 years of age (60.3%) with a median age of 62.0 years (min. 25.0, max. 92.0). Age information was unknown or missing for 10 cases (Table 16-92**).**

Table 16-92 Case Distribution by Gender and Age Group, Cumulative to 31 Dec 2021

Age Group (Years)	Female		Male		Unknown		Total # of Cases	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases	# Cases	% of Total Cases		
18-29	4	2.3%	0	0	0	0	4	2.3%
30-39	8	4.7%	1	0.6%	0	0	9	5.3%
40-49	21	12.3%	2	1.2%	0	0	23	13.5%
50-64	46	26.9%	8	4.7%	1	0.6%	55	32.2%
65-74	36	21.1%	12	7.0%	0	0	48	28.1%
75+	18	10.5%	4	2.3%	0	0	22	12.9%
Missing	5	2.9%	0	0	5	2.9%	10	5.8%
Grand total	**138**	**80.7%**	**27**	**15.8%**	**6**	**3.5%**	**171**	**100.0%**

Table 16-93 shows the most frequently reported events in the potential RA flare cases. Many of these are consistent with the coding and clinical signs and symptoms described in RA flares (such arthralgia, fatigue, pain, joint swelling and peripheral swelling).

Table 16-93 Most Frequently Reported Preferred Terms (PTs) (n ≥ 14) in Rheumatoid Arthritis Flare Cases

PT	Non-Serious		Serious		Total # Events	% of Total Events
	# Events	% of Total Events	# Events	% of Total Events		
Rheumatoid arthritis	19	1.7%	129	11.8%	148	13.5%
Condition aggravated	52	4.8%	18	1.6%	70	6.4%
Arthralgia	39	3.6%	8	0.7%	47	4.3%
Fatigue	32	2.9%	6	0.5%	38	3.5%
Pain	28	2.6%	7	0.6%	35	3.2%
Headache	24	2.2%	4	0.4%	28	2.6%
Pain in extremity	19	1.7%	8	0.7%	27	2.5%
Pyrexia	14	1.3%	5	0.5%	19	1.7%
Joint swelling	16	1.5%	0	0	16	1.5%
Peripheral swelling	14	1.3%	2	0.2%	16	1.5%
Arthritis	11	1.0%	3	0.3%	14	1.3%
Dizziness	11	1.0%	3	0.3%	14	1.3%

Based on medical review, the 171 cases were relatively ranked for diagnostic certainty, and for those possible/probable (low, medium, high relative diagnostic certainty) flare cases, WHO-UMC causality was assessed (Table 16-94). At least 10 (5.8%) reported requiring hospitalization, and 12 cases described positive rechallenges. (See Appendix 20.11.24 and Appendix 20.11.25).

Table 16-94 Diagnostic Certainty and WHO-UMC Causality Assessments for Rheumatoid Arthritis Flare Cases[1]

Diagnostic Certainty	Total Numbers	WHO-UMC Causality Probable (# of positive rechallenges)[1]	WHO-UMC Causality Possible (# of positive rechallenges)	WHO-UMC Causality Unlikely[2]	WHO-UMC Causality Unassessable[3]
High	40	3 (3)	29	3	5
Medium	50	7 (7)	35	2	6
Low	55	0	40 (2)	6	9
Total (low, medium, high cases)	**145**	**10 (10)**	**104 (2)**	**11**	**20**
Unassessable [4]	12	N/A	N/A	N/A	N/A
Duplicate cases	1	N/A	N/A	N/A	N/A

Diagnostic Certainty	Total Numbers	WHO-UMC Causality Probable (# of positive rechallenges)[1]	WHO-UMC Causality Possible (# of positive rechallenges)	WHO-UMC Causality Unlikely[2]	WHO-UMC Causality Unassessable[3]
Not a Flare	13	N/A	N/A	N/A	N/A
Grand Total[5]	**171**				

[1] Given the limitations of ICSR data, the diagnostic certainty classifications are relative and do not have the data to apply standard clinical criteria. Many of the cases coded as "high" still lack crucial data (e.g. Disease status prior to vaccination or full clinical course). In addition, causality assessment must be interpreted with caution recognizing that disease flares occur in the natural disease process in absence of identified triggers. Furthermore, "Probable" causality is applied to some cases where positive rechallenges have been described, but do not meet the standard criteria (e.g., complete resolution, absence of treatment); and this is further limited given that the disease itself is an alternate etiology of flares.
[2] Some of these cases have a very long TTO and are rather associated with COVID-19 infection; thus, likely more related to COVID-19 than to vaccination.
[3] Cases with no TTO are unassessable
[4] Unassessable cases have too little information to differentiate expected transient reactogenicity from a true flare.
[5]Grand total is the total number of all cases identified as potential flares for RA based on the search strategy and preliminary medical review described in the methodology section.

Time to onset was assessed per medical review of the narrative. Here is it challenging to differentiate onset of expected reactogenicity from a flare, as the signs/symptoms (arthralgia, myalgia, fatigue) are common to both. There are no population vaccination rates by dose for rheumatoid arthritis patients, in addition there are possible reporting biases which limits the interpretation of the reporting rates by Dose number. The majority of the cases were assessed as having a TTO within 3 days after vaccination (Table 16-95).

Table 16-95 Time-to-Onset (TTO) by Dose Number for Rheumatoid Arthritis Flare Cases (low/medium/high diagnostic certainty cases only)

	0-3 days	4-7 days	8-14 days	15-28 days	>28 days	Unknown
Dose 1	30	6	8	2	1	6
Dose 2	28	5	5	8	9	5
Dose 3	5	1	1	0	0	2
Unknown	**10**	**1**	**1**	**0**	**2**	**22**

Note: TTO counts includes events of positive rechallenges

The MAH conducted a cumulative medical review of the reports; however, there was limited information in reports about the baseline RA disease status, history of flares, reports of other potential triggering events, clinical events, clinical course, diagnostics/evaluation/diagnosis, treatment and outcome which precludes a robust analysis. Some reports describe transient fever, headache, arthralgia, and fatigue within days after vaccination and do not require treatment which is in line expected reactogenicity; however, other reports describe reactogenicity-like events of increased intensity and duration, and other reports also describe additional signs and symptoms suggestive of flares, such as peripheral swelling, joint inflammation and pain, severe fatigue, difficulty in walking or fulfilling daily activities which reflect a reactivation of RA. A few cases

describe no recent history of flares until the period after vaccination; however, most cases do not provide the baseline disease status. In a few cases, severe, clinically significant signs and symptoms such as arthralgia, pain, fatigue and joint swelling are reported which required and responded to steroids. In addition, 12 cases of positive rechallenges were identified, although there are limited data available for these cases. Most of the reports described mild/moderate or RA flares.

For case summaries of rheumatoid arthritis flares see Appendix 20.11.24.

Literature:

Multiple publications have described individual cases, case series and/or cohorts of RA and rheumatic disease flares. The mRNA 1273 associated RA flares are included in the GSDB. Several selected articles of cohort data are included here.

A prospective multicenter study assessing humoral immunogenicity and safety of the mRNA SARS-CoV-2 vaccines in Greek patients with systemic autoimmune and autoinflammatory rheumatic diseases [85]

Abstract

Objectives: To investigate humoral responses and safety of mRNA SARS-CoV-2 vaccines in systemic autoimmune and autoinflammatory rheumatic disease (SAARD) patients subjected or not to treatment modifications during vaccination.

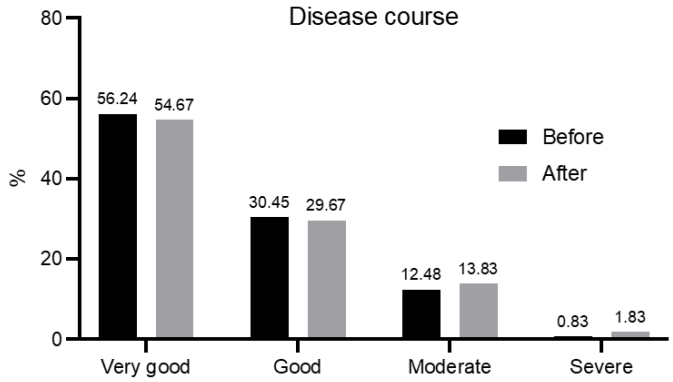
Methods: A nationwide, multicenter study, including 605 SAARD patients and 116 controls, prospectively evaluated serum anti-SARS-CoV-2 S1-protein IgG antibody titers, side-effects, and disease activity, one month after complete vaccination, in terms of distinct treatment modification strategies (none, partial and extended modifications). Independent risk factors associated with hampered humoral responses were identified by data-driven multivariable logistic regression analysis.

Results: Patients with extended treatment modifications responded to vaccines similarly to controls as well as SAARD patients without immunosuppressive therapy (97.56% vs 100%, p = 0.2468 and 97.56% vs 97.46%, p > 0.9999, respectively). In contrast, patients with partial or without therapeutic modifications responded in 87.50% and 84.50%, respectively. Furthermore, SAARD patients with extended treatment modifications developed higher anti-SARS-CoV-2 antibody levels compared to those without or with partial modifications (median:7.90 vs 7.06 vs 7.1, p = 0.0003 and p = 0.0195, respectively). Mycophenolate mofetil (MMF), rituximab (RTX) and methotrexate (MTX) negatively affected anti-SARS-CoV-2 humoral responses. In 10.5% of vaccinated patients, mild clinical deterioration was noted; however, no differences in the incidence of deterioration were observed among the distinct treatment modification SAARD subgroups. Side-effects were generally comparable between SAARD patients and controls.

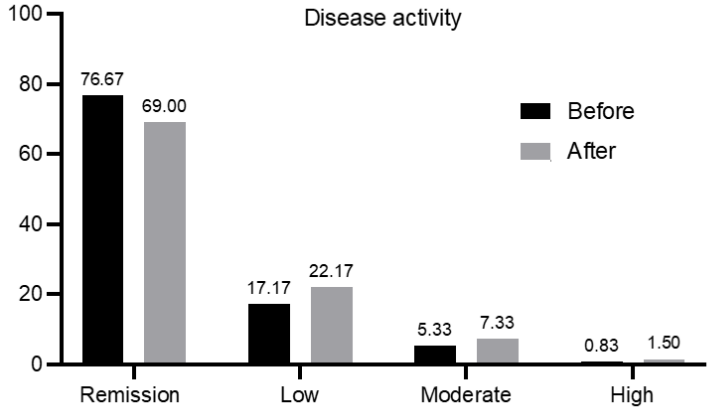
Conclusions: In SAARD patients, mRNA SARS-CoV-2 vaccines are effective and safe, both in terms of side-effects and disease flares. Treatment with MMF, RTX and/or MTX compromises

Supplementary Figure 2. Distribution of disease activity and clinical course among SAARD patients before and after the vaccination. Data (a) self-reported from patients or (b) provided by the caring physician.

(a)



anti-SARS-CoV-2 antibody responses, which are restored upon extended treatment modifications without affecting disease activity.



Disease activity was measured (per article supplement: The following disease activity indices were used: Clinical Disease Activity Index, Simplified Disease Activity Index, DAS-28(CRP/ESR) for rheumatoid arthritis, Disease Activity in Psoriatic Arthritis (DAPSA), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Ankylosing Spondylitis Disease Activity Score for axSpA (ASDAS), Systemic Lupus Disease Activity Index for SLE (SLEDAI-2K), EULAR Sjogren's syndrome disease activity index (ESSDAI), Birmingham Vasculitis Activity Score (BVAS) and European Scleroderma Study Group Activity Index (EScSG-AI).

Company Comment: The study included rheumatoid arthritis (n=178) as part of a larger number of SAARD conditions. Data on specific flares by condition and vaccine type were not provided, nor was a control group included and thus application of this data to our disease flare analysis is

limited; however, this article demonstrates the importance of assessing and considering baseline disease status and activity prior to vaccination.

Early experience of COVID-19 vaccination in adults with systemic rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance Vaccine Survey [86]

Abstract

Background: We described the early experiences of adults with systemic rheumatic disease who received the COVID-19 vaccine.

Methods: From 2 April to 30 April 2021, we conducted an online, international survey of adults with systemic rheumatic disease who received COVID-19 vaccination. We collected patient-reported data on clinician communication, beliefs and intent about discontinuing disease-modifying antirheumatic drugs (DMARDs) around the time of vaccination, and patient-reported adverse events after vaccination.

Results: We analyzed 2860 adults with systemic rheumatic diseases who received COVID-19 vaccination (mean age 55.3 years, 86.7% female, 86.3% white). Types of COVID-19 vaccines were Pfizer-BioNTech (53.2%), Oxford/AstraZeneca (22.6%), Moderna (21.3%), Janssen/Johnson & Johnson (1.7%) and others (1.2%). The most common rheumatic disease was rheumatoid arthritis (42.3%), and 81.2% of respondents were on a DMARD. The majority (81.9%) reported communicating with clinicians about vaccination. Most (66.9%) were willing to temporarily discontinue DMARDs to improve vaccine efficacy, although many (44.3%) were concerned about rheumatic disease flares. After vaccination, the most reported patient-reported adverse events were fatigue/somnolence (33.4%), headache (27.7%), muscle/joint pains (22.8%) and fever/chills (19.9%). Rheumatic disease flares that required medication changes occurred in 4.6%.

Conclusion: Among adults with systemic rheumatic disease who received COVID-19 vaccination, patient-reported adverse events were typical of those reported in the general population. Most patients were willing to temporarily discontinue DMARDs to improve vaccine efficacy. The relatively low frequency of rheumatic disease flare requiring medications was reassuring.

Summary from Table 4 presented in the article: Any flare of rheumatic disease: All 382 13.4%), Pfizer 184 (12.1%), AstraZeneca 93 (14.4%), Moderna 96 (15.7%), Janssen 7 (14%), others 2 (6.1%). Flare requiring new or increased dose of medication: All 132 (4.6%), Pfizer 58 (3.8%), AstraZeneca 40 (6.2%), Moderna 32 (5.2%), Janssen 2 (4%), others 0 (0%).

Company comment: Sattui et al described the early experience of adults with systemic rheumatic disease who received COVID-19 vaccine. An online international survey of adults with systemic rheumatic disease who received COVID-19 vaccination was conducted from April 2-30, 2021.

Patient reported data on clinician communication, beliefs and intent about discontinuing disease-modifying antirheumatic drugs (DMARDs) around the time of vaccination, and patient-reported adverse events after vaccination.

After vaccination, evaluating a convenience sample, the most reported patient-reported adverse events were fatigue/somnolence (33.4%), headache (27.7%), muscle/joint pains (22.8%) and fever/chills (19.9%). Rheumatic disease flares that required medication changes occurred in 4.6% among various COVID vaccines. Note, these data are limited with regards to interpretation as they do not include comparative flare rates in an unvaccinated cohort.

The authors conclude that among adults with systemic rheumatic disease who received COVID-19 vaccination, patient-reported adverse events were typical of those reported in the general population. The relatively low frequency of rheumatic disease flare requiring medications was reassuring. It is of note that globally there is no consensus of standard guidelines for discontinuing treatment prior to vaccination to improve immunogenicity; however, when medications have been stopped before vaccination and a flare occurs after vaccination, assessing causality or association of the vaccination and the flare become confounded and limited.

Discussion of RA Flares:

In this PBRER2, cumulative case review, of the 171 possible RA flare cases identified, 40 cases were assessed to have relatively high level of evidence of a flare), e.g., requiring treatment and/or laboratory evidence of flare), 50 were medium, 55 were low, 12 were unassessable (e.g., unable to differentiate expected reactogenicity from flare), 1 duplicate case, and 13 were not flares. Of the 145 (low/medium/high) cases, 10 of the high/medium cases reported positive rechallenges and thus were classified as probable; 104 were possible, primarily based on temporal association, 4 of the possible cases had reported confounders (stopped medication prior to vaccination, fungal pneumonia, UTI, and respiratory illness); 11 were unlikely and 20 were unassessable primarily because TTO was not reported. Most of the RA flare reports are mild/moderate, and those that require treatment respond to steroids. (See Appendix 20.11.24 and Appendix 20.11.25.). The cases of RA exacerbation were limited by missing information (lack of reported clinical course, diagnostics, treatment and outcome). Flares of RA present with similar signs and symptoms of expected reactogenicity (e.g., arthralgia, myalgia, fatigue, pain, fever) which makes case confirmation of a true flare challenging. There were cases that described more severe than expected arthralgias, joint swelling, pain, fevers, and fatigue, some of which also described the need for steroids and additional immunosuppressants. (Those reported where acetaminophen or ibuprofen resolved symptoms, also make it difficult to differentiate expected reactogenicity from a true flare.) Approximately half, 73 of the 145 (low/med/high), cases of reported RA flares occurred within 3 days after vaccination, suggesting that the chemokines and cytokines associated with the initial

innate immune response could hypothetically play a role. Of note, a higher proportion of the reports after Dose 2 had longer latencies which would be more associated with the adaptive immune response. For Dose 1 reports 11/47 (24%) occurred more than 8 days after vaccination, whereas for Dose 2, 28/55 (51%) occurred more than 8 days after vaccination. Again, the exact immune cascade by which vaccination could trigger a flare is unknown. As mentioned, analysis of the TTO pattern is severely limited as the signs and symptoms of a flare mimic reactogenicity; it remains unclear how and when reactogenicity could trigger a true flare of RA. Given the temporal association and the lack of other reported alternate etiologies/risk factors/triggers, vaccine causality as related to contributing to the exacerbation of RA cannot be excluded; however, the natural relapsing course of RA remains a confounder. Therefore, causality assessment is challenging.

Furthermore, it must be noted that RA flares have been reported after many vaccine types, including a range of COVID vaccines [85,87-89]. In this case, it can be hypothesized that other vaccines have an off-target effect of exacerbating RA through inflammatory immune mediators that remain to be defined. Such an association should be considered speculative. Cases of RA flares or disease aggravation have been described in the literature. Some interesting examples of published studies comparing flare rates for RA and rheumatic diseases more broadly suggest that the flare rates are comparable in vaccinated and unvaccinated individuals [88,90]. There are no well-established back-ground rates of RA flares, and patterns of disease are variable among individuals; this precludes an O/E analysis at this time. In general, the literature supports the general safety profile of COVID vaccinations in the autoimmune/inflammatory disease (including rheumatoid arthritis) subpopulation.

Cumulatively, as of the end of the reporting period, a total of 827,274,740 doses of SPIKEVAX had been delivered to 77 countries, and 466,804,529 doses are estimated to have been administered; and the reports of flares must also be considered in this context of the prevalence of RA and the unprecedented number of persons who have received COVID vaccines (including SPIKEVAX). Given the limited data available and known variable natural history of RA, along with limitations in data supporting causality assessment including a lack of well-established published rates of the background rate of flares, the MAH cannot confirm or quantify the risk [75,77,91,92].

In conclusion, while individual cases have been reported, limitations of available data, including incompleteness of reports, the waxing/waning natural history of RA, cohort studies that suggest comparable rates of flares between unvaccinated and vaccinated groups, the lack lack of robust, controlled studies, and the lack of useful data to inform background rates for RA flares, render the association between SPIKEVAX and RA flares to be weak and speculative. The MAH will

continue to monitor RA flare reports through routine pharmacovigilance and explore the use of RWE to further inform the topic.

Myasthenia Gravis (MG) Flares:

Background:

Myasthenia gravis (MG) is an autoimmune disorder targeting the neuromuscular junction. Characterized by acetylcholine receptor, muscle-specific kinase, and/or low-density lipoprotein antibodies, MG presents with muscular weakness involving respiration, swallowing, and vision. Infection and inflammation can trigger an exacerbation of MG. Among MG patients there is individual variation; however, all have common symptoms of muscular weakness, autoimmune dysfunction/immune dysregulation, and most are on immunosuppressive therapies. In addition, certain drugs are known to exacerbate MG, such as fluoroquinolones, aminoglycosides, telithromycin, neuromuscular blocking agents, IV local anesthetics, magnesium sulfate, penicillamine, beta blockers, and procainamide. It has been reported that programmed cell death (PD-1) inhibitors used for immune-oncology therapy have been reported to trigger autoimmune MG as they enhance immune responses; however, the exact immunobiology is not known. Individual cases of MG flares after vaccines, including various COVID-19 vaccines have been reported; however, there are no large cohort studies available to date. Severe, acute exacerbations, "myasthenic crisis", can be triggered by concurrent infection, surgery, pregnancy/childbirth, some medications, changes in immunosuppressive medications or spontaneously/idiopathically as part of the natural disease. Myasthenic crisis is characterized by life-threatening neuromuscular respiratory failure, and bulbar weakness can cause dysphagia and aspiration. Less severe exacerbations include recurrent ptosis or diplopia, mild facial or limb weakness, or slurred speech. In general, vaccines, including COVID-19 vaccines, are recommended for patients with MG, although it is recognized that there have not been clinical trials evaluating these vaccines in this patient population, and that immunosuppressive therapies to treat MG may reduce immunogenicity. Several publications describe the variable morbidity and mortality of MG patients who are infected with COVID-19, and to date the potential benefit-risk profile of COVID vaccination is considered favorable [93-95].

Results:

Cumulatively, there were 34 potential cases of myasthenia gravis flares, of which, 29 cases were serious and 1 had a fatal outcome. In total, considering all Preferred Terms (PTs), there were 184 events (103 of which were serious) reported in the 34 cases. Twenty-six (26) cases were medically confirmed. Of the 34 cases, 19 were females (55.9%) and 15 were males (44.1%) and occurred most frequently in individuals 65 to 74 years of age (47.1%) with a median age of 70.0 years (min. 16.0, max. 83.0) (Table 16-96).

Table 16-96 Case Distribution by Gender and Age Group, Cumulative to 31 Dec 2021

Age Group (Years)	Female		Male		Total # of Cases	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases		
16-17	1	2.9%	0	0	1	2.9%
30-39	1	2.9%	0	0	1	2.9%
40-49	4	11.8%	0	0	4	11.8%
50-64	2	5.9%	2	5.9%	4	11.8%
65-74	7	20.6%	9	26.5%	16	47.1%
75+	4	11.8%	4	11.8%	8	23.5%
Grand total	19	55.9%	15	44.1%	34	100.0%

Table 16-97 shows the most frequently reported events in the potential MG flare cases. Many of these are consistent with the coding and clinical signs and symptoms described in MG flares (such dysphagia, muscular weakness, asthenia, dyspnea, fatigue, and eyelid ptosis).

Table 16-97 Most Frequently (n≥3) Reported Preferred Terms (PTs) in Myasthenia Gravis Flare Cases

PT	Non-Serious		Serious		Total # Events	% of Total Events
	# Events	% of Total Events	# Events	% of Total Events		
Myasthenia gravis	3	1.6%	22	12.0%	25	13.6%
Condition aggravated	9	4.9%	14	7.6%	23	12.5%
Dysphagia	5	2.7%	4	2.2%	9	4.9%
Muscular weakness	3	1.6%	4	2.2%	7	3.8%
Asthenia	3	1.6%	3	1.6%	6	3.3%
Dyspnoea	2	1.1%	2	1.1%	4	2.2%
Fatigue	3	1.6%	1	0.5%	4	2.2%
Myasthenia gravis crisis	1	0.5%	3	1.6%	4	2.2%
Eyelid ptosis	3	1.6%	0	0	3	1.6%
Headache	3	1.6%	0	0	3	1.6%
Tremor	0	0	3	1.6%	3	1.6%

Of the potential cases of myasthenia gravis flares reviewed, 29 were assessed as possible/probable (low/med/high) cases of MG flares (Table 16-98). At least 13 (38.2%) reported hospitalization, and some required intubation, IVIG treatment, feeding tube or plasmapheresis. Where the data were available, patients recovered from the treated flares. Of note, cases were confounded by infections (UTI, COVID-19, influenza) and by comorbidities such as renal cancer and

neuroendocrine tumor; however, considering the timing of events and clinical course, even with confounding factors, the MAH considered the contribution of the vaccine to the flare as "possible" given the temporal association. (In the natural course of AI/ID conditions including MG, there may be multiple factors which contribute to a flare.)

Table 16-98 Diagnostic Certainty and WHO-UMC Causality Assessments for Myasthenia Gravis Flare Cases[1]

Diagnostic Certainty	Total Numbers	WHO-UMC Causality Probable (# of positive rechallenges)[1]	WHO-UMC Causality Possible (# of positive rechallenges)	WHO-UMC Causality Unlikely[2]	WHO-UMC Causality Unassessable[3]
High	16	1	15	0	0
Medium	9	0	8	1	0
Low	4	0	4 (1)	0	0
Total (low, medium, high cases)	**29**	**1**	**27 (1)**	**1**	**0**
Unassessable	4	N/A	N/A	N/A	N/A
Duplicate cases	1	N/A	N/A	N/A	N/A
Not a Flare	0	N/A	N/A	N/A	N/A
Grand Total[5]	**34**				

[1] Given the limitations of ICSR data, the diagnostic certainty classifications are relative and do not have the data to apply standard clinical criteria. Many of the cases coded as "high" still lack crucial data (e.g., disease status prior to vaccination or full clinical course). In addition, causality assessment must be interpreted with caution recognizing that disease flares occur in the natural disease process in absence of identified triggers. Furthermore, "Probable" causality is applied to some cases where positive rechallenges have been described, but do not meet the standard criteria (e.g., complete resolution, absence of treatment); and this is further limited given that the disease itself is an alternate etiology of flares.
[2] Some of these cases have a very long TTO and are rather associated with COVID-19 infection; thus, likely more related to COVID-19 than to vaccination.
[3] Cases with no TTO are unassessable
[4] Unassessable cases have too little information to differentiate expected transient reactogenicity from a true flare.
[5]Grand total is the total number of all cases identified as potential flares for MG based on the search strategy and preliminary medical review described in the methodology section.

Time to onset of the flare was based on medical review of the available information. While most (19 out of 29) cases occur within 0-7 days after vaccination, the limited background information of vaccination coverage by dose of MG patients precludes any pattern analysis with regards to risk after dose number (Table 16-99). Furthermore, it is unknown what percentage of those with severe flares after dose 1 go on to receive subsequent doses.

Table 16-99 Time-to-Onset (TTO) by Dose Number for Myasthenia Gravis Flare Cases (low/medium/high diagnostic certainty cases only)

	0-3 days	4-7 days	8-14 days	15-28 days	>28 days	Unknown
Dose 1	7	3	1	1	0	1
Dose 2	4	1	2	4	0	0
Dose 3	1	1	0	1	0	0
Unknown	1	1	0	0	1	0

Note: TTO counts include 1 positive rechallenge

For case summaries of myasthenia gravis exacerbation see Appendix 20.11.28.

Selected Literature

To Be or Not To Be Vaccinated: That Is a Question in Myasthenia Gravis [96].

Company Comment: This is a review article summarizing myasthenia gravis and vaccination including COVID-19 vaccination. As infection is known potentially to trigger MG onset and/or flares, the importance of vaccination to prevent infection has been recognized; however, the article notes that there is increasing vaccine hesitancy in this population. The article highlights that while a few individual case reports have been published there is a lack of cohort studies or clinical trials to inform the risk. Furthermore, the article notes, “Currently, there exist no general criteria for diagnosing vaccine-related MG, necessitating a case-by-case assessment. Consequently, the World Health Organization (WHO) has formulated four basic principles for assessing the adverse events (AEs) of vaccines, namely consistency, strength, specificity, and temporal relation. Epidemiology and case reports are valuable clues for deciphering the relationship between vaccines and MG. However, there is a need to consider background incidence, genetic predisposition, environmental factors, and time relevance.”

The only cohort study identified a study by Ruan et al, "COVID-19 Vaccination in Patients with Myasthenia Gravis: A Single Center Case Series"; however, this did not include Moderna or Pfizer vaccines, most of the vaccinees received CoronaVac. Two out of 22 patients had mild flares that resolved in days.

Discussion MG:

Based on medical review, of the 34 cases, 16 had a relatively high level of diagnostic certainty, 9 had medium, and 4 had low. Only one case had a causality assessment of “probable”, as they were first diagnosed with MG after Dose 1 and had an exacerbation after Dose 2. The remainder were classified as possible (27 cases) and unlikely (1) based on temporal association. Another case had a description of a possible rechallenge however, the data were very limited, relative diagnostic certainty was low, and thus causality was assessed as possible. Thirteen cases were required hospitalization and intensive treatment, and seven cases were confounded by infections (sepsis, COVID-19, flu, UTI (2)) and comorbidities (renal cancer and neuroendocrine tumor). (Appendix 20.11.28, Appendix 20.11.29).

Nineteen (19) of the 29 cases occurred within 7 days of vaccination, the time window of primarily innate immune response especially for Dose 1 in naive individuals. There were more reports from Dose 1 within 7 days of vaccination, compared to Dose 2 (6 of the 11 occurred 8-28 days after vaccination, consistent more with the adaptive immune response). Only three cases were reported after Dose 3.

MG exacerbations have been reported after other vaccinations; however, large aggregate reports and cohort studies have been published which have not conclusively demonstrated a risk of flares after vaccinations (e.g., influenza vaccine). [97-99] These larger cohort studies and well as controlled studies have not been published for MG and mRNA COVID-19 vaccines. In addition, there is no well-established data on background rates of MG flares, with the exception of estimates that 15-20% of MG patients develop a flare in their lifetime, on average 8-12 months from the onset/diagnosis of MG, and approximately one-third to one-half have no identifiable trigger [100]. There are case reports of severe and fatal COVID-19 infection in MG patients and reports of COVID-19 exacerbating MG. Because of the relative immunosuppressed/ immunocompromised condition with added respiratory and/or bulbar weakness, several studies have found that MG patients have more severe complications and disease when hospitalized for COVID-19 infection [101,102].

Considering the hundreds of millions of doses of SPIKEVAX that have been administered globally, there are relatively few reports of MG flare, and there is a lack of large, cohort studies/publications, which precludes a robust pattern analysis and the ability to confirm/asses the risk of MG flares after vaccination. Reports have occurred after a variety of vaccines, including a variety of COVID vaccines.

In conclusion, while individual cases of MG flares have been reported, limitations of available data, including incompleteness of reports, the natural history of MG flares/exacerbations, the lack of robust, controlled, cohort studies, and the lack of useful data to inform background rates for MG flares, render the association between SPIKEVAX and MG flares to be weak and speculative. The MAH will continue to monitor MG flare reports through routine pharmacovigilance and explore the use of RWE to further inform the topic.

Multiple Sclerosis (MS) Flares:

Background:

Multiple sclerosis (MS) is an immune-mediated, inflammatory, central nervous system demyelinating disease. MS can have variable clinical presentations and pathologic features of inflammation, demyelination, axonal degeneration, and neurodegeneration. The etiology remains largely unknown however some genetic factors have been identified, particularly Class I and II

major histocompatibility complex loci that are involved in T cell activation and regulation; however, over 200 polymorphisms have been associated with MS. Myelin reactive T-cells and myelin oligodendrocyte glycoprotein antibodies may be detected; however, conclusive evidence of the autoimmune cause (and possible infectious triggers) is lacking, and the neurodegeneration cannot be fully attributed to immune mechanisms or inflammation. Some contributing environmental factors such as viral infections (Epstein-Barre virus, cytomegalovirus, varicella zoster virus), geographic latitude, sunlight exposure/vitamin D have been found to be associated with MS. Triggers for flares include stress, infections and pregnancy. Flares can be mild with fatigue, paresthesia, or hypoesthesia, and more severe flares present with change in vision or loss of balance. Studies have evaluated MS relapse and vaccination, and one systematic review by [103] found that, "According to accumulated evidence, vaccination against seasonal influenza does not have a negative effect on the disease progression of patients with MS. No associations between relapse rate and vaccination against H1N1, HBV, tetanus, TBE, and BCG were found, but further research is needed to fully exclude an association and to investigate the potential preventive effect of the BCG vaccine." This article further points out the self-controlled case series may be the best way to evaluate the risk of flares, given the variable course of individual disease [93,103]. The etiology of MS flares is not fully understood, thought to be multi-factorial, and the disease course for many MS patients is relapsing and remitting.

COVID-19 infection has been reported to exacerbate MS, especially in those patients with higher disease activity prior to infection [104]. This recognition of the risk of COVID-19 infection for MS patients, further supports the benefit-risk profile of COVID-19 vaccines.

Results:

Cumulatively, there were 134 potential cases of multiple sclerosis flare, of which, 120 cases were serious and 1 had a fatal outcome. In total, considering all Preferred Terms (PTs), there were 757 events (386 of which were serious) reported in the 134 cases. Ninety-one (91) cases were medically confirmed. The majority of reports were in females (101; 75.4%) compared to males (33; 24.6%) and were most frequently reported in individuals 50 to 64 years of age (49.3%) with a median age of 56.0 years (min 24.0, max. 83.0). Age information was unknown or missing for 2 cases (Table 16-100)

Table 16-100 Case Distribution by Gender and Age Group, Cumulative to 31 Dec 2021

Age Group (Years)	Female		Male		Total of # Cases	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases		
18-29	4	3.0%	1	0.7%	5	3.7%
30-39	10	7.5%	5	3.7%	15	11.2%
40-49	18	13.4%	1	0.7%	19	14.2%
50-64	48	35.8%	18	13.4%	66	49.3%
65-74	16	11.9%	7	5.2%	23	17.2%
75+	4	3.0%	0	0	4	3.0%
Missing	1	0.7%	1	0.7%	2	1.5%
Grand total	**101**	**75.4%**	**33**	**24.6%**	**134**	**100.0%**

Table 16-101 shows the most frequently reported events in the potential MS flare cases. Many of these are consistent with the coding and clinical signs and symptoms described in MS flares (such fatigue, asthenia, gait disturbance, hypoesthesia, muscular weakness, pain balance disorder, mobility disorders, gait inability and optic neuritis).

Table 16-101 Most Frequently Reported (n≥6) PTs in Multiple Sclerosis Flare Cases

PT	Non-Serious		Serious		Total # Events	% of Total Events
	# Events	% of Total Events	# Events	% of Total Events		
Condition aggravated	34	4.5%	34	4.5%	68	9.0%
Multiple sclerosis relapse	0	0	55	7.3%	55	7.3%
Multiple sclerosis	1	0.1%	49	6.5%	50	6.6%
Fatigue	24	3.2%	8	1.1%	32	4.2%
Headache	17	2.2%	7	0.9%	24	3.2%
Asthenia	11	1.5%	12	1.6%	23	3.0%
Pyrexia	14	1.8%	9	1.2%	23	3.0%
Gait disturbance	9	1.2%	7	0.9%	16	2.1%
Hypoaesthesia	7	0.9%	8	1.1%	15	2.0%
Pain	10	1.3%	4	0.5%	14	1.8%
Muscular weakness	6	0.8%	6	0.8%	12	1.6%
Pain in extremity	9	1.2%	3	0.4%	12	1.6%
Balance disorder	4	0.5%	6	0.8%	10	1.3%
Chills	10	1.3%	0	0	10	1.3%
Myalgia	8	1.1%	2	0.3%	10	1.3%
Dizziness	7	0.9%	2	0.3%	9	1.2%

PT	Non-Serious		Serious		Total # Events	% of Total Events
	# Events	% of Total Events	# Events	% of Total Events		
Paraesthesia	5	0.7%	4	0.5%	9	1.2%
Mobility decreased	7	0.9%	1	0.1%	8	1.1%
Arthralgia	4	0.5%	3	0.4%	7	0.9%
Diarrhoea	2	0.3%	5	0.7%	7	0.9%
Nausea	4	0.5%	3	0.4%	7	0.9%
Optic neuritis	0	0	7	0.9%	7	0.9%
Gait inability	2	0.3%	4	0.5%	6	0.8%

Based on medical review, the 134 cases were relatively ranked for diagnostic certainty, and for those cases were a possible/probable flare was identified, WHO-UMC causality was assessed Table 16-102). At least 37 (27.6%) reported requiring hospitalization. For Multiple Sclerosis Relapse/Condition Aggravated case summaries please see Appendix 20.11.26.

Table 16-102 Diagnostic Certainty and WHO-UMC Causality Assessments for Multiple Sclerosis Flare Cases[1]

Diagnostic Certainty	Total Numbers	WHO-UMC Causality Probable (# of positive rechallenges)[1]	WHO-UMC Causality Possible (# of positive rechallenges)	WHO-UMC Causality Unlikely[2]	WHO-UMC Causality Unassessable[3]
High	22	2 (2)	20	0	0
Medium	56	1 (1)	51	4	0
Low	36	0	24	1	11
Total (low, medium, high cases)	**114**	**3 (3)**	**95**	**5**	**11**
Unassessable[4]	16	N/A	N/A	N/A	N/A
Duplicate cases	2	N/A	N/A	N/A	N/A
Not a Flare	1	N/A	N/A	N/A	N/A
N/A*	1	N/A	N/A	N/A	N/A
Grand Total[5]	**134**				

[1] Given the limitations of ICSR data, the diagnostic certainty classifications are relative and do not have the data to apply standard clinical criteria. Many of the cases coded as "high" still lack crucial data (e.g. Disease status prior to vaccination or full clinical course). In addition, causality assessment must be interpreted with caution recognizing that disease flares occur in the natural disease process in absence of identified triggers. Furthermore, "Probable" causality is applied to some cases where positive rechallenges have been described, but do not meet the standard criteria (e.g., complete resolution, absence of treatment); and this is further limited given that the disease itself is an alternate etiology of flares.
[2] Some of these cases have a very long TTO and are rather associated with COVID-19 infection; thus, likely more related to COVID-19 than to vaccination.
[3] Cases with no TTO are unassessable
[4] Unassessable cases have too little information to differentiate expected transient reactogenicity from a true flare.

[5]Grand total is the total number of all cases identified as potential flares for MS based on the search strategy and preliminary medical review described in the methodology section.
*Flare occurred after administration of CHADOX1 NCOV

The majority of the reports occurred within three days after vaccination (Table 16-103), although TTO must be interpreted with caution as it is difficult to differentiate expected reactogenicity (fatigue, paresthesia and hypoesthesia) from flares and thus challenging to identify exactly the day of onset of the flare.

Table 16-103 Time-to-Onset (TTO) by Dose Number for Multiple Sclerosis Flare Cases (low/medium/high diagnostic certainty cases only)

	0-3 days	4-7 days	8-14 days	15-28 days	>28 days	Unknown
Dose 1	19	5	7	4	1	2
Dose 2	24	2	5	5	4	1
Dose 3	6	1	0	0	0	0
Unknown	12	1	2	1	1	14

Note: TTO counts include 3 positive rechallenges.

Literature:

Vaccination Against SARS-CoV-2 in Neuroinflammatory Disease: Early Safety/ Tolerability Data [105]

Abstract

Background: Patients with autoimmune disease and on immunotherapy were largely excluded from seminal anti-SARS-CoV-2 vaccine trials. This has led to significant vaccine hesitancy in patients with neuroinflammatory diseases (NID); including, but not limited to multiple sclerosis (MS), neuromyelitis optica spectrum disorders (NMOSD), neurosarcoidosis and myelin oligodendrocyte antibody-mediated disease (MOG-AD). Data is urgently needed to help guide clinical care in the NID population.

Methods: This was a cross-sectional observational study evaluating adults with a neurologist-confirmed diagnosis of a neuroinflammatory disease (NID) and a neurologically asymptomatic control population. Participants were recruited from multiple academic centers participating in the MS Resilience to COVID-19 Collaborative study. We analyzed participant responses from a vaccine-specific questionnaire collected between February and May 2021.

Results: 1164 participants with NID and 595 controls completed the vaccine survey. Hesitancy rates were similar between NID and control groups (n = 134, 32.7% NID vs. n = 56, 30.6% control; p = 0.82). The most common reasons for hesitancy in NID participants were lack of testing in the autoimmune population and fear of demyelinating/neurologic events. Unvaccinated patients who had discussed vaccination with their doctor were less likely to be hesitant (n=184, 73.6% vs. n=83, 59.7%; p = 0.007). 634 NID patients and 332 controls had received at least one dose of a vaccine against SARS-CoV-2 at the time of survey completion. After adjusting for age, BMI, and

comorbidities, there was no difference in self-reported side effects (SE) between groups with the first dose (n = 256, 42.2% NID vs. 141, 45.3% control; p = 0.20) or second dose (n = 246, 67.0% NID vs. n = 114, 64.8% control, p = 0.85) of the mRNA vaccines nor with the viral-vector vaccines (n = 6, 46% NID vs. n = 8, 66% control; p = 0.39). All reported SEs fell into the expected SE profile. There was no difference in report of new/recurrent neurologic symptoms (n = 110, 16.2% vaccinated vs. 71, 18.2% unvaccinated; p = 0.44) nor radiologic disease activity (n = 40, 5.9% vaccinated vs. n = 30, 7.6% unvaccinated) between vaccinated and unvaccinated NID participants.

Conclusions: We found no difference in patient-reported vaccine side effects and no evidence of NID worsening after vaccination. Large-scale real-world evidence is needed for further validation.

Additional text from article: "During this inter-survey time interval, there was no difference in the rates of reported new or recurrent neurologic symptoms between the vaccinated and unvaccinated NID groups (n=110, 16.2% vaccinated vs. 71, 18.2% unvaccinated; p=0.44)."

Company comment: Studies such as this, comparing vaccinated versus unvaccinated patients, demonstrate the importance/relevance of controlled cohort data to evaluate the relative risk of flares. This study demonstrates the rates of flares are comparable between vaccinated and unvaccinated groups. For these types of studies, matching and appropriate risk windows are important considerations in study design.

Discussion:

Based on medical review, of the 134 cases, 22 had a relatively high level of diagnostic certainty, 56 had medium, and 36 had low. Sixteen (16) cases were unassessable, primarily as the signs and symptoms and duration could not be differentiated from expected reactogenicity. Three (3) medium/high cases had positive rechallenges and thus were classified as "probable". Based primarily on temporal association, 95 cases were classified as possible, 5 cases were unlikely, and 11 were unassessable (e.g., lacking TTO information). Thirty-seven cases required hospitalization, confounders were noted in 5 cases such as time since last bi-yearly treatment, stopping medication prior to vaccination, infections (bronchitis, UTI). (Appendix 20.11.26, Appendix 20.11.27).

Sixty-one (61) cases out of the 144 (low/med/high) flares occurred within 3 days of vaccination, the time window of innate immune response. There were numbers of reports within 7 days of vaccination, were comparable between Dose 1 (24) and Dose 2 (26). And 6 out of the 7 Dose 3 reports occurred within 3 days.

MS exacerbations have been reported after other vaccinations; however, large aggregate reports and cohort studies have been published which have not conclusively demonstrated a risk of flares after vaccinations (e.g., influenza vaccine) [103,105] after mRNA COVID-19 vaccines. There are no well-established data on background rates of MS flares, and as pointed out by Epstein et al, self-controlled cases series may be the best way to study flares given the individual variability of

MS disease patterns. COVID-19 infection has been reported to exacerbate MS, especially in those patients with higher disease activity prior to infection [104]. This recognition of the risk of COVID-19 infection for MS patients, further supports the benefit-risk profile of COVID-19 vaccines.

MS flare reports are difficult to assess as many of the signs and symptoms of MS flares mimic expected reactogenicity, there is a lack of large, cohort studies/publications, which precludes a robust analysis and the ability to confirm/asses the risk of MS flares after vaccination. Reports have occurred after a variety of vaccines, yet where available large studies have not confirmed a risk of flares. Furthermore, the robust study by Epstein et.al. which included 1,164 participants, of which 634 NID patients received at least one dose of COVID vaccine demonstrated that there was no difference in new/recurrent neurologic symptoms (n = 110, 16.2% vaccinated vs. 71, 18.2% unvaccinated; p = 0.44) nor radiologic disease activity (n = 40, 5.9% vaccinated vs. n = 30, 7.6% unvaccinated) between vaccinated and unvaccinated NID participants.

In conclusion, while individual cases of MS flares have been reported, limitations of available data, including incompleteness of reports, the natural history of MS flares/exacerbations, one robust NID study which did not demonstrate a difference between vaccinated and unvaccinated rates of neurologic symptoms, and the lack of useful data to inform background rates for MS flares, render the association between SPIKEVAX and MS flares to be weak and speculative. The MAH will continue to monitor MS flare reports through routine pharmacovigilance and explore the use of RWE to further inform the topic.

Systemic Lupus Erythematosus (SLE) Flares:

Background:

Systemic lupus erythematosus (SLE) is a chronic, autoimmune disease that can involve skin and mild joints, or can progress to life threatening central nervous, renal and hematologic involvement. Patients often present with symptoms of fever, fatigue, myalgia, and weight change, as well as arthritis/arthralgias and skin and mucous lesions/rashes. Cardiac disease may present as pericarditis, and these patients have an increased risk of coronary artery disease. Raynaud's phenomenon, thromboembolic events, and vasculitis may also occur. Approximately 50% of SLE patients develop renal nephritis and/or nephropathy. Gastrointestinal and pulmonary involvement may also occur. Anemia and leukopenia are common, and neutropenia can result from immunosuppressive treatments. Various lab tests can support the diagnosis of SLE, including ANA, anti-dsDNA, antiphospholipid antibodies, C3 and C4 levels, ESR, and CRP. Lupus flares present with fever, painful/swollen joints, fatigue, rashes, oral or nasal ulcers, general leg swelling, numbness or tingling, and chest pain with breathing. Emotional/physical stress, infections, exhaustion, exposure to UV rays, or injuries, and non-compliance with treatment are recognized

triggers of flares. There is inconclusive evidence if SLE is a risk factor for more severe COVID; however, many patients have other well-established risk factors. Globally, the general recommendation suggests that the potential benefits outweigh risks, although some immunosuppressant medications may impact immunogenicity and effectiveness. (UpToDate, "Clinical manifestations and diagnosis of systemic lupus erythematosus")

Results:

Cumulatively, there were 73 cases of potential SLE flare, of which, 61 cases were serious. There were no fatal cases. In total, considering all Preferred Terms (PTs), there were 565 events (192 of which were serious) reported in the 73 cases. Fifty-eight (58) cases were medically confirmed. The majority of reports were in females (68; 93.2%) compared to males (5; 6.8%) and were most frequently reported in individuals 40 to 64 years of age (58.9%) with a median age of 50.0 years (min 22.0, max. 86.0). Age information was unknown or missing for 2 cases (Table 16-104).

Table 16-104 Case Distribution by Gender and Age Group, Cumulative to 31 Dec 2021

Age Group (Years)	Female		Male		Total of # Cases	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases		
18-29	4	5.5%	1	1.4%	5	6.8%
30-39	10	13.7%	1	1.4%	11	15.1%
40-49	18	24.7%	1	1.4%	19	26.0%
50-64	22	30.1%	2	2.7%	24	32.9%
65-74	10	13.7%	0	0	10	13.7%
75+	2	2.7%	0	0	2	2.7%
Missing	2	2.7%	0	0	2	2.7%
Grand total	**68**	**93.2%**	**5**	**6.8%**	**73**	**100.0%**

Table 16-105 shows the most frequently reported events in the potential SLE flare cases. Many of these are consistent with the coding and clinical signs and symptoms described in SLE flares (such fatigue, arthralgia, pain, peripheral swelling, chest pain and dyspnea, and erythema).

Table 16-105 Most Frequently Reported (n≥6) PTs in SLE Flare Cases

PT	Non-Serious		Serious		Total # Events	% of Total Events
	# Events	% of Total Events	# Events	% of Total Events		
Systemic lupus erythematosus	6	1.1%	48	8.5%	54	9.6%
Condition aggravated	18	3.2%	12	2.1%	30	5.3%
Fatigue	20	3.5%	3	0.5%	23	4.1%

PT	Non-Serious		Serious		Total # Events	% of Total Events
	# Events	% of Total Events	# Events	% of Total Events		
Pyrexia	16	2.8%	6	1.1%	22	3.9%
Arthralgia	18	3.2%	3	0.5%	21	3.7%
Headache	14	2.5%	7	1.2%	21	3.7%
Nausea	8	1.4%	3	0.5%	11	1.9%
Pain	9	1.6%	2	0.4%	11	1.9%
Chills	10	1.8%	0	0	10	1.8%
Dizziness	7	1.2%	3	0.5%	10	1.8%
Myalgia	6	1.1%	4	0.7%	10	1.8%
Pain in extremity	8	1.4%	2	0.4%	10	1.8%
Peripheral swelling	8	1.4%	0	0	8	1.4%
Vaccination site pain	7	1.2%	1	0.2%	8	1.4%
Chest pain	3	0.5%	3	0.5%	6	1.1%
Dyspnoea	4	0.7%	2	0.4%	6	1.1%
Erythema	5	0.9%	1	0.2%	6	1.1%
Vomiting	4	0.7%	2	0.4%	6	1.1%

Based on medical review, the 73 cases were relatively ranked for diagnostic certainty, and for those possible/probable flare cases (low/medium/high), WHO-UMC causality was assessed (Table 16-106). At least 14 (19.2%) reported requiring hospitalization. Four positive rechallenges were described. For case summaries of SLE flares see: Appendix 20.11.30.

Table 16-106 Diagnostic Certainty and WHO-UMC Causality Assessments for SLE Flare Cases[1]

Diagnostic Certainty	Total Numbers	WHO-UMC Causality Probable (# of positive rechallenges)[1]	WHO-UMC Causality Possible (# of positive rechallenges)	WHO-UMC Causality Unlikely[2]	WHO-UMC Causality Unassessable[3]
High	12	2 (2)	9	1	0
Medium	17	1 (1)	15	0	1
Low	27	0	24 (1)	1	2
Total (low, medium, high cases)	56	3 (3)	48 (1)	2	3
Unassessable[4]	12	N/A	N/A	N/A	N/A
Duplicate cases	1	N/A	N/A	N/A	N/A
Not a Flare	4	N/A	N/A	N/A	N/A

Grand Total[5]	**73**

[1] Given the limitations of ICSR data, the diagnostic certainty classifications are relative and do not have the data to apply standard clinical criteria. Many of the cases coded as "high" still lack crucial data (e.g. Disease status prior to vaccination or full clinical course). In addition, causality assessment must be interpreted with caution recognizing that disease flares occur in the natural disease process in absence of identified triggers. Furthermore, "Probable" causality is applied to some cases where positive rechallenges have been described, but do not meet the standard criteria (e.g., complete resolution, absence of treatment); and this is further limited given that the disease itself is an alternate etiology of flares.
[2] Some of these cases have a very long TTO and are rather associated with COVID-19 infection; thus, likely more related to COVID-19 than to vaccination.
[3] Cases with no TTO are unassessable
[4] Unassessable cases have too little information to differentiate expected transient reactogenicity from a true flare.

[5]Grand total is the total number of all cases identified as potential flares for SLE based on the search strategy and preliminary medical review described in the methodology section.

The highest number of reports were within 3 days after Dose 1 (Table 16-107). TTO for SLE flares is particularly challenging as expected reactogenicity can mimic flares, and thus the exact timing of the onset of the flare is challenging to identify.

Table 16-107 Time-to-Onset (TTO) by Dose Number for SLE Flare Cases (low/medium/ high diagnostic certainty cases only)

	0-3 days	4-7 days	8-14 days	15-28 days	>28 days	Unknown
Dose 1	22	6	3	2	3	3
Dose 2	9	2	0	1	2	2
Dose 3	1	1	0	0	0	0
Unknown	1	2	0	0	0	0

Note: TTO counts include 4 positive rechallenges

Literature:

The Use of COVID-19 Vaccines in Patients with SLE [78].

Abstract

Purpose of review: Three COVID-19 vaccines obtained emergency authorization from the Food and Drug Administration (FDA) and are widely used in the USA. Unfortunately, there is a paucity of evidence on the safety and efficacy of these vaccines in patients with autoimmune inflammatory rheumatic diseases (AIIRD), as these patients were excluded from all phases of vaccine development. Here we reviewed current data on COVID-19 vaccination in patients with AIIRD, with emphasis on systemic lupus erythematosus (SLE), and provided a comprehensive update on the benefits and risks of vaccination.

Recent findings: Patients with SLE have worse immune responses following SARS-CoV-2 vaccination than healthy controls. The efficacy of the COVID-19 vaccines seems to be further reduced by immunosuppressive medications, such as glucocorticoids (GC), methotrexate (MTX), mycophenolate/mycophenolic acid (MMF), and rituximab (RTX). However, these data do not

substantiate that AIIRD patients are at greater risk of disease flares or have a higher incidence of side effects following vaccination. There is no significant safety concern for the use of COVID-19 vaccines in patients with AIIRD. The benefits of vaccination far outweigh the risks in patients with AIIRD, including SLE. More data are needed to determine the necessity of a booster vaccine dose and appropriate adjustment of immunosuppressants around the administration of vaccine.

Keywords: COVID-19 vaccines; Immunosuppressive agents; Rheumatic diseases; SARS-CoV-2; Systemic lupus erythematosus.

Table 2 Summary of studies on COVID-19 vaccine safety in patients with autoimmune inflammatory rheumatic disorders

Author	Design	Vaccine	Cohort	Diseases	Therapy	Time period	Results
Geisen et al.	Cohort	Pfizer, Moderna	26 AIIRDs 42 HCs	SLE 2 (7.7%), RA 8 (30.1%), PsA 6 (23.1%), SpA 3 (11.5%)	GC 7 (26.9%), TNFi 13 (50%), cDMARDs 8 (30.8%)	Pre 1st dose to 14 days post 2nd dose	Stable DAS28, PGA, PhGA pre- and post-vaccine No patient with AIIRDs needed to adjust DMARD or GC therapy in the 6 weeks of trial duration
Izmirly et al.	Cohort	Pfizer, Moderna, J&J	90 SLE 20 HCs	SLE specific	GC 26 (29%), MTX 8 (14.9%), MMF 21 (23%), RTX 3 (3%), BLyS 10 (11%)	Average 23.6 days (range 5–70) post final dose	Similar pre-/post-vaccine SLEDAI 9 (11.4%) patients had a post-vaccination flare; 8/9 mild/moderate and 1/9 severe No changes in % (+) anti-dsDNA and/or low C3/C4
Furer et al.	Cohort	Pfizer	686 AIIRD 121 HC	SLE 101 (14.7%); RA 263 (38.3%), PsA 165 (24.1%)	GC 55 (21%), MTX 116 (44%), TNFi (18%), BCDT 87 (13%), MMF 38 (4%)	Within 2 weeks post 1st dose, within 2–6 weeks post 2nd dose	Stable pre- and post-vaccine disease activity indices
Conolly et al.	Cohort	Pfizer, Moderna	325 AIIRD	SLE 91 (28%), IA 123 (38%), CTDs 62 (19%)	csDMARDs 63 (44%), biologics 62 (19%), combination 120 (37%)	Within 1st week post 1st dose	Peripheral neuropathy—1 case Local side effects—89%, pain most common Systemic side effects—69%, fatigue most common. Similar symptoms to those reported in general population vaccine trials
Boekel et al.	Cross-sectional	Pfizer, AZ, Moderna	505 IMID 203 HC	SLE 25 (5%), RA 204 (40%), PsA 49 (10%); AS 39 (8%), MS 81 (16%), PMR 17 (3%)	No treatment 157 (31%), MTX 169 (33%), other csDMARDs 67 (13%), GC 77 (15%), TNFi 93 (18%), BCDT 35 (7%)	Median of 15 days (IQR 10–25) for AIIRD and 15 days (10–34) for HC post 1st dose	Adverse events of COVID-19 vaccines in patients with IMID are comparable with controls Patients with AIIRD more frequently reported joint pain than controls (10% vs 1%) 26 (5%) patients with AIIRDs self-reported disease worsening up to 2 months post vaccine
Felten et al.	Cross-sectional	Mixed types	696 SLE	SLE specific	GC 373 (53.6%), HCQ 542 (77.9%), MTX/LEF/MMF/AZA/CTX 347 (49.9%), BLyS 76 (10.9%); RTX 22 (3.2%)	Not applicable	21 (3%) self-reported/physician confirmed SLE flares after a median of 3 days (IQR 0–29) post vaccine; 15 treatment change, and 4 admissions for SLE flares. Flare in the year pre-vaccine was associated an increased risk of post-vaccine flare (RR =5.52, 95% CI 2.17–14.03).
Watad et al.	Case series	Pfizer, AZ, Moderna	17 flares, 10 de-novo IMIDs	4 cases in SLE	Not applicable	Not applicable	4 cases of SLE flares

Pfizer, Pfizer/BioNTech BNT162b2; Moderna, Moderna mRNA-1273; J&J, Janssen Ad26.COV2.S; AZ, AstraZeneca ChAdOx1 nCoV-19
IMID immune-mediated inflammatory disease, *AIIRD* autoimmune inflammatory rheumatic diseases, *HC* healthy control, *SLE* systemic lupus erythematosus, *RA* rheumatoid arthritis, *SpA* spondyloarthritis, *PsO* psoriasis, *PsA* psoriatic arthritis, *AS* ankylosing spondyloarthritis, *PMR* polymyalgia rheumatica, *MS* multiple sclerosis, *IA* inflammatory arthritis, *CTD* overlap connective tissue disorders, *csDMARDs* conventional synthetic disease-modifying antirheumatic drugs, *HCQ* hydroxychloroquine, *GC* glucocorticoid, *MTX* methotrexate, *AZA* azathioprine, *LEF* leflunomide, *MMF* mycophenolate mofetil, *CTX* cyclophosphamide, *RTX* rituximab, *BCDT* B-cell depletion therapy, *BLyS* belimumab, *TNFi* tumor necrosis factor inhibitor, % percentage of patients, *(+)* positive, *Anti-dsDNA* anti-double stranded DNA antibody, *IQR* interquartile range, *RR* relative risk, *CI* confidence interval, *DAS28* disease activity score 28, *PGA* Patients Global Assessment, *PhGA* Physician Global Assessment, *SLEDAI* Systemic Lupus Erythematosus Disease Activity Index, *SDAI* Simple Disease Activity Index, *DAPSA* Disease Activity Index for Psoriatic Arthritis, *PASI* Psoriasis Area and Severity Index, *ASDAS* Ankylosing Spondylitis Disease Activity Score

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Company Comment: This is a systematic review of cohort studies done in patients with autoimmune rheumatic diseases, including SLE, primarily through survey methods. Flare rates generally ranged from 3-5%. Izmirly et al, [77] noted there was no change in dsDNA or C3/C4 levels after vaccination. The safety profile was comparable to the general population; however, increased arthralgia and flares or worsening of conditions were noted. Despite the occurrence of flares, the authors note the favorable benefit-risk profile of COVID vaccines in this population. Most of the studies did not have control/unvaccinated groups, and thus interpretation with regards to the risk of SLE flares after COVID vaccination is limited.

Discussion:

Based on medical review, of the 73 cases of potential SLE flares, 12 had a relatively high level of diagnostic certainty, 17 had medium, and 27 had low. Because the signs and symptoms of SLE flares mimic the expected reactogenicity, many cases were considered low or unassessable; and the cases of SLE exacerbation were limited by missing information (lack of reported clinical course, diagnostics, treatment and outcome). Twelve (12) cases were unassessable, primarily as the signs and symptoms and duration could not be differentiated from expected reactogenicity. Three (3) medium/high cases had positive rechallenges and thus were classified as "probable". Based primarily on temporal association, 48 cases were classified as possible, 2 cases were unlikely, and 3 were unassessable (e.g., lacking TTO information). Fourteen (14) cases required hospitalization, confounders were noted in six cases such as time since last bi-yearly treatment, stopping medication prior to vaccination comorbidities (Evan's syndrome, RA with concomitant reported flare, one case with multiple concurrent autoimmune conditions), infections (COVID-19, upper respiratory infection, UTI). (Appendix 20.11.30 and Appendix 20.11.31).

Thirty-three (33) cases out of the 56 (low/med/high) flares occurred within 3 days of vaccination, and 44 occurred with 7 days after vaccination, the time window of innate immune response. There were numbers of reports within 7 days of vaccination, were higher after Dose 1 (28) compared to Dose 2 (11). This must be interpreted with caution as it is unknown how many people with reactions after Dose 1 received subsequent vaccination; and there is no dose specific vaccinations rates for SLE patients. There were only two cases reported after Dose 3, both within 7 days after vaccination.

SLE exacerbations have been reported after other vaccinations; however, most published studies have not clearly demonstrated an increased risk of flares after vaccination, and many did not have unvaccinated comparator groups. [106] showed that 8/9 studies did not show a worsening of SLE disease after vaccination; [107].

COVID-19 infection has been reported to exacerbate MS, especially in those patients with lupus nephritis prior to infection. This recognition of the risk of COVID-19 infection for MS patients, further supports the benefit-risk profile of COVID-19 vaccines [108].

SLE flare reports are difficult to assess as many of the signs and symptoms of SLE flares mimic expected reactogenicity (fatigue, arthralgia, myalgia), which precludes a robust analysis and the ability to confirm/asses the risk of SLE flares after vaccination. Published cohort studies have reported flare rates ranging from 3-15%, however, many do not have comparator unvaccinated groups; and thus, interpretation is limited.

In conclusion, while individual cases of SLE flares have been reported, limitations of available data, including incompleteness of reports, the natural history of SLE flares/exacerbations, and the lack of useful data to inform background rates for SLE flares, render the association between

SPIKEVAX and SLE flares to be weak and speculative. The MAH will continue to monitor SLE flare reports through routine pharmacovigilance and explore the use of RWE to further inform the topic.

Inflammatory Bowel Disease (IBD, including Ulcerative Colitis and Crohn's) Flares

Background:

Inflammatory bowel disease (IBD) includes ulcerative colitis (UC) and Crohn's disease. IBD is understood to be a dysregulation of the mucosal immune system, either increased or decreased immune response to intestinal microbiota. Abnormal levels of immunoregulatory cytokines are found in IBD flares. For example, in Crohn's disease, large amounts of IFN and TNF-alpha are found. In addition, there is a disruption of the microbiota. Several genetic loci (such as NOD2) have been associated with IBD, and many of these loci are common to both ulcerative colitis and Crohn's disease, and many are involved with the innate immune response. It is not clear if patients with IBD are at higher risk for severe COVID, unless they are on significant doses of glucocorticoids. The GI tract in general may be susceptible to SARS-CoV2 infection because it has high expression of angiotensin-converting enzyme (ACE) inhibitors which bind to the spike protein. GI symptoms with COVID may be from direct viral damage or from the immune response. The general consensus is that the benefit-risk profile of COVID vaccines in IBD patients is favorable.

(UpToDate: "Immune and microbial mechanisms in the pathogenesis of inflammatory bowel disease")

Background Ulcerative colitis:

Ulcerative colitis (UC) is thought to be a possible autoimmune disease due to genetic and environmental factors that result in recurring episodes of inflammation of the mucosal layer of the colon, and presents with abdominal pain, diarrhea, and bloody stools/rectal bleeding. Fatigue, fever and weight loss may also occur. Flares can be caused by medications (including NSAIDs and antibiotics), smoking, stress, and foods. Thus far, the general recommendations from professional bodies (and as discussed in the literature) have recommended that people with UC receive COVID vaccinations given the potential benefit-risk profile.

Background Crohn's disease

Crohn's disease is an inflammatory bowel disease that has transmural inflammation and can occur anywhere from the oral cavity to the perianal area. Crohn's disease usually presents with abdominal pain, diarrhea (with or without bleeding), fatigue and weight loss, and severe complications which can include malabsorption, fistulas, abscesses, and perianal disease. There

can also be extraintestinal manifestations and complications such as arthritis, eye and skin disorders, hepatobiliary complications, amyloidosis and kidney stones [109].

Results:

Cumulatively, there were 83 potential cases of IBD, of which, 71 cases were serious and 0 had fatal outcomes. In total, considering all Preferred Terms (PTs), there were 504 events (252 of which were serious) reported in the 83 cases. Fifty-four (54) cases were medically confirmed. The majority of reports were in females (58; 69.9%) compared to males (23; 27.7%) (sex information was missing or unknown for 2 cases) and were most frequently reported in individuals 30-39 years of age (28.9%) followed by those 40-49 years of age. The median age was 46.0 years (min. 18 max. 82); age was unknown or missing for 4 cases (Table 16-108).

Table 16-108 Case Distribution by Gender and Age Group, Cumulative to 31 Dec 2021

Age Group (Years)	Female		Male		Unknown		Total # of Cases	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases	# Cases	% of Total Cases		
18-29	2	2.4%	6	7.2%	0	0	8	9.6%
30-39	18	21.7%	6	7.2%	0	0	24	28.9%
40-49	16	19.3%	3	3.6%	0	0	19	22.9%
50-64	11	13.3%	2	2.4%	0	0	13	15.7%
65-74	6	7.2%	4	4.8%	0	0	10	12.0%
75+	4	4.8%	1	1.2%	0	0	5	6.0%
Missing	1	1.2%	1	1.2%	2	2.4%	4	4.8%
Grand total	**58**	**69.9%**	**23**	**27.7%**	**2**	**2.4%**	**83**	**100.0%**

Table 16-109 shows the most frequently reported events in the potential IBD flare cases. Many of these are consistent with the coding and clinical signs and symptoms described in IBD flares (such diarrhea, abdominal pain, and hematochezia).

Table 16-109 Most Frequently Reported (n≥6) (Preferred Terms (PTs) in IBD Flare Cases

PT	Non-Serious		Serious		Total # Events	% of Total Events
	# Events	% of Total Events	# Events	% of Total Events		
Colitis ulcerative	7	1.4%	53	10.5%	60	11.9%
Condition aggravated	22	4.4%	12	2.4%	34	6.7%
Diarrhoea	15	3.0%	15	3.0%	30	6.0%
Abdominal pain	12	2.4%	6	1.2%	18	3.6%
Pyrexia	9	1.8%	8	1.6%	17	3.4%

PT	Non-Serious		Serious		Total # Events	% of Total Events
	# Events	% of Total Events	# Events	% of Total Events		
Fatigue	9	1.8%	6	1.2%	15	3.0%
Headache	11	2.2%	4	0.8%	15	3.0%
Nausea	10	2.0%	1	0.2%	11	2.2%
Pain in extremity	9	1.8%	2	0.4%	11	2.2%
Crohn's disease	1	0.2%	9	1.8%	10	2.0%
Chills	8	1.6%	1	0.2%	9	1.8%
Haematochezia	0	0	9	1.8%	9	1.8%
Malaise	3	0.6%	5	1.0%	8	1.6%
Pain	6	1.2%	2	0.4%	8	1.6%
Abdominal pain upper	5	1.0%	2	0.4%	7	1.4%
Arthralgia	4	0.8%	2	0.4%	6	1.2%
Vomiting	2	0.4%	4	0.8%	6	1.2%

Based on medical review, the 83 cases were relatively ranked for diagnostic certainty, and for those cases in which a possible/probable flare was identified, WHO-UMC causality was assessed (Table 16-110). At least 18 (21.7%) reported requiring hospitalization. There were four positive rechallenges described. For case summaries of IBD flare see Appendix 20.11.32.

Table 16-110 Diagnostic Certainty and WHO-UMC Causality Assessments for IBD Flare Cases[1]

Diagnostic Certainty	Total Numbers	WHO-UMC Causality Probable (# of positive rechallenges)[1]	WHO-UMC Causality Possible (# of positive rechallenges)	WHO-UMC Causality Unlikely [2]	WHO-UMC Causality Unassessable [3]
High	17	0	15	0	2
Medium	40	3 (3)	32	5	0
Low	20	0	17 (1)	1	2
Total (low, medium, high cases)	**77**	**3 (3)**	**64 (1)**	**6**	**4**
Unassessable[4]	4	N/A	N/A	N/A	N/A
Duplicate cases	0	N/A	N/A	N/A	N/A
Not a Flare	2	N/A	N/A	N/A	N/A
Grand Total[5]	**83**				

[1] Given the limitations of ICSR data, the diagnostic certainty classifications are relative and do not have the data to apply standard clinical criteria. Many of the cases coded as "high" still lack crucial data (e.g., disease status prior to vaccination or full clinical course). In addition, causality assessment must be interpreted with caution recognizing that disease flares occur in the natural disease process in absence of identified triggers. Furthermore, "Probable" causality is applied to some cases where positive

rechallenges have been described, but do not meet the standard criteria (e.g., complete resolution, absence of treatment); and this is further limited given that the disease itself is an alternate etiology of flares.
[2] Some of these cases have a very long TTO and are rather associated with COVID-19 infection; thus, likely more related to COVID-19 than to vaccination.
[3] Cases with no TTO are unassessable
[4] Unassessable cases have too little information to differentiate expected transient reactogenicity from a true flare.
[5]Grand total is the total number of all cases identified as potential flares for IBD based on the search strategy and preliminary medical review described in the methodology section.

The highest numbers of reports occurred within 3 days of vaccination, after Dose 1 and Dose 2. Table 16-111 describes the time to onset of the flare, for IBD often characterized by abdominal pain and diarrhea or hematochezia.

Table 16-111 Time-to-Onset (TTO) by Dose Number for IBD Flare Cases (low/medium/high diagnostic certainty cases only)

	0-3 days	4-7 days	8-14 days	15-28 days	>28 days	Unknown
Dose 1	18	3	3	4	2	0
Dose 2	19	4	4	0	3	3
Dose 3	3	3	0	0	0	0
Unknown	3	2	2	1	0	4

Note: TTO counts include 4 positive rechallenges

Literature:

Impact of SARS-CoV-2 Vaccination on Inflammatory Bowel Disease Activity and Development of Vaccine-Related Adverse Events: Results From PREVENT-COVID [92]

Abstract

Background: Severe acute respiratory syndrome coronavirus 2 vaccination is recommended for all individuals with inflammatory bowel disease (IBD), including those on immunosuppressive therapies; however, little is known about vaccine safety and efficacy in these patients or the impact of vaccination on IBD disease course.

Methods: We evaluated coronavirus disease 2019 (COVID-19) vaccine-related adverse events (AEs) and the effect of vaccination on IBD disease course among participants in the PREVENT-COVID (Partnership to Report Effectiveness of Vaccination in populations Excluded from initial Trials of COVID) study, a prospective, observational cohort study. Localized and systemic reactions were assessed via questionnaire. Disease flare was defined by worsening IBD symptoms and change in IBD medications. Outcomes were stratified by vaccine type and IBD medication classes.

Results: A total of 3316 individuals with IBD received at least 1 COVID-19 vaccine. Injection site tenderness (68%) and fatigue (46% dose 1, 68% dose 2) were the most commonly reported localized and systemic AEs after vaccination. Severe localized and systemic vaccine-related AEs

were rare. The mRNA-1273 vaccine was associated with significantly greater severe AEs at dose 2 (localized 4% vs 2%, systemic 15% vs 10%; P < .001 for both). Prior COVID-19 infection, female sex, and vaccine type were associated with severe systemic reactions to dose 1, while age <50 years, female sex, vaccine type, and antitumor necrosis factor and vedolizumab use were associated with severe systemic reactions to dose 2. Overall rates (2%) of IBD flare were low following vaccination.

Conclusions: Our findings provide reassurance that the severe acute respiratory syndrome coronavirus 2 vaccine is safe and well tolerated among individuals with IBD, which may help to combat vaccine hesitancy and increase vaccine confidence.

Additional extracted text: A total of 160 (4.8%) participants reported a history of COVID-19 infection before SARS-CoV-2 immunization. The Vaccine distribution included 1908 (57.5%) BNT162b2 (Pfizer-BioNTech), 1247 (37.6%) mRNA-1273 (NIH-Moderna), and 161 (4.9%) Ad26.COV2.S (Johnson & Johnson). The majority of the participants were taking biologic or small molecule therapies at baseline. 6 months after COVID-19 vaccination, 32.5% described IBD in remission, 16.8% described IBD as rarely active, 15.9% described IBD as occasionally active, 18.2% described IBD as sometimes active, 11.0% described IBD as often active, and 5.7% described IBD as constantly active with the most reported GI symptoms that worsened after vaccination were 29% fatigue, 12% bowel frequency, 12% extraintestinal manifestations, and 11% abdominal pain. All participants who completed baseline and 30-day post-enrollment surveys, outcomes were stratified by vaccine type and IBD medication classes. Participants were assessed for flare of IBD, which was defined as (1) worsening of at least 1 of the symptoms of abdominal pain, bowel frequency, rectal bleeding, and extraintestinal manifestation after vaccine 1 or 2; and (2) a need to add or change IBD medication due to symptoms within 1 month of vaccination. Only 71 (2.1%) individuals met criteria for IBD flare following vaccination and the breakdown included 48 (2.5%) of 1908 from BNT162b2, 22 (1.8%) of 1247 from mRNA-1273, and 1 (0.6%) of 161 from Ad26.COV2.S. The rates of IBD flare were low (2%) following COVID-19 in a cohort of 3316 participants with IBD, and similar to rates of IBD flare reported in prior studies evaluating the effect of influenza, pneumococcal, and shingles vaccination on IBD disease course.

Company Comment: This study describes IBD flares after multiple COVID vaccines, including mRNA1273. It does not provide a comparator of flare rates in unvaccinated patients, and it mentions that IBD flares have been reported after multiple vaccines including influenza, pneumococcal and shingles.

Adverse Events After SARS-CoV-2 mRNA Vaccination Among Patients with Inflammatory Bowel Disease [75]

Abstract

Introduction: Patients with immune-mediated inflammatory diseases such as inflammatory bowel disease (IBD) on immunosuppressive and biologic therapies were largely excluded from severe acute respiratory syndrome coronavirus-2 messenger RNA vaccine trials.

Methods: We evaluated adverse events (AE) after messenger RNA vaccination in 246 adults with IBD participating in a longitudinal vaccine registry.

Results: In general, AE frequency was similar to that reported in the general population. AEs were more common among younger patients and those with previous COVID-19. AEs were less common in individuals receiving advanced therapies with biologics or small-molecule inhibitors.

Discussion: Those with IBD and other immune-mediated inflammatory diseases can be reassured that the AE risk is likely not increased, and may be reduced, while on advanced therapies.

Botwin et al (2021) [75] discussed a Coronavirus Risk Associations and Longitudinal Evaluation-IBD (Corale-IBD) study, a prospective, nationwide registry, study of 246 subjects who received at least 1 dose of a 2-dose series of either BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) vaccines using a web-based survey. 246 subjects (mean age 47.4y; 57% female) completed an AE assessment following at least 1 mRNA vaccine dose. One hundred forty-one (57%) received BNT162b2 (Pfizer), and 105 (42.7%) received mRNA-1273 (Moderna), 58.2% were female, 33.9% were male, 84.2% were white and 3.0% Black and 1.2 % Asian. IBD diagnosis included Crohn's disease (67%) and ulcerative/indeterminate colitis (33%). Nine subjects (3.7%) reported prior COVID infection. At the time of vaccination, 50 (20.3%) were not receiving any immune-modifying therapies. The proportions of patients receiving systemic corticosteroids, thiopurine monotherapy, anti-tumor necrosis factor-α (TNF) monotherapy, anti-TNF with concomitant thiopurine, vedolizumab, ustekinumab, and tofacitinib were 6.9%, 2.4%, 28.0%, 8.5%, 13.4%, 16.7%, and 1.6%, respectively.

The overall AE frequency was 39% after dose 1 (D1), and 62% after dose 2 (D2). Localized injection-site reactions were reported in 38% after D1, and in 56% after D2. The most common systemic AE included fatigue/malaise (reported by 23% after D1, and 45% after D2), headache/dizziness (14% after D1, 34% after D2) and fever/chills (5% after D1, 29% after D2). Gastrointestinal symptoms were reported by 6% after D1, and 11.5% after D2. These frequencies are similar to the clinical trial reports as well as data from a distinct health-care worker study conducted at the same site and using similar AE capture methods.

In general, AE frequency was similar to that reported in the general population. AE were more common among younger patients, and those with prior COVID-19. AE were less common in individuals receiving biologic therapy.

Those with IBD and other IMID on these commonly prescribed therapies can be reassured that the AE risk is likely not increased, and may be reduced, while on biologics. Severe AE or those lasting more than 7 days were very uncommon.

Company comment: IBD GI symptoms were reported after both Pfizer and Moderna COVID vaccines, with a higher rate noted after Dose 2, although there is a longer follow-up time thus limiting interpretation. This study did not provide controlled/unvaccinated comparators.

Discussion IBD Flares:

Based on medical review, of the 83 potential IBD flare cases, 17 had a relatively high level of diagnostic certainty, 40 had medium, and 20 had low. Four (4) cases were unassessable. Three (3) cases had reported positive rechallenges, and thus were classified as "probable". Based primarily on temporal association, 64 cases were classified as possible, 6 cases were unlikely, and 4 were unassessable (e.g., lacking TTO information). Eighteen (18) cases required hospitalization. The serious reports in patients with a history of IBD describe abdominal pain, diarrhea, hemorrhagic/bloody stools/hematochezia, and one required surgery. Gastrointestinal symptoms have been reported following mRNA vaccines, including nausea, vomiting and diarrhea; and thus, the immune response especially chemokines and cytokines which induce gastrointestinal symptoms could hypothetically contribute to IBD exacerbation. (Appendix 20.11.32, Appendix 20.11.33).

Forty-three (43) cases out of the 77 (low/med/high) flares occurred within 3 days of vaccination, and 55 occurred with 7 days after vaccination, the time window of innate immune response. There were numbers of reports within 7 days of vaccination, were comparable after Dose 1 (21) compared to Dose 2 (23). This must be interpreted with caution as it is unknown how many people with reactions after Dose 1 received subsequent vaccination; and there is no dose specific vaccinations rates for IBD patients. There were six cases reported after Dose 3, all within 7 days after vaccination.

IBD exacerbations have been reported after other vaccinations; however, most published studies have not clearly demonstrated an increased risk of flares after vaccination, and many did not have unvaccinated comparator groups [110] which reported a pooled flare rate of 2%: however, the lack of an unvaccinated comparator limits the interpretation.).

COVID-19 infection has been reported to be low in patients with IBD, however some immunosuppressant therapy (e.g., corticosteroids and mesalamine) have been associated with

more severe disease and worse outcomes [111]. In general, considering the potential benefits and risks, COVID vaccination is recommended for IBD patients.

IBD published cohort studies have reported flare rates among various COVID vaccines, such as the publication by [92]; however, lack of a comparator unvaccinated group limits interpretation.

In conclusion, while individual cases of IBD flares have been reported, limitations of available data, including incompleteness of reports, the natural history of IBD flares/exacerbations, the lack of studies of flares including unvaccinated comparators, and the lack of useful data to inform background rates for IBD flares, render the association between SPIKEVAX and IBD flares to be weak and speculative. The MAH will continue to monitor IBD flare reports through routine pharmacovigilance and explore the use of RWE to further inform the topic. (Appendix 20.11.33).

16.3.5.7.5. Discussion

The general pattern of most commonly reported adverse events in the autoimmune and inflammatory disease subpopulation is comparable to the entire general population. In this reporting period, COVID-19 adverse events were more commonly reported (particularly in late summer and fall) as compared to PBRER#1. In addition to the well-recognized impact of immunosuppressant use in this population that can impair immunogenicity as reported in the literature, this noted increase in COVID-19 adverse events reports in the PBRER#2 reporting period may be due to stimulated reporting, social/policy issues, virological factors (variants), and host factors (waning immunity and impact of immunosuppressant therapies).

Exacerbation of underlying autoimmune and inflammatory disorders was one area identified that was explored in depth in PBRER#1 and in this PBRER#2. Among the potential flare cases identified, there are three types of cases: 1) non-autoimmune conditions aggravated; 2) some conditions (cardiac, renal, neurologic) which may not be related to the underlying AI/ID condition; and 3) those with evidence of the AI/ID flares and condition exacerbated. A revised search strategy applied in this PBRER#2 identified 1310 potential cases of flares, of which 1003 were identified as potential flares per preliminary medical narrative and data review. Many of these cases have limited information and lack a description of the baseline disease status or historic pattern of flares, the clinical course, diagnostics/labs/imaging, treatment, outcome, clear time to onset and/or dose number. Many of the signs and symptoms of reactogenicity mimic signs and symptoms of autoimmune disease (such as fever, myalgia, fatigue, arthralgia, headache), and thus it is difficult to fully differentiate transient reactogenicity from AI/ID reactivation/flare and difficult to establish the TTO of the flares. Given the data limitations of passive, post-EUA reports, full assessment of AI/ID flares is precluded. Cumulatively, within these cases of reported flares of AI/ID conditions there is a heterogeneity of autoimmune/inflammatory disorders described. In-depth sections reviewed possible flares cases rheumatoid arthritis, myasthenia gravis, multiple sclerosis, systemic

lupus erythematosus, IBD (including ulcerative colitis, and Crohn's disease) which were the focus of this section, selected based on frequency and clinical significance, and given that other immune conditions (GBS, Bell's palsy, ITP, transverse myelitis, ADEM, polymyalgia rheumatica and subacute thyroiditis) are covered in their specific respective sections of this PBRER.

An in-depth case review ranked the relative diagnostic certainty of the flare cases for RA, MG, MS, SLE, and IBD and assessed the WHO-UMC causality. (Note, high diagnostic certainty here is the relative case certainty given the limitations of spontaneous data and does not represent a high certainty based on clinical standards.) Within the five disease areas of in-depth review of the 495 identified cases, 279 had medium or high relative diagnostic certainty and WHO-UMC causality assessment, with noted positive rechallenges, are summarized below. Table 16-112 summarizes the results:

Table 16-112 Causality Assessment of Flares (RA, MG, MS, SLE, and IBD), cumulative*

Selected Condition	Diagnostic Certainty*	WHO-UMC Causality Probable (# of positive rechallenges) *	WHO-UMC Causality Possible
Rheumatoid Arthritis	RA - High	3 (3)	29
	RA - Medium	7 (7)	35
Myasthenia Gravis	MG - High	1	15
	MG - Medium	0	8
Multiple Sclerosis	MS - High	2 (2)	20
	MS - Medium	1 (1)	51
Systemic Lupus Erythematosus	SLE - High	2 (2)	9
	SLE - Medium	1 (1)	15
Inflammatory Bowel Disease	IBD - High	0	15
	IBD - Medium	3 (3)	32

*Given the limitations of ICSR data, the diagnostic certainty classifications are relative and do not have the data to apply standard clinical criteria. Many of the cases coded as "high" still lack crucial data (e.g., disease status prior to vaccination or full clinical course). In addition, causality assessment must be interpreted with caution recognizing that disease flares occur in the natural disease process in absence of identified triggers. Furthermore, "Probable" causality is applied to some cases where positive rechallenges have been described, but do not meet the standard criteria (e.g., complete resolution, absence of treatment); and this is further limited given that the disease itself is an alternate etiology of flares.

Here several challenges and notes of caution must be considered in the interpretation of the results presented above. AI/ID conditions by nature are relapsing and remitting, the etiology and immune pathophysiology of flares are not fully understood, and thus the very presence of the AI/ID condition can alone be temporally associated with flares in absence of vaccination. Thus, especially in cases where baseline disease status/patterns and clinical context is not described, causality is challenging to assess and must be interpreted with caution. Per direct input from regulators, positive rechallenges (even those that do not meet the standard criteria in

pharmacovigilance) are noted and for these cases "probable" causality is assigned. There is no clearly established/accepted risk window; however, for this analysis a one-month risk window for flares (based on the innate and adaptive immune response) was considered. Many of the cases occurred within three days of vaccination, but TTO and temporal patterns are difficult to assess as many of the symptoms of expected reactogenicity mimic flares. Furthermore, assessing positive rechallenges is limited as full resolution of a flare is often not described, treatment was often administered, and thus a conservative approach per the patient's or HCP's description of a worsening flare after the subsequent dose was considered a positive rechallenge, (this approach is more inclusive than the standard pharmacovigilance criteria for a positive rechallenge). Thus, while probable causality assessments were applied to cases with positive rechallenge, one must interpret this causality assessment with caution because the disease itself provides a natural alternate etiology or cause of flares. Flares have been described after infection and a variety of vaccines, and there is a theoretical biologic plausibility that the immune response to vaccination may contribute to flares, although the pathophysiologic mechanism is unclear. Furthermore, each AI/ID has a different immune pathophysiology, which further complicates hypotheses of the potential mechanism of action.

The MAH reviewed relevant literature. Articles report that infections can cause autoimmune disease flares, and it is acknowledged that vaccines could theoretically stimulate an AI/ID flare. Articles note that many cases of flares were self-limited or responded to anti-inflammatory treatment. Where cohort data was available flare rates ranged from 0-12%, for multiple COVID vaccine types, although studies were notably limited by small cohort sizes, and most lacked a control/unvaccinated comparator group. Importantly, in studies where control (unvaccinated) groups were included, there was not a significant difference in the flare rates between vaccinated and unvaccinated individuals. This points out the need for further high quality, rigorous controlled studies to assess if there is an elevated risk of flares after vaccination. As is typical for assessments relying upon spontaneous reports, the present analysis is limited as the MAH does not have a denominator reflecting how many people with AI/ID conditions have received the vaccine. There are not well-described background rates of flares at a population level, and preliminary exploration in RWE databases is limited by the lack of ICD-10 AI/ID flare codes. Currently the MAH is continuing to explore algorithms and RWE to identify AI/ID exacerbations in both historic and vaccinated cohorts.

Many AI/ID conditions are relapsing and recurring by nature, with multi-factorial etiologies of flares. There is hypothetical biologic plausibility that vaccines can stimulate the immune system and contribute to flares; however, the exact mechanism, immunogenomic and systems biology with regards to AI/ID flares after vaccination has not been established. The reports of flares are modest given the estimated 827,274,740 doses of SPIKEVAX have been distributed; and

estimated 466,804,529 doses administered and given the natural waxing and waning course of AI/ID, and that there are no reliable reference data of the background rates of respective flares, the modest number of case reports is practically uninterpretable. There have been reports of flares after many vaccines, including various COVID vaccines; both health care providers and patients acknowledge the potential risk of flares after any vaccination, yet flares are not specifically described in any vaccine labels, and the general, global consensus is that the benefit of vaccination outweighs the potential risks of flares. Furthermore, observed rates of reported flares after vaccination cannot be established with spontaneous reporting as the denominator of the number of SPIKEVAX vaccinated persons with AI/ID conditions is unknown; and there are no established reference rates for flares; thus, an O/E analysis is precluded. When considering all of the available evidence, the challenge is the limited data available in passive reporting data, confounding by reactogenicity that has clinical overlap with some flares, the lack of well-established background rates of flares, and the lack of rigorous well-designed controlled observational studies, currently limited ability to use RWE to estimate the O/E, and publications of cohort studies which demonstrate comparable rates of flares between vaccinated and unvaccinated cohort, there remains insufficient evidence to establish an increased risk and/or rates of flares after SPIKEVAX.

16.3.5.7.6. Conclusion

After careful review of all new safety data received during the reporting period in the MedHx AI/ID subpopulation, the benefit-risk profile for SPIKEVAX remains favorable. The MAH will continue to monitor AEs, including AI/ID flares, in the MedHx AI/ID subpopulation using the routine pharmacovigilance measures implemented for SPIKEVAX.

16.3.6. Adverse Events of Special Interest

16.3.6.1. Cardiac Disorders

16.3.6.1.1. Serious Hypertension/Hypertensive Crisis

16.3.6.1.1.1. Source of the New Information

Information presented below includes analysis performed on cases received and entered into the GSDB of ModernaTX. Inc, for the reporting period of this PBRER 01 Jul 2021 to 31 Dec 2021, for the mRNA-1273 vaccine (COVID-19 vaccine Moderna) SPIKEVAX. Cumulatively, the data reviewed covers the period from 18 Dec 2020 to 31 Dec 2021.

The MAH received a request from a health authority to provide the cumulative review of serious hypertension that was initiated on the previous PBRER for which a signal evaluation was conducted and refuted during this reporting period. Serious hypertension signal evaluation is discussed under Section 16.2.5 Signal Evaluation. This updated reporting interval review on the

topic of serious hypertension provides the new information collected during the reporting interval of this PBRER.

16.3.6.1.1.2. Background Relevant to the Evaluation

Hypertension is a common health issue among adults worldwide. In 2019, the global prevalence of hypertension in adults aged 30-79 years was 32% in women and 34% in men, with just 47% of women and 38% of men receiving treatment for their hypertension. Additionally, of those receiving treatment, less than half (23% of women and 18% of men) had well-controlled hypertension [112].

It is important to consider the impact of the COVID-19 pandemic on lifestyle, such as diet and exercise routines, and on regular medical care, which, in turn, is likely to have a noticeable impact on the detection, treatment, and control of a highly prevalent condition like hypertension. A longitudinal study of the impact of the COVID-19 pandemic on changes in blood pressure was conducted by [11] and included 464,585 participants in an employer-sponsored wellness program in the US for which it was a requirement to have their blood pressure measured by trained personnel in each of the years from 2018 to 2020. The findings revealed that there were no differences between the 2019 and 2020 blood pressure for those participants who had their measurements taken through Mar 2020; however, there was a significant increase in the annual blood pressure for participants whose blood pressure was measured from Apr to Dec 2020, blood pressure was significantly higher than it was in 2019. Weight gain during the pandemic period was investigated as a potential contributor, but this was ruled out, as there was a decrease in weight for men, overall, and the increase in weight for women was the same as during the pre-pandemic period. Both systolic and diastolic blood pressure increases were seen in men and women and across age groups, with larger increases in both measurements for women, in systolic blood pressure for older participants, and in diastolic blood pressure for younger participants.

16.3.6.1.1.3. Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

The ModernaTX, Inc GSDB was queried for valid case reports of serious hypertension received from HCP, HA, consumers, and literature for the mRNA-1273 vaccine (COVID-19 vaccine Moderna) SPIKEVAX, using the Standard MedDRA Query (SMQ) of Hypertension (narrow). The output was further refined by filtering for serious events, henceforth referred to as “serious hypertension”.

Identified events of serious hypertension were evaluated utilizing the European Society of Cardiology and European Society of Hypertension (ESC/ESH) 2018 guidelines [113] which classify blood pressure according to seated clinic blood pressure measurements and by the highest

level of blood pressure, whether systolic or diastolic; and were categorized, accordingly (Table 16-113.

Table 16-113 ESC/ESH 2018 Guidelines for classifications of office blood pressure and definitions of hypertension grade

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	**and**	<80
Normal	120–129	**and/or**	80–84
High normal	130–139	**and/or**	85–89
Grade 1 hypertension	140–159	**and/or**	90–99
Grade 2 hypertension	160–179	**and/or**	100–109
Grade 3 hypertension	≥180	**and/or**	≥110
Isolated systolic hypertension – Graded 1, 2, or 3 based on the corresponding SBP values noted above	≥140	**and**	<90

The company causality assessment was assessed utilizing the WHO-UMC standardized case causality assessment system [54].

16.3.6.1.1.4. Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Clinical Trials Data

Cumulatively, there were 14 events of serious hypertension reported in clinical trial participants. The median patient age in years was 63 (min: 24, max: 73). There were 6 cases reported in males and 8 in females (Table 16-114). All events of serious hypertension were reported in patients 50 years of age, or older, except for 2 events of pre-eclampsia.

Table 16-114 Number and Percentage of Serious Hypertension Events Reported in Clinical Trials by Age and Gender - Cumulative to 31 Dec 2021

Age Group	Female		Male		# Cases	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases		
18-29	2	14.3	0	0.0	2	14.3
30-39	0	0.0	0	0.0	0	0.0
40-49	0	0.0	0	0.0	0	0.0
50-64	2	14.3	3	21.4	5	35.7
65-74	4	28.6	3	21.4	7	50.0

Age Group	Female		Male		# Cases	% of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases		
Total	**8**	**57.1**	**6**	**42.9**	**14**	**100.0**

Most events of serious hypertension in clinical trial participants were reported following Dose 2 (10, 71.4%). More than half of the events had on onset 30 days or more following the most recent dose (8, 57.1%) (Table 16-115). All events were considered resolved. There were 10 events (71.4%) with a duration of 3 days, or less.

Table 16-115 Number and Percentage of Serious Hypertension Events Reported in Clinical Trials by Dose Number and Time to Onset - Cumulative to 31 Dec 2021

Dose Number	TTO All Doses (Days)	# Events	% Events
Dose 1	***Subtotal***	***2***	***14.3***
	14-29	2	14.3
Dose 2	***Subtotal***	***10***	***71.4***
	14-29	2	14.3
	30+	8	57.1
Dose 3	***Subtotal***	***2***	***14.3***
	0 days	1	7.1
	14-29	1	7.1
	Total	**14**	**100**

The most frequently reported serious hypertension events by MedDRA PT in clinical trial participants were hypertension (6, 42.9%) and hypertensive urgency (5, 35.7%), which, together, represented 78.6% of all events (Table 16-116).

Table 16-116 Number and Percentage of Serious Hypertension Events Reported in Clinical Trials by MedDRA PT - Cumulative to 31 Dec 2021

PT	# of Events	% of Events
Hypertension	6	42.9
Hypertensive urgency	5	35.7
Pre-eclampsia	2	14.3
Hypertensive crisis	1	7.1
Total	**14**	**100**

Severity assessments based on the ESC/ESH 2018 guidelines included 3 events that were assessed as Grade 2 hypertension, 7 events assessed as Grade 3, and 4 events were unassessable due to insufficient information. All events of serious hypertension reported in clinical trials were assessed as unrelated to mRNA-1273 due to prolonged time to onset and/or more plausible explanations for the events such as pre-existing hypertension and other cardiovascular disease.

Post Authorization Data

Serious Hypertension (Reporting Period 01 Jul to 31 Dec 2021)

During the reporting period of this PBRER there were 826 cases (855 events) of serious hypertension identified, of which, 511 cases were medically confirmed. There were 35 fatal event outcomes reported. Most cases were received from regulatory authorities (768; 93.0%).

The majority of cases (67.3%) of serious hypertension were reported in females. The median age of patients experiencing serious hypertension events was 56 (min:18/ max:103) years of age. The age group with the highest proportion of events was the 50- to 64-year-old age group (242, 29.2%), with the majority of events occurring in patients 50 years of age, or older (499, 60.4%), which is reflective of the population most likely to experience hypertension. (Table 16-117).

Table 16-117 Number and Percentage of Serious Hypertension Events by Age and Gender – Reporting Period 01 Jul to 31 Dec 2021

Age Group	Female		Male		Unknown		Total # Cases	% Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
18-29	32	3.9	17	2.1	0	0	49	5.9
30-39	77	9.3	31	3.8	0	0	108	13.1
40-49	98	11.9	45	5.4	2	0.2	145	17.6
50-64	172	20.8	68	8.2	2	0.2	242	29.3
65-74	90	10.9	52	6.3	2	0.2	144	17.4
75+	75	9.1	38	4.6	0	0	113	13.7
Missing	12	1.5	5	0.6	8	1.0	25	3.0
Grand total	**556**	**67.3**	**256**	**31.0**	**14**	**1.7**	**826**	**100.0**

Almost half of the serious hypertension cases were reported in the United States (41.2%), with the next highest number of cases reported in the EEA (38.5%) (Table 16-118).

Table 16-118 Number and Percentage of Total Cases of Serious Hypertension – Reporting Period 01 Jul to 31 Dec 2021

Region	Total # Cases	% Total Cases
Asia	67	8.1
Canada	7	0.8
European Economic Area	318	38.5
Switzerland	29	3.5
United Kingdom	64	7.7

United States	340	41.2
Unknown	1	0.1
Grand total	**826**	**100.0**

When evaluating events of serious hypertension by time to onset (TTO), there were no important differences between events reported after Dose 1 (244, 28.5%), with same-day reactions following dose 1 accounting for 83 (9.7%), when compared with those events reported post-dose 2 events (300, 35.1%) with same-day dose 2 reactions accounting for 60 (7.2%) of all events. There were 241 events (28.2%) that did not report information to determine time to onset by dose (Table 16-119).

Table 16-119 Number and Percentage of Serious Hypertension Events by Dose Number and Time to Onset – Reporting Period 01 Jul to 31 Dec 2021

Dose Number	TTO (Days)	# Events	% Events
Dose 1	***Subtotal***	***244***	***28.5***
	0 days	83	9.7
	01-02	49	5.7
	03-04	16	1.9
	05-06	11	1.3
	07-13	40	4.7
	14-29	19	2.2
	30+	26	3.0
Dose 2	***Subtotal***	***300***	***35.1***
	0 days	60	7.0
	01-02	55	6.4
	03-04	16	1.9
	05-06	14	1.6
	07-13	19	2.2
	14-29	24	2.8
	30+	112	13.1
Dose 3	***Subtotal***	***70***	***8.2***
	0 days	18	2.1
	01-02	28	3.3
	03-04	9	1.1
	05-06	2	0.2
	07-13	7	0.8
	14-29	2	0.2
	30+	4	0.5
Unknown	***Subtotal***	***241***	***28.2***

Dose Number	TTO (Days)	# Events	% Events
	Missing	241	28.2
Grand total		**855**	**100.0**

The most commonly reported event by MedDRA Preferred Term was hypertension (905, 58.8%) followed by blood pressure increased (321, 20.9%) (Table 16-120).

Table 16-120 Number and Percentage of Serious Hypertension Events Reported by MedDRA Preferred Term (PT) (where n>5) – Reporting Period 01 Jul to 31 Dec 2021

PT	# Events	% Total Events
Hypertension	510	59.6
Blood pressure increased	193	22.6
Hypertensive crisis	87	10.2
Hypertensive emergency	14	1.6
Pre-eclampsia	14	1.6
Essential hypertension	8	0.9
Hypertensive heart disease	7	0.8
Grand total	**833**	**96.5**

Of the 826 cases, 325 cases had no medical history provided. The most frequently reported medical history events (>10% of all serious hypertension cases) by MedDRA Preferred Term were hypertension (390, 26.1%) and drug hypersensitivity (279, 18.7%) (Table 16-121). Upon further analysis of the medical histories in cases of serious hypertension, 415 cases (27.8%) had at least one medical history event within the MedDRA SMQ of Hypertension (narrow). Of those 415 cases, there were only 5 with information suggesting that the patient had well-controlled hypertension prior to receiving SPIKEVAX. Four of the reports did not provide blood pressure measurements to objectively assign an ESC/ESH grade or include pertinent clinical information to evaluate potential causative etiologies for change from baseline for the reported serious hypertension events. In one report originally from a consumer, a 57-year-old female with controlled hypertension reportedly had arterial hypertension (232/127) for several consecutive days one day after the first dose of SPIKEVAX, however the event was classified as medically significant with no evidence of hospitalization or treatment for the Grade 3 hypertension.

No conclusions can be drawn from these reports.

Table 16-121 Top 20 Medical History Terms Reported in Serious Hypertension Cases by MedDRA PT - Cumulative to 31 Dec 2021

Medical History	# of Cases	% of Cases
Hypertension	390	26.1

Medical History	# of Cases	% of Cases
Drug hypersensitivity	279	18.7
Diabetes mellitus	80	5.4
Asthma	76	5.1
Food allergy	70	4.7
Hypothyroidism	63	4.2
Obesity	63	4.2
Gastroesophageal reflux disease	58	3.9
Hyperlipidemia	54	3.6
Type 2 diabetes mellitus	54	3.6
Depression	44	2.9
COVID-19	39	2.6
Chronic kidney disease	39	2.6
Atrial fibrillation	37	2.5
Chronic obstructive pulmonary disease	36	2.4
Hypersensitivity	35	2.3
Sleep apnoea syndrome	34	2.3
Anxiety	33	2.2
Coronary artery disease	32	2.1
Seasonal allergy	32	2.1
Grand Total	**1548**	**103.5**

Subpopulation Analyses

Children ages 0-11 Years (Reporting Period 01 Jul to 31 Dec 2021)

There were no reports of serious hypertension events in children of < 12 years of age during the reporting period (01 Jul 2021 to 31 Dec 2021).

Adolescents ages 12-17 Years (Reporting Period 01 Jul to 31 Dec 2021)

There were no reports of serious hypertension events in adolescents 12 to 17 years of age during the reporting period (01 Jul 2021 to 31 Dec 2021).

SPIKEVAX Booster (Reporting Period 01 Jul to 31 Dec 2021)

During the reporting period of this PBRER there were 65 cases (70 events) of serious hypertension reported following a 3rd or booster dose of SPIKEVAX (Table 16-122). There were 28 cases that were medically confirmed, and 4 cases had fatal outcomes. The median age of patients experiencing serious hypertension events was 58 years (min 25/max 95). Cases were disproportionately reported in females (52; 80.0%) compared to males (11; 16.9%). The majority

of serious hypertension events following administration of a 3rd or booster dose had a time to onset of less than 3 days (46, 65.7%).

Table 16-122 Number and Percentage of Serious Hypertension Events by Dose Number and Time to Onset Following a 3rd/Booster dose of SPIKEVAX - Reporting Period 01 Jul to 31 Dec 2021

Dose Number	TTO All Doses (Days)	# Events	% Events
Dose 3	0 days	18	25.7%
	01-02	28	40.0%
	03-04	9	12.9%
	05-06	2	2.9%
	07-13	7	10.0%
	14-29	2	2.9%
	30+	4	5.7%
Grand total		**70**	**100.0%**

Case Evaluations per the European Society of Cardiology/European Society of Hypertension (ESC/ESH) 2018 Guidelines is provided in Table 16-123.

Table 16-123 Number and Percentage of Serious Hypertension Events by ESC/ESH Hypertension Guidelines Category – Reporting Period 01 Jul to 31 Dec 2021

ESC/ESH 2018 Grade	# of Events	% of All Serious Hypertension Events (n=855)
Optimal	1	0.1
Normal	1	0.1
High Normal	2	0.2
Grade 1 Hypertension	4	0.5
Grade 2 Hypertension	6	0.7
Grade 3 Hypertension	101	11.8
Isolated systolic hypertension – any grade	0	0.0
Unassessable	740	86.5

According to the WHO-UMC causality assessment most of the reported events (177 events, 20.7%) of serious hypertension were considered possibly related (Table 16-124), based on a temporal association between the use of the product and the start of the events. (See Appendix 20.11.34).

Some of the responses associated with the reported events can be described as stress responses, which in nature are complex, involving a combination of physiological factors within an

individual, his or her psychological strengths, vulnerability, knowledge and preparedness and the social context. The reasons for which an individual presents stress symptom can be understood or explained with the biopsychosocial model. Although a stress response may present both "physical" and "psychological" symptoms, they are interconnected. For example, symptoms that we think of as "psychological" (e.g., depression) often have accompanying physical symptoms or signs (e.g., changes in appetite, sleep and weight loss). Likewise, psychological factors (e.g., anxiety) can influence physiological functioning (e.g., increase the heartbeat, raise the blood pressure) [114].

Table 16-124 Number and Percentage of Serious Hypertension Events by WHO-UMC Causality Assessment Category – Reporting Period 01 Jul to 31 Dec 2021

WHO-UMC Causality	# of Cases	% of All Serious Hypertension Events (n=855)
Certain	0	0.0
Probable/Likely	0	0.0
Possible	177	20.7
Unlikely	443	51.8
Conditional/Unclassified	222	26.0
Unassessable/Unclassifiable	13	1.5

16.3.6.1.1.5. Discussion

Following the review of the safety information included in this reporting period, the MAH considers there is insufficient evidence at this time to support a causal association between serious hypertension and SPIKEVAX. There was a temporal association with SPIKEVAX administration in post-marketing reports of serious hypertension, particularly for the first few days after the first dose of SPIKEVAX. The occurrence of hypertension after SPIKEVAX administration could also potentially be due to a component of the acute stress/anxiety/pain response or as a secondary symptom from reactogenicity symptoms or the inflammatory response associated with vaccination (Immunization stress-related responses). The majority of the reports were considered unlikely related to vaccine administration according to the WHO causality assessment criteria and a significant proportion of cases did not provide adequate information to assess causality. In many cases an alternate etiology included pre-existing hypertension which is inherently fluctuating in nature, and which can be exacerbated by factors such as the very stress of the pandemic (long lines to get the vaccine, social distancing, use of masks, fear of infection, all factors right at the time of vaccination) and other non-vaccine related disease processes. There was no evidence to suggest that vaccine administration was associated with worsening of pre-existing hypertension. Other considerations such as extended time to onset further argue towards an implausible causal association between vaccine and the events of serious hypertension.

It should be noted that the vast majority of reports contained insufficient information for the grading of hypertension according to ESC/ESH Hypertension Guidelines.

This additional analysis of the data reported during the reporting interval of this PBRER through 31 Dec 2021, does not provide evidence of a causal association between SPIKEVAX and events of serious hypertension.

16.3.6.1.1.6. Conclusion

Based on the analysis of the cumulative safety data received through 31 Dec 2021, ModernaTX, Inc considers that cases included in the review of serious hypertension temporally associated with the administration of SPIKEVAX, does not represent a safety issue. ModernaTX, Inc will continue to monitor events of serious hypertension using routine surveillance. The benefit-risk evaluation remains positive.

16.3.6.2. Endocrine and Metabolic Disorders

16.3.6.2.1. Subacute Thyroiditis

16.3.6.2.1.1. Source of the New Information

Information presented below includes analysis performed on cases received by ModernaTX, Inc. from 18 Dec 2021 to 31 Dec 2021 for the mRNA-1273 vaccine (COVID-19 vaccine Moderna) SPIKEVAX.

16.3.6.2.1.2. Background Relevant to the Evaluation

Subacute thyroiditis (SAT) is also known as granulomatous, de Quervain’s thyroiditis, giant cell thyroiditis, and subacute nonsuppurative thyroiditis. It is a self-limited inflammatory thyroid disease and a relatively uncommon cause of hyperthyroidism. It affects women more often than men (19.1 and 4.1 cases per100,000/year, respectively) and most common in young adulthood and middle age [115].

The clinical manifestation of SAT includes neck pain – hallmark of this clinical syndrome – often radiating upward to the jaw, thyroid enlargement or goiter, general systemic reactions (e.g., fever, malaise, fatigue, and myalgia) and a predictable course of thyroid dysfunction. Typically, the course of thyroid function evolution with SAT includes three consecutive phases that classically last two to eight weeks: 1) hyperthyroidism due to unregulated release of large amounts of thyroxine (T4) and triiodothyronine (T3) due to damage to thyroid follicular cells; 2) hypothyroidism due to deficiency of thyroid hormones while the thyroid follicles regenerate and thyroid hormone synthesis and secretion resume; 3) Euthryoidism due to the complete restoration of the thyroid parenchyma and achievement of sufficient hormone and normal homeostasis [116].

The diagnosis of SAT is essentially clinical, supported by laboratory evidence of hyperthyroidism (elevated thyroid hormone and suppressed TSH concentrations). Elevated acute phase reactants (e.g., ESR or CRP), normal anti-thyroid antibody levels, low isotope uptake on thyroid radioiodine imaging scan, and a normal or enlarged thyroid on ultrasonography that is diffusely or focally hypoechogenic with color Doppler showing low flow (during hyperthyroid phase), are useful in excluding other common causes of hyperthyroidism. Rarely, fine-needle biopsy is necessary to distinguish SAT from other diagnoses (e.g., infection [abscess]); widespread infiltration with giant cells, neutrophils and other inflammatory cells, with disruption and collapse of thyroid follicles, and necrosis of follicular cells are revealed. When there is limited access to these investigations, the diagnosis of SAT can be confirmed among patients with thyroid pain and mild hyperthyroidism, if the thyroid normalizes and pain resolves within several weeks.

The pathogenesis of SAT remains poorly understood; it is presumed to be caused by viral infection or post-viral inflammatory process. Thyroid autoimmunity does not appear to play a role in this disorder, but it is associated with the human leukocyte antigen (HLA)-B35 [116]. There are several hypotheses suggesting that viral infection leads to thyroid diseases which include liberating of antigens (via necrosis or apoptosis of follicular cells), forming altered antigens or causing molecular mimicry, by proinflammatory cytokine and chemokine secretion, and inducing aberrant HLA-DR expression and Toll-Like Receptor (TLR) activation [117].

Many patients have a history of an upper respiratory infection prior to onset (typically two to eight weeks prior) and many viruses have been associated with SAT including Coxsackievirus, influenza, mumps, measles, and now SARS-CoV-2. In a recent full review of literature of COVID-19 related SAT, published 17 cases were detailed [118]. A majority (82%) of the cases were females, and age ranged from 5 to 49 years, consistent with epidemiology of SAT prior to pandemic. None of the cases documented additional extra-pulmonary end-organ manifestations of COVID-19 and only a few patients reported features of systemic inflammatory response syndrome. Of the 13 cases that reported date of SAT diagnosis, majority were established at or 14 days after respiratory symptom onset (mean 26.5, IQR 16-30). Most responded quickly to oral prednisone or ibuprofen therapy. At follow up, most cases were found to be euthyroid. The link between SARS-CoV-2 has not been elucidated; SARS-CoV-2 has not been directly evidenced in the thyroid tissue. There are several theories on how SARS-CoV-2 affects the thyroid including directly via viral effect on the thyroid. There is limited evidence showing that the mRNA of angiotensin converting enzyme 2 (ACE2), the SARS-CoV-2 receptor, is expressed in thyroid cells and that elevated levels of IFN-γ and TNF-α cytokines (upregulated inpatients with COVID-19), could increase expression of ACE2 on the thyroid gland, increasing uptake of virus during an illness. It has also been proposed that that proteins generated due to cross reactivity with thyroid target proteins due to molecular mimicry trigger autoimmunity together with an inflammatory reaction in predisposed

individuals.it A study has demonstrated that human IgG1 monoclonal antibody against SARS-CoV-2 spike protein can cross-react with thyroid peroxidase (TPO), thyroglobulin and other cellular components of the follicle [119], [120], [121] and thus have an indirect effect.

Considering the accumulating evidence of subacute thyroiditis and SARS-CoV-2, the Safety Platform for Emergency vaccines (SPEAC) Project added SAT to the list of COVID-19 adverse events of special interest (AESI) for safety monitoring in Dec 2020. There are documented cases of SAT occurring after influenza, human papillomavirus (HPV), and hepatitis B virus vaccinations [122]. The pathogenesis is unclear; however, some authors have attributed it to adjuvant causing autoimmune/inflammatory syndrome induced by adjuvants (ASIA), while others have suggested direct injury to the thyroid by a vaccine component or inducing cross-reaction between the antigen in the vaccine and follicular cells because of a shared epitope.

Since the roll-out of SARS-CoV-2 vaccines, several published case reports and series have described SAT after SARS-CoV-2 vaccines, across all the different vaccine platforms including the mRNA vaccines [123]. NoMA reported signal detection based on two individual case safety reports (ICSRs) from Norway, literature and three ICSRs from EudraVigilance. It was also reported that there was a disproportionality of reporting in VigiBase for SPIKEVAX as of 02 Nov 2021 with an IC025 value of 1.9. A request was received by the Pandemic Response Accountability Committee (PRAC) for the MAH to perform a cumulative review of all cases relevant to subacute thyroiditis, consider the possibility of flare-up cases with any form of thyroiditis in the medical history, and to discuss any plausible biological mechanisms and the need for updates to the product information.

16.3.6.2.1.3. Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

The MAH reviewed all clinical trial adverse event data from the mRNA-1273 P301 study, Part A (Clinical Study Report, mRNA-1273-P301, Part A, data lock point (DLP) 04 May 2021). All unsolicited treatment-emergent adverse events (TEAEs) were reviewed to identify events with any MedDRA preferred terms (PT) requested by PRAC. These terms were "Atrophic thyroiditis, Autoimmune thyroiditis, Hashimoto's encephalopathy, Immune-mediated thyroiditis, Silent thyroiditis, Thyroiditis, Thyroiditis acute, Thyroiditis subacute and Hyperthyroidism".

The MAH queried the GSDB, cumulatively through 31 December 2021 for valid case reports received from HCP, HA, consumers, and literature, worldwide, reported for SPIKEVAX. The search strategy included using a customized list of MedDRA PTs, requested by PRAC, to identify reports with thyroiditis: Atrophic thyroiditis, Autoimmune thyroiditis, Hashimoto's encephalopathy, Immune-mediated thyroiditis, Silent thyroiditis, Thyroiditis, Thyroiditis acute, Thyroiditis subacute and Hyperthyroidism.

These reports underwent two level of reviews; the first level was performed to characterize the level of diagnostic certainty for SAT. There is currently no Brighton definition or widely accepted case definition of SAT, therefore a disease case definition for SAT was developed by the MAH to classify the reports specifically for the PBRER.

Case Definitions	
Confirmed	Meets confirmatory laboratory evidence*
	Meets one or more clinical criteria†, and laboratory evidence of hyperthyroidism and thyroid function normalizes, and pain resolves within several weeks spontaneously or with steroid therapy
Probable	Meets one or more clinical criteria† and laboratory evidence of hyperthyroidism and meets at least one other supportive laboratory evidence§ and at least one of supportive diagnostic imaging evidence in the absence of a more likely diagnosis
Possible	Has PT of subacute thyroiditis without meeting any clinical†, laboratory§ or diagnostic imaging evidence¶
	Has one or more clinical criteria and meets laboratory evidence of hyperthyroidism +/- elevated ESR or CRP and the absence of a more likely diagnosis
	Has one clinical symptom and meets at least one of the supportive diagnostic imaging evidence¶ in the absence of a more likely diagnosis
	Has one or more clinical criteria and meets at least one other supportive laboratory evidence§ and at least one of the supportive diagnostic imaging evidence¶ in the presence of a more likely diagnosis
Unlikely or diagnosis of another thyroid disease	Evaluation did not indicate SAT, or it led to the diagnosis of a thyroid disorder other than SAT
Insufficient data	Missing data on timing and relation of SAT and/or symptoms to date of vaccination.

*Confirmatory laboratory evidence: Thyroid biopsies reveal widespread infiltration with neutrophils, lymphocytes, histiocytes and giant cells, disruption and collapse of thyroid follicles, and necrosis of thyroid follicular cells. Later there may be some fibrosis.

†Clinical criteria: Presence of neck pain in the absence of another diagnosis e.g., cervical lymphadenopathy, sometimes radiating upward to the jaw, or marked thyroid tenderness, a diffuse goiter, or signs and symptoms of thyrotoxicosis including palpitations, tremors

§ Supportive laboratory evidence: evidence of hyperthyroidism (suppressed TSH and elevated free T4 and T3 concentrations), elevated ESR or CRP, normal or low titers of serum antithyroid peroxidase or antithyroglobulin antibodies

¶Supportive diagnostic imaging: a normal or enlarged thyroid on ultrasonography that is diffusely or focally hypoechogenic with colour Doppler showing low flow during hyperthyroid phase or low isotope uptake on thyroid radioiodine imaging scan

The second level of review was performed to characterize the likelihood that the event, SAT, is attributable to the vaccine, and was performed using the WHO-UMC standardized case causality for cases that met the developed case definition (confirmed, probable and possible). [54].

These reports were divided into those with and without a documented past medical history of thyroid disease. Case review identified those reports of flares after vaccination among patients with documented history of a thyroid disease.

A targeted literature search and review for subacute thyroiditis and SPIKEVAX was performed on 21st January 2022 by searching National Library of Medicine (NLM) Pubmed search engine using the following search criteria:

((((((((((((((((((Atrophic thyroiditis) OR (Autoimmune thyroiditis)) OR (Hashimoto's encephalopathy)) OR (Immune-mediated thyroiditis)) OR (Silent thyroiditis)) OR (Thyroiditis)) OR (Thyroiditis acute)) OR (Thyroiditis subacute)) OR (Hyperthyroidism)) AND (mRNA COVID vaccination or mRNA-1273 or "mRNA 1273" or mRNA1273 or "modernatx 1273" or "moderntx 1273" or "Moderna Covid19 Vaccine" or SPIKEVAX)))) AND (("2020/11/01"[Date - Publication] : "2021/12/31"[Date - Publication])).

- Appendix 20.11.36: Case Summaries of potential subacute thyroiditis by presence of documented history of thyroid disease.

16.3.6.2.1.4. Results: Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Observed vs. Expected Analysis

See Appendix 20.11.3.

Overview of Cases

Cumulative Review (Subacute Thyroiditis, cumulative to 31 Dec 2021)

Clinical trial data:

Eight subjects were identified from the clinical trial data from study mRNA-1273-P301 Part A, as of 4 May 2021, using the customized PT list. Table 16-125 below shows the list of reported PTs by treatment arm; 3 subjects received mRNA-1273 and 5 received placebo. There was no imbalance noted; the number and the distribution of the types of thyroid disease was similar.

Table 16-125 Distribution of thyroid disease by treatment arm from the clinical trial data mRNA-1273-P301 Part A, as of 04 May 2021

Preferred Term	mRNA-1273	Placebo	Total
Hyperthyroidism	2	2	4
Autoimmune thyroiditis	0	2	2
Thyroiditis subacute	0	1	1
Thyroiditis	1	0	1
Grand total	**3**	**5**	**8**

Post-Authorization Data:

Cumulatively (18 Dec 2020 to 31 Dec 2021), there were 222 cases identified of which 158 were serious and 1 was fatal. These reports included a total of 240 events, of which 159 were serious. One hundred and fifty-four cases were medically confirmed. Thirty-eight reports were among males (17.1%), 182 were among females (82%), and 2 reports with missing gender. The vast majority of the reports were among patients aged 30-64 years (80.7%) (Table 16-126). The gender

imbalance in reports received is consistent with the known general epidemiology of thyroid disease [116].

Table 16-126 Age Group and Gender Distribution of Identified Cases (N=222), 18 Dec 2020-31 Dec 2021

Age Group	Female		Male		Unknown		Total # Cases	% of Total Cases
	# Cases	% of Total Female Cases	# Cases	% of Total Male Cases	# Cases	% of Total Unknown Cases		
12-15	1	0.5	0	0	0	0	1	0.5
18-29	11	6.0	2	5.3	0	0	13	5.9
30-39	44	24.2	8	21.1	1	50	53	23.9
40-49	55	30.2	10	26.3	0	0	65	29.3
50-64	49	26.9	12	31.6	0	0	61	27.5
65-74	13	7.1	5	13.2	0	0	18	8.1
75+	5	2.7	0	0	0	0	5	2.3
Missing	4	2.2	1	2.6	1	50	6	2.7
Grand total	**182**	**100**	**38**	**100**	**2**	**100**	**222**	**100.0**

There were 159 (71.6%) cases with no documented history of thyroid disorder and 63 (28.4%) with documented history of thyroid disorder of which Hashimoto's disease (44.4%) was the most common frequently reported followed by hypothyroidism NOS (28.6%), Grave's/Basedow's disease (7.9%), hyperthyroidism NOS (7.9%), and autoimmune thyroiditis (3.1%) and thyroiditis NOS (3.1%).

Case classification

The 222 post-EUA cases identified underwent clinical review and were classified using the SAT case definition. There were 15 cases (6.8%) classified as "confirmed", six classified as "probable" (2.7%) and 39 classified as "possible" (17.6%) (See Appendix 20.11.36). One hundred and eight (48.6%) cases were classified as "insufficient data", and 54 (24.3%) classified as "unlikely or diagnosis of another thyroid disease".

The "confirmed," "probable," or "possible" cases were grouped together, and the rest of the analysis will focus on this group stratified by documented status of underlying thyroid disease.

Cases Without Documented History of Thyroid Disease

Of the 159 cases *without* documented history of thyroid disorder, 57 (35.8%) met the SAT case definition. Fifteen (66.7%) out of 57 cases were classified as confirmed, 4 (7.0%) as probable and 38 (26.3%) as possible cases of SAT.

The 57 cases (29 serious, and none were fatal) had 64 events (of which 31 were serious) and 39 cases were medically confirmed. Forty-three (75.4%) cases occurred in females, 13 (22.8 %) in males, and one (1.8 %) with missing gender information. The mean age was 45.5 (SD 12.7), and the median was 45 years (IQR:16; range:18-82). The distribution of cases by age group, is presented in Table 16-127. This is consistent with the published literature; 75% (43/57) of the cases that met the SAT case definition were females with a ratio of 3:1 (female to male) as well as people in young and middle adulthood (30-60 years with a mean age of 45 years) (UpToDate, 2022).

Table 16-127 Age Group and Gender Distribution of Cases *Without* A Documented History of Thyroid Disorder That Met the Subacute Thyroiditis Case Definition (N=57), 18 Dec 2020-31 Dec 2021

Age Group	Female		Male		Unknown		Total # Cases	% Total Cases
	# Cases	% of Total Female Cases	# Cases	% of Total Male Cases	# Cases	% of Total Unknown Cases		
18-29	3	7.0	0	0	0	0	3	5.3
30-39	14	32.6	4	30.8	1	100	19	33.3
40-49	9	20.9	3	23.1	0	0	12	21.1
50-64	13	30.2	5	38.5	0	0	18	31.6
65-74	3	7.0	1	7.7	0	0	4	7.0
75+	1	2.3	0	0	0	0	1	1.8
Grand total	**43**	**100.0**	**13**	**100.0**	**1**	**100**	**57**	**100.0**

Of the 64 events reported, thyroiditis subacute was the most frequently reported MedDRA Preferred Term (n=43, 67.2%), followed by hyperthyroidism (n=8, 12.5%) (Table 16-128).

Table 16-128 MedDRA Preferred Terms/Events of Cases *Without* A Documented History of Thyroid Disorder That Met the Subacute Thyroiditis Case Definition, 18 Dec 2020-31 Dec 2021

MedDRA Preferred Term	Events	
	N	%
Thyroiditis subacute	43	67.2
Hyperthyroidism	8	12.5
Thyroiditis	7	10.9
Thyroiditis acute	4	6.3
Autoimmune thyroiditis	1	1.6
Silent thyroiditis	1	1.6
Grand total	**64**	**100.0**

Thirty-three percent (19/57) of the events occurred after the first dose of SPIKEVAX, 49% (28/57) after the second dose and 28% (10/57) with missing dose information.

On average, it took 17 days (SD 27.9) from the preceding vaccine dose to symptom onset; median time to onset (TTO) was 8.0 days (IQR:15; range: 0-140). Of the cases (41/57) with reported preceding dose number, a vast majority (88%) reported TTO 13 days or less after dose 1, and 60% (15/25) reported TTO 13 days or less (Table 16-129).

Table 16-129 Time to Onset by Dose Based on Medical Review of Cases *Without* A Documented History of Thyroid Disorder That Met the Subacute Thyroiditis Case Definition, 18 Dec 2020-31 Dec 2021

Dose Number	Time to Onset (days)	N	Subtotal %	Grand Total%
Dose 1	Subtotal	16	-	28
	00-02	3	18.8	
	03-04	0	0.0	
	05-06	4	25.0	
	07-13	7	43.8	
	14-29	1	6.3.	
	30+	1	6.3	
Dose 2	Subtotal	25	-	44
	00-02	5	20,0	
	03-04	2	8.0	
	05-06	1	4.0	
	07-13	7	28.0	
	14-29	5	20.0	
	30+	5	20.0	
Unknown	Subtotal	16	-	28
	Missing	16	100	
Grand Total		**57**	-	**100.0**

WHO Causality Assessment

According to the WHO-UMC causality assessment, it was determined that 55 out of the 57 cases (96.5%) that met the SAT case definition, were possible associated based on temporal association between the use of the product and the start of the events. A causal relationship cannot be excluded due to the lack of information. Important information is missing from these reports including patient's medical history as well as any laboratory test conducted, often missing presenting symptoms, clinical course and diagnostic evaluation performed to establish the diagnosis of subacute thyroiditis as well as to exclude other several possible etiologies given that signs and symptoms of SAT significantly overlap with other diagnoses. Additionally, some of the cases had

current or past medical history confounding the clinical picture such as suspected COVID-19 infection, diabetes, celiac disease, and hepatitis B infection. Two cases (3.5%) were classified as unassessable due to the lack of time to onset information in relation to vaccine administration. (See Appendix 20.11.36).

Cases with Documented History of Thyroid Disease

There were 63 cases *with* documented history of thyroid disease; 28 (44.4%) reported Hashimoto's disease, followed by 18 (28.6%) with hypothyroidism, 5 (7.9%) with Grave's/Basedow's disease, 5 (5.9%) with hyperthyroidism, 2 (4.8%) with goiter with nodules, 2(3.2%) with autoimmune thyroiditis, and 2 (3.2%) with thyroiditis. 52.4% (33/63) had a flare, while 26.9% (17/63) with new onset hyperthyroidism from baseline state of hypothyroidism, 3.2% (2/63) reported new onset hypothyroidism from baseline state of hyperthyroidism, 4.8% (3/63) with new onset hyperthyroidism from a baseline state of euthyroidism, and 12.7% (8/63) cases were unassessable.

Of the 63 cases with documented history of thyroid disease, three (4.8%) met the SAT case definition. Two (66.7%) out of 3 cases were classified as probable cases of SAT, and 1 (33.3%) as possible.

The three cases (2 serious) had four events (of which three were serious) and two were medically confirmed. All three cases occurred in females with a median age of 48 (range: 39-65).

Of the 4 events reported, thyroiditis (50%) was the most frequently reported MedDRA PT, followed by thyroid subacute (25%) and hyperthyroidism (25%).

Sixty-seven percent (2/3) of the events occurred after the second dose of SPIKEVAX administration, and 33% (1/3) with missing information.

It took a median of 31 days (range: 10-33) from the preceding vaccine dose to symptom onset. Of the two cases with a reported preceding dose number, 50% reported TTO 13 days or less after dose 2 and 50% reported TTO 30 days or more after dose 2. No TTO or dose pattern was noted due to the small number of cases.

WHO Causality Assessment

According to the WHO-UMC causality assessment, all three cases were classified as possible due to temporal association and lack of obvious confounders. However, the narratives were limited lacking critical clinical and diagnostic data making it difficult to reconstruct a clear clinical picture and course in the background of an underlying thyroid dysfunction. (See Appendix 20.11.36).

Fatal cases (Cumulatively as of 31 Dec 2021)

Cumulatively as of 31 Dec 2021, one case was coded as fatal and is described below:

4.1(b) **:** 48- year- old male with current inflammatory bowel disease, cholangitis sclerosing, and multiple sclerosis, experienced fatal event of giant cell myocarditis at an unknown interval after an unknown dose of SPIKEVAX. He also experienced hyperthyroidism and atrial fibrillation at an unknown interval after vaccination. Cause of death was reported as giant cell myocarditis; autopsy performed but results unknown. Given complicated medical history as well as the extremely limited data, etiology of hyperthyroidism is unclear as well as whether it contributed to the fatal outcome. Causality is deemed unassessable.

Adolescents ages 12-17 Years (Cumulatively as of 31 Dec 2021)

Cumulatively as of 31 Dec 2021, one non-serious medically confirmed case of silent thyroiditis was reported in a 13-year-old female with medical history of COVID-19 infection. The dose, time to onset and the outcome were not reported. Insufficient data to perform analyses or draw any conclusions.

SPIKEVAX Booster (Cumulatively as of 31 Dec 2021)

Cumulatively as of 31 Dec 2021, through medical review, we identified six cases (5 serious, zero fatal) with a dose 3, with 6 (5 serious) events. The vast majority were female (83.3%) with a median age of 41.5 years (range 19-77). Four of the six (66.7%) did not report an underlying thyroid disease and the two (33.3%) that did, both reported Hashimoto's disease as the underlying thyroid disease. None of the six cases met the SAT case definition; four cases were classified as "insufficient data" and two as "unlikely or diagnosis of another thyroid disease".

Literature Review:

A total of 36 articles were identified and only four articles describing subacute thyroiditis after SPIKEVAX were relevant after full text review. These reports (4.1(b) , 4.1(b) , 4.1(b) , and 4.1(b)) were already captured in the global safety database and underwent the two level of clinical reviews described above. See Appendix 20.11.37.

16.3.6.2.1.5. Discussion

Out of the 222 cases identified by search strategy, 27.1% (60/222) met the SAT case definition. Of these 60 cases; 25% met the confirmed definition, 10% the probable definition and 65% possible case definition. SAT is a clinical diagnosis established on clinical and laboratory evidence and often times diagnostic imaging given the overlap with multiple other thyroid and non-thyroid diseases. Of the 60 cases, vast majority (57/60) had no underlying thyroid disease. Most of identified cases with underlying thyroid disease (n=63) had complicated medical histories with some of them having both Grave's and Hashimoto's disease and other confounding diseases such as Epstein-Barr infection, multiple sclerosis, Raynaud's, hypertension, hyperparathyroidism, diabetes, COVID-19 and herpes infection. Given that almost all of the reports lacked the

appropriate level of clinical and diagnostic details needed, it is very difficult to establish a clear clinical picture to make a case determination.

Thus, the 57 cases that met the SAT case definition without underlying thyroid disease provide a clearer picture to better evaluate the occurrence of subacute thyroiditis after SPIKEVAX vaccination. A majority of these cases occurred in females (82%) and among those aged 30-60 years; this is consistent with published literature that show a larger predominance of SAT among women and those in young and middle adulthood. There was not a pattern seen regarding dose number preceding symptom onset or diagnosis. However, of the cases with known preceding dose number and TTO, 88% (14/16) reported TTO 13 days or less after dose 1, and 60% (15/25) reported TTO 13 days or less with almost an even distribution between week 1 and week 2 after vaccination regardless of preceding dose number. This is consistent with a report [123] that summarized 9 cases of subacute thyroiditis after vaccination (mRNA, inactivated and adenovirus-vectored vaccines) during the period of Sep 2019 to Aug 2021; 78% with TTO within 14 days after the vaccine administration.

Although, SAT is a well-known clinical diagnosis and has been associated with viral infections or post viral inflammation, the pathogenesis is still not well defined. Additionally, the exact pathogenesis of reports of SAT occurring after vaccines against influenza and HPV is still unknown. There are published case reports of SAT occurring after SPIKEVAX, however, in the setting of an ill-defined pathogenesis leading to SAT, it difficult to determine a biologic plausible mechanism, if any, underlying SAT occurring after SPIKEVAX vaccination. Some unconfirmed hypotheses include 1) molecular mimicry; it has been shown that SARS-CoV-2 spike protein can cross-react with thyroid peroxidase, which could trigger an inflammatory reaction in predisposed individuals; 2) vaccine adjuvants causing ASIA; and 3) vaccine core component causing direct injury to thyroid [124], [121].

When WHO causality assessment was applied to the 60 cases that met the SAT case definition, and majority of the cases were classified as possible, or unassessable. 81% of these cases had no documented relevant medical history, majority of the TTO was within the time window (1-2 weeks) of the expected inflammatory response to the vaccine and given temporal association, causality could not be excluded. However, the post-authorization data used for this report is extremely limited, lacking key details of clinical history, diagnostic evaluation and clinical course to determine if the case truly has subacute thyroiditis as well as to determine the likelihood that SAT postvaccination is attributable to SPIKEVAX. SAT is usually mild and transient and should be weighed against the immense risk of contracting SARS-CoV-2 infection.

16.3.6.2.1.6. Conclusion

Based on the analysis of all the safety data received during the cumulative period of this PBRER, ModernaTX, Inc considers that cases included under the AESI of subacute thyroiditis, reported in temporal association with the administration of SPIKEVAX, does not represent a safety issue and the information provided is inadequate to provide evidence of causality between SPIKEVAX exposure and subacute thyroiditis. These data do not represent a new safety issue of concern. ModernaTX, Inc will continue to monitor events for subacute thyroiditis using routine surveillance. The benefit-risk evaluation remains positive.

16.3.6.3. Hematological Disorders

16.3.6.3.1. Thrombocytopenia with Thrombosis

16.3.6.3.1.1. Source of the New Information

Information presented below includes analysis performed on cases received by ModernaTX, Inc., for the review period, from 01 Jul 2021 to 31 Dec 2021 for the mRNA-1273 vaccine (COVID-19 vaccine Moderna) SPIKEVAX.

16.3.6.3.1.2. Background Relevant to the Evaluation

Thrombosis with Thrombocytopenia Syndrome (TTS), also known as Vaccine-induced prothrombotic immune thrombocytopenia (VIPIT) or vaccine-induced immune thrombotic thrombocytopenia (VITT), is a rare and newly identified syndrome which has been reported in people who have received adenoviral vector COVID-19 [125]. This syndrome is characterized by venous or arterial thrombosis, mild to severe thrombocytopenia, and positive PF4-heparin ELISA ("HIT" ELISA). These clinical and laboratory features are similar to rare cases of HIT-like autoimmune thrombosis with thrombocytopenia, previously described following surgery, certain medications or infections in patients not receiving heparin. Symptoms on presentation may include intense headache, abdominal pain, back pain, nausea and vomiting, vision changes, change in mental status, shortness of breath, leg pain and swelling, and/or bleeding/petechiae. Patients may complain of severe, recurrent, or persistent symptoms from 4 to 42 days following COVID-19 vaccination, with the peak time period for initial symptoms falling between days 6 to 14 [126].

The MAH has agreed to continue to closely evaluate events of "Thrombosis with Thrombocytopenia-related events".

16.3.6.3.1.3. Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

The MAH queried the GSDB for the reporting period of 01 Jul through 31 Dec 2021 for valid case reports received from HCP, HA, consumers, and literature, worldwide, reported for SPIKEVAX. The search strategy included using a customized list of MedDRA PTs from the SMQ-Embolic and thrombotic events-narrow. To identify cases with a reported thromboembolic event, which were then cross-checked for any of the following thrombocytopenia-related PTs: Acquired amegakaryocytic thrombocytopenia; Megakaryocytes decreased; Platelet count decreased; Platelet maturation arrest; Platelet production decreased; Platelet toxicity; Thrombocytopenia; Megakaryocytes abnormal; Platelet count abnormal; Platelet disorder; Plateletcrit abnormal; Plateletcrit decreased; Immune thrombocytopenia; HELLP syndrome [hemolysis (H), elevated liver enzymes (EL), and low platelets (LP)]; Thrombotic thrombocytopenic purpura; Thrombocytopenic purpura, Platelet transfusion, Petechiae, Ecchymosis, and Purpura.

All cases identified were reviewed and classified using both the CDC working definition and the Brighton Collaboration (BC) interim case definition for TTS.

The **CDC classification** for possible cases of TTS [127] divides cases into 2 tiers based on the location of thrombosis and severity of symptoms, with Tier 1 being associated with higher morbidity and mortality. Reported cases of possible TTS with insufficient evidence or information to be classified according to either of the case definitions were classified as “unassessable”; and cases with evidence that parameters were not met for either case definition were classified as “Not a TTS case”.

The **BC case definition** for TTS [128] divides cases into 5 levels:

- Level 1 – Definite Case
- Level 2 – Probable Case
- Level 3 – Possible Case
- Level 4 – Not enough information
- Level 5 – Not a case of TTS

For those cases that are classifiable according to the CDC or BC definitions, the company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment [54].

- Appendix 20.11.37 and Appendix 20.11.38: includes the reporting period information for all TTS-related case reports.

- Appendix 20.11.39 and Appendix 20.11.40: includes the reporting period cases of TTS-related cases according to the Brighton collaboration case definitions for TTS, the CDC working case definition for TTS, and case causality assessments according to the WHO-UMC standardized case causality assessment.

16.3.6.3.1.4. Results A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Observed vs Expected

See Appendix 20.11.3.

Overview of Cases (01 Jul 2021 to 31 Dec 2021)

During the reporting period, there were 88 cases (97 events) of Thrombosis with Thrombocytopenia related events, of which 86 cases were serious, and 19 cases had a fatal outcome. Seventy-three (73) cases were medically confirmed. There was no important difference in the overall number of reports received during this reporting period compared with the previous period.

There were no important differences noted upon review of the cases with TTS- related events by gender, with 47 cases (53.4%) reported in males and 40 cases (45.5%) reported in females. The majority of the reports during the reporting period were in individuals > 50 years of age (54; 61.4%) (Table 16-130).

Table 16-130 Number and Percentage of Thrombosis with Thrombocytopenia Related Cases by Gender and Age – 01 Jul 2021 to 31 Dec 2021

Age Group	Female		Male		Unknown		Total # Cases	% Total Cases
	# Cases	% of Cases	# Cases	% of Cases	# Cases	% of Cases		
12-15	2	2.3	0	0	0	0	2	2.3
18-29	7	8.0	7	8.0	0	0	14	15.9
30-39	3	3.4	3	3.4	0	0	6	6.8
40-49	6	6.8	5	5.7	0	0	11	12.5
50-64	7	8.0	8	9.1	0	0	15	17.0
65-74	8	9.1	17	19.3	0	0	25	28.4
75+	7	8.0	7	8.0	0	0	14	15.9
Missing	0	0	0	0	1	1.1	1	1.1
Grand total	**40**	**45.5**	**47**	**53.4**	**1**	**1.1**	**88**	**100.0**

The majority of reports were received from regulatory authorities (77; 87.5%). The greatest proportion of cases reporting TTS-related events were from Asia and the United States, with 29 cases from each region, representing 66% of all reported TTS-related cases. (Table 16-131).

Table 16-131 Number and Percentage of Reported Thrombosis with Thrombocytopenia Related Cases by Region – 01 Jul to 31 Dec 2021

Region	# Cases	% of Total Cases
Asia	29	33.0
United States	29	33.0
European Economic Area	18	20.5
Switzerland	5	5.7
United Kingdom	5	5.7
Canada	2	2.3
Grand total	**88**	**100.0**

During the reporting period, almost half of TTS-related events were reported as occurring after dose 2 (47; 48.5%); whereas there were 16 events (16.5%) reported following dose 1 and 3 events (3.1%) following dose 3. Regardless of most recent dose number, events were most frequently reported with a time to onset (TTO) of 14 days or more (33 events, 34%); whereas there were 22 events (22.7%) with a TTO of less than 7 days and 11 events (11.3%) with a TTO of 7 to 13 days (Table 16-132).

Table 16-132 Number and Percentage of Thrombosis with Thrombocytopenia Related Events by Dose and Time to Onset – 01 Jul 2021 to 31 Dec 2021

Dose Number	TTO (Days)	# Events	% Events
Dose 1	***Subtotal***	***16***	***16.5***
	03-04	2	2.1
	05-06	1	1.0
	07-13	4	4.1
	14-29	5	5.2
	30+	4	4.1
Dose 2	***Subtotal***	***47***	***48.5***
	0 days	3	3.1
	01-02	9	9.3
	03-04	7	7.2
	07-13	7	7.2
	14-29	8	8.2
	30+	13	13.4
Dose 3	***Subtotal***	***3***	***3.1***

Dose Number	TTO (Days)	# Events	% Events
	14-29	2	2.1
	30+	1	1.0
Unknown	***Subtotal***	***31***	***32.0***
	Missing	31	32.0
Grand total		**97**	**100.0**

Consistent with what was seen cumulatively, there were 45 events of thrombocytopenia (46.4%) and 18 (18.6 %) events of thrombotic thrombocytopenic purpura received in the reporting period (Table 16-133).

Table 16-133 Number and Percentage of Reported MedDRA PTs in Cases of Thrombosis with Thrombocytopenia Related Events – 01 Jul to 31 Dec 2021

PT	# Events	% of Total Events
Thrombocytopenia	45	46.4
Thrombotic thrombocytopenic purpura	18	18.6
Thrombosis with thrombocytopenia syndrome	15	15.5
Platelet count decreased	12	12.4
Purpura	3	3.1
Petechiae	2	2.1
Immune thrombocytopenia	1	1.0
Platelet transfusion	1	1.0
Grand total	**97**	**100.0**

The outcome was unknown or not reported in the greatest proportion of TTS-related events (31, 32.0%). Fatal outcomes were reported for 19 cases, in which 23 events were reported as fatal, representing 23.7% of the TTS-related events. (Table 16-134). Please see Appendix 20.11.37 and Appendix 20.11.38. for further details on these cases.

Table 16-134 Summary of Outcomes of Thrombosis with Thrombocytopenia Related Events – 01 Jul 2021 to 31 Dec 2021

Event Outcome	# of Events	% of Events
Fatal	23	23.7
Not Recovered/Not Resolved	22	22.7
Recovered/Resolved	10	10.3
Recovered/Resolved with Sequelae	1	1.0
Recovering/Resolving	10	10.3
Unknown	31	32.0
Grand total	**97**	**100.0**

Adolescents aged 12-17 years

There were two reports of TTS-related events in adolescents (12-17 Years) received during the reporting period. Both cases were reported in 15-year-old females, with one reported as resolved and the other as resolving. Please see Appendix 20.11.37 and Appendix 20.11.38 for further details on these cases.

Children aged <12 years

There were no reports received by the MAH through 31 Dec 2021 of TTS-related events in children <12 years of age.

SPIKEVAX Booster

There were two case of thrombosis with thrombocytopenia related events reported following dose 3 or greater in this reporting period. Two cases of TTS-related events were reported, following the administration of a 3rd dose. One case was in 76-years-old male (4.1(b); WW Identifier: 4.1(b) 4.1(b)) and the other case was in 71-years-old female (4.1(b); 4.1(b) -4.1(b)) was received during the current reporting period. Please see Appendix 20.11.37 and Appendix 20.11.38 for further details on these cases.

Brighton Collaboration/ CDC Working Case Definition/ WHO Causality Assessment

During the reporting period, evaluation of the 88 cases identified with thrombosis and thrombocytopenia related events using the Brighton Collaboration case definition for TTS (Brighton-Thrombocytopenia 2021) there were 12 reports classified as Level 1, 2 reports classified as Level 2, 2 reports classified as Level 3, 39 reports classified as Level 4 - Not enough information, and 33 reports classified as Level 5 - Not a case of TTS (See Appendix 20.11.39 and Appendix 20.11.40).

According to the CDC working case definition for TTS, there were 5 reports classified as Tier 1, 1 report classified as Tier 2, 42 reports that were unassessable due to the lack of information, including platelets levels; and 40 reports were classified as Not a case of TTS based on the report not meeting the case definition or on information available that provided a different clinical explanation for the classification of the events. (See Appendix 20.11.39 and Appendix 20.11.40).

According to the WHO causality assessment, there were 6 reports classified as possible based on temporal association between the use of the product and the start of the events, but a causal relationship cannot be excluded due to the lack of information, including medical history, concomitant medications, clinical course, laboratory information, etc. There were 21 reports considered conditional, 17 reports considered unassessable due to the lack of information, and

there were 44 reports that were considered unlikely to be related to the vaccine due to prolonged time to onset as well as comorbidities present in some of these patients that provide a more plausible explanation for the occurrence of the events (Appendix 20.11.39 and Appendix 20.11.40).

16.3.6.3.1.5. Discussion

Analysis of the data reported during this reporting period does not provide evidence to support a causal association between TTS and SPIKEVAX. None of the reports included heparin-PF4 ELISA HIT antibody test results, and multiple reports lacked laboratory results and imaging test findings. Cumulatively, the reporting rate of TTS for SPIKEVAX is substantially lower than one report per million doses. In addition, in this reporting period most of the reports met neither the CDC nor Brighton definition for TTS, and the majority of the reports were considered unlikely related to the vaccine according to the WHO causality assessment.

As evidenced in the cases detailed above, non-vaccine etiology may often be inferred due to concomitant COVID-19 disease, long times to onset, and the fact that thrombocytopenia and thrombosis (especially at common sites) can be produced by multiple non-vaccine-related disease processes.

Funded by the US Centers for Disease Control and Prevention, a rigorous population-based pharmacoepidemiologic study of the safety of mRNA COVID-19 vaccines was recently published in a major medical journal (Klein 2021) This study of more than 11.8 million doses (43% were SPIKEVAX) found that the adjusted rate ratio of TTS in the risk interval vs. the comparison interval was 0.86 (95% CI: 0.58-1.27). Klein et al concluded: “There has been no evidence that these outcomes [including TTS] are associated with mRNA vaccines.”

16.3.6.3.1.6. Conclusion

The data provided in this PBRER describe sufficiently the safety profile of SPIKEVAX in the interval and cumulatively. The benefit-risk evaluation remains positive. After careful review of all new safety data received during the reporting period, (01 Jul 2021 to 31 Dec 2021) for the risk of thrombocytopenia and thrombosis, the benefit-risk profile for SPIKEVAX remains favorable. The risk of thrombocytopenia and thrombosis will continue to be monitored using the routine pharmacovigilance measures implemented for SPIKEVAX.

16.3.6.3.2. Immune Thrombocytopenia (ITP)

16.3.6.3.2.1. Source of the New Information

Information presented below includes analyses performed on cases received by ModernaTX, Inc. from 01 Jul 2021 to 31 Dec 2021 for the mRNA-1273 vaccine (COVID-19 vaccine Moderna) SPIKEVAX. Cumulatively, the data reviewed covers the period from 18 Dec 2020 to 31 Dec 2021.

The MAH received a request from a health authority to provide an updated review on the topic of flare-up of ITP during the reporting interval of this PBRER.

16.3.6.3.2.2. Background Relevant to the Evaluation

Immune thrombocytopenia (ITP) formerly known as idiopathic thrombocytopenic purpura, is an immune-mediated acquired disease of adults and children characterized by transient or persistent decrease of the platelet count and, depending upon the degree of thrombocytopenia, increased risk of bleeding [129]. ITP is defined as a platelet count of less than 100×10^9/L (100,000/μL) with no evidence of leukopenia or anemia. This cut-off point is new and differentiates with the previous one, platelet count of less than 150×10^9/L, which is the threshold for a normal platelet count in most laboratories, and the one used by the current Brighton Collaboration case definition for Thrombocytopenia.

The etiology of autoimmune disorders is largely attributable to an individual's genetic risk factors, exposure to environmental triggers, and underlying immune dysregulation [130]. Whereas a variety of autoimmune disorders have been reported after vaccination, specific vaccines elicit unique autoimmune pathology. For example, secondary immune thrombocytopenia (ITP) is strongly linked to the measles, mumps, and rubella vaccine, and is associated with hepatitis A and B vaccines. Yet other vaccines, such as the quadrivalent human papilloma virus vaccine, demonstrate no autoimmune safety signal. As of today, the effect of SARS-CoV-2 vaccination on patients with pre-existing autoimmune hematologic conditions is poorly understood.

ITP is mediated by autoantibodies directed against platelets, and it is associated with autoimmune disorders and malignancies. ITP can be triggered by vaccines and viral infections, including SARS-CoV-2. The pathogenesis of post-viral de novo ITP is thought to involve molecular mimicry and circulating immune complexes. Flares of pre-existing ITP, however, result from an augmentation of a prior immune response [131]. COVID-19 infection has been linked to thrombocytopenia and ITP possibly due to immune-mediated destruction, direct infection of megakaryocytes or platelets, decreased thrombopoietin production related to liver damage, or consumption due to a coagulopathic state [132]. The median time to onset from symptoms of COVID-19 to presentation with ITP in one review was 13 days, with most patients presenting after two to three weeks, although approximately 20% of COVID-19 patients presented with ITP in ≤7

days [133]. Several signal evaluations were previously conducted by the MAH to fully assessed the risk of immune thrombocytopenia after vaccination with SPIKEVAX. In the final assessment report (EPITT no.: 19679) provided as part of PBRER 1 (Reporting period 18 Dec 2020 to 30 Jun 2021) the cumulative analysis of all available data conclusion provided by the PRAC indicated that based on the information provided there was not an indication of a signal on new onset of ITP after administration of SPIKEVAX. Flare-ups or condition aggravated of cases with previous history of ITP were requested to be discussed in this next PBRER.

16.3.6.3.2.3. Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

The MAH queried the global safety database, for the reporting period, 01 Jul 2021 through 31 Dec 2021, for valid case reports received from HCP, HA, consumers, and literature, worldwide, reported for SPIKEVAX. The following search strategy was designed by ModernaTx to identified and review cases of potential flares of ITP after vaccination. This search strategy required combining several fields within the global safety database as well as using interpretation and medical review of the narrative to identify reports of flares:

1. Query the global safety database for reports of thrombocytopenia-related PTs: Acquired amegakaryocytic thrombocytopenia; Megakaryocytes decreased; Platelet count decreased; Platelet maturation arrest; Platelet production decreased; Platelet toxicity; Thrombocytopenia; Megakaryocytes abnormal; Platelet count abnormal; Platelet disorder; Plateletcrit abnormal; Plateletcrit decreased; Immune thrombocytopenia; HELLP syndrome; Thrombotic thrombocytopenic purpura; Thrombocytopenic purpura, Platelet transfusion, Petechiae, Ecchymosis, and Purpura.
2. Filter all those report for those that have in the MedHx coded with Immune Thrombocytopenia and/or Thrombocytopenia
3. Identified those reports that have are coded with additional PTs of “condition aggravated”, “disease progression”, or “disease recurrence” (Medical review to identify potential flares of ITP).

For this analysis, these search strategies have been combined into one data filter, and the section of flares now uses the combined data. Preliminary medical review of the cases further classified these cases.

To characterize the level of diagnostic certainty, identified cases were classified into one of four categories, following the Brighton-Thrombocytopenia (2021) case definition:

- Meets level 1 as specified in the case definition

- Meets level 2 as specified in the case definition
- Reported case of thrombocytopenia with insufficient evidence to meet the case definition
- Not a case of thrombocytopenia

The Brighton definitions are used to evaluate the strength of the evidence to determine whether a case fulfils the criteria needed to establish a case (of immune thrombocytopenia). It is not used to ascertain causality.

In contrast, causality assessment (i.e., characterizing the likelihood that a case of immune thrombocytopenia was attributable to vaccine exposure) was conducted utilizing the WHO-UMC standardized case causality assessment [54].

For those cases classified as meeting level 1 or level 2, the company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment [54].

- Appendix 20.11.41 and Appendix 20.11.42: includes a detailed summary of interval data concerning reported events of suspected Immune Thrombocytopenia flares classified by the Brighton collaboration classification and the WHO causality assessment.

16.3.6.3.2.4. Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Observed vs. Expected Analysis

See Appendix 20.11.3.

Overview of Cases

Cumulative Review (ITP, cumulative to 31 Dec 2021)

Cumulatively, through 31 Dec 2021, a total of 36 cases were reported for events classified as Immune Thrombocytopenia (ITP) flares. There were 31 cases assessed as serious and there were no reports with fatal outcome. Of the 36 cases, 34 cases were medically confirmed. Medically confirmed cases are those case reports where the suspected adverse reaction is confirmed by a medically qualified healthcare professional.

There were no differences between males (18 cases, 51.4%) and females (18, 51.4%) reports. The majority of the cases (23, 65.7%) reported were for patients 50 years of age or older (median: 58.0 years; mean: 57.7) (Table 16-135).

Table 16-135 Number and Percentage of Reported Suspected ITP Flares Events Cases by Gender and Age – Cumulative to 31 Dec 2021

Age Group	Female		Male		Total # Cases	% Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases		
18-29	1	2.9	1	2.9	2	5.6
30-39	1	2.9	3	8.6	4	11.1
40-49	3	8.6	2	5.7	5	13.9
50-64	6	17.1	5	14.3	11	30.6
65-74	2	5.7	4	11.4	7	19.4
75+	4	11.4	1	2.9	5	13.9
Missing	1	2.9	2	5.7	3	8.3
Grand total	**18**	**51.4**	**18**	**51.4**	**36**	**100.0**

Children ages < 12 Years (Cumulatively as of 31 Dec 2021)

Cumulative there were no reports of suspected ITP flares events in children of < 12 years of age.

Adolescents ages 12-17 Years (Cumulatively as of 31 Dec 2021)

Cumulatively as of 31 Dec 2021, there were no cases of suspected ITP flares reported in adolescents 12 to 17 years of age.

SPIKEVAX Booster (Cumulatively as of 31 Dec 2021)

Cumulatively as of 31 Dec 2021 there was one report of a suspected ITP flare event on a patient after receiving a 3rd dose of SPIKEVAX. This report was received during the reporting interval of this PBRER. (See Appendix 20.11.41 and Appendix 20.11.42).

Reporting Period 01 Jul 2021 to 31 Dec 2021

During the reporting period of this PBRER (01 Jul to 31 Dec 2021), there were 18 cases of suspected flares of Immune thrombocytopenia, of which 16 cases were serious, with no reported fatal outcome. All 18 reports were medically confirmed.

There were no important differences between the cases of suspected flares of ITP by gender with 7 cases (20.0%) reported in females and 11 cases (31.4%) reported in males. The majority of the reports during the reporting period were in individuals > 50 years of age (13; 72.2%) (Table 16-136).

Table 16-136 Number and Percentage of Suspected ITP Flares Cases by Gender and Age – Reporting Period 01 Jul 2021 to 31 Dec 2021

Age Group	Female		Male		Total # Cases	% Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases		
18-29	0	0.0	1	2.9	1	2.9
30-39	0	0.0	1	2.9	1	2.9
40-49	2	5.7	1	2.9	3	8.6
50-64	2	5.7	4	11.4	6	17.1
65-74	2	5.7	3	8.6	5	14.3
75+	1	2.9	1	2.9	2	5.7
Missing	0	0.0	0	0.0	0	0.0
Grand total	**7**	**20.0**	**11**	**31.4**	**18**	**51.4**

During the reporting period most of the reports occurred after dose 1 (10; 55.6%), with most of the events occurring within the first 3 days after any vaccine dose (10; 55.6%). (Table 16-137).

Table 16-137 Number and Percentage of Suspected ITP Flares Events by Dose and Time to Onset – Reporting Period 01 Jul 2021 to 31 Dec 2021

Dose Number	TTO (Days)	# Events	% Events
Dose 1	***Subtotal***	***10***	***55.6***
	0 days	1	5.6
	01 to 03	4	22.2
	14-29	2	11.1
	30+	3	16.7
Dose 2	***Subtotal***	***3***	***16.7***
	0 to 2	1	*5.6*
	30 +	2	*11.1*
Dose 3	***Subtotal***	***1***	***5.6***
	0 days	1	*5.6*
Unknown	***Subtotal***	***4***	***22.2***
	02 days	3	*16.7*
	Missing	1	*5.6*
Grand total		**18**	**100.0**

Children ages < 12 Years (Reporting Period)

There were no reports of ITP-related flares in children of < 12 years of age during the reporting period (01 Jul 2021 to 31 Dec 2021).

Adolescents ages 12-17 Years (Reporting Period)

There were no ITP related flares during the reporting period (01 Jul 2021 to 31 Dec 2021) for adolescent (12-17 Years).

SPIKEVAX Booster (Reporting Period)

During the reporting period (01 Jul 2021 to 31 Dec 2021) there was one report of an ITP related flare for a patient following a 3rd dose of SPIKEVAX. (See Appendix 20.11.41 and Appendix 20.11.42).

Fatal outcomes reports (Reporting Period):

During the reporting period (01 Jul 2021 to 31 Dec 2021) there were no fatal outcomes reported for cases of ITP related flares.

Brighton Collaboration/ WHO Causality Assessment

As per request from regulatory authorities the MAH evaluated cases that were identified as possible flares of ITP after receiving a dose of SPIKEVAX. A total of 18 cases were identified during the reporting period of this PBRER (01 Jul to 31 Dec 2021).

There were 11 males and 7 females. There were 9 reports after dose 1, 3 after dose 2, 1 after dose 3, and 5 after an unknown dose. 16 out of the 18 cases were considered serious. Reported TTO was between hours after receiving any dose of the vaccine to 90 days after the vaccine; there was 1 report with unknown TTO. There were 3 reports received from literature articles, 14 from regulatory authorities, and 1 was a spontaneous report from a physician.

During evaluation of the 18 cases using the Brighton Collaboration case definition for Thrombocytopenia (33) 10 reports were classified as Level 1, 7 reports classified as Level 4, and 1 report was classified as Level 5 (See Appendix 20.11.41 and Appendix 20.11.42).

According to the WHO causality assessment, there were 5 reports classified as possible based on the temporal association between the use of the product and the start of the events; there are two reports of the events classified as "Possible" where there is a positive rechallenge observe in the patients after receiving the second dose of SPIKEVAX (4.1(b) [redacted], and 4.1(b) [redacted]). There were 3 reports considered conditional; 4 reports considered unassessable due to the lack of information, and there were 6 reports that were considered unlikely to be related to the vaccine due to prolonged time to onset, use of concomitant medications labelled to affect platelets, and due to comorbidities present in some of these patients that provide a more plausible explanation for the occurrence of the events (See Appendix 20.11.41 and Appendix 20.11.42).

The 2 reports with the positive rechallenge are presented below:

4.1(b) : (4.1(b) 4.1(b)): Literature article for a 72-year-old woman with chronic ITP on maintenance treatment of eltrombopag dose 25 mg daily, and recent SARS-CoV-2 antibody testing negative, who according to the authors before dose 1 of SPIKEVAX, had a platelet baseline of 65x10^9/L to 80x 10^9/L. Approximately 13 hours after receiving dose 1 of SPIKEVAX, her platelet count fell to 45x 10^9/L (42% decrease). The eltrombopag dose was increased to 50 mg daily, with an increase in platelet count to a peak of 298x 10^9/L. Approximately 1 hour before receiving dose 2, the platelet count was 193 x 10^9/L. Three days later, the platelet count fell to 27 x 10^9/L (86% decrease), prompting an increase in eltrombopag to 75 mg daily. In response to 3 doses, the platelet count increased to 205 x 10^9/L. No other information was provided. According to the authors this case demonstrates how the exacerbation of preexisting ITP can sequentially increase in severity with each of the 2 doses. The platelet count fell by 86% with the second dose compared with 42% with the first dose, consistent with a cumulative effect on the underlying humoral response.

Company assessment: Even though important information is missing in this report including any laboratory results that may also explain the sudden drop in platelet levels in this patient, including any possible infectious process, the positive rechallenge observe in the patient after receiving the second dose of SPIKEVAX makes this report according to the WHO causality assessment possible based on temporal association between the use of the product and the start of the events; a causal relationship cannot be excluded.

4.1(b) : (4.1(b)): This case concerns a 55-year-old male with history of chronic ITP who 2 days the 1st dose of SPIKEVAX experienced petechiae that resolved within days. Patient then received the 2nd dose of SPIKEVAX and two days later started experiencing petechiae on his lower legs, bruises on his left chest and left lower abdomen, a nosebleed that stopped after 10 minutes. His was found to have low platelet levels and was started a high dose steroid and immunoglobulin therapy for 4 days with increase in his platelet levels and resolution of his symptoms. According to the physician that reported the case there was no evidence of an infection.

MAH comment: Even though important information is missing in this report including any laboratory results that may also explain the sudden drop in platelet levels in this patient, the positive rechallenge observe in the patient after receiving the second dose of SPIKEVAX makes this report according to the WHO causality assessment possible based on temporal association between the use of the product and the start of the events; a causal relationship cannot be excluded.

Literature review:

Though the exact etiology of autoimmune diseases still remains unknown, there are various factors which are believed to contribute to the emergence of an autoimmune disease in a host including

the genetic predisposition, the environmental triggers such as bacterial infections, including the gut microbiota, viral fungal and parasitic infections, as well as physical and environmental agents, hormonal factors and the hosts immune system dysregulation. Suggested mechanisms of induction of the autoimmunity include both molecular mimicry as well as “bystander activation” whereby the infection may lead to activation of antigen presenting cells that may in turn activate pre-primed auto-reactive T cells, thus leading to the production of pro-inflammatory mediators, which in turn may lead to tissue damage.

A variety of autoimmune disorders have been reported after vaccination, specific vaccines elicit unique autoimmune pathology. For example, secondary immune thrombocytopenia (ITP) is strongly linked to the measles, mumps, and rubella vaccine and is associated with hepatitis A and B vaccines. SARS-CoV-2 infection has been shown to effect sustained dysregulation of adaptive and innate immunity. The immunomodulatory effects of SARS-CoV-2 vaccination, however, are poorly understood.

There were several literature reports presenting case-reports information during the reporting period, and out of those, the following four included information relevant for the analysis of ITP-flares. All cases reported in these literature reports are included in the ModernaTx global safety database.

Severe immune thrombocytopenia after COVID-19 vaccination: Report of four cases and review of the literature

- Case review of four cases of ITP following COVID-19 vaccination with both mRNA and adenoviral vaccines
- Brief literature review
- The study concluded the benefits of COVID-19 vaccine against SARS-CoV-2 infection far outweighs the risks of side effects or disease flares.
- The authors recommend hematologic monitoring in patients with ITP is advisable before and after vaccination.

Thrombocytopenia including immune thrombocytopenia after receipt of mRNA COVID-19 vaccines reported to the Vaccine Adverse Event Reporting System (VAERS)

- This case-series study analyzed VAERS reports of thrombocytopenia, including ITP, after vaccination with mRNA COVID-19 vaccines
- Fifteen cases of thrombocytopenia were identified among 18,841,309 doses of Pfizer-BioNTech COVID-19 Vaccine and 13 cases among 16,260,102 doses of Moderna COVID-19 Vaccine. The reporting rate of thrombocytopenia was 0.80 per million doses for both vaccines.

Based on an annual incidence rate of 3.3 ITP cases per 100,000 adults, the observed number of all thrombocytopenia cases, which includes ITP, following administration of mRNA COVID-19 vaccines is not greater than the number of ITP cases expected.

- Out of the 13 Moderna cases – 2 had previous history of ITP, both recovered after treatment

Autoimmune- and complement-mediated hematologic condition recrudescence following SARS-CoV-2 vaccination

- This is a case review of 3 reports that describe the recrudescence of 2 autoimmune conditions (ITP and acquired von Willebrand Disease [AvWD]/acquired hemophilia A) and 1 complementopathy (paroxysmal nocturnal hemoglobinuria [PNH]).

- According to the authors Flares of preexisting ITP, result from an augmentation of a prior immune response, that can sequentially increase in severity with each of the 2 doses.

- Among patients with autoimmune hematologic conditions, the authors advise close monitoring in the 1 to 4 days after each dose of a 2-dose SARS-CoV-2 vaccine series.

Exacerbation of immune thrombocytopenia following COVID-19 vaccination

- Fifty-two chronic ITP patients were prospectively followed after COVID-19 vaccination.

- 8/52 (15%) had no worsening of clinical symptoms but no post-vaccination platelet count done

- 38/52 (73%) had no new symptoms and no significant platelet count decline in the 14 days after vaccination

- ~50% had decreases in platelet count after vaccination that could not be distinguished from their usual fluctuation numbers – NONE decreased by more than 50% from pre-vaccination counts

- 6/52 (12%) of patients developed a severe exacerbation of their thrombocytopenia along with worsening bleeding symptoms:

    - Had a median platelet count drop of 96% within 2–5 days post vaccination with new bleeding symptoms
    - All six patients required treatment and 5/6 responded to prednisone +/- intravenous immunoglobulin (IVIG)
    - Rapid response except for 2 patients with platelets recovered to >30 × 109/l a median of 3 days later
    - 2/6 had previous dropped in the platelet count before the vaccine
    - 4/6 were in remission (3 on no therapy) for over 1 year – 2 in active treatment

- 2 patients had received a 2nd dose before platelet counts were obtained but both had increased bleeding symptoms after the 1st dose that had been wrongly attributed to their concurrent warfarin anticoagulation – Positive Rechallenge
- The remaining four patients did not receive a second vaccination.
- Of the six patients with worsening thrombocytopenia, two previously had similar declines in platelet counts with prior vaccinations for Neisseria meningitis and Streptococcus pneumoniae

An important conclusion of this study was that exacerbation of ITP occurred with all three studied COVID-19 vaccines. An additional literature article was requested by a health authority to be reviewed and presented in this reporting period. Immune thrombocytopenic purpura and acute liver injury after COVID-19 vaccine. This literature report is for a 26-year-old woman with previous medical history of irregular menses and on oral contraceptives who 1 weeks after receiving the 1st dose of SPIKEVAX experienced a petechial rash on her neck and chest associated with increased bruising, especially on her lower extremities.
She went to an urgent care facility and was diagnosed with an idiopathic allergic reaction and was prescribed prednisone 40 mg/day to treat the urticaria. After taking 3 doses of prednisone her rash improved and a repeat CBC showed an abnormal platelet count of 19×10^9/L. She was then hospitalized and on day 1 her CBC revealed a platelet count of $28x10^9$/L with normal haemoglobin and WBC. Coagulation studies were normal, SARS-CoV-2 was negative, liver enzymes were elevated, total bilirubin and alkaline phosphatase were normal. The peripheral blood smear (PBS) showed rare schistocytes, giant platelets, no platelet clumping, toxic neutrophils and atypical lymphocytes without immature WBCs or blasts. A clinical diagnosis of ITP was made, and the patient received four doses of dexamethasone 40 mg intravenously daily with two doses of intravenous immunoglobulin (IVIg) 1 g/kg/day. Her platelet counts appropriately responded and was normal at 213×10^9/L by HD 5. Her hospital course was complicated by worsening transaminitis with her AST and ALT levels peaking on HD 3 at 446 U/L and 1257 U/L, respectively. The hepatitis panel was positive for hepatitis B virus (HBV) total core antibody; however, her IgM antibody was negative; HBV surface antibody was positive at 1387.7 mIU/mL indicating immunity; HBV surface antigen and HBV e-antigen/antibody were negative with an undetectable viral load; any other viral panel test was negative; as well as any other test including an abdominal ultrasound that showed a normal liver and spleen and a liver biopsy. The authors in this article presented through a well-documented list all the differential diagnosis that could had been associated with the symptoms presented by the patient and concluded, based on the laboratory and diagnostic test results available that given the patient's platelet count returning to normal at 213×10^9/L after appropriate treatment, her liver biopsy and other workup for acute liver injury were unremarkable, and the PBS was significant for giant platelets, this supports a diagnosis of ITP. The ITP is a challenging diagnosis, with no unique identifying features when it occurs after

vaccination. Unlike other conditions, ITP is a diagnosis of exclusion. There is no specific test that confirms the diagnosis, and clinicians therefore rely on the lack of distinguishing features of other diseases, which depends in part on the thoroughness of the evaluation. In some cases, alternative diagnoses may become apparent only during follow-up. Perhaps the most reliable inclusive 'diagnostic' test is a robust response to ITP-directed therapies. Distinguishing de novo ITP from undiagnosed, pre-existing ITP is an important challenge that requires knowledge of pre-vaccination platelet counts. Many patients may have platelet counts as low as 30,000 to 50,000 platelets per microliter while still remaining asymptomatic, and unless a recent evaluation may have been conducted, most of the de nove ITP cases are identified during a routine examination or after an infectious process that may trigger the presence of symptoms. Transient reductions in platelet counts after infection and vaccination are common; and pre-vaccination platelet counts are infrequently available for patients who do not otherwise require regular medical attention. According to the WHO causality assessment this report is considered possible based on temporal association between the use of the product and the start of the events, but important information is missing including the patient's medical history as well as concomitant medications including information related to the use of contraceptives; a causal relationship cannot be excluded.

16.3.6.3.2.5. Discussion

Analysis of the data reported during this reporting period regarding the temporal association between the ITP flares and SPIKEVAX shows that more information is needed in order to understand whether vaccination, like infection, can exacerbate thrombocytopenia in patients with previous history of ITP.

In general, assessment of cases of flare up is challenging, as several aspects must be taken into consideration: stage of disease, the patient's normal frequency of flare ups, comedication, adjustments in comedications, concurrent diseases/infections. For proper assessment, the cases need to be very detailed. Distinguishing de novo ITP from exacerbation of undiagnosed, pre-existing ITP is another challenge and requires knowledge of pre-vaccination platelet counts. Many patients may have platelet counts as low as 30,000 to 50,000 platelets per microliter while still remaining asymptomatic. Second, transient reductions in platelet counts after infection and vaccination are common; and third, pre-vaccination platelet counts are infrequently available for patients who do not otherwise require regular medical attention.

Previous studies have indicated that other vaccines like human papillomavirus, hepatitis B and influenza vaccines may trigger the onset or exacerbations of autoimmune diseases, including ITP, by molecular mimicry inducing autoimmunity. In the case of the COVID-19 vaccines, several hypotheses have been postulated to try to explain the pathogenesis of these events that have been reported in individuals with previous history of autoimmune conditions, including ITP and again

exacerbations are likely to be immune-mediated and are hypothesized to be related to the increased B-cell function seen in primary ITP. Flares of pre-existing ITP, however, may result from an augmentation of a prior immune response.

Regardless of all these postulated hypotheses, whether the association between COVID- 19 vaccines and autoimmune manifestations is coincidental or causal still remains to be elucidated. The reports of flares up of ITP after COVID-19 vaccines are relatively rare given the large numbers of people that have been vaccinated globally. As mentioned above, there have been reports of flares of ITP after many vaccines, including all the currently authorized COVID-19 vaccines; both health care providers and patients acknowledge the potential risk of flares after any vaccination, yet flares are not specifically described in any vaccine labels, and the general, global consensus is that the benefit of vaccination outweighs the potential risks of flares.

Furthermore, rates of reported ITP flares after COVID-19 vaccination cannot be established with spontaneous reporting as the denominator of the number of vaccinated persons with ITP conditions is unknown. When considering all of the available evidence, the challenge is the quality of passive reporting data, the lack of well-established background rates of flares, and the lack of robust rigorous well-designed controlled observational studies, currently limited ability to use RWE to estimate the O/E, there remains insufficient evidence to establish increased risk and/or rates of flares up of ITP after vaccination with SPIKEVAX.

Attribution of a rare adverse event to vaccine exposure can exacerbate vaccine hesitancy, with important effects on public health. As of the DLP of this PBRER there have been 559,872,937 doses of SPIKEVAX that are estimated to have been administered. With 36 reports of flares of ITP cumulative, the reporting rate of flares of ITP is 0.06 cases per million doses of vaccine administered.

16.3.6.3.2.6. Conclusion

The data provided in this PBRER describe sufficiently the cumulative safety profile of SPIKEVAX. The benefit-risk evaluation remains positive. Based on the analysis of the cumulative safety data available as of 31 Dec 2021 for the risk of flares of ITP, the MAH considers that Flares of ITP-related events are not presently a safety issue of concern, and the benefit-risk profile for SPIKEVAX remains favorable. The MAH will continue to evaluate Flares of ITP-related events using routine surveillance.

16.3.6.4. Nervous System Disorders

16.3.6.4.1. Guillain-Barre Syndrome (GBS)

16.3.6.4.1.1. Source of the New Information

New information presented below includes analysis performed on new cases received by ModernaTX, Inc. from 01 Jul 2021 to 31 Dec 2021 for SPIKEVAX. Cumulatively, the data reviewed covers the period from the 18 Dec 2020 to 31 Dec 2021.

16.3.6.4.1.2. Background Relevant to the Evaluation

Several reports of Guillain-Barre Syndrome have been received by the Centers for Disease Control and Prevention (CDC) in the Vaccine Adverse Event Reporting System (VAERS) (CDC-ACIP 2021) with the use of adenovirus vector COVID-19 vaccines.

Guillain-Barre Syndrome (GBS) is an acquired degenerative, demyelinating neurological disorder classically characterized by progressive, symmetrical ascending paralysis. Absent muscle reflexes and loss of sensation are also commonly associated. The aetiology remains unclear, but onset has been associated with viral illness, most commonly an upper respiratory infection (URI), next most commonly by gastrointestinal illness. *Campylobacter jejuni* and *Haemophilus influenzae* are the most commonly involved pathogens [134].

Miller Fisher Syndrome (MFS) is a rare variant of GBS, observed in only about 1-5% of all cases of GBS in Western countries. In other geographic regions such as Taiwan and Japan, the proportion is higher, 19% and 25%, respectively. MFS presents with a clinical trial of ataxia, areflexia, and ophthalmoplegia. One of the main differences between MFS and the other, more common variants of GBS is that the first nerve groups to demyelinate are commonly located in the cranium. This results in difficulties with balance and coordination, ocular muscle movement and vision impairment, and neuronal reflexes. MFS is a clinical diagnosis but often goes undiagnosed due to the low prevalence. MFS is a clinical diagnosis that can be confirmed serologically with positive anti-ganglioside GQ1b antibodies [135].

GBS is believed to be an immune-mediated disorder resulting from the generation of autoimmune antibodies that cross-react with epitopes on peripheral nerves, leading to nerve damage. Autoantibodies may form in response to a variety of antigenic stimuli, such as bacterial or viral infections. About two-thirds of GBS cases occur several days or weeks after an apparent infectious illness, commonly a diarrheal illness or upper respiratory tract infection. The gastrointestinal bacterium *Campylobacter jejuni* has been found to stimulate cross-reactive antibodies that can result in GBS, particularly acute motor axonal neuropathy (AMAN). Other infectious agents that have been temporally associated with GBS include influenza viruses, Mycoplasma pneumoniae,

human immunodeficiency virus, Epstein-Barr virus, cytomegalovirus, and the vaccinia virus used in smallpox vaccination. Other exposures that appear to be temporally associated with GBS include surgical procedures and some malignancies, particularly Hodgkin's disease and other lymphomas. Various vaccines have also been temporally associated with GBS [136].

In several studies that evaluated a possible association between the occurrence of GBS and the use of vaccines, some of the patients have developed symptoms within 3 weeks after vaccination [137]. A statistically significant elevated risk of GBS was found among swine flu vaccinees relative to non-vaccinees within 6–8 weeks after vaccination, with relative risks ranging from 4.0 to 8.0 [136].

16.3.6.4.1.3. Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

ModernaTX, Inc queried the GSDB cumulative to 31 Dec 2021, for valid, case reports of Guillain-Barre Syndrome (GBS) received from HCP, HA, consumers, and literature, worldwide, reported for SPIKEVAX using the following MedDRA preferred terms: "Acute motor axonal neuropathy, Acute motor-sensory axonal neuropathy, Bickerstaff's encephalitis, Chronic inflammatory demyelinating polyradiculoneuropathy, Demyelinating polyneuropathy, Guillain-Barre syndrome, Miller Fisher syndrome, and Subacute inflammatory demyelinating polyneuropathy".

Cases were classified into one of five categories, following the Brighton Collaboration case definitions for GBS, which also includes evaluation for possible MFS. Both GBS and MFS have 3 levels of diagnostic certainty and the lowest, level 3, is limited to clinical findings. Critical for GBS to meet CD level 3 is demonstration of absent or decreased deep tendon reflexes in the same limbs that are weak. Without this it cannot meet any level of certainty. GBS/MFS overlap syndromes may occur, where there is weakness and features of MFS. In such cases the level of certainty should be based on the GBS criteria, but it can also be described as GBS/MF overlap syndrome [138]:

- Level 1 of diagnostic certainty
- Level 2 of diagnostic certainty
- Level 3 of diagnostic certainty
- Level 4 is a reported event of GBS/MFS with insufficient evidence to meet level 1, 2 or 3 of the case definitions
- Level 5 (Not a case)

The company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment [54].

- Appendix 20.11.43 and Appendix 20.11.44: include detailed summary of reporting period cases that met Brighton's Collaboration Level of diagnostic certainty 1 to 3, and their WHO-UMC causality assessment.

16.3.6.4.1.4. Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Observed Vs Expected Analysis

See Appendix 20.11.3

Overview of Cases

Cumulative Review (GBS, cumulative to 31 Dec 2021)

Cumulatively through 31 Dec 2021, a total of 438 cases of GBS and related PTs were identified for SPIKEVAX. Of the 438 cases, 435 were considered serious and 5 had fatal outcomes. The 438 cases of GBS yielded 464 events, of which 458 were serious. Of the 438 cumulative cases of GBS, 374 cases (85.4%) were medically confirmed. Most of the cases are from regulatory agency (85.2%). It is important to note that 68.7% of the case reports are from the US, and more specifically from the US FDA.

Cumulatively, the 438 cases reported under the GBS-related terms continue to show a generally balanced distribution between males and females (49.5% vs. 49.1%) (6 did not specify gender), with the majority of those events reported in patients >50 years of age, with a median age of 56.0 years old, and an age range of 16 to 120 years of age (Table 16-138).

Table 16-138 Number and Percentage of Guillain-Barre related Cases for SPIKEVAX by Age and Gender - Cumulative to 31 Dec 2021

Age Group	Female		Male		Unknown		Total of # Cases	% of Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
16-17	1	0.2	0	0	0	0	1	0.2
18-29	22	5.0	19	4.3	0	0	41	9.4
30-39	34	7.8	14	3.2	0	0	48	11.0
40-49	39	8.9	31	7.1	0	0	70	16.0
50-64	59	13.5	66	15.1	0	0	125	28.5
65-74	34	7.8	47	10.7	2	0.5	83	18.9
75+	20	4.6	35	8.0	0	0	55	12.6
Missing	6	1.4	5	1.1	4	0.9	15	3.4
Grand total	**215**	**49.1**	**217**	**49.5**	**6**	**1.4**	**438**	**100.0**

Amongst all the terms associated with GBS-related events, 83.7% corresponded to the PT of "Guillain-Barre syndrome" (Table 16-139).

Table 16-139 Number and Percentage of Guillain-Barre related Preferred terms for SPIKEVAX - Cumulative to 31 Dec 2021

PT	# Events	% Total Events
Guillain-Barre syndrome	390	84.1
Chronic inflammatory demyelinating polyradiculoneuropathy	24	5.2
Demyelinating polyneuropathy	20	4.3
Miller Fisher syndrome	16	3.4
Acute motor axonal neuropathy	5	1.1
Acute motor-sensory axonal neuropathy	5	1.1
Bickerstaff's encephalitis	2	0.4
Subacute inflammatory demyelinating polyneuropathy	2	0.4
Grand total	**464**	**100.0**

Cumulatively, there were no important differences between the GBS events with known dose information reported, with the 1st dose events (161; 34.9%) similar to those reported after the 2nd dose (141, 30.6%). (Table 16-140).

Table 16-140 Number of Guillain-Barre related Events for SPIKEVAX by Dose Number, and Time to Onset (TTO) - Cumulative to 31 Dec 2021

Dose Number	TTO (Days)	Total # Events	% Events
Dose 1	***Subtotal***	**161**	**34.7**
	0 days	10	2.2

Dose Number	TTO (Days)	Total # Events	% Events
	01-02	20	4.3
	03-04	8	1.7
	05-06	14	3.0
	07-13	41	8.8
	14-29	42	9.1
	30+	26	5.6
Dose 2	***Subtotal***	**142**	**30.6**
	0 days	12	2.6
	01-02	16	3.4
	03-04	13	2.8
	05-06	3	0.6
	07-13	24	5.2
	14-29	35	7.5
	30+	39	8.4
Dose 3	***Subtotal***	**13**	**2.8**
	0 days	1	0.2
	01-02	4	0.9
	03-04	2	0.4
	07-13	1	0.2
	14-29	3	0.6
	30+	2	0.4
Unknown	***Subtotal***	**148**	**31.9**
	Missing	148	31.9
Grand total		**464**	**100**

GBS in Children (<12 Years of Age) (Cumulative as of 31 Dec 2021)

There were no reports of GBS related events for children < 12 years of age cumulative as of 31 Dec 2021.

GBS in Adolescents (12-17 Years of Age) (Cumulative as of 31 Dec 2021)

Cumulatively, as of 31 Dec 2021, one serious, non-fatal, medically confirmed case of GBS ([4.1(b)] [redacted]) has been reported in adolescents (12–17-year-old).

GBS in Patients After a Third Dose or Booster Dose of SPIKEVAX (Cumulative as of 31 Dec 2021)

There were 13 medically confirmed reports (of which 12 were serious cases) of GBS in patients that have received a 3rd dose of SPIKEVAX. They are included in the reporting period (01 Jul 2021 to 31 Dec 2021) analysis.

Reporting Period 01 Jul 2021 to 31 Dec 2021

During the reporting period, a total of 262 cases (281 events) of GBS related PTs were identified for SPIKEVAX. Of the 262 cases, 260 were considered serious with 4 fatal outcomes reported. Among the 262 cases, 217 (82.8%) were medically confirmed. The 262 cases of GBS and related PTs yielded 281 events, of which 276 were serious.

The event outcomes reported were as follows: 56 events are resolving, 18 events not resolved, 6 events resolved with sequela, 131 events not resolved, 4 fatal events and 66 where no outcome was reported. There were no important differences between the reported cases for males (135, 51.5%) compared to cases in females (126, 48.1%). Most of the reports were in individuals ≥50 years of age (71, 27.1%). (Table 16-141).

Table 16-141 Number of Guillain-Barre related Case Reports for SPIKEVAX by Gender and Age Group 01 Jul 2021 to 31 Dec 2021

Age Group	Female		Male		Unknown		Total # Cases	% Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
16-17	1	0.4	0	0	0	0	1	0.4
18-29	17	6.5	12	4.6	0	0	29	11.1
30-39	18	6.9	11	4.2	0	0	29	11.1
40-49	29	11.1	24	9.2	0	0	53	20.2
50-64	30	11.5	41	15.6	0	0	71	27.1
65-74	16	6.1	30	11.5	0	0	46	17.6
75+	11	4.2	15	5.7	0	0	26	9.9
Missing	4	1.5	2	0.8	1	0.4	7	2.7
Grand total	**126**	**48.1**	**135**	**51.5**	**1**	**0.4**	**262**	**100.0**

Fatal Case Summary (Reviewing Period 01Jul to 31 Dec 2021)

There were 4 fatal cases reported in the reporting period and these are described in Appendix 20.11.43 and Appendix 20.11.44. According to Brighton collaboration case definition for GBS, 3 cases (4.1(b) [redacted] 4.1(b) [redacted] and 4.1(b) [redacted]) were classified as level 4 and 1 case (4.1(b) [redacted]) was classified as level 3. The cause of death was reported as GBS for 1 case (4.1(b) [redacted]) and not reported in the remaining 3 cases.

Brighton Case Collaboration Case Definition.

Evaluation of the 281 events received in the reporting period was conducted using the Brighton Collaboration case definition for Guillain Barre and Miller Fisher Syndromes.

A review of Level 1-3 cases was performed through the reporting period. A total of 26 cases meeting Level 1-3 Brighton Collaboration case definition for Guillain Barre and Miller Fisher Syndromes were reported. Two cases were Level-1, Thirteen cases were Level 2, and 11 cases were Level 3.

The reports classified as Level 1-3 from this reporting period are presented in Appendix (See Appendix 20.11.43 and Appendix 20.11.44**.** for more information).

An analysis of these cases by Brighton Collaboration criteria requires clinical judgement to consistently apply and interpret the different clinical information and there is a significant level of uncertainty due to missing information which can affect the final Level determination. In particular, information on flaccidity and presence or absence of reflexes was often not provided and information on lumbar puncture and other investigations was usually deficient thus impacting a final categorization. WHO causality is influenced by time to onset, and temporal relationship largely guides the assessment of the reviewer. Event onset from the time of the first or second dose of vaccine to event was frequently not available and concomitant medications, treatment for the event, and co-morbid medical conditions were infrequently described. During this reporting period there was no change in the severity of cases, all cases were serious, and there were no fatal events.

GBS in Children (<12 Years of Age) (Reporting Period)

There were no reports of GBS related events for children < 12 years of age during the reporting period (01 Jul 2021 to 31 Dec 2021).

GBS in Adolescents (12-17 Years of Age) (Reporting Period)

There were no reports of GBS related events for adolescents 12 to 17 years of age during the reporting period (01 Jul 2021 to 31 Dec 2021). Cumulatively, as of 31 Dec 2021, one serious, non-fatal, medically confirmed case of GBS (4.1(b)) of GBS has been reported in adolescents (12-17 y/o).

GBS in Patients After a Third Dose or Booster Dose of SPIKEVAX (Reporting Period)

There were 13 medically confirmed reports (of which 12 were serious cases) of GBS in patients that have received a 3rd dose of SPIKEVAX during the reporting period (01 Jul 2021 to 31 Dec 2021).

16.3.6.4.1.5. Discussion

Out of the 262 cases identified in the reporting period (01 Jul 2021 to 31 Dec 2021), 260 were serious with 22 of those cases evaluated as Level 1-3 according to the Brighton Collaboration case definition and discussed above. Cases meeting Brighton Collaboration Level 4 and 5 were generally poorly described and did not meet overall criteria for diagnostic certainty such as time

to onset or had significant alternative causalities to explain the event or were non-serious. Overall, in this reporting period, including events from Level 4 and Level 5, most cases were consumer reports or were received from regulatory authorities. This unfortunately limits the ability to obtain further follow-up in most reports, hindering the efforts to provide an accurate causality assessment.

The clinical spectrum of events in this reporting period was similar to that reported in previous MSSR's. However, although most cases had a temporal relationship from time of vaccine administration to development of Guillain-Barre syndrome, no independent risk factors were identified in any of the cases that could support a causal association of probable or certainty.

16.3.6.4.1.6. Conclusion

The data provided in this PBRER describe sufficiently the safety profile of SPIKEVAX in the reporting interval. A comparison with the cumulative data shows no new safety concerns or change in safety profile of the vaccine and the benefit-risk evaluation remains positive. Based on the analysis of all safety data available as of 31 Dec 2021, the MAH considers that for cases included under the GBS-related PTs (Table 16-139), information provided in the majority of the reports is inadequate to provide evidence of causality between SPIKEVAX exposure and Guillain-Barre syndrome. The MAH will continue to monitor events of Guillain-Barre syndrome using routine surveillance.

16.3.6.4.2. Myelitis transverse

16.3.6.4.2.1. Source of the New Information

Information presented below includes analysis performed on cases received by ModernaTX, Inc., for the review period, from 01 Jul 2021 to 31 Dec 2021 for the mRNA-1273 vaccine (COVID-19 vaccine Moderna) SPIKEVAX. Cumulatively, the data reviewed covers the period from 18 Dec 2020 to 31 Dec 2021.

16.3.6.4.2.2. Background Relevant to the Evaluation

Acute transverse myelitis (ATM) is a rare acquired neurological spinal cord disorder (1.34-4.6 cases per million/year), that can present with the rapid onset of weakness, sensory alterations, and bowel or bladder dysfunction [19]. TM can occur as an independent entity, usually as a postinfectious complication, but TM also exists on a continuum of neuroinflammatory disorders that include acute disseminated encephalomyelitis, multiple sclerosis, myelin oligodendrocyte glycoprotein (MOG) antibody disease, neuromyelitis optica spectrum disorder (NMOSD), and acute flaccid myelitis (AFM). ATM has also been identified as a neurological complication of COVID-19 infection [20] [21]. More than one-third of COVID-19 patients report neurological symptoms. COVID-19 related myelopathy has been described in the literature starting within the

first month after COVID-19 infection onset, either concomitantly with COVID-19 symptoms or within 10 days after their remission [22]. Immune disorders, as well as viral, bacterial, and fungal infections affecting the spinal cord, may also cause transverse myelitis. Viruses associated with transverse myelitis include herpes viruses, including varicella zoster virus (responsible for shingles and chickenpox). Research has shown ATM patients had lower levels of TSH and FT3 and higher levels of FT4 and FT4/FT3 compared with healthy controls, whether male or female [23]. Moreover, levels of TSH and FT3 in patients with ATM were inversely correlated with disease severity. Most patients with acute transverse myelitis associated with SARS-CoV2 infection partially recover within three months to two years after initial diagnosis. Some degree of disability may remain, but physical therapy has been shown to improve outcomes [24]. A review of the literature and the MAH's GSDB spontaneous reports post authorization did not provide sufficient evidence of a causal association between exposure to SPIKEVAX and transverse myelitis [139].

The MAH has previously considered Myelitis Transverse as a validated safety signal based on a regulatory request; the signal was refuted it (please refer to MSSR#10 for additional details).

16.3.6.4.2.3. Methods of Evaluation including Data Sources, Search Criteria and Analytical Approaches

The MAH queried the GSDB, cumulatively and for the reporting period through 31 Dec 2021, for valid case reports received from HCP, HA, consumers, and literature, worldwide, reported for SPIKEVAX. Clinical trial database was also searched for transverse myelitis. The search strategy included using the following MedDRA preferred terms: "Myelitis transverse".

Cases were classified into one of five categories, following the Brighton Collaboration case definitions for Acute Myelitis [140].

There are 3 levels of diagnostic certainty based on clinical and laboratory features:

- Characteristic spinal cord biopsy findings of myelitis are all that are needed to meet level 1.
- Of critical importance to meet level 2 or 3 is documentation of at least one feature of myelopathy plus evidence of spinal cord inflammation (fever, cerebrospinal fluid, pleocytosis, characteristic CT/MRI findings in myelitis) and absence of alternative diagnoses
    - Level 1 of diagnostic certainty
    - Level 2 of diagnostic certainty
    - Level 3 of diagnostic certainty
    - Level 4 is a reported event of Acute Myelitis with insufficient evidence to meet level 1, 2 or 3 of the case definitions

- Level 5 (Not a case of Myelitis)

The company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment [54].

- Appendix 20.11.45: includes a detailed summary of cumulative data concerning Transverse myelitis.
- Appendix 20.11.46: includes a detailed summary of review period data concerning Transverse myelitis.
- Appendix 20.11.47: include detailed summary of review period cases that met Brighton's Collaboration Level of diagnostic certainty 1 to 3, and their WHO-UMC causality assessment.

16.3.6.4.2.4. Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Observed vs Expected

Refer to Appendix 20.11.3.

Overview of Cases:

Cumulative Review

Cumulatively, through 31 Dec 2021, a total of 94 cases (94 events) of transverse myelitis were reported, with 80 cases (85.1%) medically confirmed. There were 93 cases assessed as serious but no case with a fatal outcome. A higher proportion of reported cases was observed in females (50; 53.2%) than in males (43; 45.7%). The greatest proportion of cases was reported in age group 50 - 64 (25; 26.6%), with a median age of 60 years (Range: 22/88 years) (Table 16-142).

Table 16-142 Number and Percentage of Cases of Transverse Myelitis by Age and Gender – Cumulative to 31 Dec 2021

Age Group	Female		Male		Unknown		Total Cases	% Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
18-29	4	4.3	1	1.1	0	0	5	5.3
30-39	9	9.6	3	3.2	0	0	12	12.8
40-49	8	8.5	4	4.3	0	0	12	12.8
50-64	11	11.7	14	14.9	0	0	25	26.6
65-74	8	8.5	12	12.8	0	0	20	21.3
75+	7	7.4	8	8.5	0	0	15	16.0
Missing	3	3.2	1	1.1	1	1.1	5	5.3

Age Group	Female		Male		Unknown		Total Cases	% Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
Grand total	50	53.2	43	45.7	1	1.1	94	100.0

Pediatric ages <12 Years (Cumulatively as of 31 Dec 2021)

Cumulatively as of 31 Dec 2021 there were no cases of Transverse Myelitis related events for Pediatric ages 0 -11 Years

Adolescents ages 12-17 Years (Cumulatively as of 31 Dec 2021)

Cumulatively as of 31 Dec 2021 there were no cases of Transverse Myelitis related events for adolescent (12-17 Years).

SPIKEVAX Booster (Cumulatively as of 31 Dec 2021)

Cumulatively as of 31 Dec 2021 there are 3 cases of Transverse Myelitis related events reported following dose 3 or greater. Please see the reporting period section for details on these cases.

Reporting Period 01 Jul 2021 to 31 Dec 2021

During this reporting period, there were 44 cases reported (44 events, 43 serious cases, 35 cases were medically confirmed, and no fatal outcome). A higher proportion (25; 56.8%) of the reported cases were for females, compared to males (18; 40.9%). The majority of the cases during the reporting period were in individuals greater than 50 years (27; 61.4%), with a median age of 57 years (Range: 27 years to 78 years). (Table 16-143). There were no reported cases of acute transverse myelitis in the pediatric age groups (0 -11 years) and adolescents (12 – 17 years). The outcome for most of the events was reported as not recovered (23; 52.3%).

Table 16-143 Number and Percentage of Case Reports of Acute Transverse Myelitis by Age and Gender for SPIKEVAX (Reporting Period 01 Jul 2021 to 31 Dec 2021)

Age Group	Female		Male		Unknown		Grand total # of Cases	Grand total % of Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
18-29	2	4.5%	0	0	0	0	2	4.5%
30-39	6	13.6%	3	6.8%	0	0	9	20.5%
40-49	3	6.8%	3	6.8%	0	0	6	13.6%
50-64	7	15.9%	7	15.9%	0	0	14	31.8%
65-74	1	2.3%	4	9.1%	0	0	5	11.4%
75+	3	6.8%	1	2.3%	0	0	4	9.1%
Missing	3	6.8%	0	0	1	2.3%	4	9.1%
Grand	**25**	**56.8%**	**18**	**40.9%**	**1**	**2.3%**	**44**	**100.0%**

Age Group	Female		Male		Unknown		Grand total # of Cases	Grand total % of Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
total								

During the reporting period, there were comparatively more events reported after dose 2 (18; 40.9%) than after dose 1 (11; 25.0%) and Dose 3 (3; 6.8%). and 27.3% of reported events were missing dose number and time to onset (TTO) (Table 16-144). There was no remarkable pattern of event distribution noted. The median time to onset of transverse myelitis events was 15.5 days (Range: 0;161). One (2.3%) of 44 events in the reporting period was resolved and the majority (23; 52.3%) were not resolved at the time of the report. This could be due to the prolong clinical course for acute myelitis.

Table 16-144 Number of Events of Transverse myelitis Reported by Dose number and Time to Onset (TTO) for SPIKEVAX (Review Period 01 Jul 2021 to 31 Dec 2021)

Dose Number	TTO All Doses (Days)	# Events	% Events
Dose 1	*Subtotal*	*11*	*25.0%*
	0 days	2	4.5%
	01-02	3	6.8%
	07-13	2	4.5%
	14-29	3	6.8%
	30+	1	2.3%
Dose 2	*Subtotal*	*18*	*40.9%*
	0 days	2	4.5%
	01-02	1	2.3%
	07-13	2	4.5%
	14-29	2	4.5%
	30+	11	25.0%
Dose 3	*Subtotal*	*3*	*6.8%*
	01-02	1	2.3%
	07-13	1	2.3%
	30+	1	2.3%
Unknown	*Subtotal*	*12*	*27.3%*
	Missing	12	27.3%
Grand total		**44**	**100.0%**

Subpopulation Analyses

Transverse Myelitis in Children (<12 Years of Age)

No event was reported in children < 12 years of age.

Transverse Myelitis in Adolescents (12-17 Years of Age)

No event was reported in adolescents 12-17 years of age.

Transverse Myelitis in Patients After a Third Dose or Booster Dose of SPIKEVAX

During the reporting period, there were 3 cases (3 events), and all 3 cases were serious, medically confirmed, with no fatal outcomes. There were disproportionally more reports in females (2; 66.7%) compared to males (1; 33.3%), with a median age for reported cases of 51 years (Range: 34 / 68 years). Two (66.7%) reported events did not resolve, while one (33.3%) event was reported as resolved.

Fatal outcomes reports (Reporting Period):

During the reporting period (01 Jul 2021 to 31 Dec 2021) there were no cases with fatal outcomes for cases of Transverse myelitis events. (See Appendix 20.11.46).

Brighton Classification and WHO-UMC Causality Assessment:

The forty-four cases reported for the reporting period (01 Jul 2021 to 31 Dec 2021) were evaluated using the Brighton Collaboration case definitions for Transverse myelitis [140]. The company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment [54].

During the reporting period, 16 (36.4%) of the 44 cases reported, met Brighton's case definition Levels 2 and 3 diagnostic certainty for Acute Transverse myelitis (ATM). Details of these cases are provided in Appendix 20.11.45, Appendix 20.11.46, and Appendix 20.11.47. Of these 16 cases, none had spinal cord histopathology report, so did not meet the criteria for Level 1 of diagnostic certainty, 5 cases were Level 2 of diagnostic certainty, and 11 were Level 3 of diagnostic certainty. Of the 28 (60.6%) cases that did not meet Brighton's case definitions for Transverse myelitis, 2 cases were classified as ADEM, 22 cases were classified as Level 4 (Reported event of acute myelitis with insufficient information to meet levels 1,2, or 3), 4 were also classified as Level 5 (NOT a case of Myelitis; due to zero indicators of CNS inflammation: no fever, CSF analysis normal, and CT/MRI spine reports were normal. No features of multifocal white matter lesions/ demyelination).

According to the WHO causality assessment, fifteen of the 16 cases that met Brighton's Levels 2 and 3 diagnostic certainty were assessed as "Possible", based on a temporal association between the use of SPIKEVAX and the start of the events. The lack of information in some cases, and the presence of alternative etiologies/risk factors that provide a more plausible explanation for the occurrence of the events, thereby rendering causality uncertain. One case was considered WHO

Conditional due to lack of information on medical history/confounders and more information is needed for proper assessment. (Appendix 20.11.47).

16.3.6.4.2.5. Discussion

Analysis of the data reported during this reporting period continues to provide support for a lack of a causal association between acute transverse myelitis (ATM) and SPIKEVAX. Cumulatively, the reporting rate of ATM for SPIKEVAX is substantially lower than one report per million doses. In addition, in this reporting period, most of the reports did not meet Brighton case definition Levels 1 to 3 for acute transverse myelitis, and the majority of the reports were considered Unassessable or unlikely related to the vaccine according to the WHO causality assessment.

ATM has been reported to be a frequent neurological complication of COVID-19 infection, other infections/tumors and an adverse event post-vaccination [20]. Most case studies had a latency of 10 days to 6 weeks which may indicate post-infectious neurological complications mediated by the host's immune response to the virus. In light of the multifactorial nature of the inflammatory and immune pathologies induced by multiple pathogens and vaccines, including emerging knowledge of genetic susceptibility to adverse effects, biological plausibility and temporal compatibility for a causal association between SPIKEVAX and myelitis is difficult to establish.

16.3.6.4.2.6. Conclusion

The MAH had previously refuted a validated signal (from regulatory authority). Data received during this reporting period (01 Jul 2021 to 31 Dec 2021) does not change the assessment. The benefit-risk profile for SPIKEVAX remains favorable. The risk of acute transverse myelitis will continue to be monitored using the routine pharmacovigilance measures implemented for SPIKEVAX

16.3.6.4.3. Acute Disseminated Encephalomyelitis

16.3.6.4.3.1. Source of the New Information

Information presented below includes analysis performed on cases received by ModernaTX, Inc., for the Cumulative period for the mRNA-1273 vaccine (COVID-19 vaccine Moderna) SPIKEVAX. Cumulatively, the data reviewed covers the period from 18 Dec 2020 to 31 Dec 2021.

16.3.6.4.3.2. Background Relevant to the Evaluation

Acute disseminated encephalomyelitis (ADEM), also referred to as postinfectious encephalomyelitis, is an acute, rapidly progressive, autoimmune process that occurs in the central nervous system. ADEM is characterized by demyelination in the brain and spinal cord (and occasionally the optic nerve) as a result of inflammation that occurs in response to a preceding

infection or immunization [141]. Its exact incidence is unknown. The cumulative reporting rate of 0.30 cases per 100,000 person-years fell below the range of US incidence estimates identified by a CDC systematic review [39].

The mechanism of vaccine triggered ADEM is hypothesized as an antigenic challenge that elicits an immunologic response leading to ADEM. The pathogenic mechanisms of ADEM are postulated to be based on a T-cell mediated autoimmune response to myelin basic protein. Several different viral infections, including measles, mumps, rubella, varicella-zoster, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, Hepatitis A virus, and coxsackievirus have been associated with ADEM, with associated incidence rates varying from 1 per 1000 infections for measles and varicella to 1 per 5000 infections for rubella. Additionally, a number of bacterial infections have been temporally associated with subsequent ADEM.

The link between ADEM and COVID-19 infection is well-established [142] [143] and very rare cases with COVID-19 vaccination have been reported [144]. Various immunizations have been temporally associated with subsequent ADEM, including those for Japanese encephalitis, yellow fever, measles, influenza, smallpox, anthrax, and others. However, the only epidemiologically and pathologically proven association of an antecedent event is with anti-rabies vaccination using the Semple rabies vaccine (a vaccine derived from sheep/mouse brains); such association has not been observed with modern formulations of rabies vaccine [145].

16.3.6.4.3.3. Methods of Evaluation including Data Sources, Search Criteria and Analytical Approaches

The MAH queried the global safety database (GSDB), cumulatively and for the reporting period through 31 Dec 2021, for valid case reports received from HCP, HA, consumers, and literature, worldwide, reported for SPIKEVAX. The search strategy included using the following MedDRA preferred terms: “Acute disseminated encephalomyelitis, Acute hemorrhagic leukoencephalitis, Autoimmune demyelinating disease, Demyelinating polyneuropathy, Encephalomyelitis, Immune-mediated neuropathy, Leukoencephalomyelitis, and Noninfective encephalomyelitis”.

In addition, The MAH also performed another assessment of all cases that reported encephalopathy against the Brighton Collaboration case definitions for ADEM and Encephalitis (Brighton's - ADEM 2021).

- Following the Brighton Collaboration case definitions for ADEM, and for Acute Encephalitis: Cases were classified into 3 levels of certainty based on clinical signs, brain imaging with MRI and duration of follow-up for recurrence or relapse.
- Level 1 of diagnostic certainty
- Level 2 of diagnostic certainty

- Level 3 of diagnostic certainty
- Level 4 is a reported event of ADEM/ Encephalitis with insufficient evidence to meet level 1, 2 or 3 of the case definitions
- Level 5 (Not a case of ADEM)

The company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment [146].

- Appendix 20.11.48 and Appendix 20.11.49: Includes a detailed summary of cumulative data concerning ADEM and Brighton's Collaboration Level of diagnostic certainty 1 to 5.
- Appendix 20.11.50 and Appendix 20.11.51: include detailed summary of Cumulative cases that met Brighton's Collaboration Level of diagnostic certainty 1 to 3, and their WHO-UMC causality assessment.

16.3.6.4.3.4. Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Observed vs Expected Analysis

Refer to Appendix 20.11.3.

Overview of Cases

Cumulatively, through 31 Dec 2021, a total of 69 cases were reported for ADEM (69 events), 67 cases were serious, 61 cases were medically confirmed, and 1 case had a fatal outcome. The majority of the reported events (62; 89.9%) were by regulatory authorities. Most of the reports were from females (41; 59.4%), compared to 27 reports from males (39.1%), with the majority of the reports in patients ≥50 years of age (37; 53.6%). The median age for reported cases was 53.0 years (Range: 18.0 / 83.0 years) (Table 16-145). There were no reports in pediatric and adolescent subpopulations (0 to <18 years).

Table 16-145 Number of Spontaneous Cases of ADEM Reported by Age and Gender for SPIKEVAX (Cumulative to 31 Dec 2021)

Age Group	Female		Male		Unknown		Total # Cases	% Total Cases
	# Cases	% Cases	# Cases	% Cases	# Cases	% Cases		
18-29	7	10.1	2	2.9	0	0	9	13.0
30-39	6	8.7	4	5.8	0	0	10	14.5
40-49	7	10.1	4	5.8	0	0	11	15.9
50-64	14	20.3	11	15.9	0	0	25	36.2
65-74	4	5.8	3	4.3	0	0	7	10.1

Age Group	Female		Male		Unknown		Total # Cases	% Total Cases
	# Cases	% Cases	# Cases	% Cases	# Cases	% Cases		
75+	2	2.9	3	4.3	0	0	5	7.2
Missing	1	1.4	0	0	1	1.4	2	2.9
Grand total	**41**	**59.4**	**27**	**39.1**	**1**	**1.4**	**69**	**100.0**

Cumulatively, a high proportion of reported events (33; 47.8%) had the preferred term (PT) of "Acute disseminated encephalomyelitis", followed by demyelinating polyneuropathy (20 cases; 29.0%). (Table 16-146).

Table 16-146 Number of Spontaneous Cases of ADEM Reported by Preferred Terms (PT) for SPIKEVAX (Cumulative to 31 Dec 2021)

Preferred Terms	Total # of Events	Total % of Events
Acute disseminated encephalomyelitis	33	47.8
Demyelinating polyneuropathy	20	29.0
Encephalomyelitis	10	14.5
Autoimmune demyelinating disease	3	4.3
Immune-mediated neuropathy	3	4.3
Grand total	**69**	**100.0**

Cumulative (18 Dec 2020 to 31 Dec2021), there is no major difference between the proportion of the ADEM reports between dose 1 (24; 34.8%) and dose 2 (25; 36.2%). The trend in reported time to onset was earlier after dose 1 and later after dose 2; while most of the events were reported earlier, between day 0 to day 13 for dose 1 (16; 23.2%), on the contrary, for dose 2, a similar proportion of events were reported later, after day13 (between 14 to 30+ days). In 20 events (29.0%), the dose number was not reported (Table 16-147).

Table 16-147 Number of Spontaneous Cases of ADEM Reported by Dose Number and Time to Onset (TTO) for SPIKEVAX. Cumulative to 31 Dec 2021

Dose Number	TTO All Doses (Days)	# Events	% Events
Dose 1	Subtotal	24	34.8
	0 days	4	5.8
	01-02	4	5.8
	03-04	1	1.4
	07-13	7	10.1
	14-29	5	7.2
	30+	3	4.3
Dose 2	Subtotal	25	36.2

Dose Number	TTO All Doses (Days)	# Events	% Events
	0 days	2	2.9
	01-02	4	5.8
	03-04	1	1.4
	07-13	2	2.9
	14-29	8	11.6
	30+	8	11.6
Unknown	Subtotal	20	29.0
	Missing	20	29.0
Grand total		**69**	**100.0**

Subpopulation Analyses

Children ages < 12 Years (Cumulative through 31 Dec 2021)

There were no reports of ADEM-related events for Pediatric ages 0 -11 Years.

Adolescents ages 12-17 Years (Cumulative through 31 Dec 2021)

There were no reports of ADEM-related events in adolescents (12-17 Years).

SPIKEVAX Booster (Cumulative through 31 Dec 2021)

There were no reports of ADEM-related events following dose 3 or greater doses.

Fatal outcomes reports (Cumulative through 31 Dec 2021)

Cumulatively, there was one case with a fatal outcome for cases of ADEM-related events (See Appendix 20.11.48 and Appendix 20.11.49).

Cumulatively, of the 69 events that reported an outcome, almost one half reported events not resolved (31;44.9%). This may be based on incomplete follow-up information, since reports usually occur soon after the event happens, and some events such as ADEM tend to have a longer recovery period. There was one fatal event reported cumulatively (Table 16-148).

Table 16-148 Number of Spontaneous Cases of ADEM Reported by Event Outcome for SPIKEVAX (Cumulative to 31 Dec 2021)

Event Outcome	Total # of Events	Total % of Events
Fatal	1	1.4
Not Recovered/Not Resolved	31	44.9
Recovered/Resolved	6	8.7
Recovered/Resolved with Sequelae	3	4.3
Recovering/Resolving	12	17.4
Unknown	16	23.2
Grand total	**69**	**100.0**

Brighton Collaboration Case Definition and WHO-UMC Causality Assessment

The 69 cases (69 events) reported as of 31 Dec 2021 were evaluated using the Brighton Collaboration case definitions for [147], for Acute Encephalitis [148], and for acute myelitis [147], since cases reported for ADEM sometimes overlap with cases of encephalitis and acute myelitis. The company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment [146].

Cumulatively, twenty-two (31.9%) of the 69 reported cases met Brighton Levels 2 and 3 diagnostic certainty for ADEM (Appendix 20.11.50 and Appendix 20.11.51). Of these 22 cases, 13 cases were Level 2 of diagnostic certainty, while the other 9 cases were Level-3. None of the cases was classified as Level-1, since there were no reported brain histopathology results. Of the 47 cases (68.1%) that did not meet Brighton's levels 1 – 3 case definition for ADEM, 27 cases were classified as Level-4 (not enough information for level classification) and the remaining 20 cases were Level-5, of these 5 cases were NOT ADEM cases, rather they were cases of transverse myelitis and Encephalitis.

According to the WHO causality assessment, Ten of the 22 cases that met Brighton's Levels 2 and 3 diagnostic certainty were assessed as "Possible", based on a temporal association between the use of SPIKEVAX and the start of the events, and a causal relationship could not be excluded due to the lack of information in some cases, and alternative etiologies/risk factors that provide a more plausible explanation for the occurrence of the events. Twelve (12) case was considered WHO Conditional due to lack of information on medical history/confounders and more information is needed for proper assessment.

The cumulative review of cases classified as Brighton's Level 1-3 is presented in detail, including their demographics, medical history, concomitant medications, infectious disease evaluation, TTO, and company's WHO causality assessment in Appendix 20.11.48 and Appendix 20.11.49 and Appendix 20.11.50 and Appendix 20.11.51

Encephalopathy reports

The MAH queried the company GSDB for valid, and spontaneous case reports received from HCP, HA, consumers, and literature, cumulatively worldwide, reported for the mRNA-1273 vaccine (Moderna COVID-19 vaccine Moderna) (SPIKEVAX).

Cumulatively as of 31 Dec 2021, there were 955 cases of encephalopathy-related terms (1019 events) with 929 cases considered serious (988 serious events). There were 10 cases with fatal outcomes. Cases were reported mostly in females (562; 58.8%), compared to males (380; 39.8%). The majority of the reports were in individuals 50 years or older (526; 55.1%), with a median age of 53.0 years (Range: 15.0/120.0 years).

Equal proportions of events were reported after 1st and 2nd doses (340; 33.4%) and comparatively less numbers were observed after the third dose (31; 3.0%). In a third of the reported cases, dose information was unknown (308;30.2%). The largest proportion of events identified during this search was under the preferred term (PT) "Guillain-Barre Syndrome" with 390 reports (38.3%), followed by multiple sclerosis (118; 11.6%) and acute myelitis transverse (94; 9.2%) (Table 16-149).

Table 16-149 Number of Events of Encephalopathy-Related Terms Reported by Number and Percentage for SPIKEVAX (Cumulative as of 31 Dec 2021)

PT	# Events	% of Total Events
Guillain-Barre syndrome	390	38.3
Multiple sclerosis	118	11.6
Myelitis transverse	94	9.2
Optic neuritis	81	7.9
Encephalitis	78	7.7
Multiple sclerosis relapse	67	6.6
Acute disseminated encephalomyelitis	33	3.2
Chronic inflammatory demyelinating polyradiculoneuropathy	24	2.4
Post viral fatigue syndrome	23	2.3
Demyelinating polyneuropathy	20	2.0
Neuromyelitis optica spectrum disorder	12	1.2
Noninfective encephalitis	12	1.2
Encephalitis autoimmune	10	1.0
Encephalomyelitis	10	1.0
Limbic encephalitis	6	0.6
Herpes zoster meningoencephalitis	5	0.5
Relapsing-remitting multiple sclerosis	4	0.4
Autoimmune demyelinating disease	3	0.3
Encephalitis viral	3	0.3
Immune-mediated neuropathy	3	0.3
Relapsing multiple sclerosis	3	0.3
Axonal and demyelinating polyneuropathy	2	0.2
Bickerstaff's encephalitis	2	0.2
Encephalitis allergic	2	0.2
Encephalitis brain stem	2	0.2
Herpes simplex encephalitis	2	0.2
Meningoencephalitis herpetic	2	0.2
Meningoencephalitis viral	2	0.2
Osmotic demyelination syndrome	2	0.2
Encephalitis Japanese B	1	0.1
Encephalitis post immunisation	1	0.1
Meningoencephalitis bacterial	1	0.1

PT	# Events	% of Total Events
Secondary progressive multiple sclerosis	1	0.1
Grand total	**1,019**	**100.0**

The MAH provides separate analysis for Guillain-Barre Syndrome (Section 16.3.6.4.1) and acute transverse myelitis (Section 16.3.6.4.2), including assessing the reports based on any available Brighton Collaboration case definition. Searches for the individual AESIs mentioned above include a pre-specified search strategy that may include some of the other additional encephalopathies included in the table above.

16.3.6.4.3.5. Discussion

Analysis of the data reported cumulatively continues to provide support for a lack of a causal association between ADEM and SPIKEVAX. Cumulatively, the reporting rate of ADEM-related events for SPIKEVAX continues to decline and is substantially lower than one report per million doses. In addition, two-third of the reports did not meet Brighton case definition Levels 1 to 3 for ADEM. Also, no new cases of encephalitis were identified via this review. According to the WHO causality assessment, a high proportion of the reports that met Brighton's levels 1 – 3, were considered Conditionally related to SPIKEVAX due to insufficient information.

As shown in the cumulative cases presented above, non-vaccine etiologies, alternative associations provide more plausible explanation for the occurrence of ADEM-related events. ADEM has been noted to precede symptoms of systemic viral illness and genital herpes have been implicated to cause encephalomyelitis.

16.3.6.4.3.6. Conclusion

The data provided in this PBRER describe sufficiently the cumulative safety profile of SPIKEVAX. The benefit-risk evaluation remains positive. Based on the analysis of the cumulative safety data available as of 31 Dec 2021 for the risk of ADEM, the MAH considers that ADEM-related events are not presently a safety issue of concern, and the benefit-risk profile for SPIKEVAX remains favorable. The MAH will continue to evaluate ADEM-related events using routine surveillance.

16.3.6.4.4. Encephalitis

16.3.6.4.4.1. Source of the New Information

Information presented below includes analysis performed on cases received by ModernaTX, Inc., for the Cumulative period for the mRNA-1273 vaccine (COVID-19 vaccine Moderna) SPIKEVAX. Cumulatively, the data reviewed covers the period from 18 Dec 2020 to 31 Dec 2021.

16.3.6.4.4.2. Background Relevant to the Evaluation

Central nervous system (CNS) viral infections result in the clinical syndromes of aseptic meningitis or encephalitis. Although the primary target of coronavirus disease 2019 (COVID-19) is the respiratory system, it is increasingly being recognized as a neuropathogenic [149]. Neurological complications of coronavirus disease 2019 (COVID-19) have been reported including but not limited to encephalopathy, stroke, seizures, meningoencephalitis, GBS, ADEM and myalgias. [150].

The underlying causes of acute encephalitis include infectious, vaccines, toxic, neoplastic, autoimmune, and metabolic etiologies [151]. Most cases of encephalitis are thought to be infectious in nature and may be attributed to a number of different viral, bacterial, fungal, and parasitic agents, as well as various autoimmune conditions that may lead to acute encephalitis. Immunizations may very rarely lead to acute encephalitis, particularly in the setting of live-attenuated viral vaccines.

The identified risk factors associated with encephalitis include [148]:

- Age:

  Increased incidence in children especially <1 year; and elderly

  - Increased risk by age according to specific etiologies:

    Neonate: HSV-2, CMV, toxoplasmosis, congenital syphilis, Listeria monocytogenes, enterovirus, parechovirus

    Infant/Child: HSV, VZV, enteroviruses, HHV6/7, Mycoplasma pneumoniae, EBV, parechovirus, Bartonella sp.

    >60 years: Listeria monocytogenes, VZV, HZ, HSV

- Comorbidities: HIV infected individuals can have a variety of neurologic presentations. In addition, they and other immunocompromised individuals can be at risk of specific etiologies: HSV, HHV-6, CMV, EBV, measles, tick borne viruses VZV, LCMV, Toxoplasma sp., Cryptococcus., JCV, BKV, Bartonella spp. Herpes simplex Enteroviruses, Mosquito-borne viruses, Childhood infections, Rabies virus.

- Vaccines: Several vaccines have been associated with encephalitis including smallpox vaccine, live attenuated measles vaccine, among other but information, has been inadequate or insufficient to accept or reject a causal association. The mechanism that is usually mentioned relates to immune-mediated production of autoantibody, T cells, and molecular mimicry.

- It is also possible to develop encephalitis that has non-infectious or autoimmune causes. Some cases of encephalitis are caused by an autoimmune disorder that may in some instances be triggered by an infection ("post infectious") or by a cancer – even one that is microscopic and cannot be found (so-called paraneoplastic neurological syndromes). NMDA-Receptor encephalitis is a type of autoantibody-mediated encephalitis and is being increasingly recognized.

In this report the MAH provides a cumulative assessment of cases reporting encephalitis-related events, including ADEM and Myelitis Transverse. Evaluation of those reports against the Brighton Collaboration case definitions for Acute Encephalitis [148], ADEM [147] and, Acute Transverse myelitis [152] were performed given that there is an overlap in the occurrence and diagnosis of both entities. See ADEM and Acute transverse myelitis sections for additional information on the case assessments.

Literature review:

A targeted literature search was performed as of 31 Dec 2021 using PubMed, with the following criteria of Encephalitis OR Autoimmune demyelinating disease OR Demyelinating polyneuropathy OR Encephalomyelitis OR Immune-mediated neuropathy OR Leukoencephalomyelitis AND mRNA COVID vaccination or mRNA-1273 or "mRNA 1273" or mRNA1273 or "Modernatx 1273" or "moderntx 1273" or "Moderna Covid19 Vaccine" or SPIKEVAX.

There were few case reports or case series describing temporal associations between Encephalitis and COVID-19 vaccines, including mRNA vaccines. There are no pathognomonic symptoms or signs to link a vaccine with an individual case of Encephalitis.

Among the relevant literature published, including the case report by Mashdali et al (2021), the summary findings are discussed below.

The Mashdali et al [153] case report, "Post COVID-19 vaccine acute hyperactive encephalopathy with dramatic response to methylprednisolone": A 32-year-old "previously healthy" male patient who developed acute confusion, memory disturbances, and auditory hallucination, within 24 hours from getting his first dose of the COVID-19 Moderna vaccine. Electroencephalogram (EEG) showed features of encephalopathy, CSF analyses were nonspecific, and MRI head showed no abnormality. The authors highlighted the efficacy of steroids in the treatment of acute encephalopathy related to COVID-19 vaccination based on the patient's dramatic response to methylprednisolone. They postulated an immune-mediated mechanism associated with neurological complications of COVID-19 vaccines and considered a temporal association between the vaccine and the events. Mashdali and colleagues concluded that "clinicians should be aware of

possible neurological complications post-COVID-19 vaccines and further research is needed to clarify the pathophysiology of such complications" This case was reported as a literature non-study case to the MAH. The case was reviewed and classified as Brighton level 4 Encephalitis, based on insufficient evidence to meet any level of the case definition (no abnormality MRI head, incomplete medical history, no concomitant medication report provided). According to the WHO-UMC causality assessment, the case was considered Unlikely, due to a rather short time to onset of events that make a relationship with SPIKEVAX improbable (but not impossible).

Fan et al [154] also reported a rare serious adverse event, "COVID-19 vaccine-induced encephalitis and status epilepticus" in a 22-year-old man, after the second dose of the Moderna vaccine. The symptoms were resolved by pulse corticosteroid therapy. The authors hypothesized that cytokine storm-associated encephalopathy (CySE) rather than an infectious process directly targeting the brain is one of the key mechanisms of COVID-19-related encephalopathy. Fan and colleagues agreed with the postulation by Mashdali and colleagues, that the mRNA-based vaccine could contribute to SARS-CoV-2 spike protein expression. Spike protein expression might be considered a trigger for inflammatory processes, leading to complications after vaccination. They concluded that clinical response to pulse corticosteroid therapy may be attributed to an immune-mediated process.

16.3.6.4.4.3. Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

The MAH queried the global safety database (GSDB), cumulatively through 31 Dec 2021, for valid case reports received from HCP, HA, consumers, and literature, worldwide, reported for SPIKEVAX. The search strategy included using the following MedDRA preferred terms: "Encephalitis, Acute disseminated encephalomyelitis, Acute hemorrhagic leukoencephalitis, Autoimmune demyelinating disease, Demyelinating polyneuropathy, Encephalomyelitis, Immune-mediated neuropathy, Leukoencephalomyelitis, and Noninfective encephalomyelitis".

An assessment of all cases with encephalopathy against the Brighton Collaboration case definitions for ADEM and Encephalitis was conducted by the MAH.

Characteristic brain biopsy findings of encephalitis are all that are needed to meet level 1. The key criteria to meet level 2 or 3 is documentation of either encephalopathy or focal/multifocal neurologic signs along with evidence of brain inflammation (fever, CSF pleocytosis, characteristic CT/MRI/EEG findings in encephalitis) and absence of alternative diagnoses (meningitis, parameningeal processes such as brain abscess, traumatic brain injury, encephalopathy associated with: sepsis, toxin, metabolic abnormality, neurodegenerative disease, endocrine disorder, and neoplastic disease). Events were classified into one of five categories, using the Brighton Collaboration case definitions for Acute Encephalitis and ADEM.

- Level 1 of diagnostic certainty
- Level 2 of diagnostic certainty
- Level 3 of diagnostic certainty
- Level 4 is a reported event of ADEM/ Encephalitis with insufficient evidence to meet level 1, 2 or 3 of the case definitions
- Level 5 (Not a case)

The company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment [146].

- Appendix 20.11.52: Tabulated overview of cumulative encephalitis cases listed by Brighton Collaboration case definition and with the company's WHO causality assessment of these cases.
- Appendix 20.11.53: Cumulative detailed description of all encephalitis cases fulfilling the Brighton Collaboration case definition levels 1 - 3, including WHO causality assessment as of 31 Dec 2021.
- Appendix 20.11.54: Fatal cases tabulation

16.3.6.4.4.4. Results A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Observed to Expected Analysis

See Appendix 20.11.3.

Overview of Cases

Cumulative Review

Cumulatively, through 31 Dec 2021, a total of 148 cases (156 events) of encephalitis were reported, with 113 (76.4%) cases medically confirmed. There were 4 (2.7%) cases reported with fatal outcomes. The majority of the cases were reported in females (88; 59.5%), with fewer cases reported in males (59; 39.9%). The median age of cases reported was 53 years (Range:15.0/ 89.0 years).

Encephalitis events fell under ten different MedDRA Preferred Terms (PT), cumulatively, with the most common being encephalitis (78; 50.0%) and acute disseminated encephalomyelitis (33; 21.2%) (Table 16-150).

Table 16-150 Number and Percentage of Encephalitis Events by MedDRA PT - Cumulative to 31 Dec 2021

PT	# Events	% Total Events
Encephalitis	78	50.0
Acute disseminated encephalomyelitis	33	21.2
Noninfective encephalitis	12	7.7
Encephalitis autoimmune	10	6.4
Encephalomyelitis	10	6.4
Limbic encephalitis	6	3.8
Encephalitis allergic	2	1.3
Encephalitis brain stem	2	1.3
Encephalitis post immunization	1	0.6
Immune-mediated encephalitis	1	0.6
Myelin oligodendrocyte glycoprotein antibody-associated disease	1	0.6
Grand total	156	100.0

The greatest proportion of cases were reported in patients aged 50 to 64-years-old (39; 26.4%). The majority of cases were reported in females (59.5%); however, there are no important differences in reporting rates by gender in patients 65-years-old, or older. (Table 16-151).

Table 16-151 Number and Percentage of Cases of Encephalitis by Age and Gender - Cumulative to 31 Dec 2021

Age Group	Female		Male		Unknown		Total # Cases	% Total Cases
	# Cases	% Cases	# Cases	% Cases	# Cases	% Cases		
12-15	1	0.7	0	0	0	0	1	0.7
18-29	17	11.5	8	5.4	0	0	25	16.9
30-39	14	9.5	11	7.4	0	0	25	16.9
40-49	12	8.1	5	3.4	0	0	17	11.5
50-64	23	15.5	16	10.8	0	0	39	26.4
65-74	9	6.1	10	6.8	0	0	19	12.8
75+	10	6.8	9	6.1	0	0	19	12.8
Missing	2	1.4	0	0	1	0.7	3	2.0
Grand total	88	59.5	59	39.9	1	0.7	148	100.0

Most reported cases were received from regulatory authorities (122, 82.4%). Cases originating from the United States continued to represent the greatest proportion of reported encephalitis cases (71, 48.0%). (Table 16-152).

Table 16-152 Number and Percentage of Cases of Encephalitis Reported by Region - Cumulative to 31 Dec 2021

Region	# of Cases	% of Cases
Asia	18	12.2
Canada	2	1.4
European Economic Area	45	30.4
Middle East	1	0.7
Switzerland	10	6.8
United Kingdom	1	0.7
United States	71	48.0
Grand total	148	100.0

Cumulatively, there was a slightly lower proportion of encephalitis events reported after the first dose (50, 32.1%) when compared to reports after the second dose (65, 41.7%), while 41 (26.3%) events had insufficient information to calculate time to onset by dose. Regardless of dose, a time to onset of less than 14 days from vaccination was most common for encephalitis events (65, 41.7%) (Table 16-153). For those events with a known time to onset and/or duration, the median time to onset of encephalitis events following vaccination was 9 days (Range: 0 / 200 days).

Table 16-153 Number and Percentage of Encephalitis Events by Time to Onset (TTO) and Dose Number – Cumulative to 31 Dec 2021

Dose Number	TTO All Doses (Days)	# Events	% Events
Dose 1	*Subtotal*	*50*	*32.1*
	0 days	8	5.1
	01-02	4	2.6
	03-04	6	3.8
	05-06	2	1.3
	07-13	11	7.1
	14-29	11	7.1
	30+	8	5.1
Dose 2	*Subtotal*	*65*	*41.7*
	0 days	5	3.2
	01-02	12	7.7
	03-04	5	3.2
	05-06	4	2.6
	07-13	8	5.1
	14-29	19	12.2
	30+	12	7.7

Dose Number	TTO All Doses (Days)	# Events	% Events
Unknown	*Subtotal*	*41*	*26.3*
	Missing	41	26.3
Grand total		156	100.0

Subpopulation Analyses

Children ages < 12 Years (Cumulative through 31 Dec 2021)

There were no reports of encephalitis- related events for Pediatric ages 0 -11 Years

Encephalitis in Adolescents ages12-17 Years of Age (Cumulative through 31 Dec 2021)

Cumulatively as of 31 Dec 2021 there was one case of encephalitis reported in adolescents (12- 17 years of age). Details of this case are:

4.1(b) : A 15-year-old female with no medical history information or concomitant medications reported, who SPIKEVAX5 days post-dose 1 SPIKEVAX vaccine, reported symptoms suggestive of encephalitis autoimmune. Diagnostic analysis of the CSF showed pleocytosis, mainly neutrophilia (78%). CT Head was normal; however, MRI brain was abnormal, with a T1, T2, FLAIR. Two hyperintense cortical-subcortical lesions were observed in T2, with a slight mass effect, hypointense in T1, with hippocampal involvement and extension to the left basal ganglia. This adolescent case is classified as Brighton Level 2 Encephalitis and considered WHO Conditional, due to insufficient medical history, medications, and clinical course of events information. More data are needed for proper assessment.

Encephalitis in Patients Receiving > 2 Doses of SPIKEVAX

Cumulatively as of 31 Dec 2021 there were no reports of Encephalitis in patients receiving more than 2 doses of SPIKEVAX vaccine.

Events Outcomes

Cumulatively, of the 156 reported events, a high proportion had not recovered (55;35.3%) and about 20% (31) had an unknown outcome (Table 16-154). Due to the nature of spontaneous reporting and the large proportion of reports from regulatory authorities, the ability to obtain additional information on the final outcomes for most events reported is often limited, since reports usually occur soon after the event happens, and some events such as encephalitis tend to have a longer recovery period. There were four fatal events reported cumulatively are discussed in detail in Appendix 20.11.54.

Table 16-154 Distribution of Encephalitis Events by Outcome - Cumulative to 31 Dec 2021

Event Outcome	# Events	% Events
Fatal	4	2.6
Not Recovered/Not Resolved	55	35.3
Recovered/Resolved	29	18.6
Recovered/Resolved with Sequelae	8	5.1
Recovering/Resolving	29	18.6
Unknown	31	19.9
Grand total	156	100.0

Brighton Collaboration Case Definition and WHO-UMC Causality Assessment

During the cumulative period (18 Dec 2020 to 31 Dec 2021), the reported cases were reviewed and classified according to the Brighton Collaboration case definitions for Acute Encephalitis [148], ADEM [147], and Acute myelitis [152]. The company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment [54]. (Appendix 20.11.52 and Appendix 20.11.53).

Cumulatively as of 31 Dec 2021, 148 reported cases were evaluated using the Brighton Collaboration case definitions. Of these 148 cases, 24 (16.2%) cases met Brighton's Levels 1-3 diagnostic certainty for Encephalitis (Appendix 20.11.52). Of these 24 cases, one case was Level-1 diagnostic certainty, 11 cases were Level-2 of diagnostic certainty, and 12 cases were Level-3. Of the 124 cases (83.8%) that did not meet Brighton's levels 1 – 3 case definition for Encephalitis, 112 cases were classified as Level-4 (not enough information for level classification) and the remaining 12 cases were Level-5, NOT a case of Encephalitis, rather, they were 10 cases of ADEM and 2 cases of acute transverse myelitis.

According to the WHO-UMC causality assessment, ten of the 24 cases that met Brighton's Levels 1-3 diagnostic certainty for encephalitis were assessed as "Possible", based on temporal association between the use of SPIKEVAX and the start of the events, and a causal relationship cannot be excluded due to the lack of information in some cases, and alternative etiologies/risk factors that provide a more plausible explanation for the occurrence of the events. Eleven cases were considered WHO Conditional due to lack of information on medical history/confounders and more information is needed for proper assessment; and 3 cases were considered WHO Unlikely, with a short time to onset that makes a relationship improbable.

The cumulative review of cases classified as Brighton's Level 1-3 is presented in detail, including their demographics, medical history, concomitant medications, infectious disease evaluation, TTO, and company's WHO causality assessment in Appendix 20.11.53.

16.3.6.4.4.5. Discussion

Analysis of the data reported cumulatively continues to provide support for a lack of a causal association between Encephalitis and SPIKEVAX. The cumulative reporting rate of 0.65 cases per 100,000 person-years fell below the age of US incidence estimates identified (0.80 (Dubey 2018) – 6.9 cases per 100,000 person-years, 146-1,260 cases expected rate ratio 0.81, 95% CI 0.63 – 1.03 compared to the lower estimate). In addition, more than 83% of reported encephalitis-related cases did not meet the Brighton case definition Levels 1 to 3 for encephalitis. According to the WHO causality assessment, a similar proportion of the reports that met Brighton's levels 1 – 3 case definition for encephalitis, were considered Conditionally or Possibly related to SPIKEVAX, either due to insufficient information or temporal association respectively. Twelve cases of ADEM were distinguished from other encephalitis reported cases using the Brighton case definition for ADEM.

Several different antecedent viral infections or vaccinations have been suggested as presenting an antigenic challenge leading to the immunologic response in the form of encephalitis. All 148 reported cases with diagnostic results were reviewed for known etiologically relevant pathogens (viral, bacterial, fungal, or parasitic agents), paraneoplastic antibodies, or auto-antibodies as well as known concomitant diseases including cancer and autoimmune conditions. Only 25 (16.9%) of the 148 reported cases had diagnostic results for infectious disease, tumors, and autoimmune antibody screening; and 7 had positive infectious diseases panels, including two cases with positive SARS-CoV-2 tests, one case respectively had a positive Flavivirus test, Tick-borne encephalitis virus test, and Japanese encephalitis virus. Autoimmune and tumor marker screening were all negative. In this cumulative review of encephalitis-related cases, infective pathogens were not significantly associated with cases that reported serology workup.

Exposure-related subgroup trends based on information about time to onset and dose number (1st, 2nd, 3rd dose or booster dose) were not remarkable, except that no event was reported after dose 3. It is also important to note the age subgroup trends, with the majority of reported cases among 50 years old and older. In this cumulative review, encephalitis-related cases were observed to be more among older people.

The paucity of complete medical information, full infectious disease evaluation, and tumor markers /autoimmune antibody screening in the reported cases hindered the accurate determination of alternative associations that could provide more plausible explanations for the occurrence of encephalitis-related events.

16.3.6.4.4.6. Conclusion

The data provided in this PBRER describe sufficiently the cumulative safety profile of SPIKEVAX. The benefit-risk evaluation remains positive. Based on the analysis of the cumulative safety data available as of 31 Dec 2021 for the risk of Encephalitis, the MAH considers that Encephalitis -related events are not presently a safety issue of concern, and the benefit-risk profile for SPIKEVAX remains favorable. The MAH will continue to evaluate Encephalitis-related events using routine surveillance.

16.3.6.4.5. Neuralgic Amyotrophy (CAD)

16.3.6.4.5.1. Source of the New Information

Information presented in this section includes analyses performed on cases received by ModernaTX, Inc., for the Cumulative period for the mRNA-1273 vaccine (COVID-19 vaccine Moderna) SPIKEVAX. Cumulatively, the data reviewed covers the period from 18 Dec 2020 to 31 Dec 2021.

16.3.6.4.5.2. Background Relevant to the Evaluation

Neuralgic amyotrophy (NA) (also known as brachial neuritis, brachial plexus neuritis, brachial plexus neuropathy, amyotrophic neuralgia or Parsonage-Turner syndrome) is a clinical syndrome typically characterized by acute onset of unilateral severe pain in the shoulder and upper arm followed by weakness in the arm and shoulder, often with patchy distribution related to nerves associated with the brachial plexus (multiple mononeuropathies) [155]. Symptoms are sometimes preceded by a *possibly* triggering event, such as infection, surgery, or less commonly, vaccination [156]. NA is primarily a clinical diagnosis supported by electrodiagnostic testing, and this condition has been noted to recur in 26.1% of cases over a six-year period. Neither the cause nor the pathogenesis of NA is known [157].

NA is an infrequent disease, with estimated incidence of 1 to 3 cases per 100,000 person-years. Peak incidence occurs around the third to fifth decades of life; the disease is more common in men, with a male-female ratio of 2:1.6 [158]. A prospective study in a primary care setting led by an NA expert, who trained the primary care physicians to recognize NA, found a substantially higher annual incidence of NA: 1 per 1,000 person-years. The investigators concluded that the training in the study increased clinicians' awareness of NA and its clinical presentation, leading to increased detection and diagnosis, which explains the substantially higher incidence rates observed [157].

Hereditary neuralgic amyotrophy (HNA) is an inherited autosomal dominant recurrent neuropathy with a high penetrance (most likely >90%). HNA is clinically characterized by episodes of brachial plexus neuropathy with muscle weakness and atrophy. Sensory disturbances are less prominent.

In almost all cases the attacks of plexopathy are preceded by severe pain in the affected arm. The age at onset is most commonly in the second to third decade of life but can be earlier or later. Recovery begins within weeks to months after the onset of symptoms and is often complete, but residual deficits especially affecting motor function are not uncommon [159].

16.3.6.4.5.3. Methods of Evaluation including the Data Sources, Search Criteria and Analytical Approaches

The MAH queried the GSDB, cumulatively through 31 Dec 2021, for valid case reports received from HCP, HA, consumers, and literature, worldwide, reported for SPIKEVAX. The search strategy included using the following MedDRA preferred terms: "Neuralgic amyotrophy, Radiculitis brachial, and Brachial plexus injury".

The company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment [146].

- Appendix 20.11.55: Cumulative reports of Neuralgic amyotrophy with Case Assessment and WHO Causality information.

16.3.6.4.5.4. Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Observed vs. Expected Analysis

See Appendix 20.11.3.

Overview of Cumulative Cases:

Cumulatively (18 Dec 2020 to 31 Dec 2021), there were 116 cases reported for Neuralgic Amyotrophy (120 events), 78 medically confirmed and 74/120 events were serious. Similar proportions of the cases were reported in females (58; 50.0%) and males (56 cases; 48.3%). The majority of the reports were in patients ≥50 Years of age (65; 56.0%) (Table 16-155). The mean age was 52.8 (SD 14.0), the median 53.5with an age range of 18 to 93 years.

Table 16-155 Number and Percentage of Spontaneous Cases of Neuralgic Amyotrophy Reported by Age and Gender for SPIKEVAX. Cumulative to 31 Dec 2021

Age Group	Female		Male		Unknown		Grand total of # Cases	Grand total of % of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases	# Cases	% of Total Cases		
18-29	4	3.4	2	1.7	1	0.9%	7	6.0
30-39	5	4.3	5	4.3	0	0	10	8.6
40-49	18	15.5	10	8.6	0	0	28	24.1
50-64	21	18.1	22	19.0	0	0	43	37.1

Age Group	Female		Male		Unknown		Grand total of # Cases	Grand total of % of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases	# Cases	% of Total Cases		
65-74	5	4.3	13	11.2	0	0	18	15.5
75+	1	0.9	3	2.6	0	0	4	3.4
Missing	4	3.4	1	0.9	1	0.9	6	5.2
Grand total	58	50.0	56	48.3	2	1.7	116	100.0

Time to onset of the events averaged 14.6 days (SD 18.5), with median of 8 days (0; 81). The events are reported slightly more frequently after the 2nd dose (38.3%) than the 1st dose (27.5%); this difference is largely explained by the greater number of events with TTO 30+ days after the second dose, a follow-up period that is uncommon after the first dose because the first dose vaccinees usually have received their second dose by around 28 days after dose 1. There are 2 cases reported in patients that received a 3rd dose or booster vaccine. (Table 16-156).

Table 16-156 Time to Onset by Dose Number as of 31 Dec 2021

Dose Number	TTO All Doses (Days)	# Events	% Events
Dose 1	Subtotal	33	27.5
	0 days	5	4.2
	01-02	7	5.8
	03-04	7	5.8
	05-06	2	1.7
	07-13	4	3.3
	14-29	7	5.8
	30+	1	0.8
Dose 2	Subtotal	46	38.3
	0 days	3	2.5
	01-02	7	5.8
	03-04	5	4.2
	05-06	1	0.8
	07-13	5	4.2
	14-29	14	11.7
	30+	11	9.2
Dose 3	Subtotal	2	1.7
	0 days	1	0.8
	03-04	1	0.8
Unknown	Subtotal	39	32.5
	Missing	39	32.5
Grand total		**120**	**100.0**

The majority of the reported events had the PT Neuralgic amyotrophy (92;76.7%), followed by Radiculitis brachial (24;20.0%). (See Table 16-157).

Table 16-157 Number and Percentage of Neuralgic Amyotrophic Related-Terms by PT – Cumulative to 31 Dec 2021

PT	# of Events	% of Total Events
Neuralgic amyotrophy	92	76.7
Radiculitis brachial	24	20.0
Brachial plexus injury	4	3.3
Grand total	120	100.0

Most of the reported events had at the time of the report an outcome of not recovered/not resolved (75; 62.5%), (See Table 16-158). There was 1 fatal case (4.1(b) [redacted]) described below, assessed as WHO-UMC conditional because of the lack of information provided such as the clinical course of the events, laboratory or imaging tests conducted and their results; there was also the important confounding event of sepsis prior to death.

Table 16-158 Number and Percentage of Neuralgic Amyotrophic by Outcome – Cumulative to 31 Dec 2021

Event Outcome	Total of # Events	% Total Events
Fatal	1	0.8
Not Recovered/Not Resolved	75	62.5
Recovered/Resolved	3	2.5
Recovered/Resolved with Sequelae	4	3.3
Recovering/Resolving	17	14.2
Unknown	20	16.7
Grand total	**120**	**100.0**

The sources of the reports are mostly from Regulatory Authorities (99; 85.3%); the reports come most commonly from the USA (58; 30.5%), followed by Netherlands (15;15.3%) and Germany (10; 13.6%).

Description of the Fatal Case:

4.1(b) [redacted]: A 58-year-old female patient who experienced neuralgic amyotrophy and paralysis 3 days after the second dose of SPIKEVAX. Hospitalization for a seizure episode occurred 53 days after vaccination. About three months after the second dose, another hospitalization occurred, this time for sepsis, and the patient died. No cause of death was reported, and it is unknown if an autopsy was conducted. This report lacks important information including

the patient's medical history, concomitant medication, clinical course of the events, laboratory or imaging tests conducted and their results. Sepsis is not associated with neuralgic amyotrophy and is a known life-threatening condition and confounder in this case. Based on the WHO causality assessment, this case is considered conditional. Additional information is needed to provide a full causality assessment.

Assessment of Cases using WHO-UMC Causality:

Causality assessment per WHO-UMC criteria was performed cumulatively for the 116 cases and is presented for individual cases in a tabulated format with justification in Appendix 20.11.55. Of the 116 cases received cumulatively, a total of 51 cases were assessed as WHO-UMC Possible (largely based on temporal association with lack of reported other antecedent possible triggers for NA); 36 cases were assessed as Conditional, needing more data for proper assessment; 19 cases were Unlikely to be vaccine-related: and 10 cases were Unassessable due to lack of information (Appendix 20.11.55).

Clinical Trial data Review:

The topic of Neuralgic amyotrophy was cumulatively reviewed in the MAH clinical database with a DLP of 04 May 2021, with a search using the following MedDRA v 24.1 preferred terms "Neuralgic amyotrophy, Radiculitis brachial, and Brachial plexus injury" performed in P301 study; there were zero cases observed.

Literature Review:

A cumulative literature search in PubMed as of 17 Jan 2022 was performed using the following search criteria:

- (((((Neuralgic amyotrophy) OR (Radiculitis brachial)) OR (Brachial plexus injury)) OR (brachial neuritis) OR (brachial plexus neuritis) OR (brachial plexus neuropathy) OR (amyotrophic neuralgia) OR (Parsonage-Turner syndrome) AND (SPIKEVAX)) OR (mRNA-1273)) AND (("2021/11/01"[Date - Publication]: "2021/12/31"[Date - Publication]))

One of the articles [160], describes a study that performed disproportionality analyses in Vigibase and found no association between COVID-19 vaccines and NA, using either viral vaccines or influenza vaccines as the comparator.

There was a small number of articles describing temporal associations between Neuralgic amyotrophy and COVID-19 vaccines, including mRNA vaccines. There are no pathognomonic signs or symptoms to link a vaccine with an individual case of NA. Overall, literature search results

did not provide evidence of a causal association between mRNA vaccines or mRNA-1273 and NA.

Subpopulation Analyses

Adolescents ages 12-17 Years (Cumulatively as of 31 Dec 2021)

Cumulatively as of 31 Dec 2021 there were no cases of Neuralgic Amyotrophy for adolescents (12-17 Years).

SPIKEVAX Booster (Cumulatively as of 31 Dec 2021)

Cumulatively as of 31 Dec 2021 there were two cases ([redacted] and [redacted]) of Neurologic Amyotrophy related events for the booster dose. [redacted] is a consumer report concerning a 66-year-old obese man with rheumatoid arthritis and multiple other medical conditions. NA had a TTO 4 days after third dose. Diagnosis was confirmed by electromyogram. This case of NA is possibly associated with vaccination due to temporal association, but rheumatoid arthritis is also known to be a risk factor for neuralgic amyotrophy. The second report ([redacted]) involved a female of unknown age. The patient reported pain four hours after the third dose. No weakness was reported. No test results were reported. No prescription medicine was reported. Overall, there is a lack of useful information, making this report Unassessable for causality attribution.

16.3.6.4.5.5. Discussion

Cumulatively, there were 116 cases reported for the topic neuralgic amyotrophy. The observed to expected analysis clearly showed fewer observed than expected cases. Almost similar proportions of the cases were reported in females (58; 50.0%) and Males (56; 48.3%) which is in contrast to literature reports that the disease is more common in men, but this finding is consistent with the typical distribution of spontaneous report data [161], [162] that generally show a greater frequency of reports in females.

The majority of the reports were in patients ≥50 Years of age (65; 56.0%). The mean age was 52.8 (SD 14.0), the median 53.5, with an age range of 18 to 93 years. The events were reported slightly more frequently after the 2nd dose (38.3%) than the 1st dose (27.5%). This difference in proportions is largely attributable to cases at 30+ days after vaccination for the second dose, which has greater follow-up time as noted above. There were no clear imbalance or accumulation of case counts in a narrow dose-time to onset window.

Based on simple temporal association, vaccination has been reported as a possible trigger for NA in rare case reports over the years involving various vaccines. A recent example is a report of three cases (two Comirnaty, one SPIKEVAX) of NA following mRNA vaccination against COVID-19

[163]. Before the SARS COVID-19 pandemic, in a retrospective survey of 246 NA cases, [157] that five cases had temporally associated vaccinations; however, details concerning the type of vaccine, time to onset, clinical features, etc. were not provided. Thus, for vaccines in general, as well as with COVID-19 vaccines specifically, an association with NA has been posited primarily due to simple and not clearly specified temporal association without other critically important supportive data or information.

Not in favor of a causal association of vaccination with neuralgic amyotrophy, an authoritative 2012 report by the US Institute of Medicine (IOM), now called the National Academy of Medicine (NAM), found no relevant studies of quality in the literature assessing an association between vaccination and brachial neuritis [164]. Subsequent to this report, no relevant studies of quality have been published [165]. Moreover, with regard to various proposed biologic mechanisms, the IOM concluded that there was no mechanistic evidence for an association between vaccination and brachial neuritis.

16.3.6.4.5.6. Conclusion

After careful review of cumulative safety data as of 31 Dec 2021 for the safety topic of Neuralgic Amyotrophy, the benefit-risk profile for SPIKEVAX remains favorable. The safety topic of Neuralgic Amyotrophy will continue to be monitored carefully using the routine pharmacovigilance measures implemented for SPIKEVAX.

16.3.6.5. Immune System Disorders

16.3.6.5.1. Multisystem Inflammatory Syndrome (MIS-C and MIS-A)

16.3.6.5.1.1. Source of the New Information

Information presented below includes analysis performed on cases received and entered into the global safety database of ModernaTX, Inc. from 01 Jul 2021 to 31 Dec 2021 for SPIKEVAX based on an expanded list of MedDRA preferred terms following a request received from a regulatory authority. As would be expected, this change in the search strategy increased the number of case reports that are now included under this evaluation of the AESI – Multisystem Inflammatory Syndrome. Cumulatively, the data reviewed covers the period from the 18 Dec 2020 to 31 Dec 2021.

16.3.6.5.1.2. Background Relevant to the Evaluation

Multisystem inflammatory syndrome (MIS) is a rare, but severe complication following COVID-19 infection. It was observed that a fraction of children developed a life-threatening, hyperinflammatory state, later named Multisystem Inflammatory Syndrome in Children (MIS-C).

There have been similar reports of this condition following COVID-19 infection in adults (MIS-A), and the prevalence is still unclear; however, the rate of occurrence seems to be lower in adults than in children. MIS-C is associated with high levels of inflammation and responds to anti-inflammatory therapies; it is therefore presumed to be immune-mediated. The immunopathogenesis of MIS-C remains unknown, but substantial progress has been made in defining the features of immune dysregulation in MIS-C [166].

Identifying the precise epidemiology of MIS-C is hampered by the lack of a specific case definition. Current case definitions are very broad; children who recently or previously were infected with SARS-CoV-2 and develop a multisystem illness due to infections or inflammatory conditions unrelated to SARS-CoV-2 or due to acute COVID-19 can fulfil current case definitions, resulting in overdiagnosis. However, certain epidemiologic features are consistently reported. The median age of children with MIS-C is 9 years. MIS-C occurs a median of 27 days (IQR 21–36 days) after preceding SARS-CoV-2 infection, and an increase in cases has occurred about 1 month (range 2–5 weeks) following peaks of COVID-19 in individual geographic areas. If RT-PCR for SARS-CoV-2 from the respiratory tract is positive in children with MIS-C, the cycle threshold (Ct) values are high, suggesting low viral load at that site at the time of clinical presentation. About 60% of affected children in the USA have been reported to be Hispanic or non-Hispanic Black, with a slight male preponderance. Although the racial/ethnic distribution most likely reflects COVID-19-related health disparities, a genetic predisposition to MIS-C has not been excluded. Adults can develop an illness similar to MIS-C following COVID-19 infection, called multisystem inflammatory syndrome in adults, or MIS-A; it may be underdiagnosed.

MIS was a refuted signal during this reporting period. MIS is discussed under Section 16.2.6 Signal Evaluation.

16.3.6.5.1.3. Methods of Evaluation including Data Sources, Search Criteria and Analytical Approaches

The ModernaTX, Inc. GSDB was queried cumulative and during the reporting period for this PBRER (01 Jul to 31 Dec 2021) for valid case reports of MIS received from HCP, HA, consumers, and literature, worldwide, for the mRNA-1273 vaccine (COVID-19 vaccine Moderna) SPIKEVAX using the following MedDRA PTs included in the MAH's previous search strategy of Multisystem inflammatory syndrome in children, Multisystem inflammatory syndrome in adults, Multisystem inflammatory syndrome, Cytokine storm, Cytokine release syndrome, Kawasaki's disease, and Systemic inflammatory response syndrome; and also includes the following expanded list of terms of Multiple organ dysfunction syndrome, Toxic shock syndrome, Distributive shock, Hypotensive crisis, Vaccine associated enhanced disease, Vaccine associated

enhanced respiratory disease, Haemophagocytic lymphohistiocytosis, Macrophage activation, Macrophages increased, Septic shock, and Autoinflammatory disease.

Identified cases were evaluated following the Brighton Collaboration Multisystem Inflammatory Syndrome in Children and Adults (MIS-C/A): Case Definition & Guidelines for Data Collection, Analysis, and Presentation of Immunization Safety Data, and were classified into one of five levels of diagnostic certainty:

- Level 1 - Definitive case
- Level 2 - Probable case (Divided into Levels 2a and 2b)
- Level 3 - Possible case (Divided into Levels 3a and 3b)
- Level 4 - Insufficient Evidence
- Level 5 - Not a case of MIS-C/A

The company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment [146].

- Appendix 20.11.56**:** All Cases: includes summary information for all MIS-C/A related cases for the reporting period.
- Appendix 20.11.57**:** MIS C RP: includes information on MIS-C related events for the reporting period.
- Appendix 20.11.58**:** MIS BC Level 1 to 3 RP: Brighton Collaboration summary information Level 1 to 3 for the reporting period.
- Appendix 20.11.59**:** MIS Fatal Summary Reports: includes summary information on the reported events during the reporting period with a fatal outcome.

16.3.6.5.1.4. Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Observed vs Expected Analysis

See Appendix 20.11.3.

Overview of Cases

Multisystem inflammatory syndrome - MIS (Cumulative to 31 Dec 2021)

Cumulatively, through 31 Dec 2021, a total of 336 cases (356 events) with MIS-related terms have been reported, with 300 cases medically confirmed. There were 112 cases with fatal outcomes. The distribution of cases by gender and age remained consistent upon cumulative review of the

data. There were 158 cases (47%) that involved male patients and 175 cases (52.1%) that involved female patients. The mean of the patients' ages was 62.4 years (SD 18.5), with a median age of 67 years (min 12 /max 101); 8 cases were missing age data. A large majority of cases involved patients aged 50 years, or older (253, 75.3%), with more than half of all cases reported in patients aged 65, or older (188, 56%) (Table 16-159). This is consistent with the greater incidence of inflammatory disorders occurring in the older population; however, it is inconsistent with descriptions to date of the expected demography for true cases of MIS.

Table 16-159 Number and Percentage of Cases Reporting MIS-related Events by Age and Gender - Cumulative to 31 Dec 2021

Age Group	Female		Male		Unknown		Total # Cases	% Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
12-15	3	0.9	3	0.9	0	0.0	6	1.8
18-29	8	2.4	7	2.1	0	0.0	15	4.5
30-39	15	4.5	10	3.0	0	0.0	25	7.4
40-49	19	5.7	10	3.0	0	0.0	29	8.6
50-64	35	10.4	30	8.9	0	0.0	65	19.3
65-74	49	14.6	49	14.6	0	0.0	98	29.2
75+	42	12.5	48	14.3	0	0.0	90	26.8
Missing	4	1.2	1	0.3	3	0.9	8	2.4
Grand total	**175**	**52.1**	**158**	**47.0**	**3**	**0.9**	**336**	**100.0**

The most commonly reported event by MedDRA Preferred Term was Septic shock (119, 33.4%), followed by Systemic inflammatory response syndrome (87, 24.4%), representing the majority of the cumulatively reported events. (Table 16-160).

Table 16-160 Number and Percentage of MIS-related Events Reported by MedDRA Preferred Term (PT) - Cumulative to 31 Dec 2021

PT	# Events	% Events
Septic shock	119	33.4
Systemic inflammatory response syndrome	87	24.4
Multiple organ dysfunction syndrome	75	21.1
Haemophagocytic lymphohistiocytosis	25	7
Cytokine storm	17	4.8
Multisystem inflammatory syndrome in adults	6	1.7
Multisystem inflammatory syndrome in children	6	1.7
Autoinflammatory disease	5	1.4
Vaccine associated enhanced disease	4	1.1

PT	# Events	% Events
Cytokine release syndrome	3	0.8
Distributive shock	3	0.8
Hypotensive crisis	2	0.6
Multisystem inflammatory syndrome	2	0.6
Kawasaki's disease	1	0.3
Toxic shock syndrome	1	0.3
Grand total	**356**	**100**

There were no important differences in the number of events reported following dose 1 (116; 32.6%) versus dose 2 (143; 40.2%), nor were there any trends noted upon review of the TTO of MIS-related events (Table 16-161); although there were a number of events reported with a very prolonged TTO of more than 100 days noted on individual case review. The average TTO was 46.6 days (SD: 72) and the median TTO was 9.5 days (min: 0/max: 274). There were 92 events with insufficient data to calculate TTO.

Table 16-161 Number and Percentage MIS-related Events by Dose Number and Time to Onset (TTO) - Cumulative to 31 Dec 2021

Dose Number	TTO (Days)	# Events	% Events
Dose 1	***Subtotal***	***116***	***32.6***
	0 days	15	4.2
	01-02	20	5.6
	03-04	11	3.1
	05-06	11	3.1
	07-13	24	6.7
	14-29	14	3.9
	30+	21	5.9
Dose 2	***Subtotal***	***143***	***40.2***
	0 days	13	3.7
	01-02	28	7.9
	03-04	7	2
	05-06	4	1.1
	07-13	9	2.5
	14-29	19	5.3
	30+	63	17.7
Dose 3	***Subtotal***	***5***	***1.4***
	01-02	2	0.6
	03-04	1	0.3
	07-13	2	0.6
Unknown	***Subtotal***	***92***	***25.8***
	Missing	92	25.8

Dose Number	TTO (Days)	# Events	% Events
Grand total		**356**	**100**

Multisystem Inflammatory Syndrome (MIS) in Children (<12 years old) – Cumulative to 31 Dec 2021

There have been no cases received by the MAH of MIS-related events in children less than 12-years old following SPIKEVAX.

Multisystem Inflammatory Syndrome (MIS) in Children (MIS-C) (Including Adolescents (12 to 17 years old) and 18 to 21 years old according to case definition) – Cumulative to 31 Dec 2021

Cumulatively as of 31 Dec 2021, there have been 10 cases (10 events) reporting MIS-C related events. There were 6 cases involving males and 4 cases involving females. The average age in the adolescents was 15 years (SD: 2.5) and the median age was 14 years (min: 12/max: 20). (See Appendix 20.11.57).

Multisystem Inflammatory Syndrome in Patients After a Third Dose or Booster Dose of SPIKEVAX – Cumulative to 31 Dec 2021

Cumulative as of 31 Dec 2021, there were five cases received by the MAH of MIS-related events following a 3rd or booster dose of SPIKEVAX. (See Appendix 20.11.56).

Multisystem Inflammatory Syndrome (Reporting Period – 01 Jul to 31 Dec 2021)

During the reporting period, a total of 185 cases (198 events) containing MIS-related events were reported, with 157 cases medically confirmed. There were 77 cases (86 events) with fatal outcomes. There were no differences between the number of reports for males (91; 49.2%), and females (92; 49.7%). The majority of cases were in patients 65 years of age or older (99, 53.5%) The mean of the patients' ages was 60.9 years (SD: 19.9), with a median age of 66.0 years (min: 12.0 /max:101.0). (Table 16-162). Again, this is inconsistent with the expected demography for true cases of MIS.

Table 16-162 Number and Percentage of Cases Reporting MIS-related Events by Age and Gender - Reporting Period 01 Jul to 31 Dec 2021

Age Group	Female		Male		Unknown		Total # Cases	% Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
12-15	3	1.6	3	1.6	0	0.0	6	3.2
18-29	4	2.2	6	3.2	0	0.0	10	5.4
30-39	8	4.3	6	3.2	0	0.0	14	7.6
40-49	11	5.9	6	3.2	0	0.0	17	9.2
50-64	17	9.2	18	9.7	0	0.0	35	18.9

Age Group	Female		Male		Unknown		Total # Cases	% Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
65-74	27	14.6	24	13.0	0	0.0	51	27.6
75+	20	10.8	28	15.1	0	0.0	48	25.9
Missing	2	1.1	0	0.0	2	1.1	4	2.2
Grand total	**92**	**49.7**	**91**	**49.2**	**2**	**1.1**	**185**	**100.0**

The three most reported MIS-related events were septic shock (73, 36.9%), Systemic inflammatory response syndrome (44, 22.2%), and Multiple organ dysfunction syndrome (42, 21.2%). (Table 16-163).

Table 16-163 Number and Percentage of MIS-related Events by PT - Reporting Period 01 Jul to 31 Dec 2021

PT	# Events	% of Total Events
Septic shock	73	36.9
Systemic inflammatory response syndrome	44	22.2
Multiple organ dysfunction syndrome	42	21.2
Haemophagocytic lymphohistiocytosis	10	5.1
Cytokine storm	6	3.0
Multisystem inflammatory syndrome in adults	6	3.0
Multisystem inflammatory syndrome in children	4	2.0
Autoinflammatory disease	3	1.5
Vaccine associated enhanced disease	3	1.5
Hypotensive crisis	2	1.0
Multisystem inflammatory syndrome	2	1.0
Cytokine release syndrome	1	0.5
Distributive shock	1	0.5
Kawasaki's disease	1	0.5
Grand total	**198**	**100.0**

The greatest proportion of MIS-related events were reported after dose 2 (81, 40.9%) (Table 16-164). The average time to onset of the reported events was 80.9 days (SD: 87.2) and the median was 35.0 days (min: 0/max: 274).

Table 16-164 Number and Percentage of MIS-related Events by Dose Number and Time to Onset (TTO) – Reporting Period 01 Jul to 31 Dec 2021

Dose Number	TTO (Days)	# Events	% Events
Dose 1	***Subtotal***	***47***	***23.7***
	0 days	4	2.0

Dose Number	TTO (Days)	# Events	% Events
	01-02	3	1.5
	03-04	4	2.0
	05-06	4	2.0
	07-13	10	5.1
	14-29	6	3.0
	30+	16	8.1
Dose 2	***Subtotal***	***81***	***40.9***
	0 days	4	2.0
	01-02	8	4.0
	03-04	3	1.5
	05-06	1	0.5
	07-13	4	2.0
	14-29	7	3.5
	30+	54	27.3
Dose 3	***Subtotal***	***5***	***2.5***
	01-02	2	1.0
	03-04	1	0.5
	07-13	2	1.0
Unknown	***Subtotal***	***65***	***32.8***
	Missing	65	32.8
Grand total		198	100.0

Fatal Case Summaries

There were 77 cases (86 events) with fatal outcomes received during this reporting period. There were 33 females and 53 males, between the ages of 14 and 101 years old. There were 23 cases after dose 1, 36 cases after dose 2, 1 case after dose 3, and 26 cases for which dose number was not provided. TTO was reported between 1 day after receiving any vaccine dose to 274 days after any vaccine dose. Out of 86 events reported with a fatal outcome 44 were due to a septic shock (51.2%); 34 (39.5%) due to multiorgan dysfunction syndrome that included from COVID-19 infection complications, to abdominal infections intestinal obstructions, complications due to sepsis and septic shock, chronic kidney disease, cardiovascular complications, including cardiac tamponade, etc. A summary of the cases reporting a fatal outcome during this reporting period is provided in Appendix 20.11.59 MIS Fatal Summary Reports.

Multisystem Inflammatory Syndrome (MIS) in Children (<12 years old) – Reporting Period 01 Jul to 31 Dec 2021

There have been no cases received by the MAH of MIS-related events in children less than 12-years old following SPIKEVAX.

Multisystem Inflammatory Syndrome (MIS) in Children (MIS-C) (Including Adolescents (12 to 17 years old) and 18 to 21 years old according to case definition) – Reporting Period 01 Jul to 31 Dec 2021

During the reporting period, same as during the cumulative period, there have been 10 cases (10 events) reporting MIS-C related events. There were 6 cases involving males and 4 cases involving females. The average age in the adolescents was 15 years (SD: 2.5) and the median age was 14 years (min: 12/max: 20). (See Appendix 20.11.57 MIS C RP)

Multisystem Inflammatory Syndrome in Patients After a Third Dose or Booster Dose of SPIKEVAX – Reporting Period 01 Jul to 31 Dec 2021

During the reporting period, there were five cases received by the MAH of MIS-related events following a 3rd or booster dose of SPIKEVAX. (See Appendix 20.11.56).

Brighton Collaboration Case Definition Evaluation/ WHO Causality Assessment

A review of MIS-C/A related cases with diagnostic certainty level 1–3 according to the Brighton Collaboration case definition including WHO causality assessment is included in Appendix 20.11.58 MIS BC Level 1 to 3 RP. The review is based in both the previous and the new search strategy as explained in the methods section above. Using this combine strategy, the following was the findings from the analysis:

There were 3 reports classified as Level 1, 1 report classified as Level 2a, 3 reports classified as Level 2b, and 2 reports classified as Level 3b. (See Appendix 20.11.58 MIS BC Level 1 to 3 RP).

Out of those 9 MIS-C/A related cases with diagnostic certainty level 1–3 according to the Brighton Collaboration case definition, according to the WHO standardized causality assessment, there were 17 3 reports classified as possible based on temporal association between the use of the product and the start of the events, but a causal relationship cannot be excluded due to the lack of other information.

There was 1 report-that was considered conditional due to the reported events but there was not enough information provided in order to provide a causality assessment. There were 5 reports that were considered unlikely to be related to the vaccine due to comorbidities present in some of these patients that provide a more plausible explanation for the occurrence of the events (See Appendix 20.11.56 All Cases).

16.3.6.5.1.5. Discussion

Based on the analysis of all the safety data available reported during this reporting interval, the MAH considers cases included under the AESI of MIS-C/A are heavily confounded due to the reported events including septic shock, sepsis, acute respiratory distress, associated COVID-19

pneumonia, Haemophagocytic lymphohistiocytosis, cytokine storm related events right after vaccination. All these events are considered differential diagnosis conditions providing important confounders in the evaluation of these reports.

16.3.6.5.1.6. Conclusion

A review of the data received during this reporting period showed that there is currently insufficient evidence to suggest a causal relationship between SPIKEVAX and MIS-C/A at this point.

Based on the analysis of all the safety data received during the reporting interval of this PBRER, ModernaTX, Inc considers that cases included under the AESI of MIS-C/A, reported in temporal association with the administration of SPIKEVAX, did not raise any safety issue of concern and the information provided is inadequate to provide evidence of causality between SPIKEVAX exposure and MIS-C/A. These data do not represent a new safety issue of concern. ModernaTX, Inc will continue to monitor events for MIS-C/A using routine surveillance. A follow-up questionnaire was implemented in effort to obtain additional information for cases reporting MIS-related events. The benefit-risk evaluation remains positive.

16.3.6.6. Skin and Subcutaneous Tissue Disorders

16.3.6.6.1. Chronic Urticaria/Worsening of Pre-existing Chronic Urticaria

16.3.6.6.1.1. Source of the New Information

To support cumulative review of chronic urticaria, chronic spontaneous urticaria and worsening of pre-existing chronic urticaria, the information presented below includes an analysis performed on cases received by ModernaTX, Inc. from 18 Dec 2020 to 31 Dec 2021 for the mRNA-1273 vaccine (COVID-19 vaccine Moderna) SPIKEVAX.

16.3.6.6.1.2. Background Relevant to the Evaluation

Considering emerging EudraVigilance and published literature data, the MAH (ModernaTx) has been requested by the PRAC to conduct a cumulative review in PBRER No. 2 on the association between chronic urticaria and worsening of pre-existing chronic urticaria and SPIKEVAX administration.

Background on Chronic Urticaria:

According to the Dermatology Section of the European Academy of Allergology and Clinical Immunology (EAACI), the EU-founded network of excellence, the Global Allergy and Asthma European Network (GA²LEN), the European Dermatology Forum (EDF) and the World Allergy

Organization (WAO) consensus guidelines for the definition, classification, diagnosis and management of urticaria, urticaria is defined as a condition characterized by the development of wheals (hives), angioedema or both [167]. Urticaria is a common dermatologic condition, typified by "intensely pruritic, well-circumscribed, raised wheals ranging from several millimeters to several centimeters or larger in size." Urticaria can occur with or without angioedema which is a painful localized, warm nonpitting oedema of the subcutaneous or interstitial tissue. The intensity of the pruritus can cause significant discomfort and impairment of daily functioning and disrupt normal sleep [168].

Chronic urticaria (CU) is defined by 'the presence of recurrent urticaria, angioedema, or both, for a period of more than 6 weeks" whereas acute urticaria has a duration of ≤ 6 weeks. Urticaria can also be classified as spontaneous, with no specific trigger involved, or inducible with a specific eliciting factor [167].

Urticaria has a lifetime prevalence of about 20%, whereas chronic urticaria has a lifetime prevalence of approximately 0.5% to 5% [168].

Urticaria is a clinical diagnosis and anaphylaxis must be ruled out as a potential cause. Limited additional work-up is required, unless history is suggestive of another underlying etiology.

Acute urticaria is typically benign and self-limited and resolves with avoidance of triggers. While chronic spontaneous urticaria is an episodic and self-limited disorder in most patients, the average duration of disease is two to five years. In patients in whom no trigger or underlying disorder is identified, the rate of spontaneous remission at one-year ranges from 30-50% [169].

The primary approach to treatment is to avoid identified triggers. Second-generation H1 antihistamines constitute the first-line pharmacotherapy, while "first-generation H1 antihistamines, H2 antihistamines, leukotriene receptor antagonists, high-potency antihistamines, and brief corticosteroid bursts may be used as adjunctive treatment." Subspecialist's evaluation is sought in cases of refractory chronic urticaria, who may consider additional treatments such as omalizumab or cyclosporine [168].

Etiology

Urticaria is believed to be caused by "immunoglobulin E- and non–immunoglobulin E-mediated release of histamine and other inflammatory mediators from mast cells and basophils" [168]. This may be due to immune activation in response to certain viral, bacterial or parasitic infections, IgE mediated allergic reactions, direct mast cell activation, NSAIDs (pseudoallergic or allergic reactions), or physical factors such as cold exposure or exposure to sunlight [170]. Up to 80-90% of cases of chronic urticaria are idiopathic [168]. The pathogenesis of chronic spontaneous urticaria has not been established and potential hypotheses include autoimmunity mediated by

functional autoantibodies directed against IgE or the high-affinity IgE receptor, cellular defect theories and serum or plasma factors that directly or indirectly activate mast cells or basophils, [168] [170].

Exacerbation of Chronic Spontaneous Urticaria (CSU):

Although by definition chronic spontaneous urticaria does not have a single unifying cause, certain factors may exacerbate CSU in a substantial number of patients. Factors that exacerbate chronic spontaneous urticaria (CSU) include: Nonsteroidal anti-inflammatory drugs (NSAIDs), stress, changes to dietary habits, alcohol and physical stimuli such as heat or tight clothing. However, if physical stimuli are the primary trigger for chronic urticaria symptoms, the case should not be classified as spontaneous but rather one of the physical urticaria syndromes such as cholinergic urticaria or delayed-pressure urticaria [170].

Urticaria and SPIKEVAX:

In general, a known history of a severe allergic reaction to any component of SPIKEVAX is a contraindication to SPIKEVAX administration. Injection site urticaria is listed as a common adverse reaction and hypersensitivity is listed with an unknown frequency in the adverse reaction table in the SPIKEVAX SmPC (dated 07 Jan 2022). While vaccines are not typically listed as one of the common triggers for chronic urticaria, limited literature has described a temporal association of chronic urticaria with other vaccines [171] [172].

16.3.6.6.1.3. Methods of Evaluation including Data Sources, Search Criteria and Analytical Approaches

The MAH queried the GSDB, cumulatively through 31 Dec 2021, for valid case reports received from HCP, HA, consumers, and literature, worldwide, reported for SPIKEVAX. The search strategy included using the MedDRA PTs “Urticaria chronic” and “Chronic spontaneous urticaria”. Cases of worsening of pre-existing Chronic urticaria were identified through review of medical history in cases of urticaria chronic and chronic spontaneous urticaria.

The MAH reviewed all clinical trial adverse event data from the mRNA-1273 P301 study, Part A (Clinical Study Report, mRNA-1273-P301, Part A, DLP 04 May 2021). All unsolicited treatment emergent adverse events (TEAEs) were reviewed to identify events with any MedDRA preferred terms (PT) that included the word “Urticaria”.

A targeted literature search and review for chronic urticaria and COVID vaccines was performed on 24-27 Jan 2022 by searching National Library of Medicine (NLM) Pubmed and Google Scholar search engine using the following search criteria: combinations of “Chronic urticaria” OR “Urticaria” OR “Worsening of Chronic urticaria” OR mRNA-1273 OR Moderna COVID vaccine OR COVID vaccine OR COVID-19 vaccine OR SARS-CoV-2.

All cases identified were reviewed and classified using the definition for chronic urticaria from the Dermatology Section of the European Academy of Allergology and Clinical Immunology (EAACI), the EU-founded network of excellence, the Global Allergy and Asthma European Network (GA²LEN), the European Dermatology Forum (EDF) and the World Allergy Organization (WAO) consensus guidelines for the definition, classification, diagnosis and management of urticaria [167]. This guideline defines urticaria as a condition characterized by the development of wheals (hives), angioedema or both. Urticaria is then further classified based on its duration as acute (≤6 weeks) or chronic (> 6 weeks) as well as spontaneous (no specific eliciting factor involved) or inducible (specific eliciting factor involved).

- Appendix 20.11.60**:** summary tabulation of all cases of Urticaria chronic and Chronic spontaneous urticaria
- Appendix 20.11.61: Literature summary

16.3.6.6.1.4. Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Overview of Cases

Cumulative Review (Chronic urticaria and worsening of pre-existing Chronic urticaria, cumulative to 31 Dec 2021)

Cumulatively, through 31 Dec 2021, a total of 37 cases were reported with a total of 37 events of Chronic urticaria or Chronic spontaneous urticaria. Twenty-three of the cases were assessed as serious with 19 events of chronic urticaria or chronic spontaneous urticaria assessed as serious. None of the cases had a fatal outcome. Of the 37 cases, 17 cases were medically confirmed. Most of the cases were reported from the EEA (17, 45.9%), followed by the United States (14, 37.8%), United Kingdom (4, 10.8%), and Switzerland (2, 5.4%).

The 37 reported cumulative cases of Urticaria chronic and Chronic spontaneous urticaria included a total of 125 events. Table 16-165 summarizes the top 10 most frequently reported events by preferred term within the cases of Urticaria chronic and Chronic spontaneous urticaria. Of note, multiple other hypersensitivity terms were reported including angioedema (n = 9), mechanical urticaria (n = 2), anaphylactic reaction, drug hypersensitivity, and hypersensitivity (n = 1 each) as well as other potential hypersensitivity symptoms such as eye swelling (n = 2), injection site reaction, lip swelling, oedema peripheral, and peripheral swelling (n = 1 each).

Table 16-165 presents a cumulative summary of all events within cases of Chronic urticaria and Chronic spontaneous urticaria by MedDRA PT.

Table 16-165 Number and Percentage of Top 10 Events within Cases of Urticaria Chronic and Chronic Spontaneous Urticaria by MedDRA PTs– Cumulative to 31 Dec 2021

PT	# Events*	% of Total Events
Urticaria chronic	24	19.2%
Urticaria	14	11.2%
Chronic spontaneous urticaria	13	10.4%
Angioedema	9	7.2%
Pruritus	8	6.4%
Rash	6	4.8%
Condition aggravated	3	2.4%
Rash erythematous	3	2.4%
Arthralgia	2	1.6%
Erythema	2	1.6%

*Includes only the top 10 events reported. A total of 125 events associated with Chronic urticaria and Chronic spontaneous urticaria has been reported cumulatively.

There were 7 cases (18.9%) involving males and 27 (73.0%) cases involving female and 3 (8.1%) with unknown gender. The distribution of cases by age was fairly even with 14 cases (37.84%) reported for patients 50 years of age or older (median age: 43.5 years: min: 23.0 years; max: 74.0 years) (Table 16-166).

Table 16-166 Number and Percentage of Reported Events of Urticaria chronic and Chronic Spontaneous Urticaria-Related Events Cases by Gender and Age – Cumulative to 31 Dec 2021

Age Group	Female		Male		Unknown		Total # Cases	Total % Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
18-29	5	13.5%	0	0	0	0	5	13.5%
30-39	8	21.6%	0	0	0	0	8	21.6%
40-49	4	10.8%	3	8.1%	0	0	7	18.9%
50-64	6	16.2%	3	8.1%	0	0	9	24.3%
65-74	3	8.1%	1	2.7%	1	2.7%	5	13.5%
Missing	1	2.7%	0	0	2	5.4%	3	8.1%
Grand total	**27**	**73.0%**	**7**	**18.9%**	**3**	**8.1%**	**37**	**100.0%**

There was no clear pattern related to dose number and time to onset (TTO) as shown in Table 16-167 below.

Table 16-167 **Distribution of Events of Reported Events of Urticaria Chronic and Chronic Spontaneous Urticaria by Dose Number and Time to Onset for All Doses – Cumulative to 31 Dec 2021**

Dose Number	TTO All Doses (Days)	# Events	% Events
Dose 1	Subtotal	12	32.4%
	01-02	3	8.1%
	03-04	2	5.4%
	05-06	1	2.7%
	07-13	4	10.8%
	14-29	2	5.4%
Dose 2	Subtotal	8	21.6%
	0 days	1	2.7%
	01-02	1	2.7%
	07-13	3	8.1%
	14-29	2	5.4%
	30+	1	2.7%
Dose 3	Subtotal	4	10.8%
	01-02	1	2.7%
	07-13	2	5.4%
	14-29	1	2.7%
Unknown	Subtotal	13	35.1%
	Missing	13	35.1%
Grand total		**37**	**100.0%**

Following medical review of all cases of Urticaria chronic and Chronic spontaneous urticaria, using the WHO-UMC standardized case causality assessment [146], 3 cases (8.1%) were assessed as probable, 13 cases (35.1%) were assessed as possible, 18 cases (48.6%) were assessed as unlikely (primarily due to TTO of ≥6 days), and 3 cases (8.1%) were assessed as unassessable.

In total 5 cases were assessed as meeting the case definition of chronic urticaria by having a confirmed duration of at least 6 weeks. Of note, during this review, cases with a reported medical history of urticaria, chronic urticaria or chronic spontaneous urticaria, were not considered as meeting the case definition of chronic urticaria unless the onset date of the medical history event was specified and either the duration of the medical history event and/or the duration of the reported event of chronic urticaria/chronic spontaneous urticaria was > 6 weeks.

Two cases (4.1(b) and 4.1(b)) reported concurrent events of mechanical urticaria and chronic spontaneous urticaria, which conflicts with the definition of chronic spontaneous urticaria as not having an identifiable trigger.

Fifteen of 37 reports included atopic medical history conditions such as drug/food allergies, anaphylaxis, asthma and eczema.

Condition Aggravated (Worsening of pre-existing Chronic urticaria)

Cumulatively, based on review of available medical history, 6 cases of worsening of pre-existing chronic urticaria or chronic spontaneous urticaria have been reported:

- 4.1(b): 36-year-old female from 4.1(b) with history of chronic urticaria and hemophilia A; 2 days after first dose of SPIKEVAX, patient develops urticaria with reported duration of 3 weeks, injection site reaction and angioedema.
- 4.1(b)**:** 24-year-old female from 4.1(b) with "existing chronic urticaria" though onset date not specified; urticaria worsened 7 days after first dose of SPIKEVAX leading to more rash, more itching and requiring more antihistamines; took a few weeks to return to baseline.
- 4.1(b): 23-year-old female from 4.1(b) (potential duplicate case of 4.1(b) 4 based on details provided) with medical history of chronic urticaria (onset date not specified) with worsening 7 days after second dose of SPIKEVAX with more rash, more itching and more antihistamines needed; returned to baseline 3 months later.
- 4.1(b)**:** 55-year-old male from 4.1(b) with medical history of chronic spontaneous urticaria since 2012 with severe angioedema of tongue, lips and throat; 24 days after dose 1 of SPIKEVAX experienced unexpected and constant occurrence of angioedema of lips, throat, tongue after eating previously unsuspected (i.e. "safe") foods that he would previously been able to tolerate.
- 4.1(b): 46-year-old female from 4.1(b) with medical history of chronic urticaria though of unclear duration; experienced a "surge" of chronic urticaria 24 hr after vaccination with SPIKEVAX.
- 4.1(b) was literature cases series of two patients with history of chronic spontaneous urticaria with worsening after SPIKEVAX administration; one subject had been controlled with pharmacotherapy for 2 months prior to SPIKEVAX administration had a flare of urticaria 16 hours after 2nd SPIKEVAX dose that continued to flare every 2-3 days afterwards; second subject with history of allergic rhinitis and chronic spontaneous urticaria associated with angioedema of upper lip with last flare in 1973, now controlled

with antihistamines, who developed same upper lip swelling 30 min after first dose of SPIKEVAX that resolved 30 min later without intervention.

Two additional subjects had a medical history of urticaria reported, though the urticaria was not specified as chronic:

- 4.1(b) [redacted]: 48-year-old male from 4.1(b) [redacted] with a history of hypersensitivity and urticaria (no onset date specified) and experienced new chronic urticaria 3 days after first dose of SPIKEVAX.
- 4.1(b) [redacted]: 24-year-old female from 4.1(b) [redacted] with medical history of urticaria that began 3 months prior to first dose of SPIKEVAX; chronic spontaneous urticaria and angioedema began 3 days after first dose of SPIKEVAX.

The time to onset of worsening urticaria was variable in these cases from hours to 24 days after SPIKEVAX administration. The duration of symptoms was reported in 4 cases. Two cases mentioned history of chronic spontaneous urticaria (which by definition should not have known triggers) whereas other cases mentioned history of urticaria. Two of the reported subjects with chronic spontaneous urticaria had been controlled previously with pharmacotherapy while the third was controlled by dietary restrictions.

Children ages 01-11 Years (Cumulatively as of 31 Dec 2021)

Cumulatively as of 31 Dec 2021, there have been no cases of Urticaria chronic, Chronic spontaneous urticaria or worsening of pre-existing chronic urticaria reported for children <12 years.

Adolescents ages 12-17 Years (Cumulatively as of 31 Dec 2021)

Cumulatively as of 31 Dec 2021, there have been no cases of Urticaria chronic, Chronic spontaneous urticaria or worsening of pre-existing chronic urticaria reported for Adolescents (12-17 years).

SPIKEVAX Booster (Cumulatively as of 31 Dec 2021)

Cumulatively, through 31 Dec 2021, a total of 4 cases, with a total of 3 events of Urticaria chronic and 1 event of Chronic spontaneous urticaria, were reported after receipt of > 2 doses of SPIKEVAX. One case was assessed as serious. None of the cases had a fatal outcome. Of the 4 cases, 2 cases were medically confirmed. One event had an onset within <7 days or 14-29 days from the third dose of SPIKEVAX and 2 events had an onset between 7-13 days from the third dose of SPIKEVAX. There were no cases involving male patients as all 4 cases involved females. Case count distribution by age are as follows: 30-39 (2, 50.0%); 40-49 (1, 25.0%), and 50-64 (1, 25.0%). The median age for patients reporting at least one event of chronic urticaria or chronic

spontaneous urticaria after receipt of >2 doses of SPIKEVAX was 37.0 years (min: 32.0 years; max: 54.0 years). None of the patients reported a medical history of urticaria, though one subject had a medical history of contact dermatitis. All of the other events in the cases were reported in a single patient each and were notable for one report of mechanical urticaria and 1 report of urticaria.

Clinical Trial Data:

The Phase 3 pivotal clinical trial mRNA-1273 P301 Part A was reviewed to identify all events reported with MedDRA PTs that contained the word "urticaria." Table 16-168 below summarizes all unsolicited TEAEs with a PT containing the word urticaria within the overall stage, Table 16-169 summarizes all unsolicited TEAEs with a PT containing the word urticaria within 28 days of any injection and Table 16-170 summarizes all unsolicited TEAEs assessed as related with a PT containing the word urticaria within 28 days of any injection.

Table 16-168 Summary of Incidence of Unsolicited TEAE by Preferred Term in Overall Stage from mRNA-1273 P301 Part A as of 04 May 2021

Preferred Term	Placebo N = 15162 n (%)	mRNA-1273 N = 15184 n (%)	Rate Ratio (95% CI)	Total N = 30346 n (%)
Urticaria	46 (0.3)	55 (0.4)	1.19 (0.81, 1.76)	101 (0.3)
Urticaria papular	5 (<0.1)	3 (<0.1)		8 (<0.1)
Chronic spontaneous urticaria	0	1 (<0.1)		1 (<0.1)
Mechanical urticaria	0	1 (<0.1)		1 (<0.1)
Idiopathic urticaria	1 (<0.1)	0		1 (<0.1)
Injection site urticaria	1 (<0.1)	38 (0.3)	37.94 (6.58, 218.91)	39 (0.1)

Table 16-169 Summary of Incidence of Unsolicited TEAE by Preferred Term within 28 days After Any Injection from mRNA-1273 P301 Part A as of 04 May 2021

Preferred Term	Placebo N = 15162 n (%)	mRNA-1273 N = 15184 n (%)	Rate Ratio (95% CI)	Total N = 30346 n (%)
Urticaria	33 (0.2)	44 (0.3)	1.33 (0.85, 2.08)	77 (0.3)
Urticaria papular	5 (<0.1)	3 (<0.1)		8 (<0.1)
Chronic spontaneous urticaria	0	1 (<0.1)		1 (<0.1)
Mechanical urticaria	0	1 (<0.1)		1 (<0.1)
Idiopathic urticaria	1 (<0.1)	0		1 (<0.1)
Injection site	1 (<0.1)	38 (0.3)	37.94 (6.58, 218.91)	39 (0.1)

urticaria				

Table 16-170 Incidence of Unsolicited Treatment-Related TEAE by Preferred Term up to 28 Days After Any Injection from mRNA-1273 P301 Part A as of 04 May 2021

Preferred Term	Placebo N = 15162 n (%)	mRNA-1273 N = 15184 n (%)	Rate Ratio (95% CI)	Total N = 30346 n (%)
Urticaria	7 (<0.1)	22 (0.1)	3.14 (1.37, 7.17)	29 (<0.1)
Urticaria papular	1	0		1 (<0.1)
Chronic spontaneous urticaria	0	1 (<0.1)		1 (<0.1)
Mechanical urticaria	0	1 (<0.1)		1 (<0.1)
Injection site urticaria	1 (<0.1)	34 (0.2)	33.95 (5.87, 196.28)	35 (0.1)

Overall, there was one reported event of chronic spontaneous urticaria (reported term: INTERMITTENT CHRONIC IDIOPATHIC URTICARIA-WIDESPREAD) in an mRNA-1273 subject (subject US3812158) with onset on Day 31, two days after the second dose of mRNA-1273. This event was assessed by the investigator as a non-serious moderate MAAE that was related to the investigational product. The subject had a history of seasonal allergies and intermittent eczema. The event was ongoing at the time of the data cut-off for the Part A analysis. Other than reported MAAEs of cough and nasal congestion with onset on Day 7, there were no other relevant AEs reported for this subject.

Review of the medical history of all subjects in mRNA-1273 P301 Part A is summarized in Table 16-171 below.

Table 16-171 Summary of Medical History of All Subjects in mRNA-1273 P301 Part A:

Medical History Term (PT)	mRNA-1273 Subjects	Percentage of Total Subjects	Placebo Subjects	Percentage of Total Subjects
Urticaria	83	0.5%	88	0.6%
Chronic spontaneous urticaria	5	<0.1%	0	0.0%
Cold urticaria	5	<0.1%	1	<0.1%
Mechanical urticaria	4	<0.1%	10	<0.1%
Urticaria chronic	4	<0.1%	1	<0.1%
Idiopathic urticaria	3	<0.1%	1	<0.1%
Urticaria cholinergic	3	<0.1%	0	0.0%
Solar urticaria, Urticaria pressure and/or Urticaria vibratory	0	0.0%	1	<0.1%

Literature Review:

ModernaTx conducted a comprehensive literature search to identify relevant publications on the association of association between Urticaria chronic, Chronic spontaneous urticaria and worsening of pre-existing chronic urticaria. Of 251 publications identified, 15 were directly relevant, and 2 were particularly informative. These two relevant literature summaries are presented below. Please refer to Appendix 20.11.61 for a detailed tabular listing of additional relevant literature abstracts identified from our targeted search.

Literature Review Findings:

Two Cases of Well Controlled Chronic Spontaneous Urticaria Triggered by the Moderna COVID-19 Vaccine

Author: Cylie Alflen et al. (24 Jun 2021)

Cylie Alflen et al. [173] reported the first two cases of a COVID-19 vaccine triggered relapse of Chronic Spontaneous Urticaria (CSU) that was previously well controlled on therapy.

Case No. 1:

"The first case was a 49-year-old male who presented with a history of chronic spontaneous urticaria for the past twenty-eight years. The patient's hives presented on the front and back of his body, including his feet and hips. His exacerbating factors include warm temperatures and sunlight, however, there are times that wheals appear spontaneously. Previously, the patient has tried and failed two different high dose first generation H1 antihistamines (carbinoxamine and cyproheptadine), as well as an H2 blocking antihistamine (ranitidine). Subsequently, the patient was started on omalizumab (Xolair) 300 mg every four weeks, with success experienced after the third dose. The patient had been consistent with his omalizumab injections, and his symptoms were well controlled by pharmacotherapy for about 2 months. After the second dose of the Moderna COVID19 vaccine, the patient had a flare of urticaria identical to previous episodes. The outbreak occurred 16 hours after receiving the vaccination. The patient took cetirizine, and the wheals resolved within 6 hours. Since this flare-up, the patient now continues to develop hives every 2 to 3 days, and his symptoms are no longer controlled with pharmacotherapy."

MAH Comment: In Case No. 1, temporal association was evident although causality was not established. The patient had previously experienced similar flares of chronic spontaneous urticaria without exposure to the Moderna SPIKEVAX vaccine. However, the 49-year-old male had a prior 28-year history of well-controlled chronic spontaneous urticaria (using pharmacotherapy) and experienced a flare-up 16 hours after the second dose of the Moderna COVID19 vaccine (SPIKEVAX), identical to his prior episodes of a flare of urticaria. No further doses of Moderna SPIKEVAX vaccine were reported to have been administered to the patient. The report implied

that a pattern of recurrent flares of chronic spontaneous urticaria continued since the post vaccine flare. Although other non-mRNA vaccines have been associated with urticarial flares, Moderna SPIKEVAX clinical trials, post-market SPIKEVAX spontaneous reports, or other literature findings have also reported patterns of temporal association between urticarial reactions and mRNA vaccination. Therefore, possible contribution of Moderna SPIKEVAX vaccine to the causality of such reactions cannot be completely excluded.

Case No. 2:

"The second case was a 74-year-old female who presented with a past medical history of allergic rhinitis and chronic spontaneous urticaria. The patient's CSU symptoms include angioedema of the upper lip. Her last known flare was in 1973. The patient had spontaneous angioedema for multiple years until her symptoms became controlled with a first generation H1 antihistamine. When the patient received her first Moderna COVID-19 vaccine, she experienced the same swelling of her upper lip that she had last experienced in the 1970's. The edema appeared 30 minutes after injection and resolved within 30 minutes without pharmacological intervention."

MAH Comment: Temporal association was evident in Case No. 2, although causality was not established. The patient had previously experienced similar flares of angioedema of the upper lip without exposure to the Moderna SPIKEVAX vaccine. However, the patient angioedema had not reoccurred for approximately 48 years until after she received her first dose of the Moderna SPIKEVAX vaccine. While a direct causality has not been ascertained, the MAH acknowledges a temporal association between reoccurrence of the patient's angioedema flare (after 48 years of no flares) and exposure to the Moderna SPIKEVAX vaccine.

Literature Summary

ModernaTx literature search and findings revealed a spectrum of hypersensitivity reactions, including acute and recurrent urticarial-type cutaneous reactions reported in cases of subjects who received mRNA COVID-19 vaccinations. Overall, although other non-mRNA COVID-19 vaccines and non-COVID-19 vaccines have been associated with urticarial flares, very few cases of such flares have been reported in Moderna SPIKEVAX clinical trials, post-market SPIKEVAX spontaneous reports, or other literature mentioning SPIKEVAX albeit with patterns of temporal association. Of these reports, majority have described urticaria or related reactions with recurrence that are not necessarily true chronic urticaria or worsening of pre-existing chronic urticaria. Nevertheless, possible contribution of Moderna SPIKEVAX vaccine to the causality of such reactions cannot be completely excluded.

16.3.6.6.1.5. Discussion

Cumulatively, there were 37 post-marketing cases of Urticaria chronic and/or Chronic spontaneous urticaria reported with a female predominance and no clear trends by age, though there were no reports in subjects < 18 years old. There was no clear pattern identified with respect to dose number and time to onset (TTO). Cumulatively, there were 6 cases of worsening of pre-existing chronic urticaria or chronic spontaneous urticaria reported and an additional 2 cases with a medical history of urticaria that developed chronic urticaria or chronic spontaneous urticaria following SPIKEVAX administration. The duration of the chronic urticaria/chronic spontaneous urticaria was infrequently reported. Five cases reported a duration of the chronic urticaria/chronic spontaneous urticaria of >6 weeks to meet the case definition of chronic urticaria. Two of the 13 post-marketing cases of chronic spontaneous urticaria included additional events of mechanical urticaria providing a potential alternate etiology/diagnosis as mechanical urticaria is considered an "inducible" form of chronic urticaria whereas chronic spontaneous urticaria has no identifiable trigger. One post-marketing case of chronic urticaria included a concurrent report of an anaphylactic reaction, thus supporting an acute severe hypersensitivity reaction, which is already an identified risk for SPIKEVAX. In general, 40% of subjects had a history of other hypersensitivity events and due to the limited information available in post-marketing repots, less than 15% of reports included information that duration of symptoms was long enough to be classified as "chronic urticaria." In the Phase 3 pivotal study, mRNA-1273 P301 Part A analysis (data cut 04 May 2021), there was a significant imbalance in events of injection site urticaria (rate ratio 37.94 (6.58, 218.91) for TEAEs within 28 days of any injection) and a less pronounced imbalance in urticaria (rate ratio 1.33 (0.85, 2.08) for TEAEs within 28 days of any injection) between the mRNA-1273 and placebo recipients. There was a single report of chronic spontaneous urticaria with onset 2 days after the second dose of mRNA-1273 in an atopic P301 participant with a history of intermittent eczema and seasonal allergies. As the pathophysiology of chronic spontaneous urticaria is unknown, it is challenging to propose a mechanism to justify biologic plausibility for a causal association between chronic spontaneous urticaria and SPIKEVAX whereas chronic urticaria may be related to an exaggerated hypersensitivity response, which is already an identified risk with SPIKEVAX. Cumulatively, the reporting rate of Chronic urticaria and Worsening of pre-existing Chronic urticaria for SPIKEVAX is substantially lower than one report per million doses.

Analysis of the cumulative available data is insufficient to suggest a causal association between chronic urticaria, chronic spontaneous urticaria and/or worsening of pre-existing Chronic urticaria and SPIKEVAX.

16.3.6.6.1.6. Conclusion

Based on the analysis of all the safety data received during the cumulative period of this PBRER, ModernaTX, Inc considers that cases included under the medical concept of chronic urticaria, chronic spontaneous urticaria and worsening of pre-existing chronic urticaria/chronic spontaneous urticaria, reported in temporal association with the administration of SPIKEVAX, did not raise any safety issue of concern and the information provided is inadequate to provide evidence of causality between SPIKEVAX exposure and chronic urticaria or worsening of chronic urticaria. These data do not represent a new safety issue of concern. ModernaTX, Inc will continue to monitor events for chronic urticaria and worsening of chronic urticaria using routine surveillance. The benefit-risk evaluation remains positive

16.3.6.7. Other Disorders

16.3.6.7.1. Single Organ Cutaneous Vasculitis Events (SOCV)

16.3.6.7.1.1. Source of the New Information

ModernaTX queried the GSDB for valid, spontaneous case reports received from HCP, HA, consumers, and literature cumulative from 18 Dec 2020 to 31 Dec 2021, worldwide, reported for SPIKEVAX.

16.3.6.7.1.2. Background Relevant to the Evaluation

An evaluation of single organ cutaneous vasculitis events (SOCV) is performed due to reporting rates that were above what is expected in the age-stratified O/E analysis. Additionally, ModernaTX, Inc was requested by a regulatory authority to continue to provide an overview of the event classification into Brighton level 1-5 for diagnostic certainty, and to provide a WHO Causality assessment for each event assessed as Brighton level 1-3.

SOCV refers to vasculitis in arteries or veins of any size in a single organ and has no features of systemic involvement. Some patients initially diagnosed with SOCV may develop other disease manifestations, warranting reevaluation for another systemic vasculitis. For this review of SOCV, the MAH adopted the Brighton Collaboration definition of diagnostic certainty that refers to small vessel vasculitis of the skin where systemic involvement has been excluded.

Disease-inducing or promoting factors are either post-infectious or drug-induced, but more than half of cases of SOCV are idiopathic. Although non-immunologic factors such as direct infection of endothelial cells can cause vasculitis, most lesions are mediated by immunopathogenic mechanisms. Small vessel vasculitis can also be associated with connective tissue diseases, and it may be a heralding sign of such diseases, particularly systemic lupus erythematosus.

SOCV typically presents with a single crop of lesions consisting of palpable purpura (hemorrhagic papules), erythematous papules, urticarial lesions, vesicles, and hemorrhagic vesicles 7–14 days after exposure to a triggering agent. SOCV favors dependent areas, as well as areas affected by trauma or compressed by tight-fitting clothing. The lesions are usually asymptomatic, or associated with burning, pain, or pruritus. Residual post-inflammatory hyperpigmentation may persist for months after the primary process resolves [174].

16.3.6.7.1.3. Methods of Evaluation including Data Sources, Search Criteria and Analytical Approaches

The MAH queried the GSDB using selected PTs from the MedDRA SMQ Vasculitis (Narrow scope) to include the following PTs: Administration site vasculitis, Cutaneous vasculitis, Hemorrhagic urticaria, Hemorrhagic vasculitis, Injection site vasculitis, Palpable purpura, Purpura, Purpura non-thrombocytopenic, Urticarial vasculitis, Vaccination site vasculitis, Vascular purpura, and Vasculitic rash.

To characterize the level of diagnostic certainty, identified cases were classified into one of five categories, following the Brighton Collaboration Single organ cutaneous vasculitis case definition (SOCV) [174]:

- Level 1 (Definitive case)
- Level 2 (Probable case)
- Level 3 (Possible case)
- Level 4 is a reported event of SOCV with insufficient evidence to meet level 1, 2 or 3 of the case definitions
- Level 5 (Not a case of SOCV)

The Brighton definitions are used to evaluate the strength of the evidence to determine whether a case fulfils the criteria needed to establish a case as SOCV. It is not used to ascertain causality.

- Appendix 20.11.62: include detailed summary of Cumulative cases that met Brighton's Collaboration Level of diagnostic certainty 1 to 3, and their WHO-UMC causality assessment.

16.3.6.7.1.4. Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Observed to Expected Analysis

See Appendix 20.11.3.

Overview of Cases

Cumulative review (SOCV, Cumulative to 31 Dec 2021)

Cumulatively, a total of 248 cases (and 257 events) were identified for vasculitis of which 128 cases were serious and 2 had a fatal outcome secondary to systemic complications. There were 194 (78.2%) cases that were medically confirmed. Regulatory authority reports accounted for 81.5% of received reports (202 reports), followed by spontaneous case reports (41/16.5%) and literature reports (5/ 2.01 %). The largest number of cases originated from the USA (122 / 35.4%) followed by France (34 / 23.1%) and Japan (18 / 7.7%).

Distribution of case reports by gender reflected 70 males (28.2%) and 170 females (68.5 %) (gender was missing or unknown for 8 [3.2%] cases), and the age group with the highest number of cases was the 50-64 years group (80 cases; 32.3%) (Table 16-172). The mean age was 56.6 years (SD 16.3) and the median age was 57.0 (min 17 / max 94).

Table 16-172 Case Distribution by Gender and Age Group, Cumulative as of 31 Dec 2021

Age Group	Female		Male		Unknown		Total # of Cases	Total % of Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
16-17	0	0	1	0.4	0	0	1	0.4
18-29	7	2.8	5	2.0	0	0	12	4.8
30-39	23	9.3	4	1.6	1	0.4	28	11.3
40-49	25	10.1	9	3.6	0	0	34	13.7
50-64	55	22.2	25	10.1	0	0	80	32.3
65-74	33	13.3	15	6.0	0	0	48	19.4
75+	24	9.7	11	4.4	0	0	35	14.1
Missing	3	1.2	0	0	7	2.8	10	4.0
Grand total	**170**	**68.5**	**70**	**28.2**	**8**	**3.2**	**248**	**100.0**

Of the 257 events, 119 were serious and 138 were non-serious. Purpura was the most frequently reported event (178, 69.3%) with the majority of those reports being non-serious, followed by cutaneous vasculitis (44 events / 17.1%/) (Table 16-173).

Table 16-173 Event Distribution by PT and Seriousness, Cumulative as of 31 Dec 2021

PT	Non-Serious		Serious		Total # of Events	Total % of Events
	# Events	% Total Events	# Events	% Total Events		
Purpura	126	49.0	52	20.2	178	69.3
Cutaneous vasculitis	1	0.4	43	16.7	44	17.1

PT	Non-Serious		Serious		Total # of Events	Total % of Events
	# Events	% Total Events	# Events	% Total Events		
Urticarial vasculitis	0	0	10	3.9	10	3.9
Vasculitic rash	7	2.7	4	1.6	11	4.3
Vascular purpura	0	0	4	1.6	4	1.6
Palpable purpura	2	0.8	1	0.4	3	1.2
Vaccination site vasculitis	0	0	3	1.2	3	1.2
Injection site vasculitis	2	0.8	0	0	2	0.8
Haemorrhagic vasculitis	0	0	2	0.8	2	0.8
Grand total	**138**	**53.7**	**119**	**46.3**	**257**	**100.0**

Event distribution by dose number and time to onset (TTO) are described in Table 16-174. Most of the events were reported after dose 1 (112 / 43.6%), and with a TTO within <4 days (53; 47.3. Dose number and TTO were missing for 83 events (32.3%). The median TTO for all doses was 4.0 days.

Table 16-174 Event Distribution by Dose and TTO, Cumulative as of 31 Dec 2021

Dose Number	TTO All Doses (Days)	# Events	% Events
Dose 1	**Subtotal**	**112**	**43.6**
	0 days	15	5.8
	01-02	28	10.9
	03-04	10	3.9
	05-06	8	3.1
	07-13	32	12.5
	14-29	16	6.2
	30+	3	1.2
Dose 2	**Subtotal**	**53**	**20.6**
	0 days	7	2.7
	01-02	18	7.0
	03-04	5	1.9
	05-06	3	1.2
	07-13	10	3.9
	14-29	5	1.9
	30+	5	1.9
Dose 3	**Subtotal**	**9**	**3.5**
	0 days	1	0.4

Dose Number	TTO All Doses (Days)	# Events	% Events
Unknown	**Subtotal**	**83**	**32.3**
	Missing	83	32.3
Grand total		**257**	**100.0**

Cumulatively, a total of 97 events (37.7%) were considered not recovered and 98 (38.1%) events were considered recovered or recovering (Table 16-175). Cumulatively, there have been 2 cases with a fatal outcome (4.1(b) and 4.1(b)).

Table 16-175 Event Distribution by Outcome, Cumulative as of 31 Dec 2021

Event Outcome	Grand total of # Events	Grand total of % of Total Events
Fatal	2	0.8
Not Recovered/Not Resolved	97	37.7
Recovered/Resolved	56	21.8
Recovering/Resolving	42	16.3
Unknown	60	23.3
Grand total	**257**	**100.0**

Brighton Collaboration Case Assessment

Cumulatively, there have been a total of 257 events (248 cases) involving "single organ cutaneous vasculitis." All events were medically reviewed and stratified by event classification using the criteria as specified in the SOCV case definition by the Brighton collaboration [174].

Cumulatively, 2 events (2 cases) met Level 1 criteria for diagnostic certainty, 6 events (5 cases) met the criteria for Level 2, and 17 events (17 cases) for Level 3. All remaining events either had insufficient evidence to meet the case definition or were determined to not be events of SOCV. The 25 events (24 cases) that met case definition Level 1 to 3 are outlined in Appendix 20.11.62. These cases had an age range of 28 to 77 years with a median age of 51 years. Six patients were males and 1 was female.

Of the 25 events (24 cases) that were classified as Level 1 to 3, 12 events (12 cases) occurred after Dose 1. Of these 12 events, time to onset (TTO) was < 7 days for 3 events (3 cases), ≥ 7 days and <14 days for 7 events (7 cases), and ≥ 14 days and <30 days for 2 events (2 cases). Of the 25 events (24 cases) that were classified as Level 1 to 3, four events (4 cases) occurred after Dose 2. Among those 4 events, TTO was <7 days for 3 events and ≥ 14 days and <30 days for 1 event. Dosing information was not provided for 9 events (8 cases).

The majority of cases reported as SOCV were inconsistent with criteria for the condition, generally due to multiple systemic events involving other organ systems occurring concurrently, or the information was insufficient for adequate assessment and few biopsies were reported.

Subpopulation Analyses

SOCV in Children (<12 Years of Age)

No event was reported in children <12 years of age.

SOCV in Adolescents (12-17 Years of Age)

Cumulatively, one case ([redacted]) of SOCV in adolescents (12-17 years of age) was reported.

SOCV in Patients After a Third Dose or Booster Dose of SPIKEVAX

Cumulatively through 31 Dec 2021, 9 cases of SOCV were reported in patients receiving >2 doses of SPIKEVAX.

16.3.6.7.1.5. Discussion

Based on the analysis of all the safety data available as of 31 Dec 2021, the MAH considers that cases included under the AESI of SOCV are temporally associated with the administration of SPIKEVAX, but the information provided is inadequate to support evidence of causality between SPIKEVAX exposure and SOCV. Furthermore, a substantial proportion of reports do not contain sufficient information describing clinical features, timing, concomitant meds, co-morbidities, biopsy results, other investigations, and resolution status necessary to perform a proper evaluation. None of the cases in this reporting period are consistent with the Brighton classification case definition Level 1 to 3.

16.3.6.7.1.6. Conclusion

After careful review of all new safety data received cumulatively for the risk of SOCV, the benefit-risk profile for SPIKEVAX remains favorable. ModernaTX, Inc will continue to monitor events for SOCV using routine surveillance. The benefit-risk evaluation remains positive.

16.3.6.7.2. Rhabdomyolysis

16.3.6.7.2.1. Source of the New Information

The information presented below includes analysis regarding the potential risk of rhabdomyolysis based on a cumulative review of data from all sources including findings from clinical trials, published literature, and post-authorization reports received by ModernaTX, Inc. from 18 Dec 2020 to 31 Dec 2021, worldwide, with the use of SPIKEVAX.

16.3.6.7.2.2. Background Relevant to the Evaluation

ModernaTX, Inc was requested by a regulatory authority to conduct an updated cumulative evaluation of data from all sources regarding the potential risk of rhabdomyolysis as of 31 Dec 2021. Additionally, it was requested that the PT myositis (and related terms) be included in order to identify potential cases of Rhabdomyolysis that might have been erroneously coded as myositis cases.

Rhabdomyolysis is a complex condition involving the release of intracellular muscle components, including myoglobin, creatine kinase (CK), aldolase, and lactate dehydrogenase, as well as electrolytes, into the bloodstream and extracellular space from damaged or injured skeletal muscle [80]. There are many potential causes of rhabdomyolysis, with the most common causes in adults identified as alcohol abuse, muscle overexertion, traumatic injury, and certain medications or illicit drugs. Rhabdomyolysis is also commonly diagnosed in elderly patients following a fall or stroke. Additional risk exists for individuals with certain metabolic and endocrinologic conditions, such as diabetes mellitus, thyroid dysfunction, and chronic kidney disease, as well as for those with conditions involving pathologic muscle exertion, such as seizure disorders and Parkinson's disease. Other possible causes identified include infection, inflammation, immobility, and genetic disorders [175]. Several case reports have been published describing the occurrence of rhabdomyolysis in COVID-19 infections [176]. The clinical presentation of rhabdomyolysis is often nonspecific and may include localized muscle pain, tenderness, and weakness and systemic signs and symptoms of tea-colored urine, fever, nausea, malaise, and confusion. Diagnosis of rhabdomyolysis is generally made when suspicion arises after a complete history and physical exam is followed by supporting laboratory results. Due to its long half-life, measurement of plasma CK levels is considered the gold standard for laboratory diagnosis, with the most commonly used cutoff threshold being a concentration of five times the upper limit of normal. The course of the syndrome varies from a generally asymptomatic elevation in CK level to a life-threatening condition complicated by electrolyte imbalances, acute renal failure, and disseminated intravascular coagulation. Up to 33% of patients with rhabdomyolysis develop acute kidney injury in the days following initial presentation, which is associated with high morbidity and mortality. Aggressive hydration is the primary treatment for rhabdomyolysis with the aim of supporting kidney function [80].When diagnosed and treated early, complications can be prevented, and prognosis is good.

16.3.6.7.2.3. Methods of Evaluation including Data Sources, Search Criteria and Analytical Approaches

ModernaTX, Inc queried the GSDB cumulatively from 18 Dec 2020 to 31 Dec 2021, for valid case reports of Rhabdomyolysis from HCP, HA, consumers, and literature, worldwide, reported for

SPIKEVAX and the clinical trials data from the mRNA-1273 pivotal phase 3 study (through 04 May 2021) for cases. Search terms included MedDRA PTs of Muscle necrosis, Myopathy toxic, Necrotizing myositis, and Rhabdomyolysis; and, as per regulatory authority feedback, the additional PTs of Autoimmune myositis, Dermatomyositis, Focal myositis, Immune-mediated myositis, Myositis, Myositis-like syndrome, Orbital myositis, and Polymyositis were searched in order to identify potential cases of Rhabdomyolysis that might have been erroneously coded as myositis cases.

Case reports with myositis-related PTs were thoroughly reviewed to identify any cases that, based on clinical signs and symptoms and/or laboratory test results, might have been erroneously coded as myositis but described an event consistent with rhabdomyolysis.

All cases reporting rhabdomyolysis, or reporting a myositis term, but describing a potential event of rhabdomyolysis, were assessed for a causal association to SPIKEVAX using the WHO-UMC causality assessment system.

- Appendix 20.11.63: Case Reviews for Potential Rhabdomyolysis Reports
- Appendix 20.11.64: Rhabdomyolysis Case WHO Causality Assessments
- Appendix 20.11.65: Fatal Case Review

16.3.6.7.2.4. Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Observed vs Expected Analysis

See Appendix 20.11.3.

Overview of Cases

Cumulatively (18 Dec 2020 to 31 Dec 2021), there were 261 cases (270 events) reporting rhabdomyolysis-related PTs (Autoimmune myositis, Dermatomyositis, Immune-mediated myositis, Myositis, Orbital myositis, Polymyositis, Rhabdomyolysis), of which 201 were serious, 198 were medically confirmed and 7 had a fatal outcome. Gender distribution included males 115 (44.1%) and females 142 (54.4%) with a median age of 54.0 (min 18.0/max 97.0).

Among the 270 events, 46.7% reported Rhabdomyolysis and 42.6% myositis. All cases associated with PT terms other than rhabdomyolysis were reviewed to determine if any cases should be considered as rhabdomyolysis. See Appendix 20.11.63 for these case reviews. Twelve cases were identified and are included in the WHO_UMC causality assessments. (Appendix 20.11.64).

Table 16-176 Event Counts by PT in Rhabdomyolysis Cases - Cumulative to 31 Dec 2021

PT	# Events	% of Total Events
Rhabdomyolysis	126	46.7%
Myositis	115	42.6%
Dermatomyositis	14	5.2%
Polymyositis	9	3.3%
Autoimmune myositis	2	0.7%
Immune-mediated myositis	2	0.7%
Orbital myositis	2	0.7%
Grand total	**270**	**100.0%**

*Two cases contained both Rhabdomyolysis and Myositis as PTs

Most reports were received from regulatory authorities (81.2%) and originated from the United States (57.5%) followed by 26.8 % from the EEA (Table 16-177).

Table 16-177 Number and Percentage of Cases of Rhabdomyolysis Reported by Region Cumulative as of 31 Dec 2021

Region	# of Cases	% of Total Cases
Asia	17	6.5%
Canada	5	1.9%
European Economic Area	70	26.8%
Switzerland	11	4.2%
United Kingdom	8	3.1%
United States	150	57.5%
Grand total	**261**	**100.0%**

Most cases of rhabdomyolysis were in the elderly > 65 years (35.6%) followed by 30-39 years (19.2%). There were no cases of rhabdomyolysis in the pediatric population (Table 16-178).

Table 16-178 Number and Percentage of Cases of Rhabdomyolysis Reported by Age and Gender Cumulative to 31 Dec 2021

Age Group	Female		Male		Unknown		Grand total of # Cases	Grand total of % of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases	# Cases	% of Total Cases		
18-29	12	4.6%	13	5.0%	2	0.8%	27	10.3%
30-39	27	10.3%	23	8.8%	0	0	50	19.2%
40-49	18	6.9%	14	5.4%	0	0	32	12.3%
50-64	28	10.7%	20	7.7%	0	0	48	18.4%
65-74	30	11.5%	18	6.9%	0	0	48	18.4%
75+	21	8.0%	24	9.2%	0	0	45	17.2%

Age Group	Female		Male		Unknown		Grand total of # Cases	Grand total of % of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases	# Cases	% of Total Cases		
Missing	6	2.3%	3	1.1%	2	0.8%	11	4.2%
Grand total	**142**	**54.4%**	**115**	**44.1%**	**4**	**1.5%**	**261**	**100.0%**

Cumulatively, there were 99 cases which included PTs myositis and/or rhabdomyolysis reported after the 1st dose (36.7%) and 78 cases after the 2nd dose (28.9 The greatest proportion of cases were reported within the first three days (16.2%) following the 2nd dose of SPIKEVAX. There was insufficient information provided for time to onset calculation for 31.5% of events (Table 16-179).

Table 16-179 Number and Percentage of Cases by Time to Onset and Dose Number Cumulative to 31 Dec 2021

Dose Number	TTO All Doses (Days)	# Events	% Events
Dose 1	Subtotal	99	36.7%
	0 days	14	5.2%
	01-02	24	8.9%
	03-04	14	5.2%
	05-06	10	3.7%
	07-13	20	7.4%
	14-29	11	4.1%
	30+	6	2.2%
Dose 2	Subtotal	78	28.9%
	0 days	13	4.8%
	01-02	31	11.5%
	03-04	3	1.1%
	05-06	3	1.1%
	07-13	11	4.1%
	14-29	10	3.7%
	30+	7	2.6%
Dose 3	Subtotal	8	3.0%
	0 days	1	0.4%
	01-02	2	0.7%
	05-06	2	0.7%
	07-13	1	0.4%
	14-29	2	0.7%

Dose Number	TTO All Doses (Days)	# Events	% Events
Unknown	Subtotal	85	31.5%
	Missing	85	31.5%
Grand total		**270**	**100.0%**

Of the 270 reported events, 85 events (31.4%) were reported as resolved or resolving (Table 16-180).

Table 16-180 Number and Percentage of Rhabdomyolysis Events by Outcome – Cumulative to 31 Dec 2021

Event Outcome	Cumulative	
	# Total Events	% of Total Events
Fatal	7	2.6%
Not Recovered/Not Resolved	116	43.0%
Recovered/Resolved	63	23.3%
Recovered/Resolved with sequelae	2	0.7%
Recovering/Resolving	20	7.4%
Unknown	62	23.0%
Grand total	**270**	**100.0%**

Overview of Fatal Cases

There were 7 fatal cases of rhabdomyolysis-related PTs, which are presented in Appendix 20.11.65.

WHO-UMC Causality Assessment

A cumulative review of cases reported with the rhabdomyolysis related - PTs, included cases reported with the PT Myositis was conducted. Cumulatively, through 31 Dec 2021, there were 2 cases with WHO-UMC causality assessments of probable, 14 as possible, 85 as conditional, 30 as unlikely, and 6 as unclassifiable. (Table 16-181).

During this reporting period, there were 137 new cases reporting the PT of Rhabdomyolysis and myositis related PTs that were evaluated as possible rhabdomyolysis, including 68: 46.6% new events of myositis and 43.8% of rhabdomyolysis. Additional events included dermatomyositis (6;4.1%), polymyositis (5; 3.4%), immune-related myositis (2; 1.4%), and autoimmune myositis (1; 0.7%). There were 11 newly identified cases reporting myositis-related PTs but describing events consistent with possible rhabdomyolysis. These reports were evaluated using WHO-UMC standardized causality assessment. The review focused on assessing the cases based on the clinical description, including symptoms and signs described on physical exam in addition to the review of laboratory data. Diagnostic certainty was based on elevated creatine kinase (CK) $\geq$ 1500 U/L. Additionally, the history of present illness (including recent trauma, alcohol consumption etc.),

past medical history, and concomitant medications were noted in an attempt to identify possible confounders or other more plausible explanations for the events.

In all cases assessed as "unlikely", a plausible alternative explanation was identified for the events. Eight cases reported a fall with either extensive contusions or immobility prior to the event of rhabdomyolysis, 9 reported concomitant medications associated with rhabdomyolysis including gabapentin, risperidone, amitriptyline, quetiapine, sertraline, infliximab, telmisartan or statins, 2 reported significant exercise (weight training and cross training), and the remaining cases mentioned abnormal muscle biopsy, seizure activity, progressive kidney disease, alcohol use and vasculitis, history of pancreatic cancer on Keytruda, sepsis, and lacunar infarction that confounded the reports. The reports considered unclassifiable either contained details contradictory to an event of rhabdomyolysis, such as mildly elevated CK levels, or a lack of any clinical details to confirm an event of rhabdomyolysis. Refer to Appendix 20.11.64 for additional case assessment details.

Table 16-181 Number of Rhabdomyolysis Cases by Causality Using WHO-UMC Assessment

WHO-UMC Causality	# of Cases
Probable/ Likely	2
Possible	14
Unlikely	30
Conditional/Unclassified	85
Unassessable/Unclassifiable	6
Grand Total	**137**

Two cases from literature [177], [178] were as assessed as "Probably/Likely" but still had potential confounding factors. These cases are presented below.

4.1(b) : This literature case report is for a 28-year-old female patient with unknown medical history who five days after receiving the 1st dose of SPIKEVAX, experienced a mild, predominantly left-sided, weakness of hip flexor and knee extension (MRC 4-/5 vs. MRC 4/5) with marked subcutaneous leg oedema. The patient was described as healthy, with previous absence of muscular symptoms, exercise intolerance, anesthetic reactions, and relevant family history prior to onset of the events. Concomitant medications were not reported. Patient was diagnosed with Rhabdomyolysis, Myositis and Fasciitis. Relevant laboratory results included elevated creatine kinase, hypocalcemia, hypophosphatemia, antibodies associated with myositis or myopathy were negative, and tests for hepatitis viruses, Epstein-Barr virus, and cytomegalovirus were negative. Relevant diagnostic exam results included an unremarkable echocardiogram and chest computed tomography, magnetic resonance imaging of the thighs was suggestive of fasciitis but not confirmed, and electromyography of the left rectus muscle revealed findings consistent

with acute myopathy or myositis. The patient was treated with high volume infusion of normal saline and intravenous methylprednisolone, followed by an oral methylprednisolone taper over 6 days. Within days of initiation of treatment, paresis, leg pain and oedema had resolved. Four weeks after onset, the patient's creatine kinase was normal, and she was able to resume jogging.

Company comment: This literature report case of a 28-year-old female is heavily confounded by the laboratory findings of hypocalcemia, hypophosphatemia, and electrolyte disorders, which can be a trigger for rhabdomyolysis [179].

4.1(b) **:** This literature report [178] is for an 85-year-old Caucasian woman, with a medical history of rheumatoid arthritis, hyperlipidemia, and asthma who was recently diagnosed with a cerebrovascular accident (CVA) 2 months prior. She presented to the emergency room (ER) 2 days after receiving the second dose of the Moderna COVID-19 vaccine with generalized weakness, muscle cramps, and loss of appetite. The patient had received the first dose of the Moderna vaccine 30 days before receiving the second dose. The patient started to feel weak the same afternoon after receiving the second dose. Later, she went to use the bathroom and could not stand up from the toilet seat. Her husband helped her get to bed. Since then, she mostly stayed in bed except while using the bathroom with assistance. The patient noticed her urine color changing from dark brown to black on the same day of receiving the injection. The next day, her weakness worsened along with abdominal and muscle cramps, and she was brought to the ER by ambulance. The patient's home medications included clopidogrel, metoprolol, nifedipine, rosuvastatin, telmisartan, tofacitinib, and trazodone. Clopidogrel and trazodone were started about 2 months prior to admission when the patient had a stroke. All other medications were long-term. Family history was positive for autoimmune disease in maternal grandmother. The patient had no previous history of tobacco or alcohol abuse. The patient had never contracted COVID-19 prior to this admission. There was no recent history of trauma or surgery. She had also not started to use any over-the-counter medications recently. Her vital signs remained stable, and the blood work on admission showed significantly elevated serum creatinine of 6.0 mg/dL (normal range: 0.6–1.3 mg/dL), blood urea nitrogen (BUN) of 73 mg/dL (normal range: 7– 18 mg/dL) and significantly decreased glomerular filtration rate (GFR) of 6 mL/min (normal range: >60 mL/min) and bicarbonate of 13 mmol/L (normal range: 21–32 mmol/L). The patient also had abnormally elevated liver function with aspartate aminotransferase (AST) of 1422 U/L (normal range: 15–37 U/L), alanine aminotransferase (ALT) of 600 U/L (normal range: 15–37 U/L), and alkaline phosphatase of 600 U/L (normal range: 45–117 U/L). Her creatine phosphokinase (CPK) level was found to be elevated at >14,000 U/L (normal range: 26–192 U/ L). Troponin levels were 0.18 ng/mL (normal range: 0.00– 0.04 ng/mL), followed by 0.21 ng/mL and 0.20 ng/mL. Urinalysis was positive for 3+ blood, negative for red blood cells (RBCs), and showed >5000 mcg/mL

myoglobin. Non-contrast enhanced computed tomography (CT) of the abdomen and head revealed no acute finding.

Over the course of hospitalization, the patient became progressively weaker to a point where she could not even lift/move her hands or legs. Mentation started to decline, with patient intermittently getting confused or experiencing hallucinations. She ultimately required intubation, suffered a cardiac arrest and expired.

MAH Comment: The authors note the patient had rheumatoid arthritis. The authors postulate that a dysregulated immune system may have made the patient more susceptible to immune overstimulation and might be a possible mechanism to explain rhabdomyolysis.

The case summaries for Possible cases are provided below.

4.1(b) [redacted]: This spontaneous case was reported by a consumer and concerns a 75-year-old male patient who developed acute renal failure, rhabdomyolysis, Non-ST segment elevation myocardial infarction, loss of leg strength and chills after his second dose of mRNA-1273 (Moderna COVID-19 Vaccine) SPIKEVAX. Concomitant medications reported included cetirizine hydrochloride for allergies, cyanocobalamin for increased energy, and allopurinol for uric acid. On 10 Mar 2021, the patient received his first dose of SPIKEVAX. On 07 Apr 2021, he received the second dose of SPIKEVAX and experienced chills and lost control of his legs in the middle of the night. One day after vaccination, on 08-Apr-2021, the patient experienced loss of leg strength. On an unknown date, the patient developed acute renal failure, rhabdomyolysis, and non-ST-segment elevation myocardial infarction and was hospitalized. Relevant laboratory results included creatine kinase 22,000 on 09 Apr 2021, 10,000 on 10 Apr 2021, and 6,412 on 11 Apr 2021. Intravenous saline was given as treatment. He was discharged from the hospital on 11 Apr 2021.

4.1(b) [redacted]: This regulatory authority case was reported by a health care professional and concerns a 39-year-old female patient who developed rhabdomyolysis after receiving mRNA-1273 (Moderna COVID-19 Vaccine) SPIKEVAX. Details regarding the patient's medical history and concomitant medications were not provided. On 21 Jan 2021, the patient received her second dose of SPIKEVAX, and the following day, on 22 Jan 2021, the patient experienced chills, low-grade fever, and pain described as a burning sensation, and swelling in both arms. On 27 Jan 2021, she presented to the emergency room with ongoing pain and swelling and with numbness in her left hand. Laboratory results that same day included creatine kinase 2500 and liver enzymes were elevated. The patient reported receiving an anticoagulant. On 28 Jan 2021, she was diagnosed with rhabdomyolysis and treated with aspirin, cold compresses, and fluids. On 29 Jan 2021, her pain levels had improved.

MAH Comment: The causality is based on temporal relationship in the absence of past medical history and concomitant medications.

4.1(b) **:** This regulatory authority case was reported by a health care professional and involves a 45-year-old male patient who developed rhabdomyolysis with myalgia after his second dose of mRNA-1273 (Moderna COVID-19 Vaccine) SPIKEVAX. Medical history and concomitant medication details were not provided. On 02 Apr 2021, the patient received second dose of SPIKEVAX, and on that same day, the patient developed rhabdomyolysis and myalgia. Relevant laboratory results included creatine kinase 38,906 on 02 Apr 2021. Rhabdomyolysis and myalgia were reported as not resolved. No additional information was provided.

MAH Comment: The causality is based on temporal relationship in the absence of past medical history and concomitant medication.

4.1(b) **:** This regulatory authority case was reported by a health care professional and involves a 38-year-old male patient who developed renal failure, abdominal pain, rhabdomyolysis, and headache following his first dose of mRNA-1273 (Moderna COVID-19 Vaccine) SPIKEVAX. Medical history and concomitant medication details were not provided. On 29 Apr 2021, the patient received his first dose of SPIKEVAX. Four days later, on 03 May 2021, the patient developed renal failure, abdominal pain, rhabdomyolysis, and headache. Relevant laboratory results on 03 May 2021 included creatine kinase 60,000 U/L and creatinine 2.86 mg/dL. No additional information was provided.

MAH Comment: The causality is based on temporal relationship in the absence of past medical history and concomitant medication.

4.1(b) **:** This spontaneous case, received from a licensing partner, was reported by a physician and involves a female patient in her 70’s who developed rhabdomyolysis with myalgia after receiving her first dose of mRNA-1273 (COVID 19 Vaccine Moderna) SPIKEVAX. Medical history and concomitant medication details were not provided. In mid-Jun 2021, the patient received her first dose of SPIKEVAX, and, about one week later, she developed generalized myalgia and presented to the hospital. During hospitalization, laboratory results revealed creatine kinase of 5,500, absence of myoglobinuria, and normal hepatic function. The patient underwent cardiac catheterization due to suspected myocardial infarction (results unclear “little infarction”). The patient was discharged from the hospital and the events were reported as resolved.

MAH Comment: The causality was assessed based on temporal relationship in the absence of past medical history and concomitant medications.

4.1(b) **:** This regulatory authority case was reported by a physician and involves a 32-year-old female patient who developed rhabdomyolysis after her first dose of mRNA-1273

(COVID-19 Vaccine Moderna) SPIKEVAX. The patient's past medical history includes adrenal cancer and nephrectomy. It was reported that the patient was not taking any concomitant medications. On 18-Jun-2021, the patient received her first dose of mRNA-1273 (COVID-19 Vaccine Moderna) SPIKEVAX. Fourteen days later, on 02 Jul 2021, the patient developed rhabdomyolysis with symptoms of asthenia and pain in multiple muscles. Laboratory results included creatine kinase 9979 UI/L and phosphorous, calcium, and thyroid function were normal. Rhabdomyolysis was reported as not resolved.

4.1(b) **:** This regulatory authority case was reported by a health care professional and involves a 40-year-old female patient who developed rhabdomyolysis after her first dose of mRNA-1273 (Moderna COVID-19 Vaccine) SPIKEVAX. Concurrent medical conditions included allergies to ciprofloxacin, animal dander, and pollen/seasonal allergies. Concomitant medication details were not provided. On 22 Jan 2021, the patient received her first dose of mRNA-1273 (Moderna COVID-19 Vaccine) SPIKEVAX, and, on the same day, developed rhabdomyolysis, dizziness, shortness of breath, facial numbness, near syncope, tachycardia, shaking and chills. Laboratory results that day included creatine kinase 5900. The events were reported as not resolved.

4.1(b) **:** A 73-year-old male patient with unknown medical history who was vaccinated on 03 Jul 2021 (Dose 1). On an unknown date, the patient developed suspected immune-mediated necrotizing myopathy. On 06 Jul 2021, laboratory results showed blood CK-MB of 11808. It was also reported that the patient was hospitalized with pneumonia from swallowing difficulty in Jul 2021. No additional information was available and therefore unable to fully exclude alterative causality. The causality assessment is based on temporal relationship.

4.1(b) **:** A 26-year-old male patient with unknown medical history who was vaccinated on 29 Jul 2021 (Dose 1) and two days later experienced severe bilateral upper arm pain that persisted for 5 days. Four days after being vaccinated, the patient developed weakness in his upper arms and on 05 Aug 2021, 7 days after vaccination, the patient experienced Rhabdomyolysis and was hospitalized that same day. His laboratory results showed creatine phosphokinase (CK) of 39504 U/L and myoglobin blood: 858 mcg/L. Within 24 hours, his CK had decreased to 20,000 U/L. No additional information was available and therefore unable to fully exclude alternative causality.

4.1(b) **:** A 38-year-old female patient with unknown medical history who was vaccinated on 22 Jun 2021 (Dose 2) and on 30-Jun-2021, eight days later, the patient developed rhabdomyolysis. Patient was admitted to ICU with CK value of almost 28,000. On 09 Jul 2021, rhabdomyolysis had resolved. No additional information was available and therefore unable to fully exclude alternative causality.

4.1(b) **:** A 39-year-old male received the 2nd dose of SPIKEVAX on 06 Oct 2021. On an unknown date, pyrexia of nearly 40 degrees Celsius developed. On 09 Oct 2021, the patient took a walk, but could not walk for five minutes, so returned home. On 12 Oct 2021, the patient was aware of pain in the lower back and thighs and shortness of breath when moving the body and went to see a nearby doctor. The patient was explained that it was the initial symptom of intervertebral disc herniation, prescribed a treatment, and returned home. On 18 Oct 2021, the patient was rushed to the reporting hospital because of difficulty moving the body. The patient was admitted to the department of spinal and spinal surgery as an intervertebral disc herniation. After hospitalization, pyrexia, decreased SpO2, oedema, pleural effusion, poor oral intake, bleeding tendency, thrombocytopenia, increased CK, LDH, AST, and ALT, and hypothyroidism were observed. On 29 Oct 2021, internal medicine and ICT also intervened. The rhabdomyolysis by this vaccine was suspected. As renal function was normal, fluid replacement was continued, and danaparoid sodium was administered for disseminated intravascular coagulation. On an unknown date, muscle weakness, bleeding tendency, and thrombocytopenia improved. On 07-Nov-2021, at 03:49, the patient experienced cardiac arrest. After recovery by cardiopulmonary resuscitation, the patient was transferred to the ICU, but was unconscious, and hypoxic encephalopathy was observed. Around 15-Nov-2021, gastrointestinal perforation occurred during continuous treatment in the ICU. On 18-Nov-2021, the patient underwent surgical operation of right hemicolectomy and ileostomy. On 25-Nov-2021, after the surgery, the patient's symptoms were improving, but at this time the patient was under ICU management and ventilator management, oral intake was not possible, and the patient was conscious, but comprehension was unknown. The symptoms were ongoing and unchanged.

MAH Comment: CPK values are not given but the clinical presentation is compatible with rhabdomyolysis.

4.1(b) **:** This case concerned a 41-year-old, male patient which was a trial participant (atopic eczema, treated with upadacitinib) who experienced rhabdomyolysis with chromaturia, that led to hospitalization. The events occurred approximately 5 days after the third dose of mRNA-1273 vaccine. CPK was 33846 on admission. No follow-up information was provided. Except for the atopic dermatitis the patient was reported in good health.

MAH Comment: The presentation is confounded by the use of upadactinib.

4.1(b) **:** this 86-year-old male with a history of type 2 diabetes received the 2nd dose of SPIKEVAX on 22 Jul 2021, at 10:00. On 23 Jul 2021, the patient felt weak on the lower limbs and fell. On 24 Jul 2021, at 10:00, rhabdomyolysis developed. The patient went to the hospital, and a blood test showed elevated CPK of 5,140. On 28 Jul 2021, the patient was scheduled to be

referred to another hospital but was transported by ambulance due to loss of consciousness and was hospitalized. On 28-Sep-2021, the patient had not recovered from the symptoms.

4.1(b) **:** This regulatory authority case was reported by a physician and describes the occurrence of abnormal hepatic function and rhabdomyolysis in a 50-year-old female patient who received mRNA-1273 (COVID 19 Vaccine Moderna) (batch no. 3004496) for COVID-19 vaccination. The patient's past medical history included cerebral infarction.

Concurrent medical conditions included hypertension. Concomitant medications included acetylsalicylic acid) for cerebral infarction, telmisartan (Micardis) and amlodipine for hypertension.

On 06 Aug 2021, the patient received first dose of mRNA-1273 (COVID 19 Vaccine Moderna.). Her symptoms presented an unknown time later, but laboratory tests taken 11 Aug revealed a CPK of 9957 international unit per liter. On 13 Aug 2021, Blood creatine phosphokinase was 13602 international unit per liter. On 17 Aug 2021, Blood creatine phosphokinase was 10731 international unit per liter. At the time of report symptoms had resolved.

MAH Comment: This case was confounded by the concomitant use of telmisartan.

Clinical trials

Data from the phase 3 study revealed that, out of the 15,185 numbers of subjects exposed to mRNA-1273 as of 04 May 2021, no adverse events of myositis or rhabdomyolysis were reported in the mRNA-1273 group. In the placebo arm, one event was reported for myositis and one for rhabdomyolysis.

Literature Findings

There have been multiple case reports of rhabdomyolysis following COVID 19 vaccination. In addition to the two cases presented above a paper by Mack 2021 presents a case of an 80-year-old male who developed rhabdomyolysis two days after receiving his second dose of Moderna COVID-19 vaccine. He presented with severe weakness, myalgias, and an initial creatinine kinase (CK) of 6,546 IU/L that improved with intravenous fluids. Common causes of rhabdomyolysis were excluded including statin use, strenuous exercise, and trauma. No mechanism of causation was suggested.

MAH Comment: Unlike other cases, this patient did not have evidence of known risk factors for rhabdomyolysis. Tan, et al [180] reports a patient with Carnitine palmitoyl transferase II (CPT II) deficiency who presented feeling generally unwell after his COVID-19 vaccine. The CK concentration was reported as 105,000 U/L. His baseline disorder, which affects fatty acid oxidation, manifests itself with a high serum creatine kinase (CK) concentration and can be exacerbated by periods of fasting, infection, exercise, stress, and exposure to extreme temperature.

Nassar et al [176] reported a case of rhabdomyolysis in a 21-year-old male patient with a past medical history of asthma who presented to the emergency department for progressively worsening pain and swelling in the lower back for one day after his first Pfizer/BioNTech COVID-19 vaccine injection. The patient tried over-the-counter pain medication with limited relief. He also noticed a darkened urine color before he came to the hospital. The patient did not use any medication regularly. The patient denied excessive exercise, heavy weightlifting or body trauma after vaccination. He had no family history of autoimmune or musculoskeletal diseases, and surgical history was only significant for an uncomplicated appendectomy. Patient endorsed social marijuana use but denied other drug, alcohol, or tobacco use. Pertinent lab results included Creatinine Phosphokinase (CPK) level more than 22,000 U/L (normal range 20e190 U/L). The patient recovered after a course of hydration.

MAH Comment: This patient had a history of asthma which is considered an autoimmune disorder.

Subpopulation Analyses

Rhabdomyolysis in Children < 12 Years of Age (Cumulatively as of 31 Dec 2021)

Rhabdomyolysis was not reported in children under 12 years of age.

Rhabdomyolysis in Adolescents (12-17 Years of Age) (Cumulatively as of 31 Dec 2021)

Rhabdomyolysis was not reported in adolescents (12-17 years of age).

SPIKEVAX Booster (Cumulatively as of 31 Dec 2021)

There were 8 cases of rhabdomyolysis-related events including myositis reported following dose 3 or greater. Seven of the cases were serious, 6 medically confirmed and 1 had a fatal outcome. TTO is presented below for events after the 3rd dose/booster (Table 16-182).

Table 16-182 TTO/Distribution of Events after Dose 3

Dose Number	TTO All Doses (Days)	# Events	% Events
Dose 3	Subtotal	8	100.0%
	0 days	1	12.5%
	01-02	2	25.0%
	05-06	2	25.0%
	07-13	1	12.5%
	14-29	2	25.0%
Grand total		**8**	**100.0%**

16.3.6.7.2.5. Discussion

Cumulatively, there were 137 cases identified as possible rhabdomyolysis cases (126 were reported as such and 11 were identified by medical review of myositis).

As requested by a Regulatory Authority, the PT myositis (and related terms) were included in the search to capture cases of rhabdomyolysis that might have been erroneously coded as myositis cases. There were 115 cases retrieved and a thorough medical review was performed of all cases, resulting in the identification of 11 cases suggestive of rhabdomyolysis, which were included in the 261 cases and the overall assessment.

According to the WHO-UMC causality assessment, only 2 cases were assessed as probable and 14 as possible. Based on patient's risk factors, including present and past illness, and concomitant medications, it is determined that most of these reports are confounded. (See Appendix 20.11.63 and Appendix 20.11.64).

Rhabdomyolysis is a syndrome characterized by muscle necrosis and the release of intracellular muscle constituents into the circulation. The pathophysiological hallmark of the syndrome is an increase in intracellular free ionized calcium due to either cellular energy depletion, or direct plasma membrane rupture. The increased intracellular calcium activates several proteases, intensifies skeletal muscle cell contractility, induces mitochondrial dysfunction, and increases the production of reactive oxygen species, ultimately resulting in skeletal muscle cell death [181]. There are multiple potential causes and contributory factors associated with rhabdomyolysis that include trauma, exertion, immobilization, sepsis, hyperthermia, prescribed medications and drugs of abuse, dietary supplements, metabolic poisons such as carbon monoxide, toxins, electrolyte disorders such as hypokalemia and hypophosphatemia, endocrine disorders including diabetes and thyroid diseases, and acute viral infections such as influenza A and B, Coxsackievirus, Epstein-Barr, herpes simplex, parainfluenza, adenovirus, echovirus, HIV, and cytomegalovirus. COVID infections have also been recently associated with rhabdomyolysis.

A relative frequency of the different etiologies among patients with rhabdomyolysis has been reported in series of hospitalized patients demonstrated that up to 60 %of patients had more than one etiologic factor. Underlying myopathy or muscle metabolic defects were seen in 10 % of the cases. No cause was identified in 7 percent of patients [182].

To date, there is no known biological mechanism that could explain how the mRNA vaccine could lead to rhabdomyolysis. Recent publications describe cases of rhabdomyolysis following COVID-19 mRNA or viral vector vaccine administration and noted a possible temporal relationship between vaccine administration and onset of rhabdomyolysis. Ajmera 2021 [178] suggested that patients with autoimmune disease and dysfunctional immune systems could be at risk from

overstimulation from COVID 119 vaccines. Of the cases evaluated as possible many patients did have underlying disorders that have a potential autoimmune component. Although this postulation was given in reference to mRNA vaccines rhabdomyolysis has also been reported after COVID vaccination with non-mRNA vaccines [183]. Various hypotheses were developed to explain the mechanism of vaccine-induced rhabdomyolysis, including the suggestion that statin and fibrate therapy could have led to the development of rhabdomyolysis while the vaccine acted as a trigger [184]. However, other studies [185] found no clinical or laboratory correlation between the influenza vaccine and the development of myopathy in patients taking statins.

Rhabdomyolysis has been linked to COVID infection itself, but the etiology also remains unclear. Of cases identified as myositis, only 12 were considered potential rhabdomyolysis (126 total cases, reporting rate 0.39 cases per 100,000 person-years, observed vs. expected rate ratio 0.37, 95% CI 0.3 – 0.45 compared vs US population-based data [186].

Based on the review of the post-authorization safety reports of rhabdomyolysis and myositis in the safety database and in the literature, including analysis of the observed vs. expected reporting rate for rhabdomyolysis, which was below the background rate including sensitivity analyses when myositis cases were included in the rhabdomyolysis case count, the MAH considers that there is insufficient evidence at this time to establish a causal relationship between SPIKEVAX and rhabdomyolysis.

16.3.6.7.2.6. Conclusion

Based on the analysis of all the safety data received cumulatively as of 31 Dec 2021 of this PBRER, ModernaTX, Inc considers that cases included under the AESI of Rhabdomyolysis, reported in temporal association with the administration of SPIKEVAX, did not raise any safety issue of concern and the information provided is inadequate to provide evidence of causality between SPIKEVAX exposure and Rhabdomyolysis. These data do not represent a new safety issue of concern. ModernaTX, Inc will continue to monitor events for Rhabdomyolysis using routine surveillance. The benefit-risk evaluation remains positive.

16.3.6.7.3. Extensive swelling vaccinated limb

16.3.6.7.3.1. Source of the New Information

Information presented below includes analysis performed on cases received by ModernaTX, Inc. from 01 Jul 2021 to 31 Dec 2021 for the mRNA-1273 vaccine (COVID-19 vaccine Moderna) SPIKEVAX. Cumulatively, the data reviewed covers the period from 18 Dec 2020 to 31 Dec 2021.

ModernaTX, Inc was requested to provide any new additional information received on the 49 cases of Extensive swelling of vaccinated limb (ELS) previously reported in the PBRER covering the

reporting interval (18 Dec 2020 to 30 Jun 2021), and to provide an updated cumulative review of serious cases of ELS reported during this PBRER reporting period (01 Jul 2021 to 31 Dec 2021) according to the directions provided by the health authority.

16.3.6.7.3.2. Background Relevant to the Evaluation

Extensive limb swelling is defined as oedema extending at least to the elbow or knee in a vaccinated limb. A broad range of vaccines have been implicated, with those most frequently cited being the PCV, DTaP, and adult tetanus and diphtheria toxoids (Td) vaccines. In most cases the swelling develops within 24 hours after vaccination and is limited to the proximal half of the extremity. Associated erythema, warmth, or pain is usually reported in more than 70% of cases, and constitutional symptoms such as fever is also reported in around 20% to 25% of the cases [187].

Injection site swelling (or swelling at or near injection site) is defined by Brighton Collaboration [188] as “swelling at or near the injection site, ‘increase in size or volume at the injection site that may extend to the entire limb according to severity.’” “Extensive swelling has also been defined as “local injection site swelling with a diameter over 50 mm, noticeable diffuse injection site swelling, or a noticeably increased circumference of the injected limb.” [Vaccines: In Meyler's Side Effects of Drugs (Sixteenth Edition) [189] In 2003, ‘Extent of limb swelling’ was classified into three groups by Woo EJ, et al. [190] as delineated below. Extensive limb swelling has also been defined as ‘oedema extending at least to the elbow or knee in a vaccinated limb’ [187]. The three distinct classifications defined by Woo EJ, et al. 2003 has been applied in this updated cumulative review.

In the previous PBRER, the MAH identified that the vast majority of the ELS reports came from the Netherlands (90.0%) and from Belgium (5.9%); this was in sharp contrast with the overall reporting of non-ELS adverse events by country following SPIKEVAX administration, with 80.6% of those reports received from the United States, suggesting that factors other than the vaccine itself may be involved.

As explained in the previous PBRER, the MAH investigated possible reasons for this atypical pattern and found a likely explanation, provided by the Netherlands Pharmacovigilance Centre, Lareb [191], who reported that in the period from Jan 6th, 2021 until Feb 16th, 2021 they received 80 reports of extensive limb swelling associated with administration of another mRNA vaccine against SARS COVID-2 disease, Comirnaty. Located in the main country of concern, the Netherlands Pharmacovigilance Centre, Lareb [191], provided in their report an explanation for this unusual finding: ‘The diagnosis ELS was either based on the descriptions used on the reporting form following the selection of “injection site swelling”, “injection site erythema” or both. In case of one of these descriptions is selected, an additional question about the extent of the swelling is

posed. An extensive swelling or erythema is defined by either an extension beyond the elbow and/or shoulder or an extension that is visible at both the inside and the outside of the limb. In case the reporter answers this question with "yes", the MedDRA PT "Extensive swelling of the vaccinated limb" is automatically coded next to the existing MedDRA PT "injection site swelling (29%)", PT "injection site erythema (29%)" or both (42%). Consequently, based on the vaccine adverse event reporting form described by the Netherlands Pharmacovigilance Centre, Lareb, a reporter of injection site swelling whose swelling is "visible at the inside and the outside of the limb" would be coded as the MedDRA PT "Extensive swelling of the vaccinated limb." Such a swelling meeting this criterion could be small compared to what is normally intended by extensive limb swelling.

Prior to the COVID-19 pandemic, FDA & and CDC investigators reviewed reports of extensive limb swelling reported to the FDA/CDC's Vaccine Adverse Event Reporting System (VAERS) [190] and defined 3 levels of extent of limb swelling. The MAH reviewed the narratives of all of the serious adverse events of extensive swelling of vaccinated limb after SPIKEVAX using an adapted case classification, as explained below in the methods section.

16.3.6.7.3.3. Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

ModernaTX, Inc., queried the GSDB, cumulatively and for the reporting period through 31 Dec 2021, for valid case reports received from HCP, HA, consumers, and literature, worldwide, reported for SPIKEVAX. The MedDRA PT 'Extensive swelling of vaccinated limb', was searched to identify case reports of interest.

All serious cases reported to the ModernaTX GSDB were reviewed and classified using a modified version of the case definition used in the publication, "Vaccine Adverse Event Reporting System Working Group. Extensive limb swelling after immunization: reports to the Vaccine Adverse Event Reporting System". For the present analysis, two additional classifications were added: "Not a case" and "Unnassesable", in order to provide a comprehensive review of all the serious cases identified in the search of the database.

Classification of Serious Reports of Extensive Limb Swelling:

1. **"Whole-limb swelling":** Swelling of the entire extremity (i.e., from the hip to the foot or from the shoulder to the hand).
2. **"More-than-proximal (MTP) limb swelling":** Included cases in which the entire proximal segment of the extremity was involved (i.e., from the hip to the knee or the shoulder to the elbow) and the report described swelling in the distal segment without specifying that the swelling extended all the way to the foot or hand.

3. **"Proximal limb swelling":** Swelling from the hip to the knee or from the shoulder to the elbow.
4. **Not a case:** Injection site swelling case reports (excluding those that met the ELS case definition) with coding terms suggesting signs or symptoms at the injection site (injection site reaction and/ or abscess, atrophy, cyst, oedema, granuloma, hemorrhage, vesicle, inflammation, mass, necrosis, or pain at injection site).
5. **Unassessable:** Not enough information to classify the case.

For those cases that are classifiable according to the Woo EJ, et al. [190] definitions, the company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment [146].

- Appendix 20.11.66: includes summary of cumulative and interval serious ELS reports
- Appendix 20.11.67: includes summary of 49 serious ELS reports from the previous PBRER.
- Appendix 20.11.68: includes summary of serious ELS reports meeting ELS case definition.

16.3.6.7.3.4. Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Cumulative Review (ELS, Cumulative to 31 Dec 2021)

Cumulatively, through 31 Dec 2021, a total of 206 serious cases (206 events) were reported with the PT of Extensive swelling of vaccinated limb (ELS) events. There were no cases with reported fatal outcome, and only 22 (10.7%) of the cases were medically confirmed; the rest, 184 (89.3%) were reported by consumers. Most of the events were reported in females (170; 82.5%), with no important differences between the age groups. There were 35 reports from males (17.0%), and one case had missing gender value. Mean age was 42.1 years (SD: 14.4) and the median was 40.0 years old (min: 18.0 / max: 86.0). The distribution of case count by gender and age group is shown in (Table 16-183).

Table 16-183 Number and Percentage of Reported "Extensive swelling of vaccinated limb" Serious Cases by Gender and Age – Cumulative to 31 Dec 2021

Age Group	Female		Male		Unknown		Total # Cases	Total % Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
18-29	37	18.0	5	2.4	0	0	42	20.4
30-39	43	20.9	7	3.4	0	0	50	24.3
40-49	35	17.0	8	3.9	0	0	43	20.9

Age Group	Female		Male		Unknown		Total # Cases	Total % Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
50-64	26	12.6	8	3.9	0	0	34	16.5
65-74	11	5.3	0	0	1	0.5	12	5.8
75+	5	2.4	0	0	0	0	5	2.4
Missing	13	6.3	7	3.4	0	0	20	9.7
Grand total	**170**	**82.5**	**35**	**17.0**	**1**	**0.5**	**206**	**100.0**

Cumulative, the vast majority of the ELS reports continues to be reported from the EEA (205, 99.5%), and more specifically from Belgium (181; 87.9%). (See Table 16-184 and Table 16-185).

Table 16-184 Number and Percentage of Reported "Extensive swelling of vaccinated limb" (ELS) Serious Case reports by Reporting Region. – Cumulative and by Reporting PBRER Interval

Region	PBRER 1 (18 DEC 2020 to 30 Jun 2021)		PBRER 2 (01 Jul to 31 Dec 2021		Total # Cases	% Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases		
European Economic Area	51	24.8	154	74.8	205	99.5
United Kingdom	0	0.0	1	0.5	1	0.5
Grand total	**51**	**24.8**	**155**	**75.2**	**206**	**100.0**

Table 16-185 Number and Percentage of Reported "Extensive limb swelling of vaccinated limb" (ELS) Serious Case reports, by selected Reporting Countries – Cumulative and Reporting PBRER Interval

Country	PBRER 1 (18 DEC 2020 to 30 Jun 2021)		PBRER 2 (01 Jul to 31 Dec 2021)		Total # Cases	% Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases		
BELGIUM	39	18.9	142	68.9	181	87.9
CROATIA	9	4.4	10	4.9	19	9.2
CZECH REPUBLIC	1	0.5	0	0.0	1	0.5
FRANCE	0	0.0	2	1.0	2	1.0
ITALY	1	0.5	0	0.0	1	0.5
NETHERLANDS	1	0.5	0	0.0	1	0.5
UNITED KINGDOM	0	0.0	1	0.5	1	0.5

Country	PBRER 1 (18 DEC 2020 to 30 Jun 2021)		PBRER 2 (01 Jul to 31 Dec 2021)		Total # Cases	% Total Cases
	# Cases	% Total Cases	# Cases	% Total Cases		
Grand total	**51**	**24.8**	**155**	**75.2**	**206**	**100.0**

Children ages < 12 Years (Cumulatively as of 31 Dec 2021)

Cumulatively as of 31 Dec 2021, there were no reports of ELS in children of < 12 years of age.

Adolescents ages 12-17 Years (Cumulatively as of 31 Dec 2021)

Cumulatively as of 31 Dec 2021, there were no reports of ELS in adolescents 12 to 17 years of age.

SPIKEVAX Booster (Cumulatively as of 31 Dec 2021)

Cumulatively, as of 31 Dec 2021, there were 12 serious reports of ELS after a 3rd dose of SPIKEVAX. All 12 reports were in females, between 18 to 70 years of age, with no differences between the age groups, with a mean of 44.6 (SD: 16.9) and a median of 44 years old (min: 26.0/max 70.0). All 12 reports were received from Belgium. Those 12 reports after a booster were received during the current reporting period. (See Appendix 20.11.67).

Reporting Period Review 01 Jul to 31 Dec 2021

During the reporting period there were 155 serious cases (155 events) reported with the PT of Extensive swelling of vaccinated limb (ELS) events. There were no cases with reported fatal outcome, and only 11 (7.1%) of the cases were medically confirmed; the rest, 144 (92.9%) were reported by consumers. Most of the events were reported in females (134; 86.5%), with no important differences between the age groups. There were 21 reports from males (13.5%).

During the reporting period of this PBRER, the previously observed trending continued of having all but one of the serious reports of ELS coming from the EEA (154, 99.4%), and more specifically from Belgium (142; 91.6%) where the main language is also Dutch. (See above Table 16-184 and Table 16-185).

Children ages < 12 Years (Reporting Period 01 Jul to 31 Dec 2021)

There were no reports of ELS during the reporting period in children of < 12 years of age during the reporting period (01 Jul to 31 Dec 2021.

Adolescents ages 12-17 Years (Reporting Period 01 Jul to 31 Dec 2021)

There were no reports of ELS during the reporting period in adolescents 12 to 17 years of age during the reporting period (01 Jul to 31 Dec 2021.

SPIKEVAX Booster (Reporting Period 01 Jul to 31 Dec 2021)

Cumulatively, as of 31 Dec 2021, there were 12 serious reports of ELS after a 3rd dose of SPIKEVAX. All 12 reports were in females, between 18 to 70 years of age, with no differences between the age groups, with a mean of 44.6 (SD: 16.9) and a median of 44 years old (min: 26.0 / max 70.0). All 12 reports were received from Belgium.

Extensive Limb Swelling After Vaccination Case Classification

Previous PBRER Serious Cases Review

A review of the 49 serious cases of ELS reported during the previous PBRER (18 DEC 2020 to 30 Jun 2021) showed that there were 35 from female, 13 from males, and 1 with unknown gender. Ages were between 20 to 86 years old, and 38 reports (77,5%) were from Belgium, 8 from Croatia (16.3%), and one each from Italy, The Netherlands, and the Czech Republic. (See Appendix 20.11.67).

According to the implemented case classification, there was one case report classified as Group 1-Whole Limb Swelling, on a consumer report from Croatia:

4.1(b) : (WW ID: 4.1(b)): Consumer report for a 38-year-old female with unknown medical history who same day after an unknown dose of SPIKEVAX experienced swelling of her arm reported to be from “her left arm, from her fist to her shoulder was swollen”. The next day she reported to have swollen of her face, including her eyelids, and feeling like her face "was falling". Event was reported as resolving. No other information was provided.

Company assessment: Important information is missing in the report including patient’s medical history as well as medical evaluation of the events, any laboratory test, or diagnostic test conducted, including testing for SARS-CoV-2. Follow-up information received included English translation and batch number but no other additional information. According to the Woo-classification this case is group 1 - “Whole-limb swelling” Swelling of the entire extremity (from the shoulder to the hand), unfortunately this is a consumer report with no clinical confirmation. According to the WHO causality assessment this report is conditional due to the lack of information that preclude the ability to conduct an educated assessment; a causal relationship cannot be excluded due to the lack of information.

Of the other 48 reports, 47 were classified as group 4, Not a case of ELS, as these cases based on the information presented in the reports represent more cases of Injection site swelling --- reports have coding terms suggesting signs or symptoms at the injection site (injection site reaction and/ or abscess, oedema, inflammation, mass, induration, or pain very much localized at the injection

site). There was also 1 case that was classified as group 5, Unnassessable, given that there was not enough information available to assess the case. (See Appendix 20.11.67).

According to the WHO causality assessment there was 1 conditional case due to the lack of information available for the report; there was 1 report considered unassessable due to the lack of information, including detailed symptoms. There were 47 cases that, according to the WHO causality assessment, were not considered an ELS case (Group 4). (See Appendix 20.11.67).

Reporting Period PBRER Serious Cases Review

During this reporting period there were 3 serious cases classified as Group 3 – ***Proximal limb swelling***. Two of the reports were from Belgium and one from Croatia. All three reports were from females between 43 and 56 years of age. All 3 reports were consumers reports that were not medically confirmed. Two were assessed as conditional and one as possible according to the WHO-UMC causality assessment. (See Appendix 20.11.68).

16.3.6.7.3.5. Discussion

The MAH conducted an updated review of serious cases reported under the PT of "Extensive swelling vaccinated limb" to the ModernaTX. Inc., GSDB for the reporting interval of this PBRER (01 Jul to 31 Dec 2021). There were 155 serious cases that were identified and evaluated. For clinical case classification an adapted version of the Woo et. al ELS classification was used, yielding 1 report identified as group 1 – whole limb swelling (from the shoulder to the hand); and 3 reports as group 3 – proximal limb swelling (from the shoulder to the elbow). All 4 reports were consumer reports, and none were medically confirmed.

As it was described in the cumulative review that was performed during the previous PBRER (reporting period 18 Dec 2020 to 30 Jun 2021), there is an observed trend in the reporting of these reports that suggest there are reasons other than vaccine exposure to explain the number of reports received under the PT of excessive swelling of vaccinated limb. As mentioned above under the overview of cases, during the reporting period of this PBRER, the previously observed trending continued of having all but one of the serious reports of ELS coming from the EEA (154, 99.4%), and more specifically from Belgium (142; 91.6%).

As it was explained under the background information for this analysis, The Netherlands Pharmacovigilance Centre, Lareb, provided an explanation for this unusual finding: 'The diagnosis ELS [extensive limb swelling] was either based on the descriptions used on the reporting form following the selection of "injection site swelling", "injection site erythema" or both. In case of one of these descriptions is selected, an additional question about the extent of the swelling is posed. An extensive swelling or erythema is defined by either an extension beyond the elbow and/or shoulder or an extension that is visible at both the inside and the outside of the limb. In case

the reporter answers this question with “yes”, the MedDRA PT “Extensive swelling of the vaccinated limb” is automatically coded next to the existing MedDRA PT “injection site swelling (29%)”, PT “injection site erythema (29%)” or both (42%).’

Consequently, based on the vaccine adverse event reporting form described by the Netherlands Pharmacovigilance Centre, Lareb, a reporter of injection site swelling whose swelling is “visible at the inside and the outside of the limb” would be coded as the MedDRA PT “Extensive swelling of the vaccinated limb.” Such a swelling meeting this criterion alone would not meet the definitions of extensive limb swelling noted above.

Evaluation of the 206 serious reports cumulative reported to the ModernatTX Inc., GSDB, with the exception of the 4 consumer reports for which they provided additional details indicating that there was swelling, redness, and in some instance, warmth extending further (without any measurement) up to the elbow or hand, all other reports provided more indications of representing injection site reactions.

Taken together, the above information suggests that the reports of “Extensive swelling of vaccinated limb” following SPIKEVAX are in large part explained by reporting artifact associated with the system of the Netherlands Pharmacovigilance Centre, *Lareb.*

Given that injection site swelling is already a labelled event in the product information for SPIKEVAX, the MAH does not find evidence at this time that will require updating the product information.

16.3.6.7.3.6. Conclusion

After careful review of all new safety data received during the reporting period of this PBRER for extensive swelling of vaccinated limb, ModernaTX, Inc., considers that ELS is not presently a safety issue of concern, and the benefit-risk profile for SPIKEVAX remains favorable. The MAH will continue to monitor events of ELS using routine surveillance. The benefit-risk evaluation remains positive.

16.3.6.7.4. Glomerulonephritis and Nephrotic Syndrome

16.3.6.7.4.1. Source of the New Information

Information presented below includes analysis performed on cases received by ModernaTX, Inc., for the Cumulative period for the mRNA-1273 vaccine (COVID-19 vaccine Moderna) SPIKEVAX. Cumulatively, the data reviewed covers the period from 18 Dec 2020 to 31 Dec 2021.

16.3.6.7.4.2. Background Relevant to the Evaluation

Nephrotic Syndrome can be clinically defined as a triad of 1) proteinuria greater than 3.5g/24h/1.73m^2, 2) hypoalbuminemia of less than 2.5g/dl, 3) oedema. Hyperlipidemia often also occurs. Many underlying systemic conditions can cause nephrotic syndrome, including commonly type 2 diabetes mellitus and systemic lupus erythematosus. Other causes include various autoimmune diseases, cancers, medications (including NSAIDS), infections and hypertension.

Glomerulonephritis denotes damage to the glomeruli, the tiny filters inside the kidneys. It is often caused by the immune system attacking healthy body tissue. Glomerulonephritis often does not cause any noticeable symptoms and is diagnosed when blood or urine tests are carried out for another reason. In other instances, disease can become apparent due to dark or bloody urine, swelling/oedema in the legs or in other areas, with weight gain, fatigue, etc. A normal capillary in a glomerulus keeps red blood cells, white blood cells and most proteins in the blood and only lets watery fluid into the urine. A capillary in a diseased glomerulus can let protein into urine (proteinuria) and red blood cells into the urine (hematuria).

Glomerulonephritis can be caused by multiple disease processes, including:

- Infectious:

  Post-streptococcal glomerulonephritis. May develop a week or two after recovery from a strep throat infection or, rarely, a skin infection (impetigo) or bacterial endocarditis.

- Autoimmune Diseases:

  Lupus: A chronic inflammatory disease, lupus can affect many parts of your body, including your skin, joints, kidneys, blood cells, heart and lungs.

  Goodpasture's syndrome. A rare immunological lung disorder that can mimic pneumonia, Goodpasture's syndrome causes bleeding in the lungs as well as glomerulonephritis.

  IgA nephropathy. With recurrent episodes of blood in the urine (macroscopic or microscopic) this primary glomerular disease results from deposits of immune complexes with immunoglobulin A (IgA) in the glomeruli.

  IgA nephropathy can progress for years with no noticeable symptoms.

- Vasculitis:

  Polyarteritis. This form of vasculitis affects small and medium blood vessels in many parts of your body, such as your heart, kidneys and intestines.

  Granulomatosis with polyangiitis. Wegener’s granulomatosis affects small and medium blood vessels in your lungs, upper airways and kidneys.

- Other:
    - Hypertension
    - Diabetes
    - Focal segmental glomerulosclerosis

16.3.6.7.4.3. Methods of Evaluation including Data Sources, Search Criteria and Analytical Approaches

The MAH queried the GSDB, cumulatively and for the reporting period through 31 Dec 2021, for valid case reports received from HCP, HA, consumers, and literature, worldwide, reported for SPIKEVAX. The search strategy included using the following MedDRA HLT glomerulonephritis and nephrotic syndrome. Following are the preferred terms within this MedDRA HLT: Alagille syndrome, Alport's syndrome, Anti-LRP2 nephropathy, Anti-glomerular basement membrane disease, Benign familial hematuria, C1q nephropathy, C3 glomerulopathy, Chronic autoimmune glomerulonephritis, Congenital nephrotic syndrome, Denys-Drash syndrome, Fibrillary glomerulonephritis, Focal segmental glomerulosclerosis, Frasier syndrome, Glomerulonephritis, Glomerulonephritis acute, Glomerulonephritis chronic, Glomerulonephritis membranoproliferative, Glomerulonephritis membranous, Glomerulonephritis minimal lesion, Glomerulonephritis proliferative, Glomerulonephritis rapidly progressive, Goodpasture's syndrome, Granulomatosis with polyangiitis, HIV associated nephropathy, Henoch-Schonlein purpura nephritis, Hepatitis virus-associated nephropathy, IgA nephropathy, IgM nephropathy, Immunotactoid glomerulonephritis, Membranous-like glomerulopathy with masked IgG-kappa deposits, Mesangiolipidosis, Mesangioproliferative glomerulonephritis, Microscopic polyangiitis, Nephritic syndrome, Nephritis allergic, Nephrotic syndrome, Paraneoplastic glomerulonephritis, Paraneoplastic nephrotic syndrome, Post infection glomerulonephritis, Post streptococcal glomerulonephritis, Primary coenzyme Q10 deficiency and Pulmonary renal syndrome.

- Appendix 20.11.69: Cumulative reports of Glomerulonephritis and Nephrotic Syndrome with Case Assessment and WHO Causality information.

16.3.6.7.4.4. Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Observed to Expected

See Appendix 20.11.3.

Overview of Cumulative Cases:

Cumulatively (18 Dec 2020 to 31 Dec 2021), there were 101 cases reported for glomerulonephritis and nephrotic syndrome (120 events), 88 were medically confirmed and 97/101 cases were serious.

Higher proportions of the cases were reported in males (56; 55.4%) compared to females (41; 40.6%). The majority of the reports were for patients ≥40 years of age (60; 59.4%) (Table 16-186). The mean age was 48.1 (SD 20.2), the median 48.0 with an age range of 13 to 100 years.

Table 16-186 Number and Percentage of Spontaneous Cases of Glomerulonephritis and Nephrotic syndrome Reported by Age and Gender for the SPIKEVAX. Cumulative to 31 Dec 2021

Age Group	Female		Male		Unknown		Grand total of # Cases	Grand total of % of Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases	# Cases	% of Total Cases		
12-15	1	1.0	0	0	0	0	1	1.0
18-29	7	6.9	15	14.9	1	1.0	23	22.8
30-39	6	5.9	6	5.9	0	0	12	11.9
40-49	7	6.9	7	6.9	0	0	14	13.9
50-64	9	8.9	12	11.9	0	0	21	20.8
65-74	5	5.0	8	7.9	0	0	13	12.9
75+	4	4.0	8	7.9	0	0	12	11.9
Missing	2	2.0	0	0	3	3.0	5	5.0
Grand total	41	40.6	56	55.4	4	4.0	101	100.0

Time to onset of the events averaged 21.3 days (SD 43.6), with median of 7 days (0-243). The events are reported slightly more frequent after the 2nd dose (33; 27.5%) than the 1st dose (21; 17.5%). There was 1 case reported in a patient that received a 3rd dose or booster vaccine. There were 65 events with missing TTO (Table 16-187).

Table 16-187 Time to Onset by Dose Number as of 31 Dec 2021

Dose Number	TTO All Doses (Days)	# Events	% Events
Dose 1	Subtotal	21	17.5%
	0 days	2	1.7%
	01-02	6	5.0%
	03-04	3	2.5%
	07-13	4	3.3%
	14-29	5	4.2%
	30+	1	0.8%
Dose 2	Subtotal	33	27.5%
	0 days	2	1.7%

Dose Number	TTO All Doses (Days)	# Events	% Events
	01-02	10	8.3%
	03-04	1	0.8%
	05-06	2	1.7%
	07-13	4	3.3%
	14-29	5	4.2%
	30+	9	7.5%
Dose 3	Subtotal	1	0.8%
	01-02	1	0.8%
Unknown	Subtotal	65	54.2%
	Missing	65	54.2%
Grand total		**120**	**100.0%**

The largest proportion of the reported events had the PT IgA nephropathy (35; 29.2%), followed by Nephrotic syndrome (28; 23.3%). (See Table 16-188).

Table 16-188 Number and Percentage of Nephrotic syndrome Related-Terms ≥ 2% by PT – Cumulative to 31 Dec 2021

PT	# of Events	% of Total Events
IgA nephropathy	35	29.2
Nephrotic syndrome	28	23.3
Glomerulonephritis	16	13.3
Glomerulonephritis minimal lesion	12	10.0
Glomerulonephritis membranous	8	6.7
Glomerulonephritis rapidly progressive	8	6.7
Anti-glomerular basement membrane disease	4	3.3
Focal segmental glomerulosclerosis	3	2.5

The largest proportion of the reported events had at the time of the report an outcome of unknown (50; 41.7%), followed by not recovered/not resolved (41; 34.2%). (See Table 16-189).

Table 16-189 Number and Percentage of Nephrotic syndrome by Outcome – Cumulative to 31 Dec 2021

Event Outcome	Total of # Events	% Total Events
Not Recovered/Not Resolved	41	34.2
Recovered/Resolved	8	6.7
Recovered/Resolved with Sequelae	4	3.3
Recovering/Resolving	17	14.2
Unknown	50	41.7

Grand total	120	100.0

The sources of the reports are mostly from Regulatory Authorities (58; 57.4%); the reports come most commonly from the USA (56; 55.4%), followed by EEA (20;19.8%) (Table 16-190).

Table 16-190 Number and Percentage of Nephrotic syndrome by Region – Cumulative to 31 Dec 2021

Region	Total of # Cases	Total % of Cases
Asia	12	11.9
European Economic Area	20	19.8
Middle East	2	2.0
Switzerland	9	8.9
United Kingdom	2	2.0
United States	56	55.4
Grand total	**101**	**100.0**

Description of Fatal Cases:

There were no fatalities reported for the topic of glomerulonephritis and nephrotic syndrome.

Assessment of Cases using WHO-UMC Causality:

Causality assessment per WHO-UMC criteria was performed cumulatively for the 101 cases and is presented, with justification, for individual cases in a tabulated format in Appendix 20.11.69. Of the 101 cases received cumulatively, a total of 69 cases were assessed as WHO-UMC Possible (largely based on temporal association with lack of reported other antecedent possible triggers for glomerulonephritis and nephrotic syndrome); 11 cases were assessed as Conditional, needing more data for proper assessment; 8 cases were Unlikely to be vaccine-related: and 10 cases were Unassessable due to lack of information. Additionally, 3 cases were considered invalid based on the 'Main Diagnosis'. Please note there are 2 cases (4.1(b) and 4.1(b)) which are duplicates, and the company case management team has been notified to delete those cases (Appendix 20.11.69).

Clinical Trial data Review:

The topic of Glomerulonephritis and nephrotic syndrome was cumulatively searched in the MAH's P301 study clinical database with a data lock point (DLP) of 04 May 2021, using the MedDRA v 24.1 HLT 'Glomerulonephritis and Nephrotic Syndrome.' Zero cases were observed.

Literature Review:

A literature search was performed as of 31 Dec 2021 using PubMed, with the following criteria of IgA nephropathy OR Glomerulonephritis OR Glomerulonephritis rapidly progressive OR

Nephrotic syndrome OR Nephritic syndrome OR Glomerulonephritis membranous OR Goodpasture's syndrome OR Glomerulonephritis minimal lesion OR Glomerulonephritis acute OR Antiglomerular basement membrane disease OR Haematuria OR body aches OR headache OR fatigue OR fever OR Chills AND mRNA COVID vaccination or mRNA-1273 or "mRNA 1273" or mRNA1273 or "Modernatx 1273" or "moderntx 1273" or "Moderna Covid19 Vaccine" or SPIKEVAX.

There was a small number of case reports or case series describing temporal associations between Glomerulonephritis and nephrotic syndrome and COVID-19 vaccines, including mRNA vaccines. There are no pathognomonic signs or symptoms to link a vaccine with an individual case of Glomerulonephritis and Nephrotic Syndrome.

Subpopulation Analyses

Adolescents ages 12-17 Years (Cumulatively as of 31 Dec 2021)

Cumulatively as of 31 Dec 2021 there was one case reported in an adolescent (12-17 Years) that is described below.

4.1(b) **:** A 13-year-old female on the day of vaccination with dose 1 experienced IgA nephropathy, post infection glomerulonephritis, pollakiuria (frequent urination), dysuria, proteinuria, myalgia, headache and hematuria that were resolving at the time of the report. No other information was provided. Onset of IgA Nephropathy in teenagers is not atypical. WHO Causality assessment: Conditional, because of the lack of information on the infection that led to "post infection glomerulonephritis", lack of clinical details and no further information on the timing of the adverse event on the day of vaccination with dose 1, which is an extremely short time to onset.

SPIKEVAX Booster (Cumulatively as of 31 Dec 2021)

Cumulatively as of 31 Dec 2021 there was one case (4.1(b)) of Nephrotic syndrome-related events reported after a booster dose that is described below.

4.1(b) **:** This case involves a 35-year-old female with a history of kidney transplant in 1999, breast cancer since 2019 and penicillin allergy. She was being treated with Cyclosporine, cellcept, prednisone, and tamoxifen. Within a day following the third SPIKEVAX dose the patient developed gross hematuria that led to a biopsy finding of IgA glomerulonephritis, followed by two hospitalizations. She was treated with IVIG and high dose steroids. Bladder-related causes were ruled out. **MAH Assessment:** This case shows a temporal association with hematuria and is therefore categorized for WHO Causality as Possible. However, IgA Nephropathy is typically an undiagnosed latent condition over a long period of time with no or few clinical features. Thus, IgA deposition likely had occurred for an extended period before the adverse event. The reason for the

pre-existing kidney transplant was not described and may be relevant to the current illness. This case is also confounded by breast cancer and cyclosporine use, which can be nephrotoxic.

Cases that Received Dialysis (Cumulatively as of 31 Dec 2021)

Cumulatively there have been five cases that received dialysis for renal failure. All of them had information suggesting that pre-existing illness may have played an important role in the renal failure. Four of the cases were classified according to WHO Causality as Possible and one was Unlikely. These cases were clinically heterogenous in their glomerular diagnostic findings, including crescentic depositions of IgA & anti-GBM in 4.1(b), anti-neutrophil cytoplasmic autoantibody (ANCA) pauci-immune necrotizing and crescentic glomerulonephritis with antibodies to PR3+ in 4.1(b), glomerular minimal change disease in 4.1(b), pauci-immune glomerulonephritis in 4.1(b), and IgA nephropathy and tubular necrosis in 4.1(b). Two of the cases followed dose 1, and three cases followed dose 2. The above heterogeneity does not support a common vaccine-related pathogenesis of these cases, which are summarized below.

4.1(b): This literature case was reported by pathologists (not nephrologists) and focuses on pathologic rather than clinical findings [192]. The short clinical and pathological summary of this case follows:

"The patient is an older [age not specified] woman with previously normal renal function and no significant past medical history, prior coronavirus disease 2019 (COVID-19) infection, or medication use, who developed fevers, anorexia, nausea, and gross hematuria 2 weeks after receiving the second dose of the Moderna SARS-CoV-2 vaccine. Symptoms lasted 2 weeks, and she presented with acute kidney injury (peak creatinine, 7.8 mg/dl), a urine protein-to-creatinine ratio of 1.9 g/g, and active urinary sediment. Serologic evaluation revealed a positive anti-GBM; ANCA, ANA, anti–double stranded DNA, complements, serum and urine protein electrophoresis, hepatitis C virus, hepatitis B virus, and HIV were negative. SARS-CoV-2 was negative by polymerase chain reaction, and blood and urine cultures were negative. Testing for anti–SARS-CoV-2 antibodies was not performed. Kidney biopsy revealed a diffusely crescentic glomerulonephritis, with 100% active cellular crescents and no significant chronic injury. Immunofluorescence showed linear staining of GBMs for IgG (3+), and granular mesangial staining for IgA (2–3+), with associated rare mesangial deposits by electron microscopy. There was no clinical evidence of pulmonary involvement. She was treated with methylprednisolone, Cytoxan, plasmapheresis, and hemodialysis, and she remains dialysis-dependent."

MAH comment: The presence of IgA suggests that IgA vasculitic processes may have preceded SPIKEVAX vaccination. More clinical details and medical history would be helpful to understand

better this serious case involving anti-GBM. We categorized this case as WHO-UMC causality "Possible."

4.1(b) **:** This is a literature case [192] concerning a 52-year-old male with hypertension treated with amlodipine. Two weeks after the second dose the patient presented with headache and weakness. On the basis of serologic and biopsy findings, he was diagnosed with ANCA pauci-immune necrotizing and crescentic glomerulonephritis with antibodies to PR3+. The patient remained dialysis dependent at the time of report.

MAH Comment: based on the temporal association, this case is WHO Causality: Possible.

With respect to the MAH comment for 3 below mentioned cases, kindly refer to Appendix 20.11.69.

4.1(b) **:** This case concerns a 65-year-old male with collagenous colitis who drinks three glasses of wine daily. Medications include budesonide. Eight days after dose 1 he experienced nephrotic syndrome with oedema, hypoalbuminemia and hypercholesterolemia. He underwent temporary dialysis and prednisone treatment. Kidney biopsy indicated glomerular minimal change disease. At the time of report the problem had not resolved. MAH Comment: Because of the temporal association, this case is considered WHO Causality Possible; however, the patient's autoimmune tendency, as evidence by his collagenous colitis, may be a confounder.

4.1(b) **:** This case involves an 80-year-old male with concurrent hypertension, diabetes mellitus and a history of gout. Two to three days after dose 2 he experienced pauci-immune glomerulonephritis/rapidly progressive glomerulonephritis and underwent emergent hemolysis. Other treatment of the glomerulonephritis not reported. At the time of report, the illness had resolved. MAH Comment: This case is classified as WHO Causality Possible due to the temporal association. Hypertension and diabetes can have deleterious effects on renal function and are confounders.

4.1(b) **:** This case concerns a 55-year-old male whose concurrent medical conditions include chronic hepatitis B, hyperlipidemia, hyperuricemia and erythrocytosis. Medications include entecavir for chronic hepatitis B. Forty-one days after dose 1 the patient experienced seizure, atrial fibrillation and altered state of consciousness. Forty-six days after dose 1, he experienced renal failure. Fifty days after dose 1, he was diagnosed with IgA nephropathy and tubular necrosis with elevated blood IgA. Blood IgG complement factor C3 and C4 were also reported as abnormal. The medical issues were resolving at the time of report. MAH Comment: Given the long time to onset from dose 1, the potential confounding by entecavir (renal toxicity reported in clinical trial), by hyperuricemia and by hepatitis B infection, WHO Causality assessment is Unlikely.

16.3.6.7.4.5. Discussion

The MAH evaluated spontaneous case reports supplemented by literature case reports to determine patterns or trends among all reports. There were 101 cases (120 events) with glomerulonephritis or nephrotic syndrome. Thirty-five were hospitalized. Five patients, with heterogeneous kidney biopsy results, were reported to have been treated with dialysis. There were no deaths reported.

Cases were evaluated using the WHO-UMC causality assessment. There were 69 cases evaluated as possible, 10 not assessable, 11 Conditional and 8 unlikely and 3 were not valid cases. The last dose of SPIKEVAX before onset of disease was, for those with reported information, dose 1 for 21 events, dose 2 for 33 events and dose 3 for one event; the larger number after dose 2 is mostly attributed to 9 events with TTO 30+ days after vaccination for the second dose, which has greater follow-up time than dose 1 because nearly all persons receiving dose 1 get their second dose around 28 days later and thus have no subsequent dose 1 follow-up time.

There is no pathognomonic sign to indicate a causal association between a vaccine and glomerulonephritis or nephrotic syndrome. In addition, this association has not been shown in any clinical trial, controlled observational study or pharmaco-epidemiological study. Further complicating the assessment is the fact that the normal natural history of the diseases in question is of the relapsing/remitting type. The exact causes of such relapses, or de novo disease, are rarely known. Infections of different types and some other exposures are listed as possible precipitants of relapses; however, there is not any certainty of relapse following an infection or other exposure. Thus, an infection around the time of vaccination, or vaccination itself, cannot be assumed to be a certain cause of glomerulonephritis or nephrotic syndrome. For the above reasons, the MAH generally classified cases that had a temporal association with vaccination, whether or not there were possible confounders, as having a “possible” causal association.

There was substantial heterogeneity in the diagnostic types and numbers of cases reported, with the most commonly reported: IgA nephropathy (35 cases), nephrotic syndrome (28), glomerulonephritis (16), glomerulonephritis minimal lesion (12), glomerulonephritis membranous (8) and glomerulonephritis rapidly progressive (8) as noted in Table 16-188. Consistent with this order of diagnoses by case counts, Ig A nephropathy is estimated to be the most common cause of primary glomerulonephritis in the general population. Further, similar to the heterogeneity in diagnoses, the heterogeneity of the pathological findings among the dialysis cases detailed above, as well as the heterogeneity in dose number and time to onset among all the cases, do not support a common vaccine-related pathogenesis. Moreover, the observed to expected analysis did not identify an excess of observed over expected cases.

16.3.6.7.4.6. Conclusion

After careful review of cumulative safety data as of 31 Dec 2021 for the risk of Glomerulonephritis and Nephrotic Syndrome, the benefit-risk profile for SPIKEVAX remains favorable. The risk of Glomerulonephritis and Nephrotic Syndrome will continue to be monitored carefully using the routine pharmacovigilance measures implemented for SPIKEVAX.

16.3.6.7.5. Polymyalgia Rheumatica and exacerbation or flare-up (Move to Other Disorders)

16.3.6.7.5.1. Source of the New Information

Information presented below includes analysis performed on cases received by ModernaTX, Inc. from 18 Dec 2021 to 31 Dec 2021 for the mRNA-1273 vaccine (COVID-19 vaccine Moderna) SPIKEVAX.

16.3.6.7.5.2. Background Relevant to the Evaluation

The PRAC requested the MAH to perform a cumulative review on the association between SPIKEVAX and Polymyalgia rheumatica (PMR), and exacerbation or flare-up thereof.

PMR is a common inflammatory rheumatic disease in older adults. It is clinically characterized by a sudden bilateral shoulder and hip pain, sometimes accompanied with neck aching, and a morning stiffness lasting > 45 minutes [193]. Additionally, patients with PMR can experience nonspecific systemic signs or symptoms, including malaise, fatigue, depression, anorexia, weight loss, and low-grade fever. Cases may be self-limiting and may relapse in association with viral infections and vaccinations [193]. PMR is characterized by an elevation of acute phase reactants such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) [81]. The treatment of choice is low-dose prednisone or prednisolone as the therapeutic response is prompt and typically complete or near-complete. [194]. Failure to respond to low dose prednisone should prompt a review of the diagnosis. There are other diseases in older adults which may mimic PMR. [193] These include Rheumatoid arthritis, remitting seronegative symmetrical synovitis with pitting oedema, Late onset inflammatory spondyloarthropathies including ankylosing spondylitis and psoriatic arthritis, Idiopathic inflammatory myopathies, Late-onset systemic lupus erythematosus, scleroderma, Sjogren's syndrome, vasculitis Idiopathic inflammatory arthropathies, Scapulohumeral periarthritis and adhesive capsulitis, Calcium pyrophosphate deposition disease, Paraneoplastic syndromes. These conditions may mimic PMR leading to diagnostic uncertainty as no specific laboratory tests are available although inflammatory markers ESR, CRP and IL6 may be raised and can aid diagnosis [193]. Immune-mediated disease flares or new-onset inflammatory disease following mRNA/DNA SARS-CoV-2 vaccination has been reported in the literature. [81].

16.3.6.7.5.3. Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

Identification of Case Reports of PMR in Moderna GSDB:

The MAH queried the GSDB, cumulatively, for valid case reports received from HCP, HA, consumers, and literature, worldwide, reported for SPIKEVAX. The search strategy included the MedDRA PT "Polymyalgia Rheumatica".

PMR is usually a clinical diagnosis and does not have an established algorithm to confirm diagnostic validity [195], [196]. To characterize the level of diagnostic certainty, all cases identified were medically reviewed and classified using the European Alliance of Associations for Rheumatology (EULAR) disease definition [197], adapted by the MAH, and this is further described below. The EULAR disease definition of PMR [194] includes the following criteria required for the clinical diagnosis:

Age 50 years or older at disease onset bilateral shoulder and/or pelvic girdle aching (lasting longer than 45 minutes) persisting for at least two weeks. The stiffness should involve at least two of the following three areas: neck or torso, shoulders or proximal regions of the arms, and hips or proximal aspects of the thighs

Elevated acute phase reactants (e.g., ESR and/or CRP) rapid resolution of symptoms with low-dose glucocorticoids (e.g., prednisone 15 to 25 mg/day or its equivalent).

The EULAR case definition for PMR includes only 2 categories: "Yes" and "No", however these binary categories do not fully allow for the assessment of diagnostic validity from ICSRs received by the MAH. As the cases were regulatory agency reports and spontaneous reports, they often contain incomplete information with limited ability to obtain additional information on querying. For this reason, the MAH added an additional category of "Incomplete Information" to the EULAR categories of "Yes" and "No" to provide a more accurate estimation of diagnostic validity and to take into account all information. However, to reduce bias from incorrect classification, cases from consumers or regulatory agencies were included as "Yes" if they contained reference to a confirmed diagnosis of PMR from a rheumatologist or from a hospital discharge summary. Such cases were categorized as "Yes", as were all cases with a history of PMR, those reporting flares and those cases reporting giant cell arteritis (GCA) even in the absence of all the criteria required by EULAR for clinical diagnosis. Of note, these diagnostic categories do not imply causality. The MAH adapted version of the EULAR case definition therefore divided cases into 3 categories:

Yes: Case provides diagnostic certainty by meeting all EULAR case criteria

Incomplete: Case meets insufficient number (<4) of EULAR case criteria to establish diagnostic certainty

No: Case whereby none or only one of the EULAR case criteria were met but the reported PT is PMR.

Following case classification, cases of PMR were classified as follows:

Flare/Aggravated: Cases with a reported history of PMR in patients who develop new onset symptoms (representing a flare), and other cases representing flare where symptoms might be worsened (aggravated) following the second or third dose of the vaccine.

New onset: Cases with a new diagnosis

For those cases that have been classified according to the EULAR case definition, the company causality assessment is provided utilizing the WHO-UMC standardized case causality assessment [54].

Appendix 20.11.70: includes an overview of Flare/Aggravated and New Onset PMR cases with case summaries and company comments.

16.3.6.7.5.4. Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Observed vs. Expected

See Appendix 20.11.3.

Epidemiological data was analyzed to calculate observed to expected event frequencies. The data was further analyzed by stratifying age, gender and age by gender. Overall, no increased frequency was observed in any of the above categories. PMR was reported in 151 cases cumulatively (reporting rate 0.56 per 100,000 person- years). The cumulative reporting rate was below US based estimates, which suggest an expected incidence of 95.90 per 100,000 person-years (25,738 cases expected, rate ratio 0.01 (0.00, 0.01) based on reference estimate, Partington, 2018). For the review period, there were 80 cases reported (reporting rate of 0.49 per 100,000 person-years). No subgroups showed a reporting rate that exceeded the expected incidence. The sensitivity analysis that assumes the capture of 50% and 25% of the cases in the stratified reporting rates did not meaningfully change the interpretation of the results.

Overview of Cases

Cumulative Review (PMR, cumulative to 31 Dec 2021)

Clinical Trial Data:

Clinical trial data from study mRNA-1273-P301 found that, as of 4 May 2021, no cases of PMR had been reported in subjects treated with mRNA-1273. One subject in the placebo arm experienced PMR.

Post-Authorization Data:

Cumulatively, through 31 Dec 2021, a total of 151 cases were reported that included the PT of PMR. There were 138 serious cases and zero cases with a fatal outcome. Of the 151 cases, 110 cases were medically confirmed. There were 67 cases (44.4%) involving male patients and 84 (55.6%) cases involving female patients. The majority of cases were reported by Regulatory Authorities (75.5%) the remainder were spontaneous reports (24.5%).

The majority of the cases (n=142, 94.0%) reported were for patients 50 years of age or older, which is consistent with the age of 50 years or older being a risk factor for the development of PMR [194]. The median age was 70 years (min: 42 years / max: 92 years) in keeping with the known age distribution. (Table 16-191).

Table 16-191 Age/Gender Distribution for PMR Cases, Cumulative

Age Group	Female		Male		Total # Cases	Total % Cases
	# Cases	% Total Cases	# Cases	% Total Cases		
40-49	4	2.6%	1	0.7%	5	3.3%
50-64	9	6.0%	15	9.9%	24	15.9%
65-74	31	20.5%	34	22.5%	65	43.0%
75+	37	24.5%	16	10.6%	53	35.1%
Missing	3	2.0%	1	0.7%	4	2.6%
Grand total	**84**	**55.6%**	**67**	**44.4%**	**151**	**100.0%**

SPIKEVAX Booster (Cumulatively as of 31 Dec 2021)

Cumulatively as of 31 Dec 2021 there was one serious case of PMR reported in a 75-year-old female one week after receiving Dose 3 of SPIKEVAX.

EULAR Case Definition Classification

Following evaluation of the 151 cases of post-EUA events of PMR using the MAH modified version of the EULAR case definition [194], 33 reports (21.9%) were classified as "Yes" and 43 reports were classified as "Incomplete" (28.5%) (See Appendix 20.11.70). Seventy-five (49.7%) reports were classified as "No" and these reports will not be further described as part of this assessment.

The remainder of the analysis will firstly focus on reports of PMR in patients with a reported history of PMR that represent flares or conditions aggregated. The second part of the analysis will focus on reports of PMR in patients with no reported history of PMR that represent cases of new onset.

Polymyalgia rheumatica with history of PMR (flares or conditions aggravated)

Cumulatively, 16 cases of PMR were medically assessed by the MAH as flares or conditions

aggravated, of which 15 cases were serious and met the serious criteria of "medically significant"; there were no life-threatening events or hospitalizations. Ten cases were medically confirmed. Of the 16 cases, 14 (87.5%) met the EULAR case definition of "Yes", and 2 (12.5%) cases met the case definition of "Incomplete". None of the 16 cases included reports of GCA.

Nine cases (56.3%) were in females and 7 cases (43.8%) were in males. The median age was 71 years (min: 56 years, max: 91 years). The distribution of Flare cases by age group and gender is presented in Table 16-192 below.

Table 16-192 Distribution of Cases by Age Group and Gender for PMR Flares or Conditions Aggravated (Cumulative)

Age Group	Female		Male		Total # Cases	% Total Cases
	# Cases	% Cases	# Cases	% Cases		
50-64	1	6.3%	0	0	1	6.3%
65-74	2	12.5%	6	37.5%	8	50.0%
75+	5	31.3%	1	6.3%	6	37.5%
Missing	1	6.3%	0	0	1	6.3%
Grand total	9	56.3%	7	43.8%	16	100.0%

When TTO was provided, the PMR Flares occurred within the first two weeks after Dose 1 or Dose 2, as well as for the one case that occurred after Dose 3. Of the 16 cases, there were 2 with missing TTO information. There is a small number of cases considered PMR Flares, however based on available data there was no clear pattern relating to TTO and dose number (Table 16-193).

Table 16-193 Time to Onset by Dose for PMR Flares

Dose Number	TTO All Doses (Days)	# Events	% Events
Dose 1	Subtotal	8	50.0%
	0 days	2	12.5%
	01-02	3	18.8%
	07-13	3	18.8%
Dose 2	Subtotal	5	31.3%
	0 days	1	6.3%
	01-02	1	6.3%
	03-04	1	6.3%
	07-13	2	12.5%
Dose 3	Subtotal	1	6.3%
	07-13	1	6.3%
Unknown	Subtotal	2	12.5%
	Missing	2	12.5%

Dose Number	TTO All Doses (Days)	# Events	% Events
Grand total		**16**	**100.0%**

WHO Causality Assessment for Flare Cases

According to the WHO causality assessment, 0 cases were classified as Probable; although time to onset was plausible and varied from 1-13 days and data was confounded by other auto-immune disease like rheumatoid arthritis or history of neck disorder. Nine cases (56.2%) were classified as Possible due to time to onset of PMR being reasonably related to the administration of first or second doses of SPIKEVAX. Regarding these 9 cases, on balance, the presence of confounding disease contributing to causality could not be completely ruled out, and some cases did not include full information but reported a history or flare of PMR and a temporal relationship. Six cases (37.5%) were classified as Conditional as more information was required to upgrade the causality to Possible. One case (6.3%) was unassessable due to lack of information. (See Appendix 20.11.70)

Polymyalgia rheumatica without reported history of PMR (new onset PMR)

Cumulatively, 60 cases of PMR did not report a medical history of PMR and were medically assessed by the MAH as representing cases of new onset. Forty-six cases were medically confirmed.

Of the 60 cases, 57 (95.0%) were serious and the majority were considered "medically significant" (n=53, 93.0%). Seven cases (12.3%) involved hospitalization, and one case (1.8%) was reported by a Regulatory Authority as life-threatening (4.1(b) [redacted]; other events in this case also reported as life-threatening included Arthralgia, Back pain, Giant cell arteritis, Inflammation, Loss of personal independence in daily activities, Mobility decreased; Neck pain, Pain in extremity, Polymyalgia rheumatica, Sleep disorder).

Of the 60 cases, 19 (31.7%) met the EULAR case definition of "Yes", and 41 (68.3%) met the EULAR case definition of "Incomplete". Five cases included reports of GCA and of these cases only one reported a biopsy result which was negative.

Thirty-three cases (55.0%) were in females and 27 cases (45.0%) were in males. The median age was 70 years (min: 47 years, max: 92 years). The distribution of cases by age group and gender is presented in Table 16-194 below.

Table 16-194 Distribution of Cases by Age Group and Gender for New Onset PMR (Cumulative)

Age Group	Female		Male		Total # Cases	% Total Cases
	# Cases	% Cases	# Cases	% Cases		
40-49	1	1.7%	0	0	1	1.7%
50-64	4	6.7%	7	11.7%	11	18.3%
65-74	12	20.0%	14	23.3%	26	43.3%
75+	15	25.0%	6	10.0%	21	35.0%
Missing	1	1.7%	0	0	1	1.7%
Grand total	**33**	**55.0%**	**27**	**45.0%**	**60**	**100.0%**

Of the 60 PMR new onset cases, there was a high number with missing TTO information (n=25, 41.7%). Of the remaining 35 cases, there was a similar number of cases reported after Dose 1 and Dose 2. The median TTO was 8 days (min: 1, max: 142).

There were 17 cases reported after Dose 1, of which 13 occurred within the first 14 days after receiving SPIKEVAX, with 5 events occurring within the first 2 days. As the natural history of PMR includes cases of rapid onset, it seems de novo onset PMR may be a more likely explanation for the event of PMR than a relationship to SPIKEVAX administration. Two cases occurred greater than 30 days after Dose 1 (Day 42 and Day 89), thus reducing the likelihood of a relationship to SPIKEVAX.

There were 18 cases reported after Dose 2, of which 7 cases occurred between Day 1 and Day 13 following SPIKEVAX administration. Six cases occurred after Day 30 (range: 1 to 142 days), thus reducing the likelihood of a relationship to SPIKEVAX. (Table 16-195).

Table 16-195 Time to Onset by Dose for New Onset PMR

Dose Number	TTO All Doses (Days)	# Events	% Events
Dose 1	Subtotal	17	28.3%
	01-02	5	8.3%
	03-04	3	5.0%
	05-06	2	3.3%
	07-13	3	5.0%
	14-29	2	3.3%
	30+	2	3.3%
Dose 2	Subtotal	18	30.0%
	01-02	3	5.0%
	05-06	2	3.3%
	07-13	2	3.3%

Dose Number	TTO All Doses (Days)	# Events	% Events
	14-29	5	8.3%
	30+	6	10.0%
Unknown	Subtotal	25	41.7%
	Missing	25	41.7%
Grand total		**60**	**100.0%**

WHO Causality Assessment for New PMR Cases

According to the WHO causality assessment, no cases were classified as Probable. Although there were several cases with plausible time to onset (temporal relationship) as information on comorbid conditions such as other immune mediated conditions like rheumatoid arthritis or a history of pain in the neck or shoulder, concomitant medications and rechallenge was generally not provided thus limiting an assessment of Probable causality. Thirteen cases (21.7%) were classified as Possible due to the time to onset of being reasonably related in time to administration of the vaccine and, on balance, the presence of confounding diseases, concomitant medications and age contributing to causality could not be completely ruled out. Of note, one Possible case with TTO of 58 days following Dose 2 of SPIKEVAX (4.1(b)) reported onset of symptoms (arthralgia) 19 days after receiving SPIKEVAX, and PMR was confirmed on Day 58. Twenty-six cases (43.3%) were classified as Conditional; a causal relationship could not be excluded as more data was required for assessment of causality. Fourteen cases (23.3%) were classified as Unlikely due to the presence of alternative causalities. Seven cases (11.7%) were classified as Unassessable because of insufficient information. (See Appendix 20.11.70). In general cases occurring within 1-2 days or after 30 days are unlikely to be associated with immune stimulation from SPIKEVAX but additional data is required.

16.3.6.7.5.5. Discussion

There are currently no biologic plausible hypotheses that the immunostimulatory effect of SPIKEVAX could induce PMR. The biological mechanism of vaccine associated PMR remains unclear but the similarity between the pathogenesis of PMR and the immunological activation through the vaccination (activation of CD4+ T helper 1 cells, follicular helper T cells, and CD8+ T cells and proinflammatory cytokines) could provide an explanation [198] although this hypothesis is unconfirmed [198]. It can be hypothesized that the innate immune response induced by vaccination could induce a "flare" in a previously subclinical, undiagnosed individual; however, this is speculative.

Based on the aggregate numbers in this report a relationship between PMR and SPIKEVAX cannot be confirmed. Additionally, the number of observed to expected events is less than expected in all

age categories in both males and females supporting the observation that at this time a causal relationship cannot be confirmed.

The analysis of PMR was hampered by the variability in the quality of reports provided to the MAH. Conceptualizing validity and diagnostic certainty of the diagnosis of PMR was hampered by the absence of a standardized definition [195] as provided by the Brighton Collaboration for other complex medical conditions, for example Guillain-Barre Syndrome. To enhance this analysis the EULAR algorithm [197] was applied.

However, this algorithm is of more value to clinicians as it provides guidelines for treatment of different clinical manifestations. Nonetheless the algorithm helped to identify the number of PMR cases meeting "Yes" criteria (n=33, 21.9%). This outcome may be the result of poor patient recall, inadequate medical documentation, presence of other common autoimmune conditions that may mimic PMR and the response to steroids which may be underreported. The largest category in trying to ascertain diagnostic certainty was "No" (n=75, 49.7%). These cases were poorly documented as they were mostly consumer and regulatory agency reports. Responses to follow-up queries from MAH to consumers and regulatory agencies are rare and thus quality of reports remain low. Cases with "Incomplete" information comprised 28.5% (n=43) of the PMR cases in this analysis. These cases usually had more than one but fewer than four of the clinical criteria required by EULAR for diagnostic validity of "Yes".

When application of EULAR case criteria to the event of PMR was examined, the following observations were at odds with the diagnosis of PMR; inclusion of patients with history of long-standing aching and stiffness, pattern of musculoskeletal findings at onset including other joints not typical for the usual distribution for PMR, failure to describe morning stiffness and duration of stiffness, inadequate descriptions of functional limitations, not always describing laboratory findings and omission of information on steroid dosages.

When WHO causality criteria were applied to the combined dataset of Flares and new onset PMR cases (n=76, 50.3%), no cases of Certain or Probable causality were identified. Of the 76 cases, 22 cases (28.9%) were Possible, 32 cases (42.1%) were Conditional, 14 cases (18.4%) were Unlikely, and 8 cases (10.5%) were unassessable. Time to onset of PMR was important to determine causality- most cases occurred within one week after the first or second dose. 32.9% of events ocd after the first dose and 30.3% of PMR cases occurred after the second dose. In general, no recurrence or aggravation of symptoms occurred after the second dose possibly suggesting only a limited immunostimulatory effect on the mechanisms of immune stimulation associated with development of PMR. Time to onset should be interpreted with caution when applying causality criteria as of 8 events which occurred within the first 1-2 days after doses 1 and 2, the natural history of PMR includes cases with rapid onset that may present with full blown PMR (UpToDate),

suggesting that de novo onset PMR, commonly occurring in this age group may be a more likely explanation for the event of PMR than a relationship to SPIKEVAX administration. Similarly, after Dose 1 two cases occurred beyond 42 and 89 days, reducing the likelihood of immune stimulation by SPIKEVAX leading to PMR.

Analysis of the cumulative data received as of the data lock of this PRBRER, does not support a causal association between PMR and SPIKEVAX. PMR reported in temporal association with the administration of SPIKEVAX did not raise any safety concerns and the information provided was inadequate to confirm evidence of causality between SPIKEVAX exposure and PMR.

When considering the observed reporting rate, it is helpful to bear in mind that the total number of doses administered is in excess of 466,804,529. Epidemiological data confirmed that observed to expected events of PMR showed no increase in frequency overall, when stratified by age and gender compared to a representative US population. (Appendix 20.11.3) This is consistent with the safety profile of SPIKEVAX indicating that PMR in populations exposed to SPIKEVAX are not at an increased risk.

16.3.6.7.5.6. Conclusion

Based on the analysis of all the safety data received during cumulative review of this PBRER, ModernaTX, Inc considers that cases included under the safety concern of PMR reported in temporal association with the administration of SPIKEVAX, did not raise any safety concerns and the aggregate information provided to date is inadequate to provide evidence of causality between SPIKEVAX exposure and PMR. These data do not represent a new safety issue of concern and does not support the need to update the product information or the RMP. ModernaTX, Inc will continue to monitor events for PMR using routine surveillance. The benefit-risk evaluation remains positive.

16.3.6.8. Other Clinical Topics

16.3.6.8.1. Medication Errors

16.3.6.8.1.1. Source of the New Information

The company GSDB was queried for valid case reports of medication errors and product quality issues involving SPIKEVAX received from HCPs, HAs, consumers and literature, for the reporting period of 01 Jul 2021 through 31 Dec 2021, worldwide.

16.3.6.8.1.2. Background Relevant to the Evaluation

A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient.

16.3.6.8.1.3. Methods of Evaluation including Data Sources, Search Criteria and Analytical Approaches

ModernaTX, Inc GSDB was search using the medication error broad SMQ search evaluating reports of medication errors that may represent an unintended failure in the treatment process and that may have the potential for harm to the patient.

16.3.6.8.1.4. Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

During this reporting period, there were 13,253 cases with 14,962 medication error events. There were 4,429 cases (33.4%) reported in males and 6,218 cases (46.9%) reported in females; gender information was not provided in 2,606 cases (19.7%). The majority of cases were received directly by the MAH as spontaneous reports from the public (10,556, 79.6%), with the remainder of reports received primarily from regulatory authorities (2,678, 20.2%). Most cases were received from the United States (9,028, 68.1%), followed by the EEA (1,733, 13.1%).

Upon review of medication errors reported by dose number, the events were evenly distributed, except for Dose 4, which was associated with only 16 medication error events (Table 16-196).

Table 16-196 Number and Percentage of Medication Error Events by Dose Number - Review Period 01 Jul to 31 Dec 2021

Dose Number	# Events	% of Events
Dose 1	2,699	18.0
Dose 2	3,118	20.8
Dose 3	3,087	20.6
Dose 4	16	0.1
Unknown	6,042	40.4
Grand total	**14,962**	**100.0**

In this reporting period, the MedDRA Preferred Terms of expired product administered, inappropriate schedule of product administration, and product storage error are among the most frequently reported medication errors (Table 16-197).

Table 16-197 Number and Percentage of the Top 10 Medication Error Events by PT - Review Period 01 Jul to 31 Dec 2021

PT	# Events	% of Events
Expired product administered	5,537	37.0
Inappropriate schedule of product administration	2,576	17.2
Product storage error	1,656	11.1

PT	# Events	% of Events
Product dose omission issue	1,409	9.4
Interchange of vaccine products	747	5.0
Product administered to patient of inappropriate age	511	3.4
Accidental overdose	392	2.6
Product temperature excursion issue	298	2.0
Extra dose administered	281	1.9
Incorrect route of product administration	229	1.5

During the reporting period, there were 5,172 medication error cases reported with associated adverse events, including 1,602 serious cases and 61 cases with fatal outcomes. Most of the adverse events in these cases were consistent with the labeled events for SPIKEVAX, with Headache, Pyrexia, and Fatigue as the most frequently reported adverse events (Table 16-198).

Table 16-198 Number and Percentage of Adverse Events Reported in Medication Error Cases with Associated Adverse Events by PT (≥1.5% of Events) - Review Period 01 Jul to 31 Dec 2021

PT	# Events	% Events
Headache	1,143	4.1%
Pyrexia	1,128	4.0%
Fatigue	851	3.0%
Vaccination site pain	828	3.0%
Myalgia	754	2.7%
Chills	537	1.9%
Nausea	535	1.9%
Pain in extremity	523	1.9%
Vaccination site swelling	422	1.5%

Subpopulation Analyses

Medication Errors in Adolescents (12 to 17 years old) – Reporting period 01 Jul to 31 Dec 2021

There were 502 cases (578 events) reporting medication errors in adolescents 12 to 17-years-old. There were 204 cases (40.6%) reported in males and 230 cases (45.8%) reported in females; gender information was not provided in 68 cases (13.5%). As seen with cases involving adults, the majority of cases were received directly by the MAH as spontaneous reports from the public (462, 92%), with the remainder of reports received primarily from regulatory authorities (39, 7.8%). Most cases were received from the United States (356, 70.9%), followed by the EEA (65, 12.9%).

Upon review of medication errors reported by dose number, the events were primarily associated with Dose 1, which is consistent with the high number of events coded to the PT of Product administered to patient of inappropriate age (Table 16-199).

Table 16-199 Number and Percentage of Medication Error Events Reported in Adolescents by Dose Number - Review Period 01 Jul to 31 Dec 2021

Dose Number	# Events	% of Events
Dose 1	293	50.7
Dose 2	70	12.1
Dose 3	26	4.5
Unknown	189	32.7
Grand total	**578**	**100.0**

In this reporting period, the PT of Product administered to patient of inappropriate age represented the majority of medication error events in adolescents (454, 78.5%) (Table 16-200). The frequency of this event is related to the various approval dates for the use of SPIKEVAX in adolescents, globally.

Table 16-200 Number and Percentage of Medication Error Events Reported in Adolescents by PT (>2% of events) - Review Period 01 Jul to 31 Dec 2021

PT	# Events	% of Events
Product administered to patient of inappropriate age	454	78.5
Inappropriate schedule of product administration	30	5.2
Expired product administered	25	4.3
Interchange of vaccine products	16	2.8
Product dose omission issue	16	2.8
Product storage error	13	2.2

During the reporting period, there were 141 medication error cases reported with associated adverse events in adolescents, including 16 serious cases and 1 case with a fatal outcome. Most of the adverse events in these cases were consistent with the labelled events for SPIKEVAX, with Pyrexia, Vaccination site pain, and Headache as the most frequently reported adverse events (Table 16-201).

Table 16-201 Number and Percentage of Adverse Events Reported in Medication Error Cases with Associated Adverse Events in Adolescents by PT (>2% of Events) - Review Period 01 Jul to 31 Dec 2021

PT	# Events	% of Events
Pyrexia	23	4.4
Vaccination site pain	21	4.1
Headache	18	3.5
Myalgia	12	2.3
Fatigue	11	2.1
Pain in extremity	11	2.1

Adolescent Fatal Case Summary

There was one fatal case reported in an adolescent, summarized below.

4.1(b) (WWID: 4.1(b) -4.1(b)) – This spontaneous case, received via social media, concerns a report of a 13-year-old male who was vaccinated with SPIKEVAX (dose number not reported) and died 3 days later. The event of Product administered to patient of inappropriate age was recorded in this case, as SPIKEVAX was not approved for use in adolescents in the 4.1(b) when the report was received. No additional information was provided.

Medication Errors in Children (≤11 years old) – Reporting period 01 Jul to 31 Dec 2021

There were 39 cases (45 events) reporting medication errors in children ≤11-years-old. There were 17 cases (43.6%) reported in males and 21 cases (53.8%) reported in females; gender information was not provided in 1 case (2.6%). As seen with cases involving adults and adolescents, the majority of cases were received directly by the MAH as spontaneous reports from the public (34, 87.2%), with the remainder of reports received from regulatory authorities (5, 12.8%). Most cases were received from the United States (31, 79.5%), followed by the EEA (3, 7.7%) and Canada (3, 7.7%).

Upon review of medication errors reported by dose number, the events were evenly distributed; however, 22 of the events (48.9%) were associated with an unknown dose number (Table 16-202).

Table 16-202 Number and Percentage of Medication Error Events Reported in Children by Dose Number - Review Period 01 Jul to 31 Dec 2021

Dose Number	# Events	% of Events
Dose 1	9	20.0
Dose 2	6	13.3

Dose Number	# Events	% of Events
Dose 3	8	17.8
Unknown	22	48.9
Grand total	45	100.0

In this reporting period, the PT of Product administered to patient of inappropriate age represented the majority of medication error events in adolescents (454, 78.5%). The frequency of this event is related to the various approval dates for the use of SPIKEVAX in adolescents, globally. For children, the PT of Product administered to patient of inappropriate age also represented the majority of medication error events (35, 77.8%). (Table 16-203).

Table 16-203 Number and Percentage of Medication Error Events Reported in Children by PT (n>1) - Review Period 01 Jul to 31 Dec 2021

PT	# Events	% of Events
Product administered to patient of inappropriate age	35	77.8
Inappropriate schedule of product administration	3	6.7
Accidental underdose	2	4.4

During the reporting period, there were 17 medication error cases reported with associated adverse events in children, including 1 serious case. Most of the adverse events in these cases were consistent with the labelled events for SPIKEVAX, with Vaccination site pain, Pain in extremity, and Pyrexia as the most frequently reported adverse events (Table 16-204).

Table 16-204 Number and Percentage of Adverse Events Reported in Medication Error Cases with Associated Adverse Events in Children by PT (n>1) - Review Period 01 Jul to 31 Dec 2021

PT	# Events	% of Events
Vaccination site pain	5	8.8%
Pain in extremity	4	7.0%
Pyrexia	3	5.3%
Fatigue	2	3.5%
Vaccination site reaction	2	3.5%
Vomiting	2	3.5%

16.3.6.8.1.5. Discussion

Review of the data does not suggest any identifiable patterns or trends in the reports of medication errors received by the MAH, including those reports concerning patients who received doses of SPIKEVAX vaccine beyond the primary series or any interchange of other COVID-19 vaccine

products. For more details about interaction with other vaccines/heterologous vaccines, please refer to Section 16.3.5.5.

No events were associated with harm to the patient due to the medication error.

16.3.6.8.1.6. Conclusion

After careful review of all new safety data received during the review period for medications errors, the benefit-risk profile for SPIKEVAX remains favorable. Medication errors reported to ModernaTX, Inc., will continue to be monitored using the routine pharmacovigilance measures implemented for SPIKEVAX.

Refer to Appendix 20.11.71 for a tabulation of all medication errors during the reporting period.

16.3.6.8.2. Fatal Reports

16.3.6.8.2.1. Source of the New Information

Information presented below includes analysis performed on cases received by ModernaTX, Inc. from 01 Jul 2021 to 31 Dec 2021 for the mRNA-1273 vaccine (COVID-19 vaccine Moderna) SPIKEVAX. Cumulatively, the data reviewed covers the period from 18 Dec 2020 to 31 Dec 2021.

16.3.6.8.2.2. Background Relevant to the Evaluation

Fatal reports have been reviewed as part of routine safety surveillance due to the serious outcome and clinical significance.

16.3.6.8.2.3. Methods of Evaluation including Data Sources, Search Criteria and Analytical Approaches

The MAH queried the GSDB, cumulatively and for the reporting period through 31 Dec 2021, for valid case reports received from HCP, HA, consumers, and literature, worldwide, reported for SPIKEVAX to identify all events with a fatal outcome, and events with PTs of Death or “Sudden death” and/or "Sudden cardiac death". Additional sub-analyses were conducted to evaluate fatal cases in frail subjects, in subjects with underlying comorbid risk factors for death, in subcategory of age (<18-year-old and 18–30-year-old), and subjects having received more than 2 doses per previous request by regulatory agencies.

- Appendix 20.11.72 and Appendix 20.11.73: listing of fatal cases in <12-year-olds during the reporting period.
- Appendix 20.11.74 and Appendix 20.11.75: listing of fatal cases in 12–17-year-olds during the reporting period.

- Appendix 20.11.76 and Appendix 20.11.77: listing of fatal cases in 18–30-year-olds with cardiac events during the reporting period.

16.3.6.8.2.4. Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Observed vs. Expected Analysis

See Appendix 20.11.3.

Overview of Cases

Cumulative Review (Fatal cases, cumulative to 31 Dec 2021)

Cumulatively, through 31 Dec 2021, a total of 5,282 fatal cases were reported and included a total of 15,129 events reported with a fatal outcome. Of the 5,282 cases, 4,659 cases were medically confirmed.

Table 16-205 provides a list of the top 10 cumulative most frequently reported events with a fatal outcome, with death being the most common. The reported events with a fatal outcome are for the most part symptoms of or consistent with the types of events that might be expected to result in death (such as myocardial infarction, stroke, pneumonia), particularly in elderly populations and during the COVID-19 pandemic.

Table 16-205 Number and Percentage of Top 10 Most Frequently Reported Events with a Fatal Outcome by MedDRA PT - Cumulative to 31 Dec 2021

PT	# Events	% of Total Events
Death	2,723	18.0%
COVID-19	651	4.3%
Dyspnoea	476	3.1%
Cardiac arrest	379	2.5%
Pyrexia	264	1.7%
Asthenia	193	1.3%
Unresponsive to stimuli	190	1.3%
COVID-19 pneumonia	180	1.2%
Myocardial infarction	171	1.1%
Pneumonia	171	1.1%

There were 3,024 cases (57.3%) involving male patients and 2,138 cases (40.5%) involving female patients and 120 cases (2.3%) with missing gender information. The majority of the cases (4,592 cases, 86.9%) reported were for patients 50 years of age or older (median: 74 years; mean: 72.1 years) (Table 16-206).

Table 16-206 Number and Percentage of Fatal Cases by Gender and Age – Cumulative to 31 Dec 2021

Age Group	Female		Male		Unknown		Total # Cases	Total % Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
<2	0	0	3	0.1%	2	0.0%	5	0.1%
12-15	2	0.0%	3	0.1%	0	0	5	0.1%
16-17	0	0	2	0.0%	0	0	2	0.0%
18-29	27	0.5%	68	1.3%	1	0.0%	96	1.8%
30-39	57	1.1%	88	1.7%	5	0.1%	150	2.8%
40-49	74	1.4%	144	2.7%	4	0.1%	222	4.2%
50-64	340	6.4%	491	9.3%	8	0.2%	839	15.9%
65-74	441	8.3%	770	14.6%	7	0.1%	1218	23.1%
75+	1129	21.4%	1393	26.4%	13	0.2%	2535	48.0%
Missing	68	1.3%	62	1.2%	80	1.5%	210	4.0%
Grand total	**2138**	**40.5%**	**3024**	**57.3%**	**120**	**2.3%**	**5282**	**100.0%**

Children ages <12 Years (Cumulatively as of 31 Dec 2021)

Cumulatively as of 31 Dec 2021, 5 fatal cases were reported in subjects <12 years old.

Adolescents ages 12-17 Years (Cumulatively as of 31 Dec 2021)

Cumulatively as of 31 Dec 2021, 7 fatal cases were reported in subjects 12-17 years old.

SPIKEVAX Booster (Cumulatively as of 31 Dec 2021)

Cumulatively as of 31 Dec 2021, there have been 144 fatal cases reported in subjects who received >2 doses of SPIKEVAX.

Reporting Period 01 Jul 2021 to 31 Dec 2021

During the reporting period, a total of 2,414 fatal cases were reported and included a total of 8,960 events reported with a fatal outcome. Of the 2,414 cases, 2,024 cases were medically confirmed.

Table 16-207 provides a list of the top 10 cumulative most frequently reported events with a fatal outcome, with death being the most common. The type and frequency of fatal events reported in the reporting period were similar to those reported cumulatively and consistent with those expected to result in death, particularly in elderly patients and during the COVID pandemic.

Table 16-207 Number and Percentage of Top 10 Most Frequently Reported Events with a Fatal Outcome by MedDRA PT – 01 Jul 2021 to 31 Dec 2021

PT	# Events	% of Total Events
Death	1,077	12.0%

PT	# Events	% of Total Events
COVID-19	537	6.0%
Dyspnoea	296	3.3%
Cardiac arrest	172	1.9%
Pyrexia	166	1.9%
SARS-CoV-2 test positive	149	1.7%
COVID-19 pneumonia	138	1.5%
Cough	128	1.4%
Asthenia	116	1.3%
Pneumonia	110	1.2%

There were 1,423 cases (58.9%) involving male patients and 917 cases (38.0%) involving female patients and 74 cases (3.1%) with missing gender information. The majority of the cases (1,987 cases, 82.3%) reported were for patients 50 years of age or older (median age: 72.0 years; mean age: 69.2 years) (Table 16-208).

Table 16-208 Number and Percentage of Fatal Cases by Gender and Age – 01 Jul 2021 to 31 Dec 2021

Age Group	Female		Male		Unknown		Total # Cases	% Total Cases
	# Cases	% of Total Cases	# Cases	% of Total Cases	# Cases	% of Total Cases		
<2	0	0	2	0.1%	1	0.0%	3	0.1%
12-15	1	0.0%	3	0.1%	0	0	4	0.2%
16-17	0	0	2	0.1%	0	0	2	0.1%
18-29	19	0.8%	50	2.1%	1	0.0%	70	2.9%
30-39	31	1.3%	62	2.6%	4	0.2%	97	4.0%
40-49	38	1.6%	93	3.9%	2	0.1%	133	5.5%
50-64	155	6.4%	242	10.0%	6	0.2%	403	16.7%
65-74	205	8.5%	367	15.2%	4	0.2%	576	23.9%
75+	428	17.7%	571	23.7%	9	0.4%	1008	41.8%
Missing	40	1.7%	31	1.3%	47	1.9%	118	4.9%
Grand total	**917**	**38.0%**	**1423**	**58.9%**	**74**	**3.1%**	**2414**	**100.0%**

During the reporting period more reports of death occurred after dose 2 (973; 40.3%) compared to dose 1 (570; 23.6%), and to dose 3 (142; 5.9%). The majority of the deaths after dose 1 and dose 2 occurred at 30 or more days after SPIKEVAX administration. (Table 16-209).

Table 16-209 Number and Percentage of Fatal Cases by Dose and Time-to-Death – Reporting Period 01 Jul 2021 to 31 Dec 2021

Dose Number	TTO (Days)	# Cases	% of Total Cases
Dose 1	***Subtotal***	***570***	***23.6%***
	0 days	21	0.9%
	01-02	59	2.4%
	03-04	31	1.3%
	05-06	26	1.1%
	07-13	69	2.9%
	14-29	94	3.9%
	30+	270	11.2%
Dose 2	***Subtotal***	***973***	***40.3%***
	0 days	16	0.7%
	01-02	70	2.9%
	03-04	42	1.7%
	05-06	25	1.0%
	07-13	51	2.1%
	14-29	69	2.9%
	30+	700	29.0%
Dose 3	***Subtotal***	***142***	***5.9%***
	0 days	9	0.4%
	01-02	40	1.7%
	03-04	17	0.7%
	05-06	15	0.6%
	07-13	29	1.2%
	14-29	22	0.9%
	30+	10	0.4%
Unknown	***Subtotal***	***729***	***30.2%***
	Missing	729	30.2%
Grand total		**2,414**	**100.0%**

Analyses for comorbid risk factors of death, markers of frailty and sudden death (Reporting Period):

The medical history of all subjects with at least one event reported with a fatal outcome was reviewed to identify comorbidities associated with an elevated risk for death. The list of comorbid conditions considered risk factors for death included but were not limited to arrhythmia, cardiovascular disease, infection, chronic liver/kidney, respiratory disease, COVID-19, diabetes and/or related conditions (e.g., diabetic retinopathy etc.), hypertension, neurologic diseases, obesity, oncologic conditions, solid organ or hematologic stem cell transplant, and thromboembolism/stroke/coagulopathy. Frail subjects included subjects of all ages with unstable

health conditions and comorbidities (e.g., chronic obstructive pulmonary disease [COPD], diabetes, chronic neurological disease, cardiovascular disorders). "Markers of frailty" were defined as the presence of any medical history conditions that met the above definition of frailty. In addition, where available, the primary reported causes of death were reviewed to summarize this uncoded free text field into categories. An overall summary of cumulative and reporting period fatal cases is presented below in Table 16-210.

Table 16-210 Summary of Reporting Period (01 Jul 2021 to 31 Dec 2021) and Cumulative Cases through 31 Dec 2021 by Age, Sex, Region, Markers of Frailty, Comorbid Risk Factors for Death, and Cause of Death

	Cumulative Fatal Cases		Reporting Period Fatal Cases	
	All		All	
	N	%	N	%
All	5,282	100	2,414	100
Review Period	2,414	45.7	2,414	100
Age (years)				
<18	12	0.23	9	0.37
18-30	108	2.04	78	3.23
31-50	401	7.59	245	10.15
51-64	798	15.11	380	15.74
65-74	1,218	23.06	576	23.86
≥75	2,535	47.99	1,008	41.76
Missing	210	3.98	118	4.89
Sex				
Male	3,024	57.25	1,423	58.95
Female	2,138	40.48	917	37.99
Missing	120	2.27	74	3.07
Region				
Asia	436	8.25	435	18.02
Canada	13	0.25	12	0.5
European Economic Are	667	12.63	312	12.92
Latin America	1	0.02	1	0.04
Middle East	1	0.02	1	0.04
Oceana	2	0.04	2	0.08
Switzerland	88	1.67	32	1.33
United Kingdom	30	0.57	24	0.99
United States	4,044	76.56	1,595	66.07
Dose number prior to death*				
Dose 1	2,138	40.48	570	23.61

	Cumulative Fatal Cases		Reporting Period Fatal Cases	
	All		All	
	N	%	N	%
Dose 2	1,895	35.88	973	40.31
Dose 3	143	2.71	142	5.88
Unknown	1,106	20.94	729	30.2
HCP				
Medically Confirmed	4,659	88.21	2,024	83.84
Not Medically Confirmed	623	11.79	390	16.16
Death type				
Expected	3,413	64.62	1,398	57.91
Not expected	1,869	35.38	1,016	42.09
Significant comorbidity documented in the medical record				
None	2,248	42.56	1,162	48.14
At least one	3,034	57.44	1,252	51.86
Arrhythmia	469	8.88	171	7.08
COVID	184	3.48	63	2.61
Cardiovascular disease	1,481	28.04	596	24.69
Chronic kidney disease	490	9.28	197	8.16
Chronic liver disease	69	1.31	33	1.37
Coagulopathy	19	0.36	11	0.46
Diabetes and related conditions	982	18.59	408	16.9
Elderly/frail	162	3.07	62	2.57
Gastroenterology	14	0.27	7	0.29
General	5	0.09	1	0.04
Genetic	14	0.27	3	0.12
Hematology	22	0.42	8	0.33
Hypertension	1,491	28.23	623	25.81
Infection	34	0.64	20	0.83
Neurologic	464	8.78	143	5.92
Obesity	216	4.09	93	3.85
Oncology	462	8.75	203	8.41
Other	69	1.31	40	1.66
Respiratory	665	12.59	277	11.47
Rheumatologic	33	0.62	17	0.7
Stroke	269	5.09	114	4.72
Substance use	18	0.34	8	0.33
Thromboembolic	116	2.2	54	2.24

	Cumulative Fatal Cases		Reporting Period Fatal Cases	
	All		All	
	N	%	N	%
Transplant	60	1.14	35	1.45
Markers of Frailty	2,121	40.16	822	34.05
Cause of Death				
COPD	6	0.11	2	0.08
Cardiovascular (Including Cardiorespiratory failure)	726	13.74	344	14.25
General condition or natural causes	175	3.31	113	4.68
Hemorrhage (including CNS hemorrhage)	124	2.35	59	2.44
Infection (including COVID and fever NOS)	561	10.62	430	17.81
Neurologic (excluding strokes)	111	2.1	68	2.82
Oncology	34	0.64	22	0.91
Other causes	340	6.44	230	9.53
Respiratory	262	4.96	160	6.63
Stroke	107	2.03	44	1.82
Thromboembolic (excluding myocardial infarction and stroke)	96	1.82	42	1.74
Unknown	2,740	52	900	37

*: Dose number in this analysis is based on Time-To-Death where date of death is known, whereas the main analysis, including for booster recipients, is based on Time-To-Event for events with a fatal outcome with a known event onset date.

A primary cause of death was not provided or was unknown in 37.3% of fatal cases from the reporting period. Table 16-211 below summarizes fatal cases by comorbid risk factors for death and markers of frailty.

Table 16-211 Summary of Reporting Period (01 Jul 2021 to 31 Dec 2021) Fatal Cases by Comorbid Risk Factors for Death and Markers of Frailty

	Reporting Period Fatal Cases							
	Comorbidities documented				Markers of frailty			
	None		At least one		No		Yes	
	N	%	N	%	N	%	N	%
All	1,162	100	1,252	100	1,592	100	822	100
Age (years)								
<18	8	0.69	1	0.08	8	0.5	1	0.12
18-30	56	4.82	22	1.76	67	4.21	11	1.34
31-50	141	12.13	104	8.31	196	12.31	49	5.96
51-64	182	15.66	198	15.81	260	16.33	120	14.6
65-74	242	20.83	334	26.68	361	22.68	215	26.16
≥75	426	36.66	582	46.49	586	36.81	422	51.34
Missing	107	9.21	11	0.88	114	7.16	4	0.49

	Reporting Period Fatal Cases							
	Comorbidities documented				Markers of frailty			
	None		At least one		No		Yes	
	N	%	N	%	N	%	N	%
Sex								
Male	678	58.35	745	59.5	947	59.48	476	57.91
Female	416	35.8	501	40.02	574	36.06	343	41.73
Missing	68	5.85	6	0.48	71	4.46	3	0.36
Region								
Asia	262	22.55	173	13.82	345	21.67	90	10.95
Canada	11	0.95	1	0.08	12	0.75	.	.
European Economic Area	132	11.36	180	14.38	199	12.5	113	13.75
Latin America	.	.	1	0.08	1	0.06	.	.
Middle East	1	0.09	.	.	1	0.06	.	.
Oceana	2	0.17	.	.	2	0.13	.	.
Switzerland	6	0.52	26	2.08	13	0.82	19	2.31
United Kingdom	15	1.29	9	0.72	21	1.32	3	0.36
United States	733	63.08	862	68.85	998	62.69	597	72.63
Dose number prior to death*								
Dose 1	241	20.74	329	26.28	358	22.49	212	25.79
Dose 2	432	37.18	541	43.21	594	37.31	379	46.11
Dose 3	43	3.7	99	7.91	75	4.71	67	8.15
Unknown	446	38.38	283	22.6	565	35.49	164	19.95
HCP								
Medically Confirmed	909	78.23	1,115	89.06	1,267	79.59	757	92.09
Not Medically Confirmed	253	21.77	137	10.94	325	20.41	65	7.91
Death type								
Expected	169	14.54	1,229	98.16	590	37.06	808	98.3
Not expected	993	85.46	23	1.84	1,002	62.94	14	1.7
Significant comorbidity documented in the medical record								
None	1,162	100	.	.	1,151	72.3	11	1.34
At least one	.	.	1,252	100	441	27.7	811	98.66
Arrhythmia	.	.	171	13.66	9	0.57	162	19.71
COVID	.	.	63	5.03	17	1.07	46	5.6
Cardiovascular disease	.	.	596	47.6	120	7.54	476	57.91
Chronic kidney	.	.	197	15.73	33	2.07	164	19.95

	Reporting Period Fatal Cases							
	Comorbidities documented				Markers of frailty			
	None		At least one		No		Yes	
	N	%	N	%	N	%	N	%
disease								
Chronic liver disease	.	.	33	2.64	10	0.63	23	2.8
Coagulopathy	.	.	11	0.88	2	0.13	9	1.09
Diabetes and related conditions	.	.	408	32.59	.	.	408	49.64
Elderly/frail	.	.	62	4.95	17	1.07	45	5.47
Gastroenterology	.	.	7	0.56	3	0.19	4	0.49
General	.	.	1	0.08	.	.	1	0.12
Genetic	.	.	3	0.24	.	.	3	0.36
Hematology	.	.	8	0.64	5	0.31	3	0.36
Hypertension	.	.	623	49.76	198	12.44	425	51.7
Infection	.	.	20	1.6	7	0.44	13	1.58
Neurologic	.	.	143	11.42	13	0.82	130	15.82
Obesity	.	.	93	7.43	38	2.39	55	6.69
Oncology	.	.	203	16.21	90	5.65	113	13.75
Other	.	.	40	3.19	18	1.13	22	2.68
Respiratory	.	.	277	22.12	30	1.88	247	30.05
Rheumatologic	.	.	17	1.36	9	0.57	8	0.97
Stroke	.	.	114	9.11	33	2.07	81	9.85
Substance use	.	.	8	0.64	3	0.19	5	0.61
Thromboembolic	.	.	54	4.31	16	1.01	38	4.62
Transplant	.	.	35	2.8	9	0.57	26	3.16
Markers of Frailty	11	0.95	811	64.78	.	.	822	100
Cause of Death								
COPD	.	.	2	0.16	.	.	2	0.24
Cardiovascular (Including Cardiorespiratory failure)	148	12.74	196	15.65	228	14.32	116	14.11
General condition or natural causes	60	5.16	53	4.23	79	4.96	34	4.14
Hemorrhage (including CNS hemorrhage)	28	2.41	31	2.48	43	2.7	16	1.95
Infection (including COVID and fever NOS)	209	17.99	221	17.65	260	16.33	170	20.68
Neurologic (excluding strokes)	41	3.53	27	2.16	48	3.02	20	2.43
Oncology	7	0.6	15	1.2	17	1.07	5	0.61

	Reporting Period Fatal Cases							
	Comorbidities documented				Markers of frailty			
	None		At least one		No		Yes	
	N	%	N	%	N	%	N	%
Other causes	110	9.47	120	9.58	146	9.17	84	10.22
Respiratory	56	4.82	104	8.31	82	5.15	78	9.49
Stroke	20	1.72	24	1.92	31	1.95	13	1.58
Thromboembolic (excluding myocardial infarction and stroke)	23	1.98	19	1.52	29	1.82	13	1.58
Unknown	460	39.59	440	35.15	629	39.51	271	32.96

*: Dose number in this analysis is based on Time-To-Death where date of death is known, whereas the main analysis, including for booster recipients, is based on Time-To-Event for events with a fatal outcome with a known event onset date.

In summary, based on review of the data from the reporting period, the majority of deaths were reported in subjects ≥ 65 years old (65.6%), males (59.0%), in subjects who had at least one reported comorbid risk factor for death (51.9%) and/or at least one marker of frailty (34.1%), and were reported from the United States (66.1%), as shown in Table 16-210 and Table 16-211. This is consistent with the population at highest risk for death at baseline, and consistent with vaccine indication and distribution. During this reporting period, 41.8% of fatal cases were in subjects ≥75 years old, which is only slightly less than cumulatively with 48.0% of fatal cases reported in subjects ≥75 years old. It is likely that this reflects distribution demographics for who were receiving the booster vaccine, as older subjects, who were higher risk for severe COVID and were vaccinated and/or boosted earlier in the pandemic. Thus, the population that is more recently receiving the vaccine or booster doses may be slightly younger than before. As a result, the proportion of subjects with at least one significant comorbid risk factor for death (51.9% vs 57.4%) and/or a marker of frailty (34.1% vs 40.2%) is also lower in the reporting period compared to cumulatively.

A review of all fatal cases was conducted to identify cases of sudden and/or unexpected deaths. Sudden and/or unexpected deaths was defined as any case with a fatal event with a PT = sudden death AND/OR sudden cardiac death AND/OR all fatal cases in subjects with age <85 AND no comorbid risk factors for death AND not classified as FRAIL AND free text primary cause of death did not include "natural." During the reporting period, there were 1,016 deaths (42.1%) classified as sudden and/or unexpected (Table 16-212). While sudden or unexpected death cases were still most frequently reported in subjects ≥75 years old (41.8%), the proportion of sudden or unexpected deaths decreased as age decreased. This is not unanticipated as fatal cases in subjects ≥85yo or with comorbid risk factors for death, which are more likely to occur in older subjects, were categorized as expected. As the presence of comorbid risk factors for deaths was a

requirement for exclusion as a sudden and/or unexpected death, the 23 cases (2.3%) with at least one comorbid risk factor for death reported that were classified as sudden and/or unexpected deaths were all cases with a PT of sudden death and/or sudden cardiac death. As the majority of subjects are ≥50 years, it is likely that comprehensive medical history was not provided to facilitate sufficient review of some of the sudden and/or unexpected death cases for comorbid risk factors for death.

Table 16-212 Summary of Reporting Period (01 Jul 2021 to 31 Dec 2021) and Cumulative Fatal Cases through 31 Dec 2021 by Sudden or Unexpected Death Analysis

	Cumulative Fatal Cases				Reporting Period Fatal Cases			
	Death type				Death type			
	Expected		Unexpected		Expected		Unexpected	
	N	%	N	%	N	%	N	%
All	3,413	100	1,869	100	1,398	100	1,016	100
Review Period	1,398	40.96	1,016	54.36	1,398	100	1,016	100
Age (years)								
<18	2	0.06	10	0.54	1	0.07	8	0.79
18-30	41	1.2	67	3.58	22	1.57	56	5.51
31-50	172	5.04	229	12.25	99	7.08	146	14.37
51-64	451	13.21	347	18.57	192	13.73	188	18.5
65-74	754	22.09	464	24.83	334	23.89	242	23.82
≥75	1,969	57.69	566	30.28	738	52.79	270	26.57
Missing	24	0.7	186	9.95	12	0.86	106	10.43
Sex								
Male	1,937	56.75	1,087	58.16	816	58.37	607	59.74
Female	1,460	42.78	678	36.28	573	40.99	344	33.86
Missing	16	0.47	104	5.56	9	0.64	65	6.4
Region								
Asia	186	5.45	250	13.38	185	13.23	250	24.61
Canada	2	0.06	11	0.59	2	0.14	10	0.98
European Economic Area	447	13.1	220	11.77	187	13.38	125	12.3
Latin America	1	0.03	.	.	1	0.07	.	.
Middle East	.	.	1	0.05	.	.	1	0.1
Oceana	.	.	2	0.11	.	.	2	0.2
Switzerland	80	2.34	8	0.43	28	2	4	0.39
United Kingdom	8	0.23	22	1.18	8	0.57	16	1.57
United States	2,689	78.79	1,355	72.5	987	70.6	608	59.84
Dose number prior to death*								
Dose 1	1,491	43.69	647	34.62	351	25.11	219	21.56

	Cumulative Fatal Cases				Reporting Period Fatal Cases			
	Death type				Death type			
	Expected		Unexpected		Expected		Unexpected	
	N	%	N	%	N	%	N	%
Dose 2	1,294	37.91	601	32.16	616	44.06	357	35.14
Dose 3	107	3.14	36	1.93	106	7.58	36	3.54
Unknown	521	15.27	585	31.3	325	23.25	404	39.76
HCP								
Medically Confirmed	3,152	92.35	1,507	80.63	1,246	89.13	778	76.57
Not Medically Confirmed	261	7.65	362	19.37	152	10.87	238	23.43
Death type								
Expected	3,413	100	.	.	1,398	100	.	.
Not expected	.	.	1,869	100	.	.	1,016	100
Significant comorbidity documented in the medical record								
None	458	13.42	1,790	95.77	169	12.09	993	97.74
At least one	2,955	86.58	79	4.23	1,229	87.91	23	2.26
Arrhythmia	457	13.39	12	0.64	166	11.87	5	0.49
COVID	176	5.16	8	0.43	61	4.36	2	0.2
Cardiovascular disease	1,451	42.51	30	1.61	587	41.99	9	0.89
Chronic kidney disease	484	14.18	6	0.32	196	14.02	1	0.1
Chronic liver disease	69	2.02	.	.	33	2.36	.	.
Coagulopathy	19	0.56	.	.	11	0.79	.	.
Diabetes and related conditions	955	27.98	27	1.44	403	28.83	5	0.49
Elderly/frail	159	4.66	3	0.16	61	4.36	1	0.1
Gastroenterology	14	0.41	.	.	7	0.5	.	.
General	5	0.15	.	.	1	0.07	.	.
Genetic	14	0.41	.	.	3	0.21	.	.
Hematology	22	0.64	.	.	8	0.57	.	.
Hypertension	1,456	42.66	35	1.87	615	43.99	8	0.79
Infection	34	1	.	.	20	1.43	.	.
Neurologic	458	13.42	6	0.32	142	10.16	1	0.1
Obesity	209	6.12	7	0.37	89	6.37	4	0.39
Oncology	450	13.18	12	0.64	203	14.52	.	.
Other	67	1.96	2	0.11	39	2.79	1	0.1
Respiratory	652	19.1	13	0.7	273	19.53	4	0.39
Rheumatologic	32	0.94	1	0.05	17	1.22	.	.

	Cumulative Fatal Cases				Reporting Period Fatal Cases			
	Death type				Death type			
	Expected		Unexpected		Expected		Unexpected	
	N	%	N	%	N	%	N	%
Stroke	262	7.68	7	0.37	113	8.08	1	0.1
Substance use	18	0.53	.	.	8	0.57	.	.
Thromboembolic	113	3.31	3	0.16	54	3.86	.	.
Transplant	59	1.73	1	0.05	35	2.5	.	.
Markers of Frailty	2,066	60.53	55	2.94	808	57.8	14	1.38
Cause of Death								
COPD	5	0.15	1	0.05	2	0.14	.	.
Cardiovascular (Including Cardiorespiratory failure)	482	14.12	244	13.06	211	15.09	133	13.09
General condition or natural causes	122	3.57	53	2.84	66	4.72	47	4.63
Hemorrhage (including CNS hemorrhage)	82	2.4	42	2.25	37	2.65	22	2.17
Infection (including COVID and fever NOS)	375	10.99	186	9.95	261	18.67	169	16.63
Neurologic (excluding strokes)	68	1.99	43	2.3	35	2.5	33	3.25
Oncology	22	0.64	12	0.64	16	1.14	6	0.59
Other causes	203	5.95	137	7.33	132	9.44	98	9.65
Respiratory	201	5.89	61	3.26	114	8.15	46	4.53
Stroke	81	2.37	26	1.39	28	2	16	1.57
Thromboembolic (excluding myocardial infarction and stroke)	59	1.73	37	1.98	22	1.57	20	1.97
Unknown	1,713	50	1,027	55	474	34	426	42

*: Dose number in this analysis is based on Time-To-Death where date of death is known, whereas the main analysis, including for booster recipients, is based on Time-To-Event for events with a fatal outcome with a known event onset date.

Children ages < 12 Years (Reporting Period 01 Jul to 31 Dec 2021)

There were 3 cases with fatal outcomes in children < 12 years of age during the reporting period (01 Jul 2021 to 31 Dec 2021). There was no discernable pattern or cluster of events in the reported fatal cases in subjects <12 years of age. There were 2 neonatal deaths. One case was a report of neonatal death in a 10-day-old infant, exposed to SPIKEVAX in utero during 3rd trimester, with no reported cause of death and limited details provided. The second case was a report of neonatal death in a 1-day-old infant with pulmonary hemorrhage, cardiac dysfunction and coagulopathy

after birth with a history of in utero exposure to 2 doses of SPIKEVAX during the 3rd trimester. The third fatal case in <12-year-olds during the reporting period was a report of death due to transposition of the great arteries and tricuspid valve regurgitation in a 3-month-old infant exposed to SPIKEVAX at 2 weeks gestation. Based on available data, there is insufficient evidence at this time to suggest a potential causal association between SPIKEVAX and fatalities in subjects <12 years of age. See Appendix 20.11.72 and Appendix 20.11.73 or full listing of fatal cases in <12-year-olds during the reporting period.

Adolescents ages 12-17 Years (Reporting Period 01 Jul to 31 Dec 2021)

During the reporting period (01 Jul 2021 to 31 Dec 2021) there were 6 fatal cases reported in adolescents (12–17-year-olds) which were as follows:

- One case of death in a 13yo male had limited details provided
- One case was a report of cerebral hemorrhage in 15yo male one day after vaccination in a patient with a history of cerebral arteriovenous malformation
- One case of death and myocarditis in a 17-year-old with a history of cardiomyopathy with unknown time to onset after vaccination
- One case of death in a 17-year-old male found dead in his bedroom after his second dose with limited details provided
- One case reported death due to fever, seizure and headache in a 13-year-old male with symptom onset 7 days after vaccination with SPIKEVAX
- One case in a 14-year-old female with a history of fainting 2 months prior that reported cardiac arrest, brain injury, brain herniation and multiple organ dysfunction syndrome. The patient experienced dizziness, headache and pyrexia prior to bed 16 days after the first dose of SPIKEVAX and was found unconscious the following morning.

Based on available data, there is insufficient evidence at this time to suggest a potential causal association between SPIKEVAX and fatalities in subjects 12-17 years of age. See Appendix 20.11.74 and Appendix 20.11.75 for a full listing of fatal cases in 12–17-year-olds during the reporting period.

SPIKEVAX Booster (Reporting Period 01 Jul to 31 Dec 2021)

During the reporting period (01 Jul 2021 to 31 Dec 2021), there have been 143 fatal cases reported in subjects who received >2 doses of SPIKEVAX. The majority of the cases were considered expected (57.9%), having underlying medical conditions that were considered risk factors for death and/or a marker of frailty (Table 16-213). This is likely reflective of the older demographics

of recipients of >2 doses of SPIKEVAX and that more medically complex subjects may have been receiving a booster doses.

Table 16-213 Summary of Reporting Period (01 Jul 2021 to 31 Dec 2021) Fatal Cases by Dose

	Review Period 01 Jul to 31 Dec 2021 Fatal Cases							
	Dose no prior to onset							
	Dose 1		Dose 2		Dose 3		Unknown	
	N	%	N	%	N	%	N	%
All	570	100	973	100	142	100	729	100
Age (years)								
<18	3	0.53	1	0.1	.	.	5	0.69
18-30	19	3.33	32	3.29	.	.	27	3.7
31-50	76	13.33	84	8.63	9	6.34	76	10.43
51-64	112	19.65	125	12.85	23	16.2	120	16.46
65-74	146	25.61	241	24.77	31	21.83	158	21.67
≥75	205	35.96	486	49.95	77	54.23	240	32.92
Missing	9	1.58	4	0.41	2	1.41	103	14.13
Sex								
Male	372	65.26	575	59.1	80	56.34	396	54.32
Female	188	32.98	387	39.77	61	42.96	281	38.55
Missing	10	1.75	11	1.13	1	0.7	52	7.13
Region								
Asia	108	18.95	91	9.35	3	2.11	233	31.96
Canada	.	.	.	.	.	.	12	1.65
European Economic Area	67	11.75	76	7.81	19	13.38	150	20.58
Latin America	.	.	.	.	.	.	1	0.14
Middle East	.	.	.	.	.	.	1	0.14
Oceana	1	0.18	.	.	.	.	1	0.14
Switzerland	4	0.7	15	1.54	3	2.11	10	1.37
United Kingdom	4	0.7	3	0.31	6	4.23	11	1.51
United States	386	67.72	788	80.99	111	78.17	310	42.52
Dose number prior to death*								
Dose 1	570	100	.	.	.	.	.	.
Dose 2	.	.	973	100	.	.	.	.
Dose 3	.	.	.	.	142	100	.	.
Unknown	.	.	.	.	.	.	729	100
HCP								
Medically Confirmed	489	85.79	909	93.42	128	90.14	498	68.31
Not Medically	81	14.21	64	6.58	14	9.86	231	31.69

	Review Period 01 Jul to 31 Dec 2021 Fatal Cases							
	Dose no prior to onset							
	Dose 1		Dose 2		Dose 3		Unknown	
	N	%	N	%	N	%	N	%
Confirmed								
Death type								
Expected	351	61.58	616	63.31	106	74.65	325	44.58
Not expected	219	38.42	357	36.69	36	25.35	404	55.42
Significant comorbidity documented in the medical record								
None	241	42.28	432	44.4	43	30.28	446	61.18
At least one	329	57.72	541	55.6	99	69.72	283	38.82
Arrhythmia	42	7.37	84	8.63	16	11.27	29	3.98
COVID	19	3.33	25	2.57	8	5.63	11	1.51
Cardiovascular disease	153	26.84	282	28.98	50	35.21	111	15.23
Chronic kidney disease	50	8.77	98	10.07	15	10.56	34	4.66
Chronic liver disease	11	1.93	13	1.34	1	0.7	8	1.1
Coagulopathy	4	0.7	5	0.51	2	1.41	.	.
Diabetes and related conditions	117	20.53	195	20.04	28	19.72	68	9.33
Elderly/frail	12	2.11	28	2.88	10	7.04	12	1.65
Gastroenterology	3	0.53	1	0.1	2	1.41	1	0.14
General	.	.	1	0.1	.	.	.	.
Genetic	.	.	1	0.1	1	0.7	1	0.14
Hematology	1	0.18	2	0.21	3	2.11	2	0.27
Hypertension	166	29.12	291	29.91	45	31.69	121	16.6
Infection	5	0.88	11	1.13	2	1.41	2	0.27
Neurologic	29	5.09	61	6.27	20	14.08	33	4.53
Obesity	31	5.44	36	3.7	8	5.63	18	2.47
Oncology	46	8.07	90	9.25	19	13.38	48	6.58
Other	11	1.93	22	2.26	3	2.11	4	0.55
Respiratory	83	14.56	131	13.46	23	16.2	40	5.49
Rheumatologic	3	0.53	9	0.92	3	2.11	2	0.27
Stroke	32	5.61	49	5.04	10	7.04	23	3.16
Substance use	1	0.18	6	0.62	.	.	1	0.14
Thromboembolic	12	2.11	31	3.19	4	2.82	7	0.96
Transplant	6	1.05	22	2.26	.	.	7	0.96
Markers of Frailty	212	37.19	379	38.95	67	47.18	164	22.5
Cause of Death								

	Review Period 01 Jul to 31 Dec 2021 Fatal Cases							
	Dose no prior to onset							
	Dose 1		Dose 2		Dose 3		Unknown	
	N	%	N	%	N	%	N	%
COPD	1	0.18	.	.	.	.	1	0.14
Cardiovascular (Including Cardiorespiratory failure)	80	14.04	138	14.18	29	20.42	97	13.31
General condition or natural causes	28	4.91	37	3.8	8	5.63	40	5.49
Hemorrhage (including CNS hemorrhage)	20	3.51	21	2.16	2	1.41	16	2.19
Infection (including COVID and fever NOS)	80	14.04	260	26.72	9	6.34	81	11.11
Neurologic (excluding strokes)	17	2.98	20	2.06	4	2.82	27	3.7
Oncology	3	0.53	5	0.51	2	1.41	12	1.65
Other causes	54	9.47	89	9.15	15	10.56	72	9.88
Respiratory	42	7.37	82	8.43	6	4.23	30	4.12
Stroke	13	2.28	13	1.34	1	0.7	17	2.33
Thromboembolic (excluding myocardial infarction and stroke)	11	1.93	14	1.44	1	0.7	16	2.19
Unknown	221	38.77	294	30.21	65	45.77	320	43.9

*: Dose number in this analysis is based on Time-To-Death where date of death is known, whereas the main analysis, including for booster recipients, is based on Time-To-Event for events with a fatal outcome with a known event onset date.

While there is a temporal association between fatal cases and receipt of a 3rd dose of SPIKEVAX, based on the limited details currently available, the multiple co-morbidities in the majority of the cases and the elderly age of most of the recipients, there is insufficient information to support a potential causal association between >2 doses of SPIKEVAX and fatality.

Fatal Cases in 18–30-Year-Olds with Cardiac Events (Reporting Period 01 Jul to 31 Dec 2021):

During the reporting period (01 Jul 2021 to 31 Dec 2021), there were 78 fatal cases reported in subjects 18 to 30-year-olds, of which 28 cases were associated with a cardiac event. Appendix 20.11.76 and Appendix 20.11.77 for a complete listing of fatal cases in 18–30-year-olds with cardiac events. Fatal cardiac events in young adults are being reviewed by the MAH as part of the ongoing surveillance for events of myocarditis and pericarditis (Section 16.3.1.2).

16.3.6.8.2.5. Discussion

Overall, the observed mortality rate was substantially below the expected rate. The events with a fatal outcome in subjects who received SPIKEVAX are similar in distribution to those reported by the CDC as the most frequent causes of death in the US [199]. Most doses of SPIKEVAX have been administered in the US, providing support for the validity of this finding. The demographics and comorbid medical conditions in subjects who died following SPIKEVAX is consistent with baseline populations at higher risk of death. Review of cumulative cases of sudden death and sudden cardiac death indicates that most of the events were reported in subjects with 1) other comorbid risk factors for death: or 2) had insufficient information provided to reliably assess the case.

Analysis of the data reported during the reporting period of this PBRER continues to provide support for a lack of a causal association between fatal events and SPIKEVAX.

16.3.6.8.2.6. Conclusion

The data provided in this PBRER describe sufficiently the safety profile of SPIKEVAX in the interval and cumulatively reporting interval. The benefit-risk evaluation remains positive.

Based on the analysis of all the safety data available as of 31 Dec 2021, the MAH considers that fatalities are not presently a safety issue of concern and the MAH will continue to evaluate fatal cases using routine surveillance.

Based on the analysis of all the safety data received during the reporting period of this PBRER, ModernaTX, Inc considers that fatal cases, reported in temporal association with the administration of SPIKEVAX, did not raise any safety issue of concern and the information provided is inadequate to provide evidence of causality between SPIKEVAX exposure and death. These data do not represent a new safety issue of concern. ModernaTX, Inc will continue to monitor fatal outcomes in SPIKEVAX recipients using routine surveillance. The benefit-risk evaluation remains positive.

16.3.6.8.3. Overdose

16.3.6.8.3.1. Source of the New Information

ModernaTX, Inc queried the GSDB cumulative from 18 Dec 2020 to 31 Dec 2021, for valid, spontaneous case reports received from HCP, HA, consumers, and literature, worldwide, reported for SPIKEVAX.

16.3.6.8.3.2. Background Relevant to the Evaluation

Assessing harm due to administration of an extra dose of a vaccine is not well understood. Among all the VAERs reports received from 2007- 2018, more than three-fourths of the reports of an excess dose of vaccine did not describe an adverse event. Among reports where an adverse event was reported, most of the common events included expected conditions such as pyrexia, injection site erythema, pain and headache. Although most of the reports were of other vaccines (e.g., trivalent inactivated influenza, varicella, hepatitis A, and measles, mumps, rubella, varicella, the percentage of the adverse events among these vaccine reports were comparable to all reports submitted to VAERS during the same period [200]. Other case reports of excess administration (or overdose) in a woman in Italy, who accidentally received six doses of the Pfizer-BioNTech COVID-19 vaccine all at once, without experiencing any serious side effects have been published [201]. Although these data have been mainly anecdotal, overdose appears to be rare with limited harm/effects.

16.3.6.8.3.3. Methods

Cases reports in ModernaTX, Inc global database reporting overdose, or administration of more than 2 doses or more than indicated volume of SPIKEVAX were reviewed.

An “Overdose” is judged by regulatory definitions, such as, “Administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the authorized product information.” (EMA GVP Annex 1 Definitions – Rev 4).

Previously, two doses of ModernaTx SPIKEVAX were recommended and an “Overdose” was considered a dose(s) above the EUA-approved recommended 2 doses. Following the approval of a 3rd booster dose of ModernaTx SPIKEVAX COVID-19 vaccine for use as determined by specific country/region approvals, reported “Overdose” is assessed accordingly. In many jurisdictions a 3rd dose may be administered to immune compromised persons or as a booster dose to other (immune competent) persons.

The search criteria applied for identification of Overdose cases included the following terms: Accidental Overdose, Overdose, Intentional Overdose, and Prescribed Overdose.

The PBRER/PSUR No. 2 reporting interval (01 Jul 2021 –31 Dec 2021) data was examined critically to determine any new and significant overdose patterns that may indicate new trends, risks or signals of SPIKEVAX not previously known or identified in the last reporting interval and in the context of cumulative information on risks and benefits. Also, any inter-relatedness of Overdose and Off Label Use was evaluated. Overall, medical review of overdose data for this

PBRER reporting interval relative to the cumulative information was also focused on identifying and summarizing new overdose safety information that may impact benefit-risk balance.

16.3.6.8.3.4. Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Overview of Overdose Cases

A review of overdose associated SPIKEVAX was performed using the search MI-OD (Yes). A narrative review of Off Label Use cases was conducted to determine qualitative correlates to overdose, especially accidental overdose, for further medical evaluation.

Cumulative Review

Cumulatively, 618 overdose cases (1,335 events; 190 serious events) have been reported of which 56 cases were serious, 5 with a fatal outcome, and 450 cases were medically confirmed. Of the 618 overdose cases, 322 cases (55 serious cases, 6 with a fatal outcome) were associated with a reported event. Most of the cases were from the USA (443, 71.7%) followed by the United Kingdom (75, 12.1%).

Cumulatively, amongst the top 10 most frequently reported Overdose events (MedDRA Preferred Terms – PTs), Accidental overdose ranked highest followed by Overdose (231 events; 17.3%) and 2nd (87 events; 6.5%), respectively. Amongst reported events associated with Overdose, Pyrexia, (48; 3.6%) Headache (47; 3.5%), Chills (38; 2.8%) and Fatigue (37; 2.8%) ranked highest, consecutively. Overall, cumulative Overdose-associated events reported are consistent with a reactogenicity profile.

Other than Overdose event terms which are specific to the Overdose cases, adverse events most frequently reported in Overdose cases were comparable or lower in reporting frequency to events reported in the general reporting population and are presented in the table below. The top 10 most frequently reported event terms with Off label use are presented below (Table 16-214).

Table 16-214 The Top 10 Most Frequently Report PTs with Overdose and General Population (Cumulative)

Cumulative - Overdose			Cumulative – General Population**		
PT	# Events	% of Total Events	PT	# Events	% of Total Events
Accidental overdose	231	17.3%	Headache	89,454	5.4%
Overdose	87	6.5%	Pyrexia	89,235	5.4%

Cumulative - Overdose			Cumulative – General Population**		
PT	# Events	% of Total Events	PT	# Events	% of Total Events
Pyrexia	48	3.6%	Fatigue	76,889	4.7%
Headache	47	3.5%	Chills	62,451	3.8%
Chills	38	2.8%	Myalgia	54,167	3.3%
Fatigue	37	2.8%	Nausea	45,937	2.8%
Myalgia	36	2.7%	Pain in extremity	39,365	2.4%
Pain in extremity	32	2.4%	Injection site pain	38,764	2.3%
Expired product administered	28	2.1%	Malaise	36,335	2.2%
Inappropriate schedule of product administration	27	2.0%	Pain	34,007	2.1%

**Percentages are calculated based on the cumulative number of events (1,335) in Overdose cases with other associated events. Cumulative overview of cases and demographics data for Overdose cases are presented at the beginning of this Overdose section.
**Percentages are calculated based on the cumulative number of all events (1,650,223) in cases reported for the general population. Additional data for the general population includes the following: a cumulative total of 429,577 cases (88,427 serious cases; 5,282 cases with a fatal outcome; 235,671 medically confirmed) yielded 1,650,223 events (288,442 serious events; 15,129 fatal events); 581,167 events resolved by PBRER No. 2 DLP of Dec 31, 2021. The median age of patients was 49 years (37,358 missing age values) with events occurring in 116,628 males (27.2%), 295,065 females (68.7*%), and 17,864 (4.2%) missing gender values.

Cumulatively, the median age was 59.0 years (min: 12.0 and Max: 97.0) with events occurring in 222 males (35.9%), 302 females (48.9%), and 94 missing gender values. Females in the 50-64 age group represent the highest population of cases (74; 12.0%) followed by the 65-74 age group (67; 10.8%). The distribution of case count by gender and age group is shown in Table 16-215 below.

Table 16-215 Number and Percentage of Reported Overdose Cases by Gender and Age – Cumulative to 31 Dec 2021

Age Group	Female		Male		Unknown		Total # Cases	Total % Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
12-15	2	0.3%	0	0	0	0	2	0.3%
16-17	1	0.2%	1	0.2%	0	0	2	0.3%
18-29	26	4.2%	14	2.3%	1	0.2%	41	6.6%
30-39	30	4.9%	22	3.6%	0	0	52	8.4%
40-49	37	6.0%	20	3.2%	1	0.2%	58	9.4%
50-64	74	12.0%	48	7.8%	2	0.3%	124	20.1%
65-74	67	10.8%	53	8.6%	6	1.0%	126	20.4%
75+	31	5.0%	22	3.6%	2	0.3%	55	8.9%
Missing	34	5.5%	42	6.8%	82	13.3%	158	25.6%
Grand	**302**	**48.9%**	**222**	**35.9%**	**94**	**15.2%**	**618**	**100.0%**

Age Group	Female		Male		Unknown		Total # Cases	Total % Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
total								

Cumulatively, events of overdose occurred most frequently with Dose 3 (384 reports: 28.8%). Following Dose 1, majority of the events (180, 13.5%) occurred on vaccination day (Day 0) and then between 24 to 48 hours (34, 2.5%) (Table 16-216). A similar pattern of event occurrence was noted following Doses 2 and 3. For Dose 4, there's insufficient data to support meaningful interpretation. The table below shows details of latency by dose number.

Table 16-216 Overdose Events: Latency by Dose number (Cumulative)

Dose Number	First Dose Latency	# of Events	% Events
Dose 1	Subtotal	236	17.7%
	0 days	180	13.5%
	01-02	34	2.5%
	03-04	1	0.1%
	05-06	6	0.4%
	07-13	4	0.3%
	14-29	3	0.2%
	30+	8	0.6%
Dose 2	Subtotal	233	17.5%
	0 days	133	10.0%
	01-02	45	3.4%
	03-04	10	0.7%
	05-06	6	0.4%
	07-13	8	0.6%
	14-29	22	1.6%
	30+	9	0.7%
Dose 3	Subtotal	384	28.8%
	0 days	279	20.9%
	01-02	92	6.9%
	03-04	6	0.4%
	05-06	3	0.2%
	07-13	1	0.1%
	30+	3	0.2%
Dose 4	Subtotal	4	0.3%
	0 days	2	0.1%
	01-02	2	0.1%
Unknown	Subtotal	478	35.8%

Dose Number	First Dose Latency	# of Events	% Events
	Missing	478	35.8%
Grand total		**1,335**	**100.0%**

Children ages < 12 Years (Cumulatively as of 31 Dec 2021)

There have been no cumulative Overdose reports in children of < 12 years of age.

Adolescents ages 12-17 Years (Cumulatively as of 31 Dec 2021)

Cumulatively as of 31 Dec 2021, 4 overdose cases (8 events; 1 serious event) have been reported, of which one case was serious, none with a fatal outcome, and 3 cases were medically confirmed. Of the 4 overdose cases, 3 cases (one non-fatal serious case) were associated with a reported event. Accidental overdose and 'Product administered to patient of inappropriate age' both ranked highest (2 events, 25.0%) as the most frequently reported Overdose terms. All other event terms reported only one event. Erythema (1, 12.5%) was the only reported adverse event term associated with Overdose. Previously presented in SPIKEVAX monthly reports, the adverse event of erythema was reported in a case for a 12 y/o female (4.1(b)) that experienced 'Maternal exposure during pregnancy' and Accidental Exposure without any reported medical history, treatment or concomitant medications. By the data lock point of this reporting interval, no significant follow-up was received about this case. The median age of the adolescent was 14.5 years (min: 12.0 and Max: 17.0) with events occurring in one male (25.0%) and 3 females (75.0%). The distribution of case count by gender and age group is as follows: two 12-15 y/o females, and 1 female and 1 male in the 16-17 y/o group. Adolescent data is still nascent and limited to support critical evaluation.

SPIKEVAX Booster (Cumulatively as of 31 Dec 2021)

Cumulatively as of 31 Dec 2021, 277 overdose cases (388 events; 23 serious events) have been reported, of which 7 cases were serious with one case had a fatal outcome. A total of 199 cases were medically confirmed. Of the 277 cumulative overdose cases, 125 cases (8 serious cases, one with a fatal outcome) were associated with a reported event. Accidental overdose (111, 28.6%) and 'Expired product administered' (25, 6.4%) both ranked highest as the most frequently reported Overdose terms, followed by 'Inappropriate schedule of product administration' (15, 3.9%), Headache (13, 3.4%) and Overdose (11, 2.8%). The reporting frequency of all other event terms were at 2.6% or below. As of the data lock point of this reporting interval, 250 events of the 277 Overdose events had resolved. The median age of individuals who received SPIKEVAX Booster was 64.0 years (min: 23.0 and Max: 89.0; 33 missing age data values) with events occurring in 108 males (39.0%) and 152 females (54.9%), with 17 (6.1%) missing data values. Females in the

50-64 age group represent the highest population of cases (51; 18.4%) followed by the 65-74 age group (43; 15.5%).

Reporting Interval (01 Jul 2021 – 31 Dec 2021)

During this PBRER No. 2 interval period, 461 overdose cases (943 events; 159 serious events) have been reported of which 39 cases were serious, 3 with a fatal outcome, and 321 of the 461 cases were medically confirmed. Of the 461 overdose cases, 227 cases (39 serious cases, 3 with a fatal outcome) were associated with a reported event.

During the reporting interval, Accidental overdose was the most frequently reported event (Reporting Interval: 169, 17.9%), followed by Overdose (55, 5.8%) (Table 16-217). Except for minor non-significant differences in ranking, the patterns of occurrence of adverse events were similar to the cumulative data landscape (Table 16-218). Also, adverse events reported following overdose were generally consistent with labelled reactogenicity events as shown in Table 16-217 below.

Table 16-217 The Top 10 most Frequently Reported Preferred Terms (PTs) with Overdose (Reporting Interval)

PT	# Events	% of Total Events*
Accidental overdose	169	17.9%
Overdose	55	5.8%
Pyrexia	36	3.8%
Headache	33	3.5%
Expired product administered	28	3.0%
Fatigue	28	3.0%
Myalgia	28	3.0%
Chills	25	2.7%
Inappropriate schedule of product administration	24	2.5%
Pain in extremity	24	2.5%

*Percentages are calculated based on the total number of events (943) in cases of Overdose with other associated events for the review period.

Table 16-218 The Top 10 Most Frequently Report PTs with Overdose and General Population (Reporting Period)

Reporting Period- Overdose			Reporting Period – General Population**		
PT	# Events	% of Total Events*	PT	# Events	% of Total Events**
Accidental overdose	169	17.9%	Pyrexia	44,460	6.2%
Overdose	55	5.8%	Headache	40,502	5.7%
Pyrexia	36	3.8%	Fatigue	35,142	4.9%
Headache	33	3.5%	Myalgia	26,841	3.7%
Expired product administered	28	3.0%	Chills	24,215	3.4%
Fatigue	28	3.0%	Malaise	21,513	3.0%
Myalgia	28	3.0%	Nausea	19,187	2.7%
Chills	25	2.7%	Injection site pain	17,623	2.5%
Inappropriate schedule of product administration	24	2.5%	Vaccination site pain	16,031	2.2%
Pain in extremity	24	2.5%	Arthralgia	15,564	2.2%

**Percentages are calculated based on the cumulative number of events in cases (943) of Overdose with other associated events. Overview of Reporting Interval cases and demographics data for Overdose cases are presented above.
**Percentages are calculated based on the total number of reporting interval events (715,965) in cases reported for the general population. Additional reporting interval data for the general population includes the following: a total of 189,489 cases (52,667 serious cases; 2,414 cases with a fatal outcome; 75,675 medically confirmed) yielded 715,965 events (288,442 serious events; 8,960 fatal events); 231,450 events resolved by PBRER No. 2 DLP of Dec 31, 2021. The median age of patients was 44 years (15,885 missing age values) with events occurring in 59,418 males (31.4%), 121,917 females (64.3*%), and 8,154 (4.3%) missing gender values.

During the reporting interval, the median age of patients was 60.0 years (min: 12.0 and Max: 89.0) with events occurring in 169 males (36.7%), 228 females (49.5%), and 64 (13.9%) missing gender values. Females in the 50-64 age group represent the highest population of cases (59; 12.8%) followed by the 65-74 age group (54; 11.7%). The distribution of case count by gender and age group is shown in Table 16-219 below.

Table 16-219 Number and Percentage of Reported Overdose Cases by Gender and Age – Reporting Period to 01 Jul 2021 - 31 Dec 2021

Age Group	Female		Male		Unknown		Total # Cases	Total % Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
12-15	2	0.4%	0	0	0	0	2	0.4%
18-29	21	4.6%	8	1.7%	1	0.2%	30	6.5%
30-39	16	3.5%	11	2.4%	0	0	27	5.9%
40-49	27	5.9%	14	3.0%	0	0	41	8.9%
50-64	59	12.8%	42	9.1%	1	0.2%	102	22.1%
65-74	54	11.7%	41	8.9%	6	1.3%	101	21.9%

Age Group	Female		Male		Unknown		Total # Cases	Total % Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
75+	23	5.0%	14	3.0%	1	0.2%	38	8.2%
Missing	26	5.6%	39	8.5%	55	11.9%	120	26.0%
Grand total	**228**	**49.5%**	**169**	**36.7%**	**64**	**13.9%**	**461**	**100.0%**

During this PBRER No. 2 interval period, a similar pattern was observed with the highest number of Overdose-associated events reported following Dose 3 (378, 40.1%). While the percentage of events after Dose 3 was higher during the interval period, this can be explained possibly by increased exposure to Dose 3 following recent regulatory approvals in various countries. Majority of the events were reported within 1-4 days regardless of the dose number; Dose 4 data is too limited to support meaningful interpretation (Table 16-220).

Table 16-220 Overdose Events: Latency by Dose number (Reporting Interval)

Dose Number	First Dose Latency	# of Events	% Events
Dose 1	Subtotal	119	12.6%
	0 days	96	10.2%
	01-02	11	1.2%
	03-04	0	0.0%
	05-06	2	0.2%
	07-13	2	0.2%
	14-29	2	0.2%
	30+	6	0.6%
Dose 2	Subtotal	118	12.5%
	0 days	55	5.8%
	01-02	22	2.3%
	03-04	6	0.6%
	05-06	6	0.6%
	07-13	6	0.6%
	14-29	14	1.5%
	30+	9	1.0%
Dose 3	Subtotal	378	40.1%
	0 days	273	29.0%
	01-02	92	9.8%
	03-04	6	0.6%
	05-06	3	0.3%
	07-13	1	0.1%
	30+	3	0.3%

Dose Number	First Dose Latency	# of Events	% Events
Dose 4	Subtotal	4	0.4%
	0 days	2	0.2%
	01-02	2	0.2%
Unknown	Subtotal	324	34.4%
	Missing	324	34.4%
Grand total		**943**	**100.0%**

Overdose frequently referred to either the receipt of the 3rd dose of vaccine or receiving more volume of vaccine than indicated. The volume of vaccine in overdose most frequently reported was 1ml.

Other than Accidental Overdose, which is specific to the Overdose cases, adverse events frequently reported following overdose were comparable or lower in reporting frequency to events reported in the general reporting population and are presented in the table below. The top 10 most frequently reported event terms with overdose are presented below:

Children ages < 12 Years (Reporting Interval)

Reporting Interval (01 Jul 2021 – 31 Dec 2021)– Children (0-11 years)

There have been no Overdose reports in children of < 12 years of age during the reporting period (01 Jul 2021 to 31 Dec 2021).

Adolescents ages 12-17 Years (Reporting Period)

Reporting Interval (01 Jul 2021 – 31 Dec 2021)– Adolescent (12-17 years)

During the reporting period (01 Jul 2021 to 31 Dec 2021), 2 overdose cases (3 events; 1 serious event) was reported for two female 12-year-olds, of which one case was serious, none with a fatal outcome, and one case was medically confirmed. Two events of Accidental overdose were reported.

Overall, the SPIKEVAX Adolescent Overdose data is still evolving at a nascent stage and has not provided any new significant information that deviates from known cumulative data profile of the vaccine product.

SPIKEVAX Booster (Reporting Period)

SPIKEVAX Booster (Reporting Period - (01 Jul 2021 – 31 Dec 2021)

During the reporting period (01 Jul 2021 to 31 Dec 2021), 271 overdose cases (382 events; 23 serious events) have been reported, of which 7 cases were serious and one case had a fatal outcome. A total of 194 cases were medically confirmed. Of the 271 cumulative overdose cases, 122 cases (7 serious cases, one with a fatal outcome) were associated with a reported event. Accidental

overdose (109, 28.5%) and 'Expired product administered' (25, 6.5%) both ranked highest as the most frequently reported Overdose terms, followed by 'Inappropriate schedule of product administration' (15, 3.9%), and Headache (13, 3.4%). The reporting frequency of all other event terms were at 2.6% or below. As of the data lock point of this reporting interval, 245 events of the 382 Overdose events had resolved. The median age of individuals who received SPIKEVAX Booster was 64.0 years (min: 23.0 and Max: 89.0; 31 missing age data values) with events occurring in 103 males (38.0%) and 152 females (56.1%), with 16 (5.9%) missing data values. Females in the 50-64 age group represent the highest population of cases (51; 18.8%) followed by the 65-74 age group (43; 15.9%).

Overall, the reporting interval SPIKEVAX Booster data has not provided any new significant information that deviates from known cumulative data profile of the vaccine product.

Serious Cases (Reporting Period)

During the reporting period (01 Jul 2021 to 31 Dec 2021), there were 39 serious overdose cases. (See Appendix 20.11.78 for a comprehensive listing).

Below we describe selected serious cases of interest.

4.1(b) **:** On 17-Jun-2021 this 21-year-old pregnant female patient received a second dose of mRNA-1273 (Moderna COVID-19 Vaccine) (Intramuscular) dosage that was reported as an Overdose, but the exact dosage was not given. The patient's last menstrual period was on an unknown date and the estimated date of delivery was 4.1(b) -2021 On 21-Jun-2021, the patient presented to the emergency room with new onset chest pain and dizziness. Diagnostic tests reported SARS-CoV-2 test: negative Troponin: 3.180 and white blood cell count 15000. She was diagnosed with spontaneous coronary artery dissection and was admitted to the hospital and treated with a beta blocker and blood thinners. According to the report there was no evidence of myocarditis. No further information available. Causality assessment is possible based on temporal association, but the disease is known to occur during pregnancy as is the more likely explanation.

4.1(b) **:** This 36-year-old male experienced injection site pain, fever, and a seizure the day he received a second dose of SPIKEVAX. The dose was reported as an Overdose, but a dose was not specified. All symptoms resolved. Causality assessment is possible.

4.1(b) **:** This regulatory authority case was reported by a physician and describes the occurrence of optic ischemic neuropathy in a 79-year-old female patient who received mRNA-1273 (COVID-19 Vaccine Moderna) for COVID-19 vaccination. On an unknown date, the patient received dose of mRNA-1273 (COVID-19 Vaccine Moderna) (Intramuscular) 200 micrograms as a first dose and 10 days later experienced optic ischemic neuropathy. No past medical history or concomitant medication history was available. At the time of the report the neuropathy had

resolved with sequelae after long-term steroid therapy. Causality assessment is considered possible based on temporal relationship as no past medical history of concomitant medication history was available.

4.1(b) **:** This spontaneous report from a consumer concerns a 30-year-old female who reported to have received a full vial (6 doses) of SPIKEVAX on 17 Mar 2021. He was hospitalized for 1 DAY with peroneal nerve palsy, left sided hypoesthesia, incontinence, malabsorption and eye pattern disorder. She received physical therapy for the peroneal nerve palsy. She was subsequently hospitalized on 24 Mar and 19 Jul for unspecified reasons. Past medical history and concomitant medications were not provided. Based on temporal relationship the causality is possible but there is significant missing information, and no medical records are available.

4.1(b) **:** This regulatory authority case was reported by another health care professional and describes the occurrence of pyrexia and anaphylaxis in a 27-year-old female patient who received mRNA-1273 (Moderna CoviD-19 Vaccine) (batch no. 3003651) for COVID-19 vaccination on 17 Aug 202. Her symptoms occurred that day after vaccination. The patient's past medical history included decreased lactation and anaphylaxis. Previously administered products included for contraception: DEPO-PROVERA (Had reaction one month ago.). Past adverse reactions to the above products included anaphylaxis with DEPO-PROVERA. The patient was treated with EPINEPHRINE (EPIPEN) at an unspecified dose and frequency. At the time of the report, pyrexia had resolved, and anaphylactic reaction was resolving. Based on temporal association and the patient’s prior history causality is possible.

4.1(b) **:** This case concerns a 62-year-old female patient with a history of stroke, Raynaud’s phenomenon, “Sherwin’s” disease and complex regional pain syndrome, who experienced Accidental overdose, Condition aggravated, Cough, Headache, Illness, Mobility decreased, Myalgia, Nasal congestion, Nausea, Neuropathy peripheral, Pain, Peripheral swelling, Photophobia, Pruritus, and Vaccination complications starting on same day after the third SPIKEVAX dose .It was reported that she received a full dose rather than a half dose as the booster dose. Causality assessment is possible based on temporal association.

4.1(b) **:** This case concerns a 59-year-old, female patient with a history of Sjogren’s syndrome since 2005 who received her first dose of SPIKEVAX on 26 Feb 2021 and her second dose on 26 Mar 2021. On 19 Aug 2021, she received her third dose of SPIKEVAX (reported as a booster dose), as well as an influenza vaccine. On 19 Aug 2021, the patient experienced Accidental overdose, and 2 days later experienced Guillain-Barre syndrome (not diagnosed until 5 Nov 2021) with symptoms of bilateral lower extremity weakness and loss of coordination. On 24 Aug 2021, the patient experienced mixed connective tissue disorder and additional non-serious events.

From the narrative the booster was given less than 6 months from the primary series. The mixed connective tissue disease is most likely a pre-existing condition. No further information is available for this report. Causality assessment is confounded by history of Sjogren's syndrome and mixed connective tissue disease.

4.1(b) **:** This is a spontaneous case of accidental overdose and interchange of vaccine products for this patient, of unknown age and gender, with relevant past drug history of receiving two doses of Pfizer COVID-19 vaccine, who experienced unilateral deafness after administration of the booster dose of the Moderna mRNA-1273 vaccine. The date of vaccine administration and start date of the event were not provided. The patient received a full dose of the Moderna booster vaccine and after 5 days developed complete hearing loss of the right ear. The patient sought consultation. Magnetic Resonance Imaging and other investigations on the right ear were done but no cause for the deafness has been found. No further details were provided. Treatment information was also not provided. The outcome of the event was unknown at the time of the report. The history of administration of the Pfizer COVID-19 vaccine remains a confounder. The causality assessment is possibly based solely on temporal association and is confounded by the prior administration of Pfizer vaccine.

4.1(b) **:** This spontaneous case concerns a 70-year-old female patient with a medical history of pain in extremity (leg pain), who experienced the unexpected serious (hospitalization and medically significant) events/AESI of Deep vein thrombosis and Pulmonary embolism after the booster mRNA- 1273 Moderna vaccine. Additionally, Accidental overdose occurred (booster dose was reported as 100 micrograms). The events were diagnosed approximately 36 days after the booster dose of mRNA- 1273 vaccine. Clinical manifestations included leg pain, which started 2 weeks after the third dose. Leg ultrasound and Computer tomogram were performed, which showed bilateral deep vein thrombosis and pulmonary embolism. The patient was admitted for 3 days. Echocardiogram was also performed, but results are not available. Treatment with heparin was prescribed, and later switched to Apixaban. The benefit-risk relationship of mRNA- 1273 vaccine is not affected by this report. The patient has a prior history of leg pain and is elderly. The onset of symptoms is 36 days after vaccination whereas the normal window for a vaccine-associated event is 1-28 days. The causality is rated as possible based solely on temporal association.

Additional Overdose cases identified by medical review of Off label use cases

4.1(b) **:** This regulatory authority case was reported by a physician and describes the occurrence of Genital Herpes Simplex (Genitale Herpes simplex 4.1(b)) in a 56-year-old male patient who received mRNA-1273 (COVID-19 Vaccine Moderna) for COVID-19 vaccination. No Medical History information was reported. On 19 Apr

2021, the patient received first dose of mRNA-1273 (COVID-19 Vaccine Moderna) (Intramuscular) 200 micrograms. On an unknown date, the patient received second dose of mRNA-1273 (COVID-19 Vaccine Moderna) 200 micrograms. On 29 Apr 2021, the patient experienced Genital Herpes Simplex (Genitale Herpes simplex 4.1(b)) (seriousness criterion medically significant). On an unknown date, the patient experienced Pain in extremity (pain in arm) and Fatigue (tiredness). On 21 May 2021, Genital Herpes Simplex (Genitale Herpes simplex 4.1(b)) had resolved. On 12 May 2021, Herpes simplex test positive: 3.5 (Positive) (>3.5 MOC; normal value <1.0). For mRNA-1273 (COVID-19 Vaccine Moderna) (Unknown Route), the reporter considered Genital Herpes Simplex (Genitale Herpes simplex 4.1(b)) to be possibly related. No treatment product information was provided. Based on temporal relationship a causality of possible is assigned.

4.1(b) **:** This regulatory authority case was reported by a physician and describes the occurrence of Balance Disorder (4.1(b)), Paraesthesia (4.1(b)) and Dizziness (4.1(b)) in a 43-year-old male patient who received mRNA-1273 (COVID-19 Vaccine Moderna) for COVID-19 vaccination. The occurrence of additional non-serious events is detailed below. No Medical History information was reported. On an unknown date, the patient received first dose of mRNA-1273 (COVID-19 Vaccine Moderna) (Intramuscular) 200 micrograms. On 12-Jun-2021, the patient received second dose of mRNA-1273 (COVID-19 Vaccine Moderna) (Intramuscular) dosage of 200 micrograms. On 23-Jun-2021, the patient experienced Balance Disorder (4.1(b)) (seriousness criteria disability and medically significant), Paraesthesia (4.1(b)) (seriousness criteria disability and medically significant) and Dizziness (4.1(b)) (seriousness criteria disability and medically significant). On 13 Jul 2021, Paraesthesia (4.1(b)) had not resolved. At the time of the report, Balance Disorder (4.1(b)) had not resolved, Dizziness (4.1(b) Off label use (200 mcg dose) had resolved, Concomitant medications were not provided by the reporter. Treatment information was not provided. Based on temporal association the causality is rated as possible.

Fatal outcomes reports (Reporting Period):

During the reporting period (01 Jul 2021 to 31 Dec 2021) there were 3 cases with fatal outcomes. All 3 Overdose cases with a fatal outcome are described below.

4.1(b) **:** This case was received via United States FDA VAERS (Reference number: 4.1(b)) on 31 Aug 2021 and was forwarded to Moderna on 31 Aug 2021. This regulatory authority case was reported by other health care professional and describes the occurrence of Completed suicide, Depression, Depressed mood, Confusional state, Fatigue, Overdose and

Weight decreased in a 70-year-old male patient who received mRNA-1273 (Moderna COVID-19 Vaccine) (batch no. 028L20A) for COVID-19 vaccination. The patient's past medical history included Leg pain. Concurrent medical conditions included Hypertension and High cholesterol. Concomitant products included Atenolol, Lisinopril, Simvastatin, Ezetimibe, (Zetia), Ibuprofen, and Escitalopram Oxalate (Lexapro) for an unknown indication. This is not a case of vaccine overdose.

4.1(b) : This case was received via United States FDA VAERS (Reference number: 4.1(b)) on 14-Sep-2021 and was forwarded to Moderna on 14 Sep 2021. This regulatory authority case was reported by other health care professional concerns a death of 57-year-old, male patient with relevant medical history of HIV disease, who experienced the unexpected events of lymphoma, gastrointestinal reflux disease, victim of abuse, accidental overdose and interchange of vaccine products. The events occurred approximately 1 day after the third dose of Moderna COVID-19 Vaccine. It was reported that both Pfizer and Moderna vaccine were administered on the same day. The patient was hospitalized having lymph nodes cancer. The patient died approximately three months after the third dose of vaccine. and the reporter stated that either vaccine caused this or overdose when shift change happened because he was given too many pain medicines. Patient's medical history of HIV remains a confounder. Causality for event of victim of abuse is assessed as unlikely as his underlying illness is the more likely explanation.

4.1(b) **:** This case was received via United States FDA VAERS (Reference number: 4.1(b)) on 05 Oct 2021 and was forwarded to Moderna on 05 Oct 2021A 36-year-old, female patient with a medical history of tobacco and methamphetamine abuse and asthma, was seen in the emergency room for worsening asthma and intentional opioid overdose. She was noted to be doing “ok” except for minor wheezes on examination and was then given her 2nd SPIKEVAX dose. She was discharged home on a course of prednisone in case of exacerbation, because she had reported asthma worsening after first SPIKEVAX dose. She was found dead at home several days later with drug paraphernalia at the scene. Coroner reported cause of death as possible asthma exacerbation versus drug overdose. There is no information in this case that suggests an overdose of SPIKEVAX.

16.3.6.8.3.5. Discussion

Cumulatively, 618 overdose cases have been reported of which 56 cases were serious, 6 with a fatal outcome were associated with a reported event. During this reporting interval period, 461 overdose cases have been reported of which 39 cases were serious, and 3 with a fatal outcome associated with a reported event.

During this reporting interval, of the 39 cases of overdose with serious outcomes reported with SPIKEVAX Overdose and 2 Intentional overdoses of other drugs. The most frequently reported

preferred terms of harm, were in line with event terms expected with SPIKEVAX use. Two of the 39 serious cases (including fatal case) were not of SPIKEVAX overdose but overdoses of other drugs and accounted for 2 of the 3 reported deaths. All 11 of the serious cases presented above without a fatal outcome had confounding factors or alternative explanations for the events observed. Temporal association was the primary association that made SPIKEVAX considered possibly related to these events.

16.3.6.8.3.6. Conclusion

Cumulatively and based on the analysis of all the safety data received during this reporting interval of this PBRER, ModernaTX, Inc considers that Overdose cases reported in temporal association with the administration of SPIKEVAX, did not raise any safety concerns, and the information provided does not support or is inadequate to provide evidence of causality between SPIKEVAX exposure and reported Overdose and Overdose-associated events. The cumulative and reporting period data do not represent a new safety issue of concern. ModernaTX, Inc will continue to monitor events for Overdose and Overdose-associated events using routine surveillance.

Overall, based on the analysis of all the Overdose safety data in this period, there is no change in the known safety profile of SPIKEVAX. No significant information was identified that impacts SPIKEVAX benefit-risk balance. Therefore, the benefit-risk evaluation of SPIKEVAX remains positive.

16.3.6.8.4. Off-label use

16.3.6.8.4.1. Source of the New Information

Off label Use data presented below includes analysis performed on cases received by ModernaTX, Inc. from 01 Jul 2021 to 31 Dec 2021 (Reporting Interval for PBRER No. 2) for the mRNA-1273 vaccine (COVID-19 vaccine Moderna) SPIKEVAX. Cumulatively, the data reviewed covers the period from 18 Dec 2020 to 31 Dec 2021.

16.3.6.8.4.2. Background Relevant to the Evaluation

ModernaTX, Inc performs routinely monitors cases of Off label use of SPIKEVAX in patient populations, dosage or dosage form for which it is not currently authorized.

Off-label use is defined as, “Situations where a medicinal product is intentionally used for a medical purpose not in accordance with the terms of the marketing authorization. Examples include the intentional use of a product in situations other than the ones described in the authorized product information, such as a different indication in terms of medical condition, a different group of patients (e.g., a different age group), a different route or method of administration or a different

posology. The reference terms for off-label use are the terms of marketing authorization in the country where the product is used." (EMA GVP Annex 1 – Definitions [Rev 4]).

16.3.6.8.4.3. Methods of Evaluation including Data Sources, Search Criteria and Analytical Approaches

ModernaTX, Inc queried the GSDB cumulative to 31 Dec 2021, for valid, spontaneous case reports received from HCP, HA, consumers, and literature, worldwide, reported for SPIKEVAX using the search "STD- OL". MedDRA Preferred terms (PTs) included Off label use, Intentional Product use Issue, Intentional dose omission and Intentional product misuse.

The PBRER/PSUR No. 2 reporting interval (01 Jul 2021 –31 Dec 2021) data was examined critically to determine any new and significant Off label use patterns that may indicate new trends, risks or signals of SPIKEVAX not previously known or identified in the last reporting interval and in the context of cumulative information on risks and benefits. Also, any inter-relatedness of Off Label Use and Overdose was evaluated. Overall, medical review of Off label use data for this PBRER reporting interval relative to the cumulative information was also focused on identifying and summarizing new Off label use safety information (if any) that may impact benefit-risk balance.

16.3.6.8.4.4. Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

No relevant literature was published during this reporting period regarding off label use.

Overview of Cases

Cumulative Review (Off label Use, cumulative to 31 Dec 2021)

Cumulatively, 939 Off label use cases (4,474 events) have been reported, of which 203 were serious cases and 413 were medically confirmed. Of the 939 Off label use cases, 752 cases (203 serious cases, 3 with a fatal outcome) were associated with a reported event. The 752 cases with associated events reported at total of 621 serious events. Most of the cases were from the USA (528, 70.2%) followed by the EEA (104, 13.8%).

Off label use was the most frequently reported PT (438 events, 9.8%), followed by 'Intentional product use' (157, 3.5%), and 'Intentional dose omission' (151, 3.4%). Amongst the adverse event terms associated with Off Label Use, Headache (125) ranked highest with a reporting frequency of 2.8%, followed by Fatigue (117, 2.6%). All other events amongst the top ten most frequently reported PTs included Pyrexia (108, 2.4%), and Myalgia, Pain in extremity, and Chills, each with a reporting frequency of 2.0%. (Table 16-221).

Other than Off label use event term(s) which is specific to the Off-label use cases, adverse events most frequently reported in Off label use cases are comparable or lower in reporting frequency to event terms reported in the general reporting population. The top 10 most frequently reported event terms with Off label use are presented below (Table 16-221).

Cumulatively, Off-label use-associated events are consistent with reactogenicity of vaccines, and the MAH did not determine any significant deviation from the known adverse event profile of SPIKEVAX.

Table 16-221 The Top 10 Most Frequently Report PTs with Off label use and General Population (Cumulative)

Cumulative - Off label use			Cumulative – General Population**		
PT	# Events	% of Total Events	PT	# Events	% of Total Events
Off label use	438	9.8%	Headache	89,454	5.4%
Intentional product use issue	157	3.5%	Pyrexia	89,235	5.4%
Intentional dose omission	151	3.4%	Fatigue	76,889	4.7%
Headache	125	2.8%	Chills	62,451	3.8%
Fatigue	117	2.6%	Myalgia	54,167	3.3%
Pyrexia	108	2.4%	Nausea	45,937	2.8%
Myalgia	90	2.0%	Pain in extremity	39,365	2.4%
Pain in extremity	90	2.0%	Injection site pain	38,764	2.3%
Chills	88	2.0%	Malaise	36,335	2.2%
Product administered to patient of inappropriate age	76	1.7%	Pain	34,007	2.1%

**Percentages are calculated based on the cumulative number of events (4,474) in Off label use cases with other associated events. Cumulative overview of cases and demographics data for Off label use cases are presented at the beginning of this Off-label use section.

**Percentages are calculated based on the cumulative number of all events (1,650,223) in cases reported for the general population. Additional data for the general population includes the following: a cumulative total of 429,577 cases (88,427 serious cases; 5,282 cases with a fatal outcome; 235,671 medically confirmed) yielded 1,650,223 events (288,442 serious events; 15,129 fatal events); 581,167 events resolved by PBRER No. 2 DLP of Dec 31, 2021. The median age of patients was 49 years (37,358 missing age values) with events occurring in 116,628 males (27.2%), 295,065 females (68.7*%), and 17,864 (4.2%) missing gender values.

Cumulatively, the median age was 58.0 years (min: 0.0 and Max: 97.0) with events occurring in 282 males (30.0%), 565 females (60.2%), and 92 unknown gender values. Females in the 50-64 age group represent the highest population of cases (142; 15.1%) followed by the 65-74 age group (101; 10.8%). The distribution of case count by gender and age group is shown in Table 16-222.

Table 16-222 Number and Percentage of Reported Off Label Use Cases by Gender and Age – Cumulative to 31 Dec 2021

Age Group	Female		Male		Unknown		Total # Cases	Total % Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
<2	1	0.1%	1	0.1%	0	0	2	0.2%
02-11	0	0	2	0.2%	0	0	2	0.2%
12-15	12	1.3%	5	0.5%	2	0.2%	19	2.0%
16-17	38	4.0%	32	3.4%	11	1.2%	81	8.6%
18-29	23	2.4%	16	1.7%	4	0.4%	43	4.6%
30-39	52	5.5%	19	2.0%	7	0.7%	78	8.3%
40-49	40	4.3%	26	2.8%	3	0.3%	69	7.3%
50-64	142	15.1%	52	5.5%	7	0.7%	201	21.4%
65-74	101	10.8%	55	5.9%	5	0.5%	161	17.1%
75+	88	9.4%	44	4.7%	0	0	132	14.1%
Missing	68	7.2%	30	3.2%	53	5.6%	151	16.1%
Grand total	**565**	**60.2%**	**282**	**30.0%**	**92**	**9.8%**	**939**	**100.0%**

Cumulatively. events of Off label use occurred most frequently with Dose 1 (1,824 reports, 40.8%). Following Dose 1, majority of the events (768, 17.2%) occurred on vaccination day (Day 0) and then between 24 to 72 hours (331, 7.4%). A similar pattern of event occurrence was noted following Doses 2 and 3. No data was reported for Dose 4. Table 16-223 below shows details of latency by dose number.

Table 16-223 Off label use Events: Latency by Dose number (Cumulative)

Dose Number	First Dose Latency	# of Events	% Events*
Dose 1	Subtotal	1,824	40.8%
	0 days	768	17.2%
	01-02	331	7.4%
	03-04	109	2.4%
	05-06	72	1.6%
	07-13	220	4.9%
	14-29	182	4.1%
	30+	142	3.2%
Dose 2	Subtotal	309	6.9%
	0 days	203	4.5%
	01-02	20	0.4%
	03-04	24	0.5%
	05-06	8	0.2%

Dose Number	First Dose Latency	# of Events	% Events*
	07-13	14	0.3%
	14-29	4	0.1%
	30+	36	0.8%
Dose 3	Subtotal	301	6.7%
	0 days	198	4.4%
	01-02	54	1.2%
	03-04	11	0.2%
	05-06	6	0.1%
	07-13	8	0.2%
	14-29	14	0.3%
	30+	10	0.2%
Unknown	Subtotal	2,040	45.6%
	Missing	2,040	45.6%
Grand total		**4,474**	**100.0%**

*Percentages are calculated based on the cumulative number of events (4,474) in Off label use cases with other associated events.

Children ages < 12 Years (Cumulatively as of 31 Dec 2021)

Cumulatively as of 31 Dec 2021, 4 Off-label use non-serious cases have been reported for children < 12 years, and 3 cases were medically confirmed. Of the 4 Off-label use non-serious cases, 3 cases were associated with a reported event with a total of 15 non-serious events. Off label use ranked highest (2 events, 13.3%) amongst the most frequently reported Off label use terms. All other event terms such as Chills, Fatigue, Myalgia, Pain in extremity, Pyrexia, Hallucination-visual, and Heavy menstrual bleeding each reported only one event (6.7%). The adverse events of Hallucination-visual and Heavy menstrual bleeding reported for SPIKEVA have been evaluated by the MAH, and evidence of causality due to SPIKEVAX exposure was not determined. Therefore, Hallucination-visual and Heavy menstrual bleeding do not represent a new safety issue. Other non-adverse event terms such as Intentional dose omission and Interchange of vaccine products also reported one event. For more details on Interaction with other COVID vaccines (Heterologous Vaccine Schedule) please refer to Section 16.3.5.5. By the data lock point of this reporting interval approximately 47% of the events (7 of the 15 events) had resolved and the outcome of 8 other events is unknown. The median age of the adolescent was 4.2 years (min: 0.0 and Max: 11.0) with events occurring in 3 males (75.0%) and 1 female (25.0%). The distribution of case count by gender and age group is as follows: 1 female and 1 male in the <2 y/o group and two males in the 02-11 y/o group. Overall, children's SPIIKEVAX data is still nascent and limited to support critical evaluation. As at the data lock point of this reporting interval, the cumulative Off label use data for children < 12 years remains consistent with known SPIKEVAX safety profile.

Adolescents ages 12-17 Years (Cumulatively as of 31 Dec 2021)

Cumulatively as of 31 Dec 2021, 100 Off label use cases (232 events) have been reported for the Adolescent age group (12-17 y/o), of which 3 cases were serious (7 serious events), none with a fatal outcome, and 74 cases were medically confirmed. Of the 100 Off label use cases, 87 cases (3 non-fatal serious cases) were associated with a reported event. Amongst all reported Off label use terms, the event of Off label use ranked highest (82 events, 35.3%) as the most frequently reported, followed by 'Product administered to patient of inappropriate age (74, 31.9%), and No adverse event (27, 11.6%). The reporting frequency of all other event terms are either at 1.7% or lower. By the data lock point of this reporting interval 113 events of the cumulative 232 events had resolved. The median age of the adolescent was 16.0 years (min: 12.0 and Max: 17.0) with events occurring in 37 males (37.0%) and 50 females (50.0%). Females in the 16-17 y/o age group represent the highest number of cases (38, 38.0%) relative to males (32, 32.0%) in the same age bracket. As Adolescent data continue to evolve to support critical evaluation, the significance of the data is being cautiously interpreted to avoid premature or over interpretation of the nascent emerging trends. Nevertheless, as at the data lock point of this reporting interval, the cumulative Adolescent Off label use data remains consistent with known SPIKEVAX safety profile.

SPIKEVAX Booster (Cumulatively as of 31 Dec 2021)

Cumulatively as of 31 Dec 2021, 88 Off label use cases (301 events) have been reported for the SPIKEVAX Booster group, of which 8 cases were serious, none with a fatal outcome, and 32 cases were medically confirmed. Of the 88 Off label use cases, 86 cases (11 non-fatal serious cases) were associated with a reported event. Amongst all reported Off label use terms, the event of Off label use ranked highest (71 events, 23.6%) as the most frequently reported, followed by Headache (11, 3.7%), 'Inappropriate schedule of product administration' and Pyrexia (10, 3.3%) each, and Vaccination pain (9, 3.0%). The reporting frequency of all other event terms are either at 2.7% or lower. By the data lock point of this reporting interval, of the cumulative 301 Off label use-associated events, 160 events had resolved. The median age was 70.0 years (min: 30.0 and Max: 89.0; 5 unknown age data values) with events occurring in 35 males (39.8%) and 51 females (58.0%), and 2 missing gender values. Females in the 65-74 y/o age group represent the highest number of cases (19, 21.6%) relative to males (10, 11.4%) in the same age bracket. As Booster data continue to evolve to support critical evaluation, the significance of the data is being cautiously interpreted to avoid premature or over interpretation of the nascent emerging trends. Nevertheless, at the data lock point of this reporting interval, the cumulative SPIKEVAX Booster data remains consistent with its known safety profile.

Reporting Interval (01 Jul 2021 – 31 Dec 2021)

During this PBRER No. 2 interval period, 488 Off label use cases (2,200 events; 391 serious events) have been reported of which 112 cases were serious, none with a fatal outcome, and 215 of the 488 cases were medically confirmed. Of the 488 Off label use cases, 397 cases (112 serious cases, 1 with a fatal outcome) were associated with a reported event.

During the reporting interval, Off label use was the most frequently reported event (278, 12.6%), followed by Intentional dose omission (68, 3.1%), Pyrexia (67, 3.0%), Fatigue (59, 2.7%,), and Headache (54, 2.5%). The reporting frequency of all other event terms was at 2.1% or lower. Except for minor non-significant differences in ranking, the patterns of occurrence of adverse events reported during this interval period were similar to the cumulative data landscape. Also, adverse events reported following Off label use were generally consistent with labelled reactogenicity events as shown in Table 16-224.

During this reporting interval, other than Off label use adverse event term(s) which is specific to the Off-label use cases, adverse events most frequently reported in Off label use cases are comparable or lower in reporting frequency to events reported in the general reporting population and are presented in the table below. The top 10 most frequently reported event terms with Off label use are presented below Table 16-224 below.

Overall, relative to the cumulative data, review of this reporting interval data for PBRER No. 2 showed that Off label use-associated events are consistent with reactogenicity of vaccines, and the MAH did not determine any significant deviation from the known adverse event profile of SPIKEVAX.

Table 16-224 The Top 10 Most Frequently Report PTs with Off label use and General Population (Reporting Period)

Reporting Period- Off label use			Reporting Period – General Population**		
PT	**# Events**	**% of Total Events***	**PT**	**# Events**	**% of Total Events****
Off label use	278	12.6%	Pyrexia	44,460	6.2%
Intentional dose omission	68	3.1%	Headache	40,502	5.7%
Pyrexia	67	3.0%	Fatigue	35,142	4.9%
Fatigue	59	2.7%	Myalgia	26,841	3.7%
Headache	54	2.5%	Chills	24,215	3.4%
Intentional product use issue	47	2.1%	Malaise	21,513	3.0%
Pain in extremity	45	2.0%	Nausea	19,187	2.7%
Product administered to patient of inappropriate age	43	2.0%	Injection site pain	17,623	2.5%
Chills	41	1.9%	Vaccination site pain	16,031	2.2%

Reporting Period- Off label use			Reporting Period – General Population**		
PT	# Events	% of Total Events*	PT	# Events	% of Total Events**
Myalgia	41	1.9%	Arthralgia	15,564	2.2%

**Percentages are calculated based on the cumulative number of events in cases (2,200) of Off label use with other associated events. Overview of Reporting Interval cases and demographics data for Off label use cases are presented above.
**Percentages are calculated based on the total number of reporting interval events (715,965) in cases reported for the general population. Additional reporting interval data for the general population includes the following: a total of 189,489 cases (52,667 serious cases; 2,414 cases with a fatal outcome; 75,675 medically confirmed) yielded 715,965 events (288,442 serious events; 8,960 fatal events); 231,450 events resolved by PBRER No. 2 DLP of Dec 31, 2021. The median age of patients was 44 years (15,885 missing age values) with events occurring in 59,418 males (31.4%), 121,917 females (64.3*%), and 8,154 (4.3%) missing gender values.

During the reporting interval, the median age of patients was 55.0 years (min: 0.0 and Max: 92.0; 80 missing age values) with events occurring in 145 males (29.7%), 275 females (56.4%), and 68 (13.9%) missing gender values. Females in the 50-64 age group represent the highest number of cases (67, 13.7%) relative to males (28, 5.7%) in the same age group; followed by the females in the 65-74 age group (47; 9.6%) relative to males (23, 4.7%) in the same age group. The distribution of case count by gender and age group is shown in Table 16-225.

Table 16-225 Number and Percentage of Reported Off label use Cases by Gender and Age – Reporting Period to 01 Jul 2021 - 31 Dec 2021

Age Group	Female		Male		Unknown		Total # Cases	Total % Cases
	# Cases	% Total Cases	# Cases	% Total Cases	# Cases	% Total Cases		
<2	1	0.2%	1	0.2%	0	0	2	0.4%
02-11	0	0	1	0.2%	0	0	1	0.2%
12-15	10	2.0%	5	1.0%	1	0.2%	16	3.3%
16-17	12	2.5%	16	3.3%	10	2.0%	38	7.8%
18-29	8	1.6%	11	2.3%	4	0.8%	23	4.7%
30-39	33	6.8%	8	1.6%	7	1.4%	48	9.8%
40-49	25	5.1%	14	2.9%	2	0.4%	41	8.4%
50-64	67	13.7%	28	5.7%	6	1.2%	101	20.7%
65-74	47	9.6%	23	4.7%	4	0.8%	74	15.2%
75+	40	8.2%	24	4.9%	0	0	64	13.1%
Missing	32	6.6%	14	2.9%	34	7.0%	80	16.4%
Grand total	**275**	**56.4%**	**145**	**29.7%**	**68**	**13.9%**	**488**	**100.0%**

During this PBRER No. 2 interval period, a similar pattern relative to the cumulative data was observed with the highest number of Off label use-associated events reported following Dose 1 (618, 28.1%). While the percentage of events following Dose 3 was higher during the interval period, this can be explained possibly by increased exposure to Dose 3 following recent regulatory approvals in various countries. Majority of the events were reported within 1-4 days regardless of

the dose number; Dose 4 data is too limited to support meaningful interpretation. (Table 16-226).

Table 16-226 Off label use Events: Latency by Dose number (Reporting Interval)

Dose Number	First Dose Latency	# of Events	% Events
Dose 1	Subtotal	618	28.1%
	0 days	286	13.0%
	01-02	144	6.5%
	03-04	24	1.1%
	05-06	17	0.8%
	07-13	65	3.0%
	14-29	35	1.6%
	30+	47	2.1%
Dose 2	Subtotal	133	6.0%
	0 days	68	3.1%
	01-02	8	0.4%
	03-04	16	0.7%
	07-13	11	0.5%
	14-29	2	0.1%
	30+	28	1.3%
Dose 3	Subtotal	300	13.6%
	0 days	197	9.0%
	01-02	54	2.5%
	03-04	11	0.5%
	05-06	6	0.3%
	07-13	8	0.4%
	14-29	14	0.6%
	30+	10	0.5%
Unknown	Subtotal	1,149	52.2%
	Missing	1,149	52.2%
Grand total		**2,200**	**100.0%**

Children ages < 12 Years (Reporting Interval)

Reporting Interval (01 Jul 2021 – 31 Dec 2021)– Children (0-11 years)

During the reporting period (01 Jul 2021 to 31 Dec 2021), 3 non-serious Off label use cases (15 events) were reported for children in the age group of < 12 years. A total of 3 cases were medically confirmed. All 3 Off label use cases were associated with a reported event. Off label use (2, 13.3%) ranked highest as the most frequently reported Off label use term, followed by known reactogenicity event terms reported as single events (1, 6.7%). As of the data lock point of this reporting interval, 7 of the 15 Off label use events had resolved. The median age of children < 12

years who received SPIKEVAX was 0.4 years (min: 0.0 and max: 11.0; and no missing age data value) with events occurring in 2 males (66.7%) and one female (33.3%). Gender distribution by age are as follows: 1 female < 2 y/o (1, 33.3%), 1 male < 2 y/o (1, 33.3%), and 1 male in the 02-11 y/o age group (1, 33.3%). Overall, the reporting interval SPIKEVAX data for children in the 0-11 y/o age group is sparse and has not provided any new significant information that deviates from known cumulative data profile of the product.

Adolescent ages 12-17 Years (Reporting Interval)

Reporting Interval (01 Jul 2021 – 31 Dec 2021)– Adolescent (12-17 years)

During the reporting period (01 Jul 2021 to 31 Dec 2021), 54 Off label use cases (1 serious case) were reported for Adolescents (12-17 years). A total of 29 cases were medically confirmed. Of the 54 Off label use cases, 48 cases were associated with a reported event, yielding a total of 144 events (2 serious events). Off label use (46, 31.9%%) ranked highest as the most frequently reported Off label use term, followed by 'Product administered to patient of inappropriate age' (41, 28.5%), and No adverse event (21, 14.6%). Additional event terms including known vaccine reactogenicity event terms were reported as single events at a frequency of 2.1% or lower. As of the data lock point of this reporting interval, 50 events of the 144 Off label use-associated events had resolved. The median age of Adolescents who received SPIKEVAX was 16.0 years (min: 12.0 and max: 17.0; no missing age data value) with events occurring in 21 males (38.9%) and 22 females (40.7%). Gender distribution by age are as follows: 12-15 y/o (Females: 10, 18.5%; Males: 5, 9.3%); 16-17 y/o (Females: 12, 22.2%; Males: 16, 29.6%). Overall, this reporting interval SPIKEVAX data for Adolescents (12-17 years) is evolving and has not provided any new significant information that deviates from known cumulative data profile of the product.

SPIKEVAX Booster (Reporting Period)

SPIKEVAX Booster (Reporting Period - (01 Jul 2021 – 31 Dec 2021)

During the reporting period (01 Jul 2021 to 31 Dec 2021), 87 Off label use cases (300 events; 23 serious events) have been reported, of which 8 cases were serious and none with a fatal outcome. A total of 32 cases were medically confirmed. Of the 87 cumulative Off label use cases, 85 cases (11 serious cases, none had a fatal outcome) were associated with a reported event. Off label use (70, 23.3%) ranked highest as the most frequently reported Off label use terms, followed by Headache (11, 3.7%). The reporting frequency of all other event terms were at 3.3% or below. As of the data lock point of this reporting interval, 159 events of the 300 Off label use events had resolved. The median age of individuals who received SPIKEVAX Booster was 70.5 years (min: 30.0 and Max: 89.0; 5 missing age data values) with events occurring in 34 males (39.1%) and 51 females (58.6%), with 2 (2.3%) missing data values. Females in the 65-74 age group represent the

highest population of cases (19; 21.8%) relative to males (10, 11.5%) in the same age group; followed by females in the 75+ year age group (16; 18.4%) relative to males (12, 13.8%) in the same age group. Overall, the reporting interval SPIKEVAX Booster data has not provided any new significant information that deviates from known cumulative data profile of the product.

Serious Cases (Reporting Period)

During the reporting period (01 Jul 2021 to 31 Dec 2021), there were 112 serious Off label use cases (See Appendix 20.11.79 for a comprehensive listing). Nearly all of these cases were considered off label use because a subsequent vaccine dose was either omitted or delayed due to the adverse events seen after a dose of SPIKEVAX or were events occurring in older patients after a booster dose when boosters were only indicated in immunocompromised patients. Two cases were overdoses and are described in the Overdose Section 16.3.6.8.3.

Fatal outcomes reports (Reporting Period):

During the reporting period (01 Jul 2021 to 31 Dec 2021) there were no fatal outcomes for Off label use cases.

16.3.6.8.4.5. Discussion

During this reporting interval, off label use was the most frequently reported PT (278 events, 12.6%). A review of case narratives with the PT of Off label use found that 93 cases (33.5%) were booster doses given when not indicated by prescribing instructions; 71 cases (25.5%) where the patient received other vaccines for COVID 19 in addition to SPIKEVAX, 48 cases (17.3%) were related to vaccine administration scheduling outside of recommended time intervals, 34 cases (12.2%) were associated with vaccine being given to persons not in approved age groups at the time of vaccine administration, and 30 cases (10.8%) were associated with intentional dose delay or omission. Intentional product use issue PT primarily captured poorly defined dose scheduling issues.

The fatalities reported in these Off-label use cases were not related to the Off-label use. The reported adverse events representing harm reported and cases of Off label use were in line with expectation for reactogenicity following SPIKEVAX. There was no pattern of off label use observed that changes the safety profile of SPIKEVAX.

16.3.6.8.4.6. Conclusion

Cumulatively and based on the analysis of all the safety data received during this reporting interval of this PBRER, ModernaTX, Inc considers that Off label use cases, reported in temporal association with the administration of SPIKEVAX, did not raise any safety concerns, and the information provided does not support or is inadequate to provide evidence of causality between

SPIKEVAX exposure and reported Off label use/ Off label associated events. The cumulative and reporting period data do not present a new safety issue of concern. ModernaTX, Inc will continue to monitor Overdose cases and associated events using routine surveillance.

Overall, based on all the information presented in this analysis, ModernaTX, Inc considers that there is no change to the known safety profile of SPIKEVAX. The benefit-risk evaluation of SPIKEVAX remains positive.

16.3.6.8.5. Interactions with Other Vaccines

16.3.6.8.5.1. Source of the New Information

The company (herein referred to as ModernaTx) GSDB was queried for valid, clinical, and spontaneous case reports received from HCP, HA, consumers, and literature, through 31 Dec 2021), reported for SPIKEVAX for cases of vaccine co-administration with all other vaccines (not including COVID-19 products). Search included the preferred term (PT) Drug/Vaccine interactions, and a search of medical history, concomitant medication and narrative text for other vaccines.

16.3.6.8.5.2. Background Relevant to the Evaluation

Limited data are currently available on the interactions of SPIKEVAX with other non-COVID-19 vaccines. As such, the safety profile of SPIKEVAX when co-administered with these vaccines is being monitored.

Only limited evidence on COVID-19 vaccine coadministration with influenza vaccine exist, but available evidence does not show increased adverse events. Therefore, WHO considers that coadministration of an inactivated seasonal influenza vaccine and any dose of a COVID-19 vaccine is acceptable, given that the known risk of serious illness for adults infected with influenza virus or SARS-CoV-2 is substantial.

As COVID-19 vaccines become available to children who are also being vaccinated against childhood infectious diseases, the safety and efficacy of coadministration needs to be better understood.

Literature Search and Findings

ModernaTX conducted a targeted literature search covering the period 01 Jul to 31 Dec 2021, focusing on SPIKEVAX coadministration with other non-COVID-19 vaccines.

Thomas et al., [202] reported a case of Immune Thrombocytopenic Purpura following coadministration of mRNA-Based SARS-CoV-2 (Pfizer BioNTech) and MMR Vaccinations.

No literature articles were identified for co- administration of SPIKEVAX with other non-COVID-19 vaccine during this reporting period.

16.3.6.8.5.3. Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

ModernaTx, queried the GSDB for the reporting period through 31 Dec 2021, for valid cases reporting SPIKEVAX and other Non-COVID-19 vaccines without exclusion for concurrency of dates of administration, from HCP, HA, consumers, and literature, worldwide, reported for SPIKEVAX using the following criteria:

16.3.6.8.5.4. Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Vaccine-Vaccine Interactions:

Overview of Cases of SPIKEVAX with Other Non-COVID-19 Vaccines

Cumulatively, there were 143 cases (549 events) reported after SPIKEVAX was administered (not necessarily concurrently) with other non-COVID-19 vaccines. Seventy-four (51.7%) of the cases were serious of which 2 had a fatal outcome. More cases (95 cases; 66.4%) were reported in females than in males (42 cases; 2.4%) with gender missing in 6 cases (4.2%).

During the reporting period, there were 124 cases (460 events) reported after SPIKEVAX was administered (not necessarily concurrently) with other non-COVID-19 vaccines. Sixty-nine of these cases (55.6%) were serious of which 2 cases had a fatal outcome. More cases were reported in females (80; 64.5%), than males (39 cases; 31.5%) with 5 cases missing gender (4.0%) information. The median age of reported cases was 53.0 years, with a range from 18 years to 85 years. Most cases were reported in the age group 50-64 years old. See Table 16-227.

Table 16-227 Distribution by Age of cases of SPIKEVAX with Non-COVID-19 Vaccines (Reporting Period)

Age Group	Total Cases	% Total Cases
18-29	8	6.5%
30-39	16	12.9%
40-49	16	12.9%
50-64	52	41.9%
65-74	14	11.3%
75+	5	4.0%
Missing	13	10.5%
Grand total	**124**	**100.0%**

Most reports were received from regulatory authorities (104; 83.9%) followed by spontaneous sources (19; 15.3%), and 1 case (0.8%) from a clinical trial. Most of the case reports were from the United Kingdom (76.6%), followed by US (15.3%) and EEA (8.1%).

The most frequently reported PTs were consistent with expected reactogenicity with SPIKEVAX and presented in Table 16-228.

Table 16-228 Most frequently reported PTs after SPIKEVAX administration with Non-COVID-19 Vaccines >=2% (Reporting Period)

PT	# Events	% of Total Events
Headache	31	6.7%
Pyrexia	25	5.4%
Fatigue	21	4.6%
Chills	18	3.9%
Myalgia	16	3.5%
Nausea	13	2.8%
Pain in extremity	12	2.6%
Arthralgia	11	2.4%
Pain	9	2.0%

There was a significantly higher proportion of events reported to have occurred after dose 3 of SPIKEVAX (62.6%) than any other dose. Most (57.6%) events were reported to have occurred in the period < 3 days after Dose 3. See Table 16-229.

Table 16-229 Dose and Time to Onset after SPIKEVAX with Non-COVID-19 Vaccine (Reporting Period)

Dose Number	TTO All Doses (Days)	# Events	% Events
Dose 1	Subtotal	17	3.7%
	0 days	1	0.2%
	01-02	2	0.4%
	05-06	2	0.4%
	07-13	6	1.3%
	14-29	2	0.4%
	30+	4	0.9%
Dose 2	Subtotal	14	3.0%
	01-02	4	0.9%
	07-13	1	0.2%
	14-29	1	0.2%
	30+	8	1.7%

Dose Number	TTO All Doses (Days)	# Events	% Events
Dose 3	Subtotal	288	62.6%
	0 days	111	24.1%
	01-02	154	33.5%
	03-04	13	2.8%
	05-06	9	2.0%
	07-13	1	0.2%
Unknown	Subtotal	141	30.7%
	Missing	141	30.7%
Grand total		**460**	**100.0%**

Event outcome in the reporting period was most frequently reported as recovered (33.9%) followed by Not recovered (27.8%) and recovering (19.3%).

Serious cases of non-COVID-19 vaccines with SPIKEVAX administration

In this reporting period, there were 38 serious case reporting SPIKEVAX and other non-COVID-19 vaccines, of which 30 cases were with Influenza vaccine, 6 cases with a single or combination Tetanus vaccine and one case each with Pertussis vaccine and Diphtheria vaccine.

Of the 38 serious cases, 11 included administration of non-COVID-19 vaccine on the same day as SPIKEVAX, therefore, meeting the definition of coadministration. All 11 cases were with Influenza vaccine and are presented in Table 16-230.

Table 16-230 Serious Cases of Non-COVID-19 Vaccine co-administered with SPIKEVAX

Case ID	Country	Age (Yrs)/Sex	Case Narratives
4.1(b)	4.1(b)	23/M	A patient with no relevant medical history, experienced Pyrexia and Pain in Extremity on same day after influenza vaccination and the third dose of SPIKEVAX
4.1(b)	4.1(b)	64/F	A patient with history of COPD, and asthma on steroid therapy, experienced Feeling hot, Swelling Face, Peripheral swelling, Headache, and Nausea, 2 days after booster dose of SPIKEVAX co-administered with Influenza vaccine
4.1(b)	4.1(b)	39/F	A patient with a history of asthma and on steroids experienced pyrexia, chills, arthralgia, pain, pain in extremity, peripheral swelling, headache, lethargy and myalgia, the day after dose 3 of SPIKEVAX co-administered with Influenza vaccine
4.1(b)	4.1(b)	63/F	A patient with medical history of Transient Ischeamic attack, experienced Syncope, Cellulitis, Malaise, Rash on the same day after dose 3 of SPIKEVAX co-administered with Influenza vaccine
4.1(b)	4.1(b)	Unk/F	A patient experienced Migraine, Nausea, Paraesthesia, and Vomiting 1 day after the booster dose of SPIKEVAX co-administered with Influenza vaccine

Case ID	Country	Age (Yrs)/Sex	Case Narratives
4.1(b)	4.1(b)	59/Unk	A patient with no relevant medical history experienced extrasystole (heartbeats skipped) on the same day after the third dose of SPIKEVAX co-administered with Influenza vaccine.
4.1(b)	4.1(b)	52/M	A patient experienced the Headache, Nasopharyngitis, Chills and Injection site pain, 1 day after third dose of SPIKEVAX co-administered with Influenza vaccine.
4.1(b)	4.1(b)	53/F	A patient experienced Rash and Lymphadenopathy, 2 days after 3rd dose of SPIKEVAX co-administered with Influenza vaccine
4.1(b)	4.1(b)	42/F	A patient with asthma on steroid therapy experienced Myalgia, Back pain, burning sensation, Paraesthesia, Pyrexia and Migraine one day after dose 3 of SPIKEVAX co-administered with influenza vaccine
4.1(b)	4.1(b)	31/F	A patient with med history of hypothyroidism and lactose intolerance, experienced Coeliac disease 29 days after dose 1 of SPIKEVAX co-administered with Influenza vaccine.
4.1(b)	4.1(b)	47/F	A patient experienced Dizziness, Dizziness postural, Lymphadenopathy, Nausea, 3 days after dose 3 of SPIKEVAX Co-administered with influenza vaccine

Ten of these 11 cases (42 events) occurred after dose 3 and were from the UK while one case was reported from the US after dose 1 of SPIKEVAX.

Table 16-231 Top MedDRA PTs reported in 11 serious cases of Vaccine Co-administration >=2 events

PT	# Events	% of Total Events
Pyrexia	4	9.50%
Headache	3	7.10%
Back pain	2	4.80%
Chills	2	4.80%
Migraine	2	4.80%
Myalgia	2	4.80%
Nausea	2	4.80%
Pain in extremity	2	4.80%
Paraesthesia	2	4.80%
Peripheral swelling	2	4.80%
Rash	2	4.80%

Time to onset was 0-2 days for all 41 events after SPIKEVAX dose 3 and 14-29 days for the one event after SPIKEVAX Dose 1.

Of the 11 cases, 20 (47.6%) of the 42 events had not recovered while 14 events (33.3%) had recovered and 6 (14.3%) were recovering.

Fatal cases of Vaccine Coadministration:

Both fatal cases (4.1(b) and 4.1(b)) were reported in patients who received heterologous COVID-19 vaccine administration as well as Influenza vaccination and are therefore discussed in the heterologous vaccine section.

Subpopulation Analyses

Non-COVID-19 vaccine coadministration with SPIKEVAX in Children (<12 Years of Age).

There were no reports of non-COVID-19 vaccine coadministration with SPIKEVAX in children (< 12 years of age) in the cumulative or interval reporting period.

Non-COVID-19 vaccine coadministration with SPIKEVAX in Adolescents (12-17 Years of Age)

There were no reports of non-COVID-19 vaccine coadministration with SPIKEVAX in adolescents 12-17 years of age in the cumulative or interval reporting period.

Non-COVID-19 vaccine reported in cases of Third Dose or Booster Dose of SPIKEVAX

In this reporting period, there were 97 cases (288 events) reporting Non-COVID-19 vaccines with 3rd dose of SPIKEVAX without exclusion for concurrency of dates of administration.

Fifty-four (54) of these 97 cases (55.7%) were serious, 1 was fatal and 16 were medically confirmed. Most of the cases (68.5%; 97 of 147 cases) occurred after 3rd SPIKEVAX dose. The most frequently reported MedDRA PTs are presented in Table below.

Table 16-232 The Top 10 Most frequently reported MedDRA PTs after Dose 3

PT	# Events	% of Total Events
Headache	24	8.3%
Pyrexia	20	6.9%
Fatigue	15	5.2%
Nausea	12	4.2%
Chills	10	3.5%
Pain in extremity	9	3.1%
Arthralgia	8	2.8%
Injection site pain	8	2.8%
Lymphadenopathy	8	2.8%
Myalgia	8	2.8%

Time to onset was most frequently reported as 1-2 days in 53.5% of events and 0 days in 38.5% of events.

Events after dose 3 were most frequently reported to have resolved (41.3%) followed by not resolved in 31.3%, with 1 event reporting a fatal outcome.

The 10 serious cases that occurred with concurrent administration of SPIKEVAX on same day as Non COVID-19 vaccine (coadministration) are described above in Serious cases of vaccine coadministration.

16.3.6.8.5.5. Discussion

In order to capture all cases of non-COVID-19 vaccine, the MAH has conservatively searched its database for all SPIKEVAX cases also containing any non-COVID-19 vaccine, without exclusion for concurrency of dates of administration. Analysis of these cases revealed an adverse event profile (top PTs and time to onset) similar to that seen with independent administration of SPIKEVAX and labeled reactogenicity of the concurrent vaccine (mostly Influenza vaccine).

A review of all the serious cases retrieved in this reporting period, identified 11 cases of concurrent administration (coadministration) with all concerning Influenza vaccination. The predominance of Influenza vaccine is likely related to the usual timing of annual seasonal flu vaccinations typical for this timeframe (fall 2021). From this limited data the adverse event profile was not indicative of any trends, different than observed for SPIKEVAX administration alone.

Ten of these 11 cases occurred after 3rd / booster SPIKEVAX dose and were reported from the UK regulatory authority. It is of note that most SPIKEVAX use in the UK is likely to be as 3rd dose/booster given its later introduction compared to other COVID-19 vaccines in that country.

There have been no cases reported in children or adolescents who are more likely to be the recipients of non-COVID-19 vaccines, but less likely to have received SPIKEVAX due to more recent approvals in some countries.

16.3.6.8.5.6. Conclusion

After careful review of all new safety data received during the reporting period for the risk of non-COVID-19 coadministration with SPIKEVAX, the benefit-risk profile for SPIKEVAX remains favorable. The risk of coadministration will continue to be monitored using the routine pharmacovigilance measures implemented for SPIKEVAX.

16.3.6.8.6. Lack of Efficacy/Vaccine failure

16.3.6.8.6.1. Source of the New Information

ModernaTX, Inc queried the GSDB for the reporting period 01 Jul 2021to 31 Dec2021 for valid, spontaneous case reports of vaccination failure received from HCP, HA, consumers, and literature, worldwide, reported for SPIKEVAX.

16.3.6.8.6.2. Background Relevant to the Evaluation

Lack of efficacy/vaccine failure is defined as COVID-19 infection occurring 14 days or more after the second dose of SPIKEVAX. In order to better characterize the effect of the booster dose on Vaccine failure, ModernaTX has further broken down its definition of lack of efficacy into primary series vaccine failure (breakthrough infection 14 days or more after 2nd dose of primary vaccination) and booster dose vaccine failure (breakthrough infection 14 days or more after booster dose of vaccine). Breakthrough SARS-CoV-2 infections among fully vaccinated individuals continue to be reported, many of which have involved infection with the Delta variant. Since no vaccine is 100% effective, Moderna continues to monitor breakthrough infections and lack of efficacy/vaccine failure cases, particularly in light of new variants, such as Omicron, and the impact of booster doses.

Tang et al, [203] conducted a matched test-negative case-control study to assess the real-world effectiveness of COVID-19 messenger RNA vaccines against infection with Delta in Qatar's population. Corresponding mRNA-1273 effectiveness ≥14 d after the first or second dose was 73.7% (95% CI, 58.1-83.5%) and 73.1% (95% CI, 67.5-77.8%), respectively. Notably, effectiveness against Delta-induced severe, critical, or fatal disease was 96.1% (95% CI, 71.6-99.5%) for mRNA-1273 ≥ 14 d after the second dose. Their findings show robust effectiveness for mRNA-1273 in preventing Delta hospitalization and death in Qatar's population. Despite reports of breakthrough infections, the benefit-risk balance of SPIKEVAX continue to show unambiguous benefits of the vaccine as it relates to reduced disease severity and reducing COVID-related hospitalizations among vaccinated populations.

16.3.6.8.6.3. Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

ModernaTX, Inc queried the GSDB for the reporting period from 01 Jul 2021 to 31 Dec 2021 for valid, spontaneous case reports received from HCP, HA, consumers, and literature, worldwide, reported for SPIKEVAX.

The database was searched using the criteria IPR-VED (>=14), which includes COVID-19 Preferred Terms and Lack of Efficacy Preferred Terms occurring 14 days or more after the second dose of vaccination.

Vaccine failure cases occurring 14 days or more after 2nd SPIKEVAX dose or less than 14 days after the 3rd SPIKEVAX dose are considered primary vaccine failure, as they are attributable to the primary vaccine series. Vaccine failure occurring 14 days or more after the 3rd dose (booster) are considered secondary vaccine failure as they are attributed to the booster.

16.3.6.8.6.4. Results A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Overview of Cases

During this review period there were 5,171 cases (8,743 events) of vaccine failure (primary and booster) representing 2.7% of all cases reported in this interval (189,489 cases). Three thousand, three hundred and thirty-five (3,335) cases (64.5 %) were serious, 4,968 cases (96.1%) were medically confirmed, and 404 cases (7.8 %) had a fatal outcome. Most of the cases were from the USA (74.1%) followed by Austria (19.0%). Gender distribution of these 5,171cases was 2,442 males (47.2%), 2,709 females (52.4%) and 20 missing gender (0.4%). The mean age was 61.5 (SD: 19.6), and median age was 65.0 (min: 18.0 / max: 120.0) with 2,592 cases; 50.1 % reported in the elderly 65 years and over. Refer to Section 16.3.6.8.7 .

Of the 5,171 cases of vaccine failure in this reporting period, 5,058 (97.8%) of them were attributable to the primary vaccine series while 113 (2.2%) were attributable to the booster vaccine.

Primary Series Vaccine failure

There were 8,536 events reported in the 5,058 cases, of which 3,264 cases (64.5%) were serious, 400 cases (7.9%) were fatal, and 4,865 cases (92.6%) were medially confirmed.

Gender distribution was 47.3% male and 52.3% male with a mean age of 61.4 (SD 19.7) and median of 65.0 (min: 18.0/ max 120).

Time to onset all dose calculation was 170.1 (SD 258.2) with a median of 171.0 (min 14; max 22519). Outcome was unknown in 62.1% of events, recovered and non-recovered in 15.4% and 14.0% respectively.

Table 16-233 Case Distribution by Age Group by Review Period for Primary Vaccine Failure

Age Group	Review Period	
	# Cases	% of Total Cases
18-29	7.7%	387
30-39	9.9%	499
40-49	10.7%	542
50-64	21.5%	1,085
65-74	20.3%	1,027
75+	29.6%	1,496
Missing	0.4%	22
Grand total	100.0%	5,058

Serious Cases of Primary Vaccine Failure

There were 3,264 serious cases (5,817 events) of primary series vaccine failure reported in this reporting period, of which 3,174 cases were medical confirmed. There were 400 cases with a fatal outcome representing 7.7% of all vaccine failure cases (5,171 cases) in this reporting interval. The elderly (65 years and older) was the most frequently represented age group in serious cases of primary vaccine failure (61.4 % of serious cases).

Table 16-234 Distribution of Serious Cases of Primary Series Vaccine Failure by Age Group

Age Group	Review Period	
	# Cases	% of Total Cases
18-29	168	5.1%
30-39	238	7.3%
40-49	261	8.0%
50-64	579	17.7%
65-74	736	22.5%
75+	1271	38.9%
Missing	11	0.3%
Grand total	**3264**	**100.0%**

The most frequently reported PTs in serious cases of primary vaccine failure in this reporting period were COVID-19, Vaccination failure and SARS-CoV-2 test positive and as expected, reflect events associated with COVID-19 disease.

Table 16-235 Most Frequently Reported PTs in Serious Cases of Primary Vaccine Failure Cumulative ≥ 2%

PT	# Events	% of Total Events
COVID-19	2,974	51.1%
Vaccination failure	843	14.5%
SARS-CoV-2 test positive	796	13.7%
COVID-19 pneumonia	419	7.2%
Drug ineffective	371	6.4%
Vaccine breakthrough infection	335	5.8%

The average time to primary vaccine failure in serious cases was 163.3 days (SD:72) with a median of 168.0 (14:338) in this reporting interval. The most frequently reported outcome in this reporting period, when known (unknown 60%), was recovered (14.2%) followed by not recovered. (13.9%). (Table 16-236).

Table 16-236 Event Outcomes for Serious Cases of Primary Vaccine Failure by Reporting Period

Event Outcome	# Events	% of Total Events
Fatal	646	11.1%
Not Recovered/Not Resolved	808	13.9%
Recovered/Resolved	828	14.2%
Recovered/Resolved with Sequelae	1	0.0%
Recovering/Resolving	41	0.7%
Unknown	3,493	60.0%
Grand total	5,817	100.0%

Fatal Cases of Primary Vaccine Failure

There were 400 fatal cases of primary vaccine failure in this reporting period. The elderly 65 and older are overrepresented with 352 cases (88.0%), followed by age group 50- 64 years with 36 cases (9%). Of the 11 cases reported in those under the age of 50 years, 7 had a concurrent history of chronic renal disease, malignancy or immunosuppression.

Vaccine Failure / Lack of Efficacy in Patients After a Third Dose or Booster Dose of SPIKEVAX

In this reporting interval, there were 113 cases (207 events) of vaccine failure occurring 14 days or more after receiving booster dose of SPIKEVAX. All cases were reported to have occurred after Dose 3. There were 71 serious cases (62.8%) of which 4 cases (3.5%) were fatal. Gender distribution was 50 males (44.2%) and 63 females (55.8%).

Serious cases of Vaccine failure after Booster dose

Of the 71 serious cases (131 events) of vaccine failure after booster dose, 52 cases (73.3%) occurred in the elderly age 65 and older. Most (58%) events had an unknown outcome, 24.4% had not recovered and 12.2% of events recovered.

Table 16-237 Age distribution of Serious Cases of Booster Vaccine Failure

Age Group	# Cases	% of Total Cases
18-29	2	2.8%
30-39	1	1.4%
40-49	2	2.8%
50-64	14	19.7%
65-74	18	25.4%
75+	34	47.9%
Grand total	**71**	**100.0%**

The average time to onset all dose calculation for serious cases of vaccine failure after booster dose (Secondary series) was 124.6 (SD: 107.4) with a median of 90 days (min 15: max 306).

When outcome was known (unknown in 58.0%), it was most frequently reported as not recovered (24.4%) followed by recovered (12.2%%) in the interval periods. There were 4 fatal cases discussed below:

Fatal cases of Vaccine failure after Booster Dose

All four cases occurred in the elderly with significant comorbidities. They are presented below

4.1(b) [redacted]: A fatal regulatory authority report concerning an 83-year-old female patient with a medical history of drug allergies, end stage renal disease, hypertension, and coronary artery disease with pacemaker, who experienced Cardiac arrest, Chest pain, Dyspnea and COVID-19. The events occurred approximately 1 month 3 days after the third dose of Moderna COVID-19 Vaccine.

4.1(b) [redacted]: A fatal regulatory authority report concerning an 87-year-old, female patient with a history of COPD and on unknown medications, who experienced abdominal discomfort 5 days after 3rd SPIKEVAX dose, and COVID 19 pneumonia and acute respiratory distress syndrome, 18 days later. The patient additionally experienced acute renal failure approximately one month after third dose and died 32 days after receiving the booster dose. It was unknown if an autopsy was performed.

4.1(b) [redacted]: A fatal regulatory authority report concerning a 64-year-old male patient with a history of Hypertension, Diabetes mellitus, Alcohol abuse, Hepatitis C and Hepatic cirrhosis, who experienced Encephalopathy, COVID-19, Staphylococcal infection, Pneumatosis intestinalis, Rhabdomyolysis and Death, with all symptom onset approximately 26 days after booster dose of SPIKEVAX. Patient was found unresponsive at his home, was hospitalized and had a fatal outcome 7 days later. SARS-CoV-2 test was positive and blood cultures were positive for Staphylococcus aureus. The patient developed decreased level of consciousness intubation, hypoxemia and required. Imaging showed gastric, colonic and portal venous system pneumatosis. Preliminary cause of death was reported as COVID-19. It is unknown if an autopsy was performed.

4.1(b) [redacted]: A regulatory authority report concerning a 74-year-old, male patient with a medical history of Cerebrovascular accident, Obesity and Hypertension, who experienced COVID-19 and had a fatal outcome, with death occurring 21 days after the second and third doses of mRNA-1273. This case reports 2nd and 3rd SPIKEVAX dose on same day and is missing the date of COVID-19 diagnosis.

Subpopulation Analyses

Vaccine Failure / Lack of Efficacy in Children (<12 Years of Age)

There were no cases of vaccine failure reported in children (< 12 years old) either cumulatively or in the reporting period.

Vaccine Failure / Lack of Efficacy in Adolescents (12-17 Years of Age)

There were no cases of vaccine failure reported in adolescents (12 to 17 years old) either cumulatively or in the reporting period.

Comorbid Conditions in all cases of vaccine failure (Primary + booster)

Of the 5,171 cases, 1,337 (25.9%) of the reports of vaccine failure involved frail subjects and 140 (2.7%) were identified as having a history of immunosuppression per medical history or per use of concomitant medications (MI-IMMUN-SUPP (MHX of CM). Many of the reports were confounded by comorbidities that affect baseline health and may affect ability for optimal immune response.

The most frequently reported medical history PT in those reporting vaccine failure was hypertension in 19% of cases. Many of the conditions listed are known to increase severity of COVID-19 disease as well as being independent risk factors for death (Table 16-238).

Table 16-238 Top 10 Reported Medical History PTs in Vaccine Failure Patients

Medical History	Cases (N)	Cases (%)
Total Unique Cases	5,171	100%
Non-Documented Cases	3,021	58%
Hypertension	960	19%
Drug hypersensitivity	835	16%
Hyperlipidaemia	382	7%
Diabetes mellitus	347	7%
Type 2 diabetes mellitus	302	6%
Chronic obstructive pulmonar	281	5%
Coronary artery disease	272	5%
Gastrooesophageal reflux dis	271	5%
Obesity	254	5%
Atrial fibrillation	239	5%

The most frequently reported concomitant medications cumulatively in those reporting vaccine failure are indicative of comorbidities that increase the risk for severe COVID-19 disease or of thromboembolic events (Table 16-239).

Table 16-239 Top 10 Most Frequently Reported Concomitant Medications in Vaccine Failure Patients (Cumulatively)

Concomitant Medication	Cases (N)	Cases (%)
Total Unique Cases	5,761	100%
Non-Documented Cases	5,289	92%
ATORVASTATIN	83	1%
ASPIRIN [ACETYLSALICY	57	1%
AMLODIPINE	55	1%
LISINOPRIL	53	1%
METFORMIN	46	1%
METOPROLOL	46	1%
ACETAMINOPHEN	43	1%
TAMSULOSIN	42	1%
FUROSEMIDE	39	1%
OMEPRAZOLE	39	1%

16.3.6.8.6.5. Discussion

Though vaccine failure reports represent 2.7% of all cases in this reporting period (189,489 cases), it however accounts for 3,3354 (6.3%) of the 52,667 serious cases in this reporting interval. The US continues to lead reporting with 78.2% of cases in this period.

The elderly, the frail and those with immunosuppressive conditions are more prone to vaccine failure due to multifactorial reasons including host immune response and preponderance of comorbid conditions.

Though the elderly (age group 65 years and older), represent 61.4% of serious primary vaccine failure cases, they represented 88% of fatalities. The same was true for booster vaccine failure where the elderly were 73.3% of the serious cases but 100% of the deaths. Frail patients made up 23.2% of cases of vaccine failure and those with immunosuppressive conditions accounted for 2.4% in this reporting period.

Immunosenescence is known to be associated with decreased immune response and is more common in the elderly. Though older age is also a known risk factor for severe COVID disease, it is also an independent risk factor for death from comorbid conditions or natural causes. Fatalities attributed to vaccine failure may therefore be an overrepresentation, especially in the elderly.

The institution of 3rd dose boosters has become more widespread in different countries, with percentage of vaccine failure cases reporting after dose 3 representing 2.2% of all vaccine failure cases in this reporting interval. Current data is still limited from spontaneous reporting with 113 case reports in the period >= 14 days after 3rd dose (booster vaccine failure). In all the 4 fatal cases

reported after booster dose, the patients reported significant comorbidities that either may have interfered with the mounting of an adequate immune response to vaccine or in other ways contributed to fatality.

16.3.6.8.6.6. Conclusion

After careful review of all new safety data received during the reporting period for vaccine failure, the benefit-risk profile for SPIKEVAX remains favorable. The safety topic of vaccine failure will continue to be monitored using the routine pharmacovigilance measures implemented for SPIKEVAX.

16.3.6.8.7. Subpopulation Analysis: Elderly >= +65 years

16.3.6.8.7.1. Source of the New Information

Information presented below includes analysis performed on cases received by ModernaTX, Inc. from 01 Jul 2021 to 31 Dec 2021 for the mRNA-1273 vaccine (COVID-19 vaccine Moderna) SPIKEVAX.

16.3.6.8.7.2. Background Relevant to the Evaluation

The impact of COVID-19 on older populations is well documented. This subpopulation is at most risk due to comorbidities and age-related complex conditions. At the time of this report, this subpopulation was eligible for the use of booster shots 5 or 6 months or more after the initial series, in most countries. Use of a booster dose is also under active discussion in other countries. This is based on concerns of waning immunity and the increasing prevalence of variants (e.g., Delta) and the recent discovery of Omicron variant characterized by (during the reporting period) by unclear transmissibility, morbidity, and mortality.

Young-Xu et al estimated the effectiveness of COVID-19 Messenger RNA Vaccination Against SARS-CoV-2 Infection Among Male US Veterans aged 65 years and older (110). The estimated pre-Delta mRNA vaccine effectiveness against any SARS-CoV-2 infection was 94.5% (95% CI, 90.7-96.7) in the first month after complete vaccination and decreased to 87.9% (95% CI, 85.9-89.5) by month 3. During the high-Delta period, the estimated vaccine effectiveness was 62.0% (95% CI, 45.6-73.5) in the first month and decreased to 57.8% (95% CI, 52.5-62.5) by month 3, similar to the pattern from the pre-Delta period. The decrease in vaccine effectiveness accelerated after month 4, reaching a low of approximately 20% in months 5 through 7.

16.3.6.8.7.3. Methods of Evaluation including Data Sources, Search Criteria, and Analytical Approaches

The MAH queried the GSDB for the reporting period 01 Jul 2021 through 31 Dec 2021, for valid case reports received from HCP, HA, consumers, and literature, worldwide, reported for SPIKEVAX. The search strategy and criteria included using a "Age group >=65-years."

16.3.6.8.7.4. Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Overview of Cases

During this reporting period, a total of 28,592 cases (105,695 events) were reported in the elderly 65 years and older, of which 11,421 (39.9%) were assessed as serious, 1584 cases (5.5%) reported a fatal outcome, and 16,331 (57.1%) cases were medically confirmed. Cases were disproportionately reported in females compared to males (59.9% vs 38.4%, respectively) with 1.7% missing gender information. The median age was 72.0 years (min 65.0 / max 600) with a mean age of 74.1 (SD:11.5). Most cases were from the USA (51.0%) followed by the Japan (8.1%). Case reports in the elderly represent 15.1% of all cases (189,489 cases) in this reporting period.

During this reporting period, the top 3 SOC were General disorders and administration site conditions (30.4%), Nervous disorders (11.0%, and Musculoskeletal and connective tissue disorders (8.8%.); HLT (Vaccination site reactions (5.5%), febrile disorders (4.2%), and Coronavirus infections (4.0%). 10 most frequently reported MedDRA PTs among the elderly are presented below in Table 16-240 below.

Table 16-240 Top 10 MedDRA PT Elderly Age ≥ 65 Years by Frequency (Review Period)

PT	Events (n)	Events (%)
Pyrexia	4,405	4.2%
COVID-19	3,554	3.4%
Fatigue	3,371	3.2%
Headache	3,078	2.9%
Myalgia	2,253	2.1%
Pain in extremity	2,078	2.0%
Chills	2,058	1.9%
Vaccination site pain	2,041	1.9%
Dyspnoea	1,957	1.9%
Nausea	1,719	1.9%

Time to Onset

In this reporting interval, more events (34.2%) were reported after the second dose than after the

first dose (19.9%). The most frequently reported time to onset (when known) was 30+ days after 2nd SPIKEVAX dose (17.5%), with a clustering also noted less than 5 days after each dose. There were 13,342 events reported after Dose 3, representing 12.6% of all events. Events after the 3rd dose were most frequently reported as occurring less than 5 days after 3rd SPIKEVAX dose (10,904 events; 10.3%).

There were 13 events (0.0%) reported after dose 4, all on day 0. Time to onset is presented in more detail in Table 16-241.

Table 16-241 Distribution of Events by Dose Number and Time to Onset for Age ≥ 65 Years (Review Period)

Dose Number	TTO All Doses (Days)	Review Period	
		# Events	% Events
Dose 1	**Subtotal**	21,017	19.9%
	0 days	5,233	5.0%
	01-02	4,482	4.2%
	03-04	1,197	1.1%
	05-06	868	0.8%
	07-13	2,888	2.7%
	14-29	1,809	1.7%
	30+	4,540	4.3%
Dose 2	**Subtotal**	36,170	34.2%
	0 days	6,416	6.1%
	01-02	6,177	5.8%
	03-04	1,090	1.0%
	05-06	701	0.7%
	07-13	1,553	1.5%
	14-29	1,749	1.7%
	30+	18,484	17.5%
Dose 3	**Subtotal**	13,342	12.6%
	0 days	5,186	4.9%
	01-02	4,785	4.5%
	03-04	933	0.9%
	05-06	519	0.5%
	07-13	820	0.8%
	14-29	538	0.5%
	30+	561	0.5%

Dose Number	TTO All Doses (Days)	Review Period	
		# Events	% Events
Dose 4	**Subtotal**	13	0.0%
	0 days	13	0.0%
Unknown	**Subtotal**	35,153	33.3%
	Missing	35,153	33.3%
Grand total		**105,695**	**100.0%**

When event outcome was known, in this reporting period, it was most frequently recovered in 26.9% of cases (Table 16-242).

Table 16-242 Event Outcome for Age ≥ 65 Years by Review Periods

Event Outcome	Review Period	
	Events (n)	Events (%)
Fatal	6,353	6.0%
Not Recovered/Not Resolved	25,834	24.4%
Recovered/Resolved	28,475	26.9%
Recovered/Resolved with Sequelae	539	0.5%
Recovering/Resolving	8,924	8.4%
Unknown	35,570	33.7%
Grand Total	105,695	100.0%

Serious Cases

During this reporting interval, there were 11,421 serious cases (54,172 events) of which 1584 cases were fatal (5.5%). Age distribution was 52.9% females to 46.2% males (0.9% missing gender) with the median age of serious reports in the elderly being 74.0 years (min: 65.0 / max 120.0) and mean of 75.2 (SD: 7.8).

In serious cases in this reporting period, General disorders and administration site conditions, Nervous system disorders and Investigations, were the top 3 SOCs while Coronavirus infections, Asthenic conditions and Breathing abnormalities were the top 3 HLTs. The most frequently reported preferred terms reflected either active Covid-19 or reactogenicity and are presented in (Table 16-243).

Table 16-243 Top 10 most Frequently reported MedDRA Preferred Terms in Serious Cases in Elderly Age ≥ 65 Years (Review Period)

PT	# Events	% Of Total Events
COVID-19	2,664	4.9%
Dyspnoea	1,550	2.9%

PT	# Events	% Of Total Events
Pyrexia	1,367	2.5%
Fatigue	1,187	2.2%
Asthenia	997	1.8%
Headache	876	1.6%
SARS-CoV-2 test positive	839	1.5%
Cough	794	1.5%
Death	728	1.3%
Nausea	679	1.3%

Abbreviations: MedDRA = Medical Dictionary for Regulatory Affairs; PT = preferred term.

Serious Cases of COVID-19 in the Elderly (Reporting Period)

COVID-19 was the most frequently reported Preferred term in serious cases in the elderly. There were 2,663 serious cases of COVID-19, representing 9.3% of the 28,592 cases in the elderly in this reporting interval of which 490 cases had a fatal outcome (1.7% of 28592). See Section 16.3.6.8.2 for death cases. The cases had a mean age of 78.4 (SD 8.2) and median age of 78.0 (min 65.0 / max 104.0). Gender distribution was 1,204 (45.2%) female and 1,446 (54.3%) males with 13 missing gender (0.5%). The mean time to onset all dose calculations was 186.1 days (SD: 72.7) with a median of 201.0 days (min:0; max 368) with 1336 missing or not reported. Most cases were from the US (92.4%) followed by 6.9% from the EEA.

The majority (11,654; 69.5%) of events in serious cases reporting the PT of COVID-19 occurred 14 or more days after 2nd dose of SPIKEVAX and may represent vaccine failure ().

Table 16-244).

Table 16-244 Time to Onset by Dose Number for Serious Events of COVID-19 Related PTs in Elderly Age ≥ 65 Years (Review Period)

Dose Number	TTO All Doses (Days)	# Events	% Events
Dose 1	Subtotal	2,869	17.1%
	0 days	24	0.1%
	01-02	9	0.1%
	03-04	22	0.1%
	05-06	5	0.0%
	07-13	86	0.5%
	14-29	107	0.6%
	30+	2,616	15.6%
Dose 2	Subtotal	11,785	70.3%
	0 days	90	0.5%

Dose Number	TTO All Doses (Days)	# Events	% Events
	03-04	10	0.1%
	07-13	31	0.2%
	14-29	149	0.9%
	30+	11,505	68.6%
Dose 3	Subtotal	770	4.6%
	0 days	8	0.0%
	01-02	133	0.8%
	03-04	40	0.2%
	05-06	202	1.2%
	07-13	102	0.6%
	14-29	67	0.4%
	30+	218	1.3%
Unknown	Subtotal	1,336	8.0%
	Missing	1,336	8.0%
Grand total		**16,760**	**100.0%**

Outcome of events in serious cases reporting COVID-19 in the elderly in this reporting interval was most frequently reported as unknown (36.4%), followed by not recovered in 23.8% of events, recovered in 22.0% of events. There was a fatal outcome reported in 17.3% of events.

Dyspnoea

There were 1,540 serious cases (13,951 events) reporting dyspnea, with a mean age of 75.7 years, (SD 7.9) and a median age of 75.0 (min: 65 to max: 101.0). Gender distribution included: 771 males (50.1%) to 754 females (49.0%) and 15 (1.0%) with missing gender information. The events in serious cases of dyspnea most frequently (47.7%) occurred 14 or more days after 2nd dose. When known, outcome was most frequently reported as not recovered for 29.5% of events. COVID-19 was the most frequently reported event term in serious cases of Dyspnea in the elderly.

Fatal Cases in the Elderly

The 1584 fatal cases (6,353 events) in the elderly in this reporting interval, occurred in 938 males (59.2%) and 633 females (40.0%) with13 cases (0.8%) missing gender information. Mean age was 78.6 (SD: 8.4) and median was 78.0 (min:65/max: 101.0). The top 3 PTs in fatal cases were Death (11.4%), COVID-19 (7.2%) and Dyspnea (3.5%). Most fatal cases were from the USA (73.2%) followed by Taiwan (12.9%). See Section 16.3.6.8.2 for review of Deaths. Most of these fatal events during the reporting period (3,469 of 6,353; 54.6%) occurred greater than 14 days after Dose 2 (including after dose 3).

Cases in Elderly Patients After a Third Dose or Booster Dose of SPIKEVAX

During this reporting period, a total of 3,845 cases (13,355 events), were reported in the elderly after the 3rd SPIKEVAX dose, (1,376; (35.8%) of these cases were serious, 109 (2.8%) cases were fatal, and 2,028 cases were medically confirmed. Cases reported after 3rd dose, represent 13.4% of all case reports in the elderly in this reporting period. Gender distribution was 36.9% male and 59.8% female, and the median age was 72.0 (min 65.0/ max 108.0) with an average age of 73.8 (SD: 7.2).

The most frequently reported event terms after 3rd SPIKEVAX dose in the elderly were expired product administered (5.2%), pyrexia (3.8%), and headache (3.7%), and mostly consistent with expected reactogenicity also seen with primary series for SPIKEVAX. The time to onset of reported events after the 3rd dose was < 5 days in 81.6 % of events. There were 13 events reported after dose 4 and all occurred on day 0.

Events occurring after dose 3 were most frequently reported as recovered (36.3%) followed by unknown (26.5%) and Not recovered (25.1%).

Serious cases in elderly after Booster dose of SPIKEVAX.

There were 1,376 serious case reports after the 3rd dose, of which 109 cases were fatal. These serious cases occurred in 533 males (38.7%) and 811 females (58.9%), with a mean age of 73.3 (SD:7.4) and median age of 71.0 (min 65.0. max 101.0). The most frequently reported PTs in serious cases after dose 3 were Headache, Pyrexia and Fatigue.

Most of the events (70.8%%) in serious cases in the elderly after dose 3 occurred in the <5 daytime frame. The most frequently reported event outcome in serious cases in the elderly after 3rd dose was not recovered 33.5% followed by recovered in 29.7% of cases.

16.3.6.8.7.5. Discussion

The most frequently reported events in the elderly, as in the general population, are those associated with reactogenicity as expected with and other vaccines.

COVID-19 was reported in 9.3% of serious cases in the elderly with 69.5% of event terms in these cases reported to have occurred in a time frame representing / suggestive of vaccine failure (14 days or more after 2nd dose).

The elderly subpopulation accounts for about half of vaccine failure cases (50.1%) and a disproportionate amount of the fatal vaccine failure cases (87.9%), in this review period. Advanced age and frailty are also independent risk factors for death with 18.2% of the elderly also classified as frail due to comorbid conditions. Immunosenescence and failure to mount sufficient immunity are all factors that are more likely to occur in the elderly.

Though 3rd dose data were (during the reporting period) more limited than for primary vaccine series, the adverse event profile observed so far is similar to that of primary vaccination with SPIKEVAX in the elderly population.

16.3.6.8.7.6. Conclusion

After careful review of all new safety data received during the reporting period in the elderly subpopulation, the benefit-risk profile for SPIKEVAX remains favorable. The risk profile in the elderly will continue to be monitored using the routine pharmacovigilance measures implemented for SPIKEVAX.

16.3.6.8.8. Subpopulation Analysis: Children < 18 Years (incl adolescent and young children)

16.3.6.8.8.1. Source of the New Information

Information presented below includes analysis performed on cases received by ModernaTX, Inc. from 01 Jul 2021 to 31 Dec 2021 for the mRNA-1273 vaccine (COVID-19 vaccine Moderna) SPIKEVAX. Cumulatively, the data reviewed covers the period from 18 Dec 2020 to 31 Dec 2021 and for the PBRER reporting period (01 Jul 2021 to 31 Dec 2021).

16.3.6.8.8.2. Background Relevant to the Evaluation

In addition to approval in adults over 18 years, SPIKEVAX has received approval under EUA (or similar international public health measures) for age groups 12 – 17 years, in certain countries and regions including the EEA, Australia and UK.

As of this report, SPIKEVAX has not been approved in the US for this population.

With this recent extension to include 12- to 17-year-olds for another mRNA vaccine, it is of high importance to keep the safety profile of this subgroup under close monitoring. A Regulatory Authority has also requested that the MAH report, present and comment on the data in the subgroups <12-year-olds (Appendix 20.11.80 and Appendix 20.11.81).

In the context of subpopulation analyses, Moderna TX, Inc continues to evaluate topics of interest such as myocarditis and pericarditis identified as having a higher risk in younger populations. This is discussed in detail in a specific section of Myocarditis/Pericarditis of this PBRER report Section 16.3.1.2.

16.3.6.8.8.3. Methods of Evaluation including Data Sources, Search Criteria and Analytical Approaches

Moderna TX, Inc queried the GSDB for the PBRER reporting period (01 Jul 2021 to 31 Dec 2021) for valid, spontaneous case reports received from health care professionals (HCP), HA, consumers,

and literature, worldwide, reported for SPIKEVAX using the search criteria "Age groups <18 years."

A review of pediatric cases associated with SPIKEVAX was performed using the search age groups including children, across age groups of neonates, infant, children, and adolescents < 18 years. Data are analyzed and presented for all the age groups <18 years with a sub analysis on children 12-17 years, also children taking more than two doses (e.g., booster dose).

- Appendix 20.11.80: Cumulative vaccine exposure in the < 18 years age
- Appendix 20.11.81: Interval vaccine exposure in the < 18 years age

16.3.6.8.8.4. Results: A Summary and Critical Analysis of the Data Considered in the Risk Evaluation

Cumulative Overview of Cases

Cumulatively, there were 6,163 cases (10,850 events), of which 509 cases were assessed as serious, 12 were fatal, and 5,095 were medically confirmed. There were 2,555 cases reported in males (41.5%) compared to 3,288 in females (53.4%) with 320 missing gender (5.2%). The mean age was 15.1 (SD: 3.6) and median age was 16.0 (Min: -1.0/max: 17.0).

An overview of most frequent events cumulatively in children < 18 years of age is described below in Table 16.265. The most frequently reported MedDRA PTs in children < 18 years of age were Product administered to patient of inappropriate age followed by Pyrexia and Headache. See Table 16.265. Additional details on interval and cumulative vaccine exposure in the < 18 years age group are presented in Appendix 20.11.80.

Table 16-245 Cumulative Summary of Top 3 SOC, HLT, PTs for Children < 18 years by Frequency

Classification	Event	Total Events (N)	Total Events (%)
SOC	Injury, poisoning and procedural complications	4,884	45.0
	General disorders and administration site conditions	2,618	24.1
	Nervous system disorders	865	8.0
HLT	Product administration errors and issues	4,495	41.4
	Febrile disorders	555	5.1
	Vaccination site reactions	520	4.8
PT	Product administered to patient of inappropriate age	4,281	39.5
	Pyrexia	540	5.0
	Headache*	490	4.5

Abbreviations: MedDRA = Medical Dictionary for Regulatory Affairs; HLT = higher level term; PT = preferred term; SOC = system organ class. Note: as per the source PT of 'No Adverse Event' was in top 3 and Headache was on Top 4 list of PT

Reports of Adverse Events in Children 12-17 Years Cumulatively as of 31 Dec 2021

Cumulatively, there were 5,820 cases (10,020 events), of which 433 cases were assessed as serious, 7 were fatal, and 4,949 were medically confirmed. There were 2418 cases reported in males (41.5%) compared to 3,162 in females (54.3%) and 240 missing gender (4.1%). The mean age was 15.9 years (SD: 1.5) and median age was 16.0 years (Min: -12.0 / max: 17.0).

Reports of Adverse Events in Children <18 Years After a Third Dose or Booster Dose of SPIKEVAX (Cumulative)

Cumulatively as of 31 Dec 2021, there were 44 cases reported after Dose 3. Of the 44 cases, 22 cases reported only the medication error "Product administered to patient of inappropriate age" and 7 cases co-reported "Product administered to patient of inappropriate age" along with adverse events.

Overview of Cases for the Reporting Period (01 Jul 2021 to 31 Dec 2021):

During the reporting period, a total of 2112 cases (5381 events) were reported in children. Of these, 1313 cases were medically confirmed, 449 cases were serious, and 9 cases had a fatal outcome. There were 942 cases (44.6%) reported for males compared to 1053 for females (49.9%), and 117 cases were missing gender (5.5%). The average age was 13.5 (SD: 4.2) with a median age of 14.0 (min: -1.0 / max: 17.0). The top 3 countries reporting cases in children under 18 years old were United States (20.7%), followed by Italy (13.3%) and Finland (12.4%).

An overview of most frequent events during this interval in children < 18 years of age is described below in Table 16-246. Additional details on interval vaccine exposure in the < 18 years age group are presented in Appendix 20.11.81.

Table 16-246 Interval Summary of Top 3 SOC, HLT, PTs for Children < 18 years by Frequency

Classification	Event	Total Events (N)	Total Events (%)
SOC	General disorders and administration site conditions	1794	33.3
	Injury, poisoning and procedural complications	804	14.9
	Nervous system disorders	747	13.9
HLT	Product administration errors and issues	580	10.8
	Febrile disorders	495	9.2
	Vaccination site reactions	469	8.7
PT	Product administered to patient of inappropriate age	489	9.1

	Pyrexia	480	8.9
	Headache	309	5.7

Abbreviations: MedDRA = Medical Dictionary for Regulatory Affairs; HLT = higher level term; PT = preferred term; SOC = system organ class.

In this review period, the greatest proportion of case reports were from the EEA (1126; 53.3%), followed by United States (437; 20.7%) and Asia (410; 19.4%) (Table 16-247).

Table 16-247 Distribution of Cases in Children by Region and Reporting Period (01 Jul 2021 to 31 Dec 2021)

Region	Review Period	
	# Cases	% of Total Cases
Asia	410	19.4
Australia	9	0.4
Canada	45	2.1
European Economic Area*	1126	53.3
Middle East	1	0.0
Switzerland	28	1.3
United Kingdom	56	2.7
United States	437	20.7
Grand total	**2112**	**100.0**

Note: counts from European Economic Area includes a one case from France which appears as the Empty region in the source data

The most frequently (≥2%) reported event terms in children for SPIKEVAX are presented in Table 16-248.

Table 16-248 Most Frequently Reported MedDRA PTs in Children Under 18 years ≥2% During the Reporting Period (01 Jul 2021 to 31 Dec 2021)

PT	# Events	% of Total Events
Product administered to patient of inappropriate age	489	9.1
Pyrexia	480	8.9
Headache	309	5.7
Vaccination site pain	182	3.4
Fatigue	151	2.8
Nausea	126	2.3
Vomiting	108	2.0
Dizziness	107	2.0
Myalgia	107	2.0

During the reporting interval, the most frequently reported time to onset in children < 18 years (when known) was < 1 day after first dose (22.7 %) and second dose (7.2%) (Table 16-249). More

events (39.1%) were reported after the first dose than the second dose (15.4%), representing the same trend as the previous PBRER reporting interval.

Table 16-249 TTO by Dose in Children Under 18 years During the Reporting Period (01 Jul 2021 to 31 Dec 2021)

Dose Number	TTO All Doses (Days)	Review Period	
		# Events	% Events
Dose 1	Subtotal	2,102	39.1
	0 days	1,224	22.7
	01-02	460	8.5
	03-04	60	1.1
	05-06	60	1.1
	07-13	197	3.7
	14-29	74	1.4
	30+	27	0.5
Dose 2	Subtotal	827	15.4
	0 days	389	7.2
	01-02	295	5.5
	03-04	48	0.9
	05-06	30	0.6
	07-13	30	0.6
	14-29	18	0.3
	30+	17	0.3
Dose 3	Subtotal	95	1.8
	0 days	57	1.1
	01-02	31	0.6
	07-13	6	0.1
Unknown	**Subtotal**	2,357	43.8
	Missing	2,357	43.8
Grand total		5,381	100.0

Adverse Event Outcomes in Children < 18 Years During the Reporting Period (01 Jul 2021 to 31 Dec 2021)

The most frequently reported event outcome in Children < 18 years in the reporting period was recovered, in 41.9% of events (Table 16-250).

Table 16-250 Adverse Event Outcomes in Children < 18 years During the Reporting Period (01 Jul 2021 to 31 Dec 2021)

Event Outcome	Review Period	
	# Events	% of Total Events
Fatal	15	0.3
Not Recovered/Not Resolved	1,039	19.3
Recovered/Resolved	2,252	41.9
Recovered/Resolved with Sequelae	31	0.6
Recovering/Resolving	1,119	20.8
Unknown	925	17.2
Grand total	5,381	100.0

Cases were most frequently reported in the 12–15-year age group (54.4%) followed by the 16–17-year age group (36.2%). The distribution of case reports by age is provided in (Table 16-251).

Table 16-251 Distribution of Case Reports by Age Group During the Reporting Period (01 Jul 2021 to 31 Dec 2021)

Age Group	Review Period	
	# Cases	% of Cases
<2	151	7.1
02-11	47	2.2
12-15	1,149	54.4
16-17	765	36.2
Grand total	2,112	100.0

During the review period, 151 cases (7.1%) were reported in children under 2 years of age. eighty-one of these 151 cases were either pregnancy related or exposure through breast milk. These 81 cases will be discussed in Section 16.3.5.1 and Section 16.3.5.2, Use in Pregnancy and While Breastfeeding.

There were 47 cases (2.2%) reported in the age group 2 – 11 years of age. These cases are discussed below. The other 1914 cases occurred in age group 12 – 17 years and are discussed below.

Serious Cases in Children under 18 Years During the Reporting Period (01 Jul 2021 to 31 Dec 2021)

There were 444 serious cases (1127 events) reported in children under 18 years, with 9 cases (15 events) having a fatal outcome. Forty-nine (49) of these cases were reported in children under the age of 12 years (See below). The fatal cases: 4.1(b) [redacted]; 4.1(b) [redacted]; 4.1(b) [redacted]; 4.1(b) [redacted]; 4.1(b) [redacted]; 4.1(b) [redacted]; 4.1(b) [redacted]

4.1(b) ; 4.1(b) ; 4.1(b) , are discussed in Section 16.3.6.8.2, Fatal Cases.

The 395 serious cases in children that occurred in age 12 – 17 years are discussed under that section for Adolescents 12 – 17 (see below).

Overall reports in Adolescents Ages 12 – 17 years During the Reporting Period (01 Jul 2021 to 31 Dec 2021)

There were 1914 cases (4916 events) reported in the 12 – 17-year age group, representing 90.6% of cases in children (<18 years) in this reporting period. Of these, 400 cases were serious (see below) and six (6) cases had a fatal outcome (see below).

The 3 most frequently reported PTs in this age group were Product administered to patient of inappropriate age, Pyrexia, and Headache (Table 16-252). Pyrexia and Headache are events consistent with expected events following vaccinations including SPIKEVAX. Myocarditis ranked #10. Myocarditis is an Important Identified Risk and is discussed in Section 16.3.1.2, Myocarditis and Pericarditis.

Table 16-252 presents the top 10 events (by PT) during the reporting period for children in the age group 12 – 17 years.

Table 16-252 Top 10 MedDRA PTs by Event Count for Children 12-17 years During the Reporting Period (01 Jul 2021 to 31 Dec 2021)

PT	# Events	% of Total Events
Product administered to patient of inappropriate age	454	9.2%
Pyrexia	453	9.2%
Headache	300	6.1%
Vaccination site pain	174	3.5%
Fatigue	136	2.8%
Nausea	125	2.5%
Dizziness	107	2.2%
Myalgia	102	2.1%
Vomiting	97	2.0%
Myocarditis	96	2.0%

When time to onset and dose number was known, events most frequently occurred less than one days after 1st dose of SPIKEVAX (1,148 events; 23.4%). The time to onset by dose number is presented in Table 16-253.

Table 16-253 Distribution of Events by Dose Number, and TTO for Adolescents 12- 17 years During the Reporting Period (01 Jul 2021 to 31 Dec 2021)

Dose Number	TTO All Doses (Days)	# Events	% Events
Dose 1	Subtotal	1,989	40.5
	0 days	1,148	23.4
	01-02	435	8.8
	03-04	57	1.2
	05-06	58	1.2
	07-13	195	4.0
	14-29	74	1.5
	30+	22	0.4
Dose 2	Subtotal	756	15.4
	0 days	360	7.3
	01-02	270	5.5
	03-04	47	1.0
	05-06	29	0.6
	07-13	23	0.5
	14-29	18	0.4
	30+	9	0.2
Dose 3	Subtotal	52	1.1
	0 days	42	0.9
	01-02	4	0.1
	07-13	6	0.1
Unknown	Subtotal	2,119	43.1
	Missing	2,119	43.1
Grand total	Grand total	4,916	100.0

The most frequently reported event outcome in the age group 12 – 17 years during the reporting interval, was Recovered/Resolved (42.5%) (Table 16-254).

Table 16-254 Event Counts by Outcomes for Adolescents 12 – 17 Years During the Reporting Period (01 Jul 2021 to 31 Dec 2021)

Event Outcome	# Events	% of Events
Fatal	12	1.2
Not Recovered/Not Resolved	981	20.0
Recovered/Resolved	2,088	42.5
Recovered/Resolved with Sequelae	30	0.6
Recovering/Resolving	1,058	21.5

Event Outcome	# Events	% of Events
Unknown	747	15.2
Grand total	4,916	100.0

Serious Cases in Adolescents age 12 – 17 Years During the Reporting Period (01 Jul 2021 to 31 Dec 2021)

There were 395 serious cases (1001 events) and 6 cases (12 events) were fatal in this age group during this reporting period. The most frequently reported event terms in these serious cases were Myocarditis, Pyrexia and Headache (Table 16-255).

Table 16-255 Most Frequently Reported PTs in Serious Cases in Children Age 12 – 17 Years ≥2%During the Reporting Period (01 Jul 2021 to 31 Dec 2021)

PT	Serious	
	# Events	% of Total Events
Myocarditis	95	9.5
Pyrexia	68	6.8
Headache	45	4.5
Chest pain	44	4.4
Syncope	33	3.3
Dyspnoea	27	2.7
Dizziness	21	2.1
Pericarditis	20	2.0

Of the 44 cases of chest pain, 23 were in association with Myocarditis, seven (7) case is in association with Pericarditis. See Myocarditis and Pericarditis in Section 16.3.1.2.

The other 14 cases of chest pain where myocarditis was not mentioned are discussed below.

4.1(b) : On 02 Jul 2021 a 15-year-old male patient received second dose of mRNA-1273 (Moderna COVID-19 Vaccine). (On an unknown date, the patient received first dose of mRNA-1273 (Moderna COVID-19 Vaccine). On 03 Jul 2021, the patient experienced chest pain dizziness, dyspnoea, ventricular tachycardia), fatigue) and hypoacusis)). The patient was hospitalized on 04 Jul 2021. At the time of the report-symptoms had not resolved. Diagnostic Results (normal ranges are provided in parenthesis if available): On 03 Jul 2021, Cytomegalovirus test: negative (Negative) Negative, Electrocardiogram: abnormal (abnormal) abnormal and elevated ST segment, Epstein-Barr virus test: negative (Negative) negative. HIV test: negative (Negative) negative. On 03 Jul 2021, Respiratory viral panel: negative Negative. Treponema test: negative (Negative) negative, Troponin: high (High) 8154 (Serial troponins - 14.23 greater than 13.98 greater than 13.06 greater than 10.20 greater than 14.67 greater than 11.71 greater than 9.23).

Urine analysis: normal (normal) normal. Varicella virus test: negative (Negative) Negative. Patient received immunoglobulin therapy on 05 Jul 2021 as corrective. No concomitant medications were reported Based on the information presented. Based on the temporal relationship causality is possible. The laboratory and clinical findings are consistent with myocarditis but the data available does not meet the definition of a case by Brighton criteria.

4.1(b) **:** This regulatory authority case was reported by a physician and describes the occurrence of chest pain in a 16-year-old male patient who received mRNA-1273 (SPIKEVAX) (batch no. 3005835) for COVID-19 vaccination. No Medical History information was reported. On 02 Oct 2021, the patient received second dose of mRNA-1273 (SPIKEVAX. On 05 Oct 2021, after starting mRNA-1273 (SPIKEVAX), the patient experienced chest pain at the time of the report, his symptom was resolving. Based only on temporal relationship causality is possible. The case does not meet the Brighton criteria for myocarditis.

4.1(b) **:** On 04 Oct 2021, the patient received first dose of mRNA-1273 (SPIKEVAX. On 04 Oct 2021, the patient experienced arrhythmia irregular heart rate, asthenia, chest pain), and decreased exercise tolerance. At the time of the report, symptoms had not resolved. No medical history was provided by the reporter. Concomitant products included salbutamol sulfate (buventol) from 11-May-2020 to an unknown date, Midazolam Hydrochloride (Buccolam) from 03-Jun-2021 to an unknown date and Oxcarbazepine (Apydan [Oxcarbazepine]) from 07 Jul 2021 to an unknown date for an unknown indication. Based on the temporal relationship causality is possible. Given the medications there may be potential confounding by underlying medical conditions treated by these medications. The Brighton criteria for myocarditis are not satisfied.

4.1(b) **:** A 16-year-old female with no relevant medical history, experienced Chest pain, Pain in extremity, Vertigo, Headache and Fatigue, 2 days after first dose of SPIKEVAX. Diagnostic tests, including echocardiogram and chest X-ray, were performed but results, medical history, treatment and outcome, were not provided. Causality – Possible based on temporal relationship. The Brighton criteria for myocarditis are not met.

4.1(b) **:** This regulatory authority case concerns a 16-year-old female patient with relevant medical history of anxiety and concurrent medical condition of asthma bronchial, who experienced chest pain, palpitations and dyspnea, approximately 4 days after 1st dose of SPIKEVAX. Examination findings, diagnostic test results, treatment and outcome were not provided. Causality: Possible based on temporal association. The Brighton criteria for myocarditis are not met.

4.1(b) **:** This regulatory authority case concerns a 15-year-old male who experienced chest pain, malaise, tachycardia, and respiratory distress 4 days after receiving his second dose of SPIKEVAX. Symptoms were reported to have resolved. No past medical history or concomitant

medications were reported. Based on the temporal relationship the WHO causality is assessed as possible. The Brighton criteria for myocarditis are not met.

4.1(b) : This regulatory authority case was reported by a pharmacist and describes the occurrence of chest pain (Retrosternal pain at rest) a 17-year-old male patient one day after receiving SPIKEVAX dose 1. After the 2nd dose SPIKEVAX chest pain recurred. The timing of the second event is not stated but it was reported that heart rate, blood pressure and oxygen saturation were measured 3 days after the second dose. No values for these tests were given in the report. The pain was resolving at the time of the report. No past medical history, concomitant medications or treatment were reported. Based on the temporal relationship and positive rechallenge the WHO causality is assessed as possible. Since we do not have the information needed to know whether there are alternative explanations, we cannot meet the definition of probable by being able to definitely exclude alternative explanations in the absence of past medical history, treatment and concomitant medications. The case does not meet the Brighton classification for myocarditis.

4.1(b) : This regulatory authority case was reported by a physician. A 14-year-old male received a second dose SPIKEVAX and 3 days later experienced chest pain, palpitations, and pyrexia. On an unknown date the patient was also reported to have a repolarization disorder and an elevated troponin level (greater than 5000 pg/ml.). Pyrexia resolved after 2 days and other findings were resolving at the time of the report approximately one month later. No treatment history or past medical history were provided. Causality assessed as possible because of temporal association. This case does not meet Brighton criteria for myocarditis.

4.1(b) **:** A 15-year-old experienced chest pain, fever, generalized aching precordial chest pain and palpitations for three days after a first dose of SPIKEVAX beginning the day of vaccination. Events were resolving at the time of the report. No prior medical history, concomitant medications or treatment information was provided. Insufficient evidence is present to classify as a possible case of myocarditis according to the Brighton criteria.

4.1(b) **:** A 17-year-old female experienced dyspnea, chest pain and increased heart rate 12 days after a second dose of SPIKEVAX. Events were resolving at the time of the report. No past medical history, concomitant medications or treatment history were provided. Insufficient evidence is present to classify as a possible case of myocarditis according to the Brighton criteria.

4.1(b) **:** A 17-year-old female experienced palpitations, chest pain, and vomiting beginning the day of SPIKEVAX administration. Three days after vaccine administration she experienced dyspnea, and on an unknown date tachycardia was reported. Symptoms had resolved at the time of the report. Insufficient evidence is present to classify as a possible case of myocarditis according to the Brighton criteria.

4.1(b) [redacted]: This regulatory authority case was reported by another health care professional and describes the occurrence of chest pain), dyspnoea and palpitations in a 17-year-old female patient who received mRNA-1273 (COVID-19 Vaccine Moderna) (batch no. 083F21B. On 30-Nov-2021, the patient received dose of mRNA-1273 (COVID-19 Vaccine Moderna) (Intramuscular). On 30-Nov-2021 at 4:00 PM, the patient experienced chest pain, dyspnoea and palpitations. At the time of the report all symptoms were resolving. Insufficient evidence is available to classify as a possible case of myocarditis according to the Brighton criteria. This case could represent reactogenicity.

4.1(b) [redacted]: On 30-Nov-2021, the patient received dose of mRNA-1273 (COVID-19 Vaccine Moderna) (Intramuscular). On 30-Nov-2021 at 2:00 PM, the patient experienced chest pain, dyspnoea, palpitations and hyperventilation. At the time of the report all symptoms were resolving. Insufficient evidence is available to classify as a possible case of myocarditis according to the Brighton criteria.

4.1(b) [redacted]: This regulatory authority report concerns a 13-year-old patient who experienced hyperpyrexia and chest pain after receiving her second SPIKEVAX vaccination. Hyperpyrexia occurred several hours after the vaccination and chest pain was reported the following day. All symptoms had resolved 5 days after the vaccination. No past medical history, treatment or concomitant medications were reported. Insufficient evidence is available to classify as a possible case of myocarditis according to the Brighton criteria.

The most frequently reported time to onset (when known) for events in serious cases in adolescents 12 – 17 years was < 1 days from 1st SPIKEVAX dose (141 events; 14.1%) and 2nd SPIKEVAX dose (78 events, 7.8%). (Table 16-256).

Table 16-256 Distribution of Events in Serious Cases by Dose Number, and TTO in Adolescents 12 – 17-year-old During the Reporting Period (01 Jul 2021 to 31 Dec 2021)

Dose Number	TTO All Doses (Days)	# Events	% Events
Dose 1	Subtotal	341	34.1%
	0 days	141	14.1%
	01-02	96	9.6%
	03-04	11	1.1%
	05-06	7	0.7%
	07-13	20	2.0%
	14-29	59	5.9%
	30+	7	0.7%
Dose 2	Subtotal	252	25.2%

Dose Number	TTO All Doses (Days)	# Events	% Events
	0 days	78	7.8%
	01-02	89	8.9%
	03-04	34	3.4%
	05-06	25	2.5%
	07-13	11	1.1%
	14-29	10	1.0%
	30+	5	0.5%
Unknown	Subtotal	408	40.8%
	Missing	408	40.8%
Grand total		1,001	100.0%

The adolescents with serious cases in this reporting period most frequently reported event outcomes as recovering (333; 33.3%) followed by Recovered (293; 29.3%). (Table 16-257).

Table 16-257 Event Outcomes in Serious Cases in Adolescents 12 – 17 Years of Age During the Reporting Period (01 Jul 2021 to 31 Dec 2021)

Event Outcome	# Events	% of Total Events
Fatal	12	1.2
Not Recovered/Not Resolved	245	24.5
Recovered/Resolved	293	29.3
Recovered with sequelae	18	1.8
Recovering/Resolving	333	33.3
Unknown	100	10.0
Grand total	1,001	100.0

Fatal Cases in Adolescents Age 12 – 17 Years During the Reporting Period (01 Jul 2021 to 31 Dec 2021)

There are 6 cases with fatal outcomes in this reporting period in adolescents 12 – 17 years of age.

4.1(b) : This spontaneous case was reported by a consumer and describes the occurrence of death in a 13-year-old male patient who received mRNA-1273 (Moderna COVID-19 Vaccine) for COVID-19 vaccination. No Medical History information was reported. On an unknown date, the patient received dose of mRNA-1273 (Moderna COVID-19 Vaccine). The patient died on an unknown date reportedly three days after vaccination. The cause of death was not reported. It is unknown if an autopsy was performed Concomitant product was not provided by the reporter. Treatment information was unknown. There is insufficient information to assess causality.

4.1(b) **:** A regulatory Authority report of a 15-year-old male with a medical history of cerebral arteriovenous malformation, who experienced headache and vomiting, 9 hours after 1st dose of SPIKEVAX. The patient was taken to the hospital, where JCS3 was 300 and CT showed cerebral hemorrhage and cerebral ventricular rupture from cerebral arteriovenous malformation. Patient died 4 days later. Causality: Possible. Though confounded by underlying condition, there is close temporal association with SPIKEVAX administration. Although the cerebral hemorrhage and subsequent death is likely related to the rupture on an existing cerebral arteriovenous malformation, there is a close almost coincidental (9h) temporal association, and thus a causal association cannot be ruled out.

4.1(b) **:** A spontaneous case of a 17-year-old male patient who experienced bilateral myocarditis at an unknown latency after unknown dose of SPIKEVAX. Medical history, concomitant drugs, diagnostic tests and treatment were unknown. Cause of death was Myocarditis, and it is unknown if an autopsy was performed. Causality: Unassessable – Insufficient information is provided for causality assessment.

4.1(b) **:** This spontaneously reported case involves a 17-year-old male with unknown medical history who was found dead in his bedroom a few days after receiving his second dose of SPIKEVAX. No further information is currently available on the reason of his death or events that may have resulted in death. The reporter declined further information on his name or address. The causality assigned is possible based solely on a temporal relationship to vaccine administration.

4.1(b) **:** This regulatory authority case was reported by a physician and describes the occurrence of pyrexia, seizure and headache in a 13-year-old male patient who received mRNA-1273 (COVID-19 Vaccine Moderna) (batch no. 940067) for an unknown indication. No Medical History information was reported. On 15-Nov-2021, the patient received dose of mRNA-1273 (COVID-19 Vaccine Moderna). On 22-Nov-2021 at 9:00 PM, the patient experienced pyrexia (Fever). On 23-Nov-2021, the patient experienced a seizure). On 24-Nov-2021 at 5:43 PM, the patient experienced headache the reported cause of death was Fever, Seizure and Headache. It is unknown if an autopsy was performed. A possible association to vaccine administration is based on temporal association in the absence of past medical history and concomitant medications.

4.1(b) **:** This case concerns a 14-year-old, female patient with a relevant medical history of syncope 2 months prior to the events below, who experienced cardiac arrest, brain injury, brain herniation and multiple organ dysfunction. The events occurred approximately 16 days after the first dose of mRNA-1273 and had a fatal outcome, with death occurring in the following day. The causality assessment is possible based on temporal association. There is no information on the cause of syncope two months prior and no other information on past medical history or concomitant medications.

Reports in Children < 12 Years During the Reporting Period (01 Jul 2021 to 31 Dec 2021)

There were 198 cases (465 events) reported in the <12 years age group in this reporting period. forty-nine (49) of those cases were serious and Three (3) cases of these had a fatal outcome.

The top 3 most frequently reported PTs in this age group during the reporting period were "Exposure via breast milk", "Product administered to patient of inappropriate age" followed "Fatigue" and "Pyrexia".

Table 16-258 presents the top 10 events (by PT) during the reporting period in the <12 years age group.

Table 16-258 Top 10 MedDRA PTs by Event Count for Children <12 years for Reporting Period (01 Jul 2021 to 31 Dec 2021)

Reporting Period		
PT	**# Event**	**% Event**
Exposure via breast milk	89	19.1
Product administered to patient of inappropriate age	35	7.5
Pyrexia	27	5.8
Fatigue	15	3.2
Vomiting	11	2.4
Diarrhoea	9	1.9
Headache	9	1.9
Malaise	9	1.9
Vaccination site pain	8	1.7
Maternal exposure during breast feeding	7	1.5

During the reporting period, when time to onset and dose number was known, events most frequently occurred less than 1 days after Dose-1 (76; 16.3%) were comparatively high to that of events reported on 2nd dose of SPIKEVAX (29 events; 6.2%) and 3rd dose of SPIKEVAX (15 events, 3.2%). The average time to onset was 5.2 days (SD: 20.4) with a median number of days of 0.0 (min 0/max161).

The time to onset by dose number is presented in Table 16-259.

Table 16-259 Distribution of Events by Dose Number, and TTO for Children <12 years for Reporting Period (01 Jul 2021 to 31 Dec 2021)

Dose Number	TTO All Doses (Days)	Review Period	
		# Events	% Events
Dose 1	**Subtotal**	113	24.3
	0 days	76	16.3

Dose Number	TTO All Doses (Days)	Review Period	
		# Events	% Events
	01-02	25	5.4
	03-04	3	0.6
	05-06	2	0.4
	07-13	2	0.4
	30+	5	1.1
Dose 2	Subtotal	71	15.3
	0 days	29	6.2
	01-02	25	5.4
	03-04	1	0.2
	05-06	1	0.2
	07-13	7	1.5
	30+	8	1.7
Dose 3	Subtotal	43	9.2
	0 days	15	3.2
	01-02	27	5.8
	30+	1	0.2
Unknown	Subtotal	238	51.2
	Missing	238	51.2
Grand total		465	100.0

The most frequently reported event outcome in this age group during the reporting interval was Unknown followed (38.3%) and Recovered/Resolved (35.3%) (Table 16-260).

Table 16-260 Event Counts by Outcomes for Children <12 years for Reporting Period (01 Jul 2021 to 31 Dec 2021)

Event Outcome	Review Period	
	# Events	% of Total Events
Fatal	3	0.6
Not Recovered/Not Resolved	58	12.5
Recovered/Resolved	164	35.3
Recovered/Resolved with Sequelae	1	0.2
Recovering/Resolving	61	13.1
Unknown	178	38.3
Grand total	465	100.0

Serious Cases in Children <12 years During the Reporting Period (01 Jul 2021 to 31 Dec 2021)

There were 49 serious cases (126 events) and 3 cases with fatal outcome in this age group during this reporting period. Two cases were associated with fetal exposure during pregnancy or exposure

through breast milk and 1 case was associated with paternal exposure before pregnancy. These cases are discussed in Section 16.3.5.1 and Section 16.3.5.2, Use in Pregnancy and While Breastfeeding. During the reporting period, there is a single case report of seizures in this age group.

The most frequently reported time to onset (when known) for events in serious cases in children <12 years during the reporting interval was 2 days from 3rd SPIKEVAX dose (17; 13.5%) and 2nd dose (14; 11.1%) compared to 1 days from 1st SPIKEVAX dose (7 events, 5.6%) (Table 16-261).

Table 16-261 Distribution of Events in Serious Cases by Dose Number, and TTO in Children <12 years for Reporting Period (01 Jul 2021 to 31 Dec 2021)

Dose Number	TTO All Doses (Days)	Review Period	
		# Events	% Events
Dose 1	Subtotal	17	13.5
	0 days	7	5.6
	01-02	7	5.6
	03-04	1	0.8
	30+	2	1.6
Dose 2	Subtotal	30	23.8
	0 days	2	1.6
	01-02	14	11.1
	07-13	7	5.6
	30+	7	5.6
Dose 3	Subtotal	19	15.1
	0 days	2	1.6
	01-02	17	13.5
Unknown	Subtotal	60	47.6
	Missing	60	47.6
Grand total		126	100.0

During the reporting period, children <12 years with serious cases most frequently reported event outcomes as Unknown (44; 34.9%) followed by Recovered/Resolved (37; 29.4%) (Table 16-262).

Table 16-262 Event Outcomes in Serious Cases in Children <12 years for Reporting Period (01 Jul 2021 to 31 Dec 2021)

Event Outcome	Review Period	
	# Events	% of Total Events
Fatal	3	2.4
Not Recovered/Not Resolved	23	18.3

Recovered/Resolved	37	29.4
Recovering/Resolving	19	15.1
Unknown	44	34.9
Grand total	126	100.0

Fatal Cases in Children <12 years During the Reporting Period (01 Jul 2021 to 31 Dec 2021)

During the reporting period, three (3) fatal cases in children <12 years of age were reported. These were all in children less than 2 and are discussed in Pregnancy and Lactation section.

16.3.6.8.8.5. Discussion

Over three-quarters (79.1%) of cases reported in children under the age of 18 years during this reporting period were non-serious and most of the cases (1914; 90.6%) were reported in adolescents 12 – 17 years. Cases reported in children less than 12 years old continued to be primarily in the context of maternal exposures. There were a few cases of vaccine administration in this age group and the symptoms were typical of vaccine reactogenicity. All but one of the serious cases reported in the 5-11-year-old age group appeared to be age coding errors.

In the12-17-year age group the events most frequently reported were in line with reactogenicity of SPIKEVAX but myocarditis (96 events, 2.0%) during the reporting interval and 99 events, 1.0% cumulatively) has also now emerged as an adverse event in the 12–17-year-old age group.

Most of the events in children under 18 years were non-serious, had a time to onset <1 day and described events related to expected reactogenicity. With the approval of conditional marketing authorization (CMA) in adolescents, reports in this age group are increasing, and the MAH expects an increasing amount of information about the safety of the product in this subpopulation.

16.3.6.8.8.6. Conclusion

After careful review of all new safety data received during the reporting period for the children <18 years, the benefit-risk profile for SPIKEVAX remains favorable. The safety of vaccination in children <18 years will continue to be monitored using the routine pharmacovigilance measures implemented for SPIKEVAX.

16.4. Characterization of Risks

Table 16.263 Important Identified/Important Potential Risks

Important Identified Risk	**Anaphylaxis**
Potential mechanisms	Immediate type (Type 1), hypersensitivity mediated by immunoglobulin (Ig) E. Naturally existing IgM and IgG can bind to various components commonly present in nanomedicines, (cholesterol, phospholipids and polyethylene glycol).
Evidence source(s) and strength of evidence	Data to evaluate the safety concern were derived from clinical studies and post authorization.
Characterization of risk	In study mRNA-1273-P301 (Part A), in the anaphylaxis SMQ, 9 events were reported for 5 participants in the mRNA-1273 group and 18 events were reported for 8 participants in the placebo group. Anaphylactic reaction of unknown cause was reported for 2 participants in the mRNA-1273 group as non-serious, moderate severity events approximately 2 months after the second dose; both were considered not related to investigational product and resolved on the same day with concomitant medications. Among the other terms in the SMQ, reported events in the mRNA-1273 group were all non-serious and described as follows: mild cough and mild eye pruritus for one participant on Day 47 after the second dose (not considered related); mild tachypnea on Day 29 after the first dose (which was reported on the day of the second dose), severe tachypnea on Day 1 after the second dose (which was the same day; event resolved on Day 64), and moderate urticaria beginning 30 minutes after the second dose and resolved in 1 hour with concomitant medication (all events considered related); and moderate dyspnea (considered related; reported as resolving) and severe swelling face (not considered related; resolving with prednisone) beginning on Day 34 after the second dose . In Part B of mRNA-1273-301, amongst the SAEs, a grade 3 anaphylaxis was reported in 2 participants in the placebo-mRNA-1273 group, both of which were considered unrelated to mRNA-1273. These 2 participants had history of asthma. The first participant was a 51-year-old female who experienced anaphylaxis 19 days after the first injection which resolved the same day; the participant did not receive the second dose. The second participant was a 57-year-old female who experienced anaphylaxis a few months after receiving the second dose of vaccine; however, it was not temporally related to mRNA-1273 and considered associated to a steroid injection per the investigator. In the placebo group, no anaphylaxis was reported. In the mRNA-1273 group, 1 participant experienced anaphylaxis due to antigen challenge allergy testing (CSR) mRNA-1273-P301 addendum 1 (Safety from open label phase [Part B]). During the post authorization, cumulatively as of 31 Dec 2021, a total of 1,949 cases (and 1,992 events) were identified using the narrow SMQ ‘anaphylactic reaction’, of which 1,916 cases were serious and 41 had a fatal outcome. There were 1,487 (76.3%) cases that were medically confirmed. Regulatory authority reports accounted for 76.3% of received reports (1,488 reports), followed by spontaneous case reports (451 cases / 23.1%) and literature reports (10 cases / 0.5%). The largest number of cases originated from the United States (853 cases / 43.0%) followed by Japan (552 cases / 32.4%) and Germany (135 cases / 7.2%). Far fewer reports have been received from other countries. Of the 1,992 events (in 1,949 cases), 1,949 (97.8.%) were serious and 43

Important Identified Risk	**Anaphylaxis**
	(2.2%) were non-serious. Anaphylactic reaction represented 73.8% of the total events (1,470 events), followed by Anaphylactic shock (177 events / 8.9%/) and Circulatory collapse (163 events / 8.2%). Cumulatively, a total of 912 events (45.9%) were considered "recovered/resolved", 244 events (12.3%) were "recovering/resolving", and 182 events (9.2%) were "not recovered/not resolved". Outcome was unknown or not reported for 594 events (29.9%).
Risk factors and risk groups	Any participant receiving the vaccine. However, participants with a known history of hypersensitivity to any component of the vaccine may be at risk of hypersensitivity reactions.
Preventability	mRNA-1273 vaccine is contraindicated in individuals with known severe allergic reactions (e.g., anaphylaxis) to any component of the vaccine or to a previous dose of the vaccine. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine. Close observation is recommended following vaccination for 30 minutes for people with a history of an immediate allergic reaction of any severity to another vaccine or injectable therapy, and/or people with a history of anaphylaxis due to any cause. All other persons should be observed for 15 minutes following vaccination. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of COVID-19 Vaccine Moderna.
Impact on the benefit-risk balance of the product	Anaphylactic reaction is a potentially life-threatening event requiring medical intervention.
Public health impact	Anaphylaxis associated with vaccines typically occurs at a low incidence, which results in a low public health impact. Although the potential clinical consequences of an anaphylactic reaction are serious, this is a risk known to healthcare professionals.

Important Identified Risk	**Myocarditis**
Potential mechanisms	Myocarditis is an under-diagnosed cardiac disease resulting from any one of a broad range of infectious, immune, and toxic causes. Most cases of myocarditis are caused by infectious agents, toxic substances, drugs or autoimmune disorders. Hence, it is increasingly recognized that myocarditis is an inflammatory condition of the myocardium triggered by various factors rather than a distinct cardiovascular disease. Infectious causes include viruses, bacteria, Chlamydia, rickettsia, fungi, and protozoa. Non-infectious triggers have been identified such as toxins, autoimmune disease and hypersensitive reactions. Numerous medications like antipsychotics (e.g., clozapine), antibiotics (penicillin, ampicillin, sulfonamides, tetracyclines), and antiphlogistic (e.g., mesalamine) can induce hypersensitivity eosinophilic myocarditis. Myocarditis has been reported following many different vaccines including flu vaccine, however the smallpox vaccine has the strongest association. During the influenza epidemic of the winter 1998-1999 there were several reports of patients who had preceding flu-like symptoms and fever and developed cardiac involvement between 4 and 7 days after the onset of influenza symptoms [204]. Evaluation of the post-authorization safety data suggest a very rare risk of myocarditis following COVID-19 vaccination, the mechanisms involved in such vaccine-related myocarditis are not clear based on the data currently

Important Identified Risk	**Myocarditis**
	available.
Evidence source(s) and strength of evidence	Data to evaluate the safety concern were derived from clinical trials and the post-authorization safety.
Characterization of risk	In Study mRNA-1273-P301 (Part A), there were 15,184 participants exposed to the mRNA-1273 vaccine, and 15,166 participants in the placebo arm. There were no reported TEAEs of Myocarditis follow-up period after vaccination. No cases have been reported in Part B of the study (CSR mRNA-1273-P301 addendum 1 (Safety from open label phase [Part B]). During the post authorization, cumulatively, through 31 Dec 2021, a total of 2,668 cases (2,692 events) of myocarditis, with or without pericarditis, have been reported, with 1,982 cases medically confirmed and 35 cases with fatal outcomes. There were 1,152 (42.8%) events of myocarditis reported with an onset after the 2nd dose. Regardless of dose number, more than half of the events had an onset less than 7 days from vaccination (1,316, 48.9%), inclusive of 70 events following a 3rd or booster dose. There were 2,010 cases (75.3%) that involved males and 615 cases (23.1%) that involved females; 43 cases (1.6%) did not include gender. The mean of the patients' ages was 33 years (SD 15.2), with a median age of 28 years (min 12 /max 94); 313 cases were missing age data. Most of the cases reporting myocarditis events involved individuals between the ages of 18 to 39-years-old (1648, 61.8%). Of the 1,648 cases reported in the 18 to 39-year-old age group, 82.3% were reported in males. Cumulatively, most reports were received from regulatory authorities (82.2%). The greatest proportion of the cases reported by region, originated from the EEA (954, 35.8%), closely followed by the United States (744, 27.9%). The cumulative proportion of myocarditis cases reported by country is similar to that of cases reporting myocarditis and/or pericarditis overall, with the proportion of reports from the United States remaining at the top.
Risk factors and risk groups	Approximately 1% to 5% of patients that test positive for acute viral infection(s) may exhibit a form of myocarditis. The annual prevalence of myocarditis has been reported from 10.2 to 105.6 per 100,000 worldwide, and its annual occurrence is estimated at about 1.8 million cases. Most studies of acute myocarditis report a greater prevalence and severity in male patients, speculated to be caused by a protective effect of natural hormonal influences on immune responses in women when compared with men [205]. Patients are usually between the ages of 20 and 50. Acute myocarditis and hyperthyroidism are also common diseases that often present in young, otherwise healthy patients.
Preventability	Myocarditis presents with a spectrum of symptoms ranging from mild dyspnea or chest pain that spontaneously resolves without treatment to cardiogenic shock and sudden death. The major long-term consequence is dilated cardiomyopathy (DCM) with chronic heart failure. Common viral infections are the most frequent cause of myocarditis, but other pathogens, hypersensitivity reactions, and systemic and autoimmune diseases have also been implicated [206]. Very rare cases of myocarditis and pericarditis have been observed following vaccination with SPIKEVAX. These cases have primarily occurred within 14 days following vaccination, more often after the second vaccination, and more often in younger men. Available data suggest that the

Important Identified Risk	Myocarditis
	course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general. Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination. Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition. For patients presenting with myocarditis or pericarditis after the 1st dose CDC recommends deferring the 2nd dose of mRNA COVID-19 vaccine until more information is known. However, if heart has recovered, it could consider proceeding with 2nd dose [207]. Current SmPC and PIL adequately covers the information on this risk awareness to the health care professionals, caregivers and vaccinees.
Impact on the benefit-risk balance of the product	Based on the analysis of all the safety data, there have been very rare reports of myocarditis occurring after vaccination with Moderna COVID-19 Vaccine. Causal association between SPIKEVAX and myocarditis is considered of at least a reasonable possibility. The majority of the cases have been reported in young males, and shortly after the second dose of the vaccine. These are typically mild cases and individuals tend to recover within a short time following standard treatment and rest. Healthcare professionals should be alert to the signs and symptoms of myocarditis. The benefits (prevention of COVID-19 disease and associated hospitalizations, ICU admissions, and deaths) outweighed the risks (expected myocarditis cases after vaccination) in all populations for which vaccination has been recommended [53].
Public health impact	Myocarditis associated with vaccines typically occur at a low incidence, which results in a low public health impact. Although the potential clinical consequences of the occurrence of myocarditis is serious, this is a risk known to healthcare professionals and can be managed with early diagnosis with supportive treatment. Most observed cases have been of mild severity, and spontaneously resolved.

Important identified risk	Pericarditis
Potential mechanisms	Acute pericarditis is an inflammatory process involving the pericardium that results in a clinical syndrome characterized by chest pain, pericardial friction rub, changes in the ECG and occasionally, a pericardial effusion. Generally, the diagnosis requires 2 of these 4 features. Epidemiologic data on the incidence of acute pericarditis are lacking, likely because this condition is frequently inapparent clinically, despite its presence in numerous disorders [208]. However, it appears to be the most common form of pericardial disease and a relatively common cause of chest pain. It is diagnosed in approximately 0.1% of patients hospitalized for chest pain and in 5% of patients admitted to the emergency department for chest pain unrelated to acute myocardial infarction (MI). Although acute pericarditis occurs in all age groups and in men and women, it presents most often in men 20 to 50 years of age. The most common form of acute pericarditis is idiopathic, which accounts for about 90% of cases. Other common causes include infection, renal failure, myocardial infarction (MI), post-cardiac injury syndrome, malignancy, radiation, and trauma. Acute pericarditis is more common in men than in women. However, although this condition is

Important identified risk	Pericarditis
	more common in adults than in children, adolescents are more commonly affected than young adults.
Evidence source(s) and strength of evidence	Data to evaluate the safety concern were derived from the clinical trials and post-authorization safety data.
Characterization of risk	In study mRNA-1273-P301 (Part A), in the safety set, there were 15,184 participants exposed to the mRNA-1273 vaccine, and 15,166 participants in the placebo arm. There were four TEAE of "Pericarditis" in P301: Two TEAEs in the Placebo arm, and two in the Vaccine arm of the safety set in the overall stage after any injection. The 2 events in the placebo arm were reported in the >18 to <65 years of age. The events in the vaccination arm were reported in a 65-year-old male and a 59-year-old female. In Part B, one case of acute pericarditis (verbatim: "acute infective pericarditis") was reported in a 63-year-old male in the placebo group; the event occurred 24 days after a COVID-19 diagnosis. In addition, one case of pericardial effusion was reported as an SAE (resolving) in a 23-year-old male in the placebo–mRNA-1273 group. No participant in the mRNA-1273 group experienced pericarditis (CSR mRNA-1273-P301 addendum 1 (Safety from open label phase [Part B]). During the post authorization, cumulatively, through 31 Dec 2021, a total of 1,377 cases (1,383 events) of pericarditis have been reported, with 1,036 cases medically confirmed. There were 7 cases with fatal outcomes. Cumulatively, the greatest proportion of the pericarditis events were reported after the 2nd dose (512; 37%). Regardless of dose number, the greatest proportion of the events had an onset of less than 7 days from vaccination (505, 36.7%), inclusive of 43 events following a 3rd or booster dose There were 801 cases (58.2%) that involved males and 555 cases (40.3%) that involved females; 21 cases (1.5%) did not include gender. The mean of the patients' ages was 42 years (SD 17.9), with a median age of 39 years (min 12 /max 93); 97 cases were missing age data. The greatest proportion of reports of pericarditis continue to be in males between the ages of 18 to 39-years-old (406; 29.5%). Most reports were received from regulatory authorities (86.9%). Reports of pericarditis primarily originated from the United States (591, 42.9%) and the EEA (487, 35.4%). A review of reports received by country (excluding the United States), cumulatively, shows that 137 (9.9%) of the cases reporting pericarditis events originated in France, 92 (6.7%) in Italy, and 91 (6.6%) in Canada, which remains consistent with previous reviews. Cumulatively, the greatest proportion of the pericarditis events were reported after the 2nd dose (512; 37%). Regardless of dose number, the greatest proportion of the events had an onset of less than 7 days from vaccination (505, 36.7%), inclusive of 43 events following a 3rd or booster dose.
Risk factors and risk groups	Acute pericarditis occurs when the bilayer pericardial sac becomes inflamed. In most cases, the cause of pericarditis is idiopathic or is assumed to be due to a viral infection for which the antecedent virus is not identified. There are several less common infectious and non-infectious causes of pericarditis, but most patients with acute pericarditis present with a history suggestive of recent or concurrent viral illness. Most cases resolve with no long-term sequelae. While pericardial effusions might develop as a result of

Important identified risk	Pericarditis
	pericarditis, they are usually minor and rarely result in cardiac tamponade [209]. Acute pericarditis is more common in men than in women. However, although this condition is more common in adults than in children, adolescents are more commonly affected than young adults. A prospective clinical cohort study in Italy identified an incidence of 27.7 cases per 100,000 person-years [208]. Another study, a retrospective analysis of Finnish registry data capturing admissions to 29 hospitals over a span of 9.5 years identified an age standardized incidence of 3.32 per 100,000 person-years, with higher rates in men ages 16-65 [210]. Pericarditis is the most common pericardial disorder. Congenital pericardial disorders are rare.
Preventability	Pericarditis may be caused by many disorders (e.g., infection, myocardial infarction, trauma, tumors, metabolic disorders) but is often idiopathic. Symptoms include chest pain or tightness, often worsened by deep breathing. Cardiac output may be greatly reduced if cardiac tamponade or constrictive pericarditis develops. Diagnosis is based on symptoms, a friction rub, electrocardiographic changes, and evidence of pericardial fluid accumulation on x-ray or echocardiogram [211]. Pericarditis may result in one of two serious complications: cardiac tamponade and chronic constrictive pericarditis. Cardiac tamponade is considered a medical emergency and, if left untreated, can quickly become fatal. Very rare cases of myocarditis and pericarditis have been observed following vaccination with SPIKEVAX. These cases have primarily occurred within 14 days following vaccination, more often after the second vaccination, and more often in younger men. Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general. Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination. Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition. CDC recommends deferring the 2nd dose of mRNA COVID-19 vaccine until more information is known. However, if heart has recovered, could consider proceeding with 2nd dose [207].
Impact on the benefit-risk balance of the product	Based on the analysis of all the safety data, it shows that there have been very rare reports of pericarditis occurring after vaccination with Moderna COVID-19 Vaccine. Although causality cannot be established at this time, the majority of the cases have been reported in young males, and shortly after the second dose of the vaccine. These are typically mild cases and individuals tend to recover within a short time following standard treatment and rest. Healthcare professionals should be alert to the signs and symptoms of pericarditis. The benefits (prevention of COVID-19 disease and associated hospitalizations, ICU admissions, and deaths) outweighed the risks (expected myocarditis cases after vaccination) in all populations for which vaccination has been recommended.

Important identified risk	Pericarditis
Public health impact	Pericarditis associated with vaccines typically occur at a low incidence, which results in a low public health impact. Although the potential clinical consequences of the occurrence of pericarditis are serious, this is a risk known to healthcare professionals.

Table 16.264 Presentation of Important Potential Risks

Important Potential Risk	Vaccine-associated Enhanced Disease (VAED) Including Vaccine-associated Enhanced Respiratory Disease (VAERD)
Potential mechanism(s)	Research points to disease enhancement being triggered by one of two major mechanisms although other mechanisms may also contribute. The first and least well characterized is when priming by the initial infection results in a Th2 biased immune response mediated more by myeloid lineage cells, including neutrophils and eosinophils with immune complex formation and complement activation. While this inflammatory phenotype may be preferred for parasitic infections it is not ideal for viruses, for which an adaptive T-cell and antibody mediated Th1 type response is preferable. This "Th2 biased" phenotype is most associated with enhanced disease as resulting from the formalin-inactivated measles and RSV vaccines. In these cases, post vaccination exposure of previously naïve vaccines resulted in an immune response characterized by high interleukin (IL) 4, 5 & 13 levels and localized tissue inflammation associated with neutrophil and eosinophil infiltration, immune complex deposition and pulmonary inflammation and obstruction. The second and far better characterized mechanism is antibody dependent enhancement (ADE). This results from the generation of binding but poorly neutralizing antibodies induced by heterologous antigens generated either by heterologous viral strains (e.g., dengue), by chemically disrupted antigens (e.g., formalin-inactivated RSV and measles) or by epitope altering mutations such as feline infectious peritonitis. These antibodies bind to but do not neutralize the virus and facilitate Fc receptor mediated entry of viable virus into macrophages. This can result in an accelerated and more marked viremia and more severe disease. This scenario is the one associated with dengue virus and its virus and vaccine-associated ADE. ADE for dengue can also result from sub-neutralizing concentrations of neutralizing antibodies, such as that seen in infants as maternal antibodies wane. It is likely that in many cases there are components of both mechanisms in enhanced disease.
Evidence source(s) and strength of evidence	No evidence of harm has been identified in non-clinical studies nor from the Phase 3 mRNA-1273-P301 harm monitoring at the time of the data lock point for the risk management plan where safety follow-up is based on a median duration of follow-up after the second injection to the data cut-off for database lock (including Part A and Part B) was 183 days (range: 1 to 218 days), or approximately 6 months. As of 31 Dec 2021, no new information has been identified through post-authorization safety data.
Characterisation of risk	Cumulatively, there were 9,824 COVID-19 and/or lack of efficacy cases included in this assessment based on known dose and latency. Of these, a total of 5,805 (59.1%) cases of COVID-19 had a latency of at least 14 days after the second vaccine dose. These cases were considered vaccine failure. Of these vaccine failure events, 153 (1.9%) occurred at least 14 days after third vaccine dose.

Important Potential Risk	Vaccine-associated Enhanced Disease (VAED) Including Vaccine-associated Enhanced Respiratory Disease (VAERD)
	The most commonly identified condition potentially consistent with VAED among COVID-19 and/or lack of efficacy cases was death, which occurred in 7.4% of vaccine failure cases and 4.0% in the comparison group, i.e., COVID-19 cases that were not yet eligible to be considered VAED (not being defined as a "vaccine failure" based on latency). Multiple other conditions were also identified in both the subset of cases eligible for consideration as VAED per the Brighton criteria referenced above and the comparator. These conditions may occur in typical presentations of COVID-19. Although a larger proportion of vaccine failure cases had at least one of these concomitant conditions reported (14.8% vs 8.2%), it should be noted that COVID-19 cases in the context of vaccine failure compared with individuals diagnosed with COVID-19 within 7 days of the first vaccine dose more frequently reported comorbidities such as hypertension (18.8% vs. 10.1%), drug hypersensitivity (16.6% vs. 11.4%), and coronary artery disease (5.2% vs 0.7%). As such, differences in patient characteristics placing individuals at higher risk for severe outcomes of COVID-19 between those with vaccine failure and those with COVID-19 before vaccination would have been expected to take full effect makes attribution of the difference to VAED questionable.
Risk groups or risk factors	This is a potential risk and no increased risk to mRNA-1273 has been established. Therefore, no risks groups or risks factors can be identified. However, the generation of binding but poorly neutralizing antibodies in individuals may result in an accelerated and more marked viremia and more severe disease.
Preventability	Information is not available as the risk remains theoretical.
Impact on the benefit-risk balance of the product	In addition to possible early efficacy, the Data Safety Monitoring Board has monitored Phase 3 mRNA-1273-P301 study for vaccine harm. Based on these analyses no vaccine harm was identified. This risk is further evaluated in the ongoing Phase 3 mRNA-1273-P301 through continued trial follow-up as well as pharmacovigilance activities.
Public health impact	The public health impact of mRNA-1273 in worsening COVID-19 disease is unknown but this could impact the benefit-risk should this event be reported in a significant number of vaccinees.

Table 16.265 Presentation of Missing Information

Missing Information	Use in Pregnancy and While Breastfeeding
Evidence source	As pregnancy was an exclusion criterion for the mRNA clinical trials, there is limited data from the use of mRNA-1273 in pregnant women from the clinical trials. A developmental and reproductive study with mRNA-1273 in female Sprague-Dawley rats was completed in Dec 2020 with no adverse findings. In post authorization, preliminary analysis of the v-Safe pregnancy registry conducted by the US CDC did not identify safety signals [200]
Anticipated risk/consequence of the missing information	Targeted populations of the indication will include women of childbearing potential, thus, the use of mRNA-1273 in pregnant and breastfeeding women may happen. Pregnancy outcome data will be collected in enhanced pharmacovigilance. An observational cohort pregnancy study will inform on the risk of adverse outcome in women who were exposed to mRNA-

	1273 during pregnancy.
Missing Information	**Long-Term Safety**
Evidence source	Per protocols, the clinical development program has a safety follow-up period of 12 months in the ongoing Phase 1 study 20-0003, Phase 2a Study mRNA-1273-P201 and, 24 months in the Phase 3 study mRNA-1273-P301. , In the Phase 3mRNA-1273-P301 the safety follow-up is based on a median duration of follow-up after the second injection to the data cut-off for database lock (including Part A and Part B) was 183◦days (range: 1 to 218 days), or approximately 6 months. The follow-up time is through Day 209 for the Phase 1 study DMID 20-0003 and through at least 180 days (6 months) after the most recent injection (Day 209) for the 555/600 (92.5%) participants who had not discontinued from the study before Day 209 in the Phase 2a Study mRNA-1273-P201.
Anticipated risk/consequence of the missing information	As of the DLP of this PBRER, 8 ongoing clinical trials sponsored by ModernaTX, Inc were ongoing, and no study has been completed. Cumulatively, 48,823 subjects have been exposed to either mRNA-1273, mRNA-1273.351, mRNA-1273.211, mRNA-1273.213, mRNA-1273.617.2, or placebo in the mRNA clinical development program sponsored by ModernaTX, Inc. The comprehensive monthly safety reports have regularly updated the known safety data, and that compared with other (non-COVID) vaccines in their first year of authorization/approval. The safety profile should be considered comparatively well characterized for the populations that have been eligible to receive the vaccine (particularly for immune competent persons 18+ years of age). The long-term safety profile remains to be characterized through continued trial follow-up, active surveillance for safety, a European post-authorization safety study, and routine pharmacovigilance.
Missing Information	**Use in Immunocompromised subjects**
Evidence source	In the Phase 1 and 2a studies of mRNA-1273, participants with immunosuppression were excluded. Immunosuppression in these studies were defined as immunosuppressive or immunodeficient state, including HIV infection, asplenia, recurrent severe infections or systemic immunosuppressants or immune-modifying drugs for > 14 days in total within 6 months prior to the Screening Visit. These criteria were subsequently modified in the Phase 3 mRNA-1273-P301 to allow the participation in the study of HIV positive participants considered not immunosuppressed.
Anticipated risk/consequence of the missing information	In general, it is expected that participants with immunocompromised status may not reach the protective antibody level achieved in healthy individuals with vaccines. However, in the Phase 3 study mRNA-1273-P301, the results show an overwhelming vaccine efficacy in the overall population of the trial. mRNA-1273 vaccine is not a live attenuated vaccine, nor does it contain a viral vector. Therefore, no risk of transmission of an infection due to the vaccine construct is expected in this population. This population will be monitored via routine pharmacovigilance. To the extent that immunosuppressed patients are captured in the European post-authorization safety study (PASS) and the US effectiveness study, these studies may inform use in subjects with immunosuppression. A Phase 3b open-label safety and immunogenicity study (Study mRNA-1273-P304) in a target population of approximately 220 adult solid organ transplant recipients is ongoing.
Missing Information	**Interactions with other vaccines**

Evidence source	No experience exists with vaccines within 28 days prior to the first dose or any dose of mRNA-1273 except for seasonal influenza vaccine <14 days.
Anticipated risk/consequence of the missing information	There is the theoretical question as whether a vaccine can create interference in the immune response to either vaccines or induce safety concerns. Due to the exclusion criteria in the mRNA-1273 clinical program no experience exists with vaccines within 28 days prior to the first dose or any dose of mRNA-1273 except for seasonal influenza vaccine <14 days. It is common medical practice to administer vaccines concurrently. Participants receiving mRNA-1273 may be administered seasonal flu vaccines during the vaccination period of the pandemic.
Missing Information	**Use in Frail Subjects with Unstable Health Conditions and Co-morbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)**
Evidence source	The vaccine has been studied in participants with stable chronic diseases (e.g., patients with hepatic impairment and patients with cardiovascular impairment), however it has not been studied in frail participants with severe co-morbidities that may compromise immune function due to the condition or treatment of the condition.
Anticipated risk/consequence of the missing information	In general, there is a potential that frail participants with unstable health conditions and co-morbidities may experience a different outcome than achieved in healthy individuals administered vaccines. To the extent that frail participants can be classified in the European PASS and the US effectiveness study, these studies may inform use in frail participants.
Missing Information	**Use in Subjects with Autoimmune or Inflammatory Disorders**
Evidence source	There is limited information on the safety of the vaccine in patients with autoimmune or inflammatory disorders.
Anticipated risk/consequence of the missing information	In general, there is a potential that subjects with autoimmune or inflammatory disorders may experience a different outcome than achieved in healthy individuals administered vaccines. To the extent that participants with autoimmune or inflammatory disorders are captured in the European PASS and the US effectiveness study, these studies may inform use in participants with autoimmune or inflammatory disorders.

16.5. Effectiveness of Risk Minimization

Not applicable. There are no additional risk minimization measures in place for SPIKEVAX.

17. BENEFIT EVALUATION

17.1. Important Baseline Efficacy and Effectiveness Information

Epidemiology and Natural History of COVID-19 disease

Coronaviruses (CoVs) are a large diverse family of enveloped positive-sense single-stranded RNA viruses that cause illness ranging from the common cold to more severe diseases. CoVs infect humans, other mammals and avian species, including livestock and companion animals. Four CoVs are causes of the common cold and represent the only significant CoVs to infect humans prior to the 21st century. Before 2019, novel coronaviruses had resulted in two major respiratory illness outbreaks during the 21st century: SARS, which occurred during 2002–04; and Middle East respiratory syndrome (MERS), which began in 2012. [212]

As of 26 Dec 2021, over 278 million cases and around 5.4 million deaths have been reported globally related to COVID-19. [213]

As the name suggests, SARS-CoV-2 is primarily a respiratory infection, with manifestations ranging from asymptomatic infection to death due to pneumonia or to related organ failure as a consequence of primary pulmonary infection. The initial steps of coronavirus infection involve the specific binding of the coronavirus spike (S) protein to the cellular entry receptors, which have been identified for several coronaviruses and include human aminopeptidase N (APN; HCoV-229E), angiotensin-converting enzyme 2 (ACE2; HCoV-NL63, SARS-CoV and SARS-CoV-2) and dipeptidyl peptidase 4 (DPP4; MERS-CoV). The expression and tissue distribution of entry receptors consequently influence viral tropism and pathogenicity [214]. The replication cycle of the SARS-CoV-2 virus infection into the host cell can be divided into several key steps: (a) attachment and cell entry, (b) transcription of viral replicase, (c) genomic transcription and replication, (d) translation of structural proteins, and (e) virion assembly and release [215].

A cluster of pneumonia cases of unknown cause was reported in the city of Wuhan, China, by health officials on 31 Dec 2019. Sequencing of the fluid samples collected from the cluster of those patients with pneumonia identified the causal agent as a novel coronavirus [216], and soon the virus was named as SARS-CoV-2. By 07 Jan 2020, the China National Institute of Viral Disease Control and Prevention had confirmed the genetic sequence of SARS-CoV-2 and that the virus was associated with the previously reported pneumonia cluster in Wuhan. On 20 Jan 2020, the US CDC activated its emergency operations center in response to the emerging public health threat of COVID-19. On 30 Jan 2020, WHO declared the COVID-19 outbreak a Public Health Emergency of International Concern, and 6 weeks later, on 11 Mar 2020, WHO characterized the COVID-19

epidemic as a pandemic [217]; however, widespread community transmission was already occurring in many locations.

On 11 Mar 2020, the WHO officially declared the outbreak a pandemic, and governments across the world began implementing strategies to slow the infection spread, including social distancing and complete lockdown [217]. On 16 Mar 2020, no more new cases were reported in China, but by 19 Mar 2020 the death toll surpassed 10,000 worldwide [217]. Italy quickly became the new emerging epicenter with peak daily new cases reported at 6,557 on 21 Mar 2020 [217]. The infection quickly spread in the US, with at least 100,000 cumulative cases by 27 Mar 2020, and over 2,700 deaths. On 29 Mar 2020, the global number of cases surged to >600,000, including more than 29,000 deaths [217]. On 29 Mar 2020, Spain recorded 838 new deaths in 24 hours [217]. By the end of Mar 2020, few countries with unreported cases remained. The death toll in the US surpassed that in China, and the international community had begun an unprecedented lockdown [218,219].

By 09 Feb 2021, a spike in the death toll was reported with 910 dead and 40,000 cases in China alone [219]. On 15 Feb 2021, Egypt and France reported deaths due to COVID-19 [219]. By the end of Feb, 11 additional European countries reported cases with 82,000 confirmed infections and 2,800 people killed worldwide [219].

By the end of this reporting period (31 Dec 2021), the cumulative number of cases reported exceeds 278 million and the number of deaths were almost 5.4 million. [213]

Evidence suggests that SARS-CoV-2 is transmitted via exposure to infectious respiratory fluids in three principal ways: 1) inhalation of respiratory droplets and aerosol particles; 2) deposition of respiratory droplets and aerosol particles on mucous membranes in the mouth, nose, or eye by direct splashes and/or sprays; and, 3) touching mucous membranes with hands that have been soiled either directly by respiratory fluids or indirectly by touching surfaces with virus on them [220]. Transmission of SARS-CoV-2 from asymptomatic or pre-symptomatic individuals has also been documented and may account for an estimated 59% of transmission [221]. Common symptoms of COVID-19 include fever and cough, shortness of breath or difficulty breathing, muscle aches, chills, sore throat, headache, and loss of taste or smell. Individuals at highest risk of severe COVID-19 are older adults (≥ 65 years old) and people of any age who have certain underlying medical conditions, such as cancer, chronic kidney disease, chronic lung diseases, dementia or other neurological conditions, diabetes, Down syndrome, heart conditions, human immunodeficiency virus (HIV) infection, immunocompromised state, liver disease, obesity, pregnancy, sickle cell disease, solid organ transplant, and stroke or cerebrovascular disease [222]. Smokers and individuals with substance use disorders are also at increased risk for severe COVID-19 [222].

The majority of individuals with COVID-19 have mild symptoms or moderate illness. Approximately 10% to 15% of COVID-19 cases progress to severe disease, and approximately 5% become critically ill (WHO 2021b). Long-term sequelae in COVID-19 patients with persistent symptoms after recovery from acute COVID-19 have been reported. Fatigue, dyspnea, joint pain, chest pain, and neuropsychiatric symptoms have been reported as common and persistent sequelae [223,224]. Myocardial injury has reported among patients with severe COVID-19 [225]. Additionally, some patients develop serious medical complications such as myocardial inflammation, ventricular dysfunction, pulmonary function abnormalities, and acute kidney injury [226-231]. While more serious long-term health complications appear to be less common, they have individual, global health, and severe socioeconomic consequences.

Like all RNA viruses, SARS-CoV-2 is prone to mutation. Multiple viral variants have been detected, most of which appear to have little if any biological significance. However, a small number of 'variants of concern' (VOC) appear to influence SARS-CoV-2 transmissibility and possibly also host immune responses. Towards the end of 2020, a new variant was identified in the UK (B.1.1.7) that is associated with greater transmissibility. In South Africa, the B.1.351/501.YV2 variant has rapidly become the dominant strain nationally and carries mutations that appear to influence the potency of protective immune responses. A third variant (B.1.1.248/B1.1.28/P1), detected in Japan in a traveler from Brazil, may also be less sensitive to host immune responses. Towards the end of 2021, the WHO declared Omicron (B.1.1.529) a VOC [232]. All these variants have since spread to other countries [233].

WHO created a case definition to identify VOC: A SARS-CoV-2 variant that meets the definition of a Variant of Interest (VOI) and, through a comparative assessment, has been demonstrated to be associated with one or more of the following changes at a degree of global public health significance: Increase in transmissibility or detrimental change in COVID-19 epidemiology; OR Increase in virulence or change in clinical disease presentation; OR Decrease in effectiveness of public health and social measures or available diagnostics, vaccines, therapeutics. As of 31 Dec 2021, the following are considered the VOI [233] (Table 17.1):

Table 17.1 Currently designated Variants of Concern

WHO label	Pango lineages	GISAID clade	Nextstrain clade	Additional amino acid changes monitored*	Earliest documented samples	Date of designation
Alpha	B.1.1.7	GRY	20I (V1)	+S:484K +S:452R	United Kingdom, Sep 2020	18 Dec 2020
Beta	B.1.351 B.1.351.2 B.1.351.3	GH/501Y.V2	20H (V2)	+S:L18F	South Africa, May 2020	18 Dec 2020

WHO label	Pango lineages	GISAID clade	Nextstrain clade	Additional amino acid changes monitored*	Earliest documented samples	Date of designation
Gamma	P.1 P.1.1 P.1.2 P.1.4 P.1.6 P.1.7	GR/501Y.V3	20J (V3)	+S:681H	Brazil, Nov-2020	11 Jan 2021
Delta	B.1.617.2 AY.1 AY.2 AY.3 AY.3.1	G/478K.V1	21A	+S:417N	India, Oct 2020	VOI: 4 Apr 2021 VOC: 11 May 2021
Omicron	B.1.1.529	GRA	21K, 21L 21M	+S:R346K	Multiple countries, Nov 2021	VUM: 24-Nov-2021 VOC: 26 Nov 2021

Notable spike (S) amino acid changes under monitoring, which are currently reported in a minority of sequenced samples.

Nature of the Benefit

Early in 2020, the WHO declared COVID-19 to represent a Public Health Emergency of International Concern, denoting its highest level of public health emergency. As of DLP, SARS-CoV-2 infections have been reported in nearly every country in the world, with more than 278 million, including almost 5.4 million deaths [213]. These figures are considered underestimates. As per estimates, COVID-19 deaths in 2021 imply a 1.7-year reduction in life expectancy at birth and a 1.1-year reduction in life expectancy at age 65 for the total US population relative to pre-pandemic levels [234]. Like other respiratory viruses, SARS-CoV-2 spreads efficiently. The global population is at risk of infection with this virus.

It is widely acknowledged that the lynchpin to control of this pandemic is through vaccination. Efforts to control the pandemic through other public health measures (e.g., social distancing, mask wearing) are helpful but not sufficient. The use of therapeutic agents to prevent or treat SARS-CoV-2 infections are similarly important but secondary to the role of primary prevention through vaccinations as a means of controlling and mitigating the impact of this pandemic.

Global efforts to evaluate novel antivirals and therapeutic strategies to treat severe SARS-CoV-2 infections have intensified, and there is an urgent public health need for rapid development of novel prophylactic therapies, including vaccines, to prevent the spread of this disease. ModernaTX, Inc's scalable mRNA/LNP technology platform allowed for a rapid response to the

pandemic and was used to develop SPIKEVAX, a novel LNP-encapsulated mRNA-based vaccine against SARS-CoV-2.

SPIKEVAX, an LNP-encapsulated mRNA vaccine expressing the prefusion-stabilized spike glycoprotein, is enzymatically produced, directs vaccine antigen production in vivo, thus avoiding the need for the lengthy processes to optimize the production and in vitro characterization of the target antigen as required with traditional vaccines. This approach provides potential benefits in terms of reducing time from discovery to production. Additionally, production of the antigen in vivo likely mimics the expression of the antigen during the course of a natural infection.

mRNA does not interact with the genome, is nonreplicating, delivers only the genetic elements required for expression of the encoded protein, and is only a transient carrier of information and does not persist in the body.

During translation, mRNA serves as the template for the synthesis of the intended proteins. mRNA vaccines targeting SARS-CoV-2 represent the first vaccines employing this technology. They offer the potential to vaccinate against any encoded protein antigen with potential use in both prophylactic and therapeutic vaccines.

ModernaTX, Inc's SPIKEVAX vaccine is indicated for active immunization to prevent coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 in individuals 6 years of age and older till DLP.

Efficacy and Immunogenicity against COVID-19 disease is currently being evaluated in 13 clinical trials including 8 sponsored by Moderna. Primary analysis for efficacy was demonstrated in adults 18 years and older in Study mRNA-1273-P301. The primary end point was the efficacy of the SPIKEVAX vaccine in preventing a first occurrence of symptomatic COVID-19 with onset at least 14 days after the second injection in the per-protocol population, among participants who were seronegative at baseline."COVID-19 cases were defined as occurring in participants who had at least two of the following symptoms: fever (temperature ≥38°C), chills, myalgia, headache, sore throat, or new olfactory or taste disorder, or as occurring in those who had at least one respiratory sign or symptom (including cough, shortness of breath, or clinical or radiographic evidence of pneumonia) and at least one nasopharyngeal swab, nasal swab, or saliva sample (or respiratory sample, if the participant was hospitalized) that was positive for SARS-CoV-2 by reverse-transcriptase–polymerase-chain-reaction (RT-PCR) test." [235] Vaccine efficacy was assessed in the full analysis population (randomized participants who received at least one dose of mRNA-1273 or placebo), the modified intention-to-treat population (participants in the full analysis population who had no immunologic or virologic evidence of COVID-19 on day 1, before the first dose), and the per-protocol population (participants in the modified intention-to-treat population who received two doses, with no major protocol deviations). Participants were evaluated in the

treatment groups to which they were assigned. Vaccine efficacy was defined as the percentage reduction in the hazard ratio for the primary end point (mRNA-1273 vs. placebo). A stratified Cox proportional hazards model was used to assess the vaccine efficacy of mRNA-1273 as compared with placebo in terms of the percentage hazard reduction [235].

The primary efficacy endpoint in Study mRNA-1273-P301 was met, mRNA-1273 prevented COVID-19 starting 14 days after the second injection of vaccine, based on a total of 95 adjudicated cases accrued (5 cases in the mRNA-1273 group and 90 cases in the placebo group). For the primary analysis, 196 cases of COVID-19 were diagnosed: 11 cases in the vaccine group (3.3 per 1,000 person-years; 95% CI, 1.7 to 6.0) and 185 cases in the placebo group (56.5 per 1,000 person-years; 95% CI, 48.7 to 65.3), indicating 94.1% efficacy of the mRNA-1273 vaccine (95% CI, 89.3 to 96.8%; P<0.001) for the prevention of symptomatic SARS-CoV-2 infection as compared with placebo. Findings were similar across key secondary analyses, including assessment starting 14 days after dose 1 (225 cases with placebo, vs. 11 with mRNA-1273, indicating a vaccine efficacy of 95.2% [95% CI, 91.2 to 97.4]), and assessment including participants who were SARS-CoV-2 seropositive at baseline in the per-protocol analysis (187 cases with placebo, vs. 12 with mRNA-1273; one volunteer assigned to receive mRNA-1273 was inadvertently given placebo], indicating a vaccine efficacy of 93.6% [95% CI, 88.6 to 96.5]). Between days 1 and 42, seven cases of COVID-19 were identified in the mRNA-1273 group, as compared with 65 cases in the placebo group.

A key secondary end point evaluated the efficacy of mRNA-1273 at preventing severe COVID-19. Thirty participants in the trial had severe COVID-19; all 30 were in the placebo group (indicating vaccine efficacy of 100% [95% CI, could not be estimated to 1.0]), and one death among these participants was attributed to COVID-19. The vaccine efficacy to prevent COVID-19 was consistent across subgroups stratified by demographic and baseline characteristics: age groups (18 to <65 years of age and ≥65 years), presence of risk for severe COVID-19, sex, and race and ethnic group (non-Hispanic White and communities of color). Among participants who were positive for SARS-CoV-2, by serologic or virologic testing, at baseline (337 in the placebo group and 343 in the mRNA-1273).

The mRNA-1273-P301 study population included adults with risk factors for complications of COVID-19, including older age and underlying medical comorbidities, in addition to racial and ethnic minority groups that have been disproportionately affected by COVID-19. The efficacy of mRNA-1273 was consistent for the primary efficacy endpoint in study participants with and without risk factors for severe COVID-19, in older and younger adults, in males and females, and in White participants and those from communities of color. There was a limited number of participants in each ethnic group in the subgroup analysis who contributed to the primary efficacy

endpoint, and therefore efficacy analyses were not performed for each specific racial and ethnic subgroup.

Importantly, analysis of the 04 May 2021 dataset also showed that mRNA-1273 100 µg was 98.2% effective in preventing severe COVID-19, with 106 adjudicated cases of severe COVID-19 in the placebo group and 2 adjudicated cases in the mRNA-1273 group. Subgroup analyses of VE to prevent severe COVID-19 showed consistent high efficacy in subgroups of participants with 1 risk factor, at least 2 risk factors, chronic lung disease, significant cardiac disease, severe obesity, diabetes, liver disease, and HIV infection. Additionally, mRNA-1273 was effective in preventing COVID-19 regardless of prior SARS-CoV-2 infection for cases starting 14 days after the second dose of mRNA-1273 (VE of 92.8% based on HR).

mRNA-1273 also demonstrated protection against asymptomatic SARS-CoV-2 infection. The VE to prevent asymptomatic SARS-CoV-2 infection was 63.0% (95% CI 56.6%, 68.5%) and VE to prevent SARS-CoV-2 infection, regardless of symptomatology or severity, was 82.0% (95% CI 79.5%, 84.2%).

Study mRNA-1273-P301 demonstrated that the 100 µg dose level was highly immunogenic through Day 57 as measured by both bAb and nAb in both SARS-CoV-2 baseline-negative and baseline-positive individuals. In SARS-CoV-2 baseline-positive participants, antibody levels at Day 29 were similar to those observed at Day 57 in baseline-negative participants, indicating that the first injection of mRNA-1273 acts like a booster in participants with previous SARS-CoV-2 infection. Studies mRNA-1273-P201 and mRNA-1283-P101 provided evidence of persistence of immune response through Day 209, 6-months after the second injection of mRNA-1273, although antibody levels at Day 209 were lower than peak values.

The immunogenicity of the mRNA-1273 vaccine was evaluated in DMID Study mRNA-1273-P101/20-0003/NCT04283461 and mRNA-1273-P201 and is supportive of the efficacy of the vaccine to prevent COVID-19 as demonstrated in the pivotal mRNA-1273-P301 Phase 3 study. In DMID Study mRNA-1273-P101/20-0003/NCT04283461 (Phase 1), 2 doses of 100 µg or higher generated the highest titers of neutralizing or binding antibody and this observation was the basis for selecting the 100-µg dose for use in the pivotal mRNA-1273-P301 Phase 3 study. Importantly, the antibody levels after 2 doses of mRNA-1273 exceeded those in a pool of convalescent sera. Neutralizing activity was observed for the 100-µg mRNA-1273 dose as of Day 36, which was higher than that of the convalescent sera control group, and the median titers remained in the same range as the median titer in the convalescent sera control group at Day 119 across the age strata. Additionally, in DMID Study mRNA-1273-P101/20-0003/NCT04283461, Th1-directed CD4+ T-cells were observed to be induced across age groups, with limited indication of a Th2-directed response and similar responses were observed among all age groups for the 100-µg dose. In the

dose-confirming study, mRNA-1273-P201, generally comparable neutralizing and binding antibody responses were measured in the serum of participants who received either 50 µg or 100 µg doses of mRNA-1273 administered 28 days apart.

Efficacy in adolescents 12 through 17 years of age

mRNA-1273-P203 is an ongoing Phase 2/3 randomized, placebo-controlled, observer-blind, clinical trial to evaluate the safety, reactogenicity, and effectiveness of the Moderna COVID-19 Vaccine in adolescents ages 12 to 17 years in the US (NCT04649151). Participants with a known history of SARS-CoV-2 infection were excluded from the study. A total of 3,732 participants were randomized 2:1 to receive 2 doses of the Moderna COVID-19 Vaccine or saline placebo 1 month apart. Participants will be followed for efficacy and safety until 1 year after the second dose.

An efficacy analysis was performed in 3,236 participants who received at least Dose 1 of either Moderna COVID-19 Vaccine (n=2,163) or placebo (n=1,073) and had a negative baseline SARS-CoV-2 status (referred to as the modified Intent-to-Treat Set). In the mITT set, 48.5% were female, 11.2% were Hispanic or Latino; 83.9% were White, 2.8% were African American, 6.3% were Asian, and 0.9% other races. Between participants who received Moderna COVID-19 Vaccine and those who received placebo, there were no notable differences in demographics or pre-existing medical conditions.

COVID-19 was defined as the presence of at least one symptom from a list of COVID-19 symptoms occurring at least 14 days after Dose 1 and a positive nasopharyngeal (NP) swab or saliva sample for SARS-CoV-2 by RT-PCR (reverse transcription polymerase chain reaction). Listed symptoms were fever (temperature > 38ºC/≥ 100.4ºF), or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle aches, or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea, or vomiting or diarrhea.

There were 2 COVID-19 cases in the Moderna COVID-19 vaccine group and 13 cases in the placebo group, with a vaccine efficacy of 92.7% (95% confidence interval of 67.8% to 99.2%) (Table 17.2).

Table 17.2 Efficacy analysis: COVID-19* in participants 12 to 17 years of age starting 14 days after Dose 1 – modified intent-to-treat set

Moderna COVID-19 Vaccine			Placebo			% Vaccine efficacy (95% CI)†
Participants (N)	COVID-19 cases (n)	Incidence rate of COVID-19 per 1,000 person-years	rticipant (N)	COVID-19 cases (n)	Incidence rate of COVID-19 per 1,000 person-years	
2,163	2	3.828	1,073	13	52.473	92.7 (67.8, 99.2)

Moderna COVID-19 Vaccine			Placebo			% Vaccine efficacy (95% CI)†
Participants (N)	COVID-19 cases (n)	Incidence rate of COVID-19 per 1,000 person-years	rticipant (N)	COVID-19 cases (n)	Incidence rate of COVID-19 per 1,000 person-years	

* COVID-19: Presence of at least one symptom from a list of COVID-19 symptoms occurring at least 14 days after Dose 1 and a positive NP swab or saliva sample for SARS-CoV-2 by RT-PCR.
† Vaccine efficacy defined as 1 — ratio of incidence rate (Moderna COVID-19 Vaccine vs. placebo). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years.

Immunogenicity in adolescents 12 through 17 years of age

In mRNA-1273-P203, an analysis was conducted of SARS-CoV-2 50% neutralizing titers and seroresponse rates 28 days after Dose 2 in a subset of adolescents aged 12 through 17 in mRNA-1273-P203 and in participants aged 18 through 25 in mRNA-1273-P301 (Part A) who had no immunologic or virologic evidence of prior COVID-19 at baseline. Noninferior immune responses and seroresponse rates were demonstrated in a comparison of immune responses in adolescents aged 12 through 17 years compared with those of participants aged 18 through 25 (Table 17.3).

Table 17.3 Summary of geometric mean titer and seroresponse rate – comparison of adolescents aged 12 through 17 to participants aged 18 through 25 – per-protocol immunogenicity subset

Assay	Time point	Moderna COVID-19 Vaccine		12 through 17 years/ 18 through 25 years	
		12 through 17 years n=340	18 through 25 years n=305		
		GLSM (95% CI)*	GLSM (95% CI)*	GMR (95% CI)†	Met Non-inferiority objective (Y/N)‡
SARS-CoV-2 neutralisation assay – ID50 (titer)§	28 days after Dose 2	1401.7 (1276.3, 1539.4)	1301.3 (1177.0, 1438.8)	1.08 (0.94, 1.24)	Y
		Seroresponse % (95% CI)¶	Seroresponse % (95% CI)¶	Difference in seroresponse rate % (95% CI)#	
		98.8 (97.0, 99.7)	98.6 (96.6, 99.6)	0.2 (-1.8, 2.4)	

GLSM = Geometric least squares mean
GMR = Geometric mean ratio
n = Number of subjects with non-missing data at the corresponding timepoint
* Antibody values reported as below the lower limit of quantification (LLOQ) are replaced by 0.5 x LLOQ. Values greater than the upper limit of quantification (ULOQ) are replaced by the ULOQ if actual values are not available.
† The log-transformed antibody levels are analyzed using an analysis of covariance (ANCOVA) model with the group variable (adolescents in mRNA-1273-P203 and young adults in mRNA-1273-P301 [Part A]) as fixed effect. The resulted LS means, difference of LS means, and 95% CI are back transformed to the original scale for presentation.
‡ Non-inferiority is declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67 and the lower bound of the 2-sided 95% CI for difference in seroresponse rate is greater than -10%.
§ SARS-CoV-2 50% inhibitory dose (ID50) neutralization titers were determined using a SARS-CoV-2 Spike-Pseudo-typed Virus Neutralization Assay. Quantification of SARS-CoV-2 neutralizing antibodies utilizes lentivirus particles expressing SARS-CoV-2 Spike protein on their surface and contains a firefly luciferase (Luc) reporter gene for quantitative measurements of infection by

relative luminescence units (RLU). Neutralization is measured as the serum dilution at which RLU is reduced by 50% (ID50) relative to mean RLU in virus control wells virus but after subtraction of mean RLU in cell control wells.
¶ Seroresponse due to vaccination specific to pseudovirus neutralizing antibody ID50 titer at a subject level is defined as a change from below LLOQ to equal or above LLOQ, or at least a 3.3-fold rise if baseline is equal to or above LLOQ.
# Difference in seroresponse rate 95% CI is calculated using the Miettinen-Nurminen (score) confidence limits

The final efficacy analysis of the primary endpoint for Part A (04 May 2021) was performed on 799 adjudicated first occurrences of COVID-19 starting at least 14 days after the second injection in the PP Set.

The follow-up period for the final blinded efficacy analysis provided a median of 148 days (approximately 5.3 months, where 1 month = 28 days) from randomization to the PDV for participants who completed their PDV on or before the data cut-off date. Additionally, the median duration of follow-up from the PDV to the data cut-off was 67 days, during which time blinded follow-up continued for participants who did not complete their PDV on or before to the data cut-off. Together, these provide a total follow-up duration of approximately 7.6 months from randomization (or approximately 6.5 months from the second injection).

The results of this analysis were consistent with the results of the interim and primary efficacy analyses, confirming persistent, high efficacy over a substantially larger case database and over the median 5.3-month blinded observation period of Part A. For the final efficacy analysis, the VE point estimate (95% CI) was 93.2% (91.0%, 94.8%; $p < 0.0001$) and the 95% CI was observed to be within the 95% CIs for the interim and primary efficacy analyses. In the final analysis of efficacy (database lock of 04 May 2021), 108 participants had adjudicated severe COVID-19 starting 14 days after second injection in the PP Set (106 cases in the placebo group and 2 cases in the mRNA-1273 group); the VE point estimate (95% CI) based on the hazard ratio was 98.2% (92.8%, 99.6%), confirming and extending the findings of the primary analysis of 25 Nov 2020 based on a median of 148 days (final analysis) versus 78 days (primary analysis) of efficacy follow-up after randomization. Among these participants, 3 deaths in the placebo group were attributed to COVID-19.

Importantly, analysis of the 04 May 2021 dataset also showed that mRNA-1273 100 µg was 98.2% effective in preventing severe COVID-19, with 106 adjudicated cases of severe COVID-19 in the placebo group and 2 adjudicated cases in the mRNA-1273 group. Subgroup analyses of VE to prevent severe COVID-19 showed consistent high efficacy in subgroups of participants with 1 risk factor, at least 2 risk factors, chronic lung disease, significant cardiac disease, severe obesity, diabetes, liver disease, and HIV infection. Additionally, mRNA-1273 was effective in preventing COVID-19 regardless of prior SARS-CoV-2 infection for cases starting 14 days after the second dose of mRNA-1273 (VE of 92.8% based on HR).

Important endpoints that support the benefit

Primary Efficacy Endpoints: efficacy of the mRNA-1273 vaccine in preventing a first occurrence of symptomatic COVID-19 with onset at least 14 days after the second injection in the per-protocol population, among participants who were seronegative at baseline.

Secondary Efficacy Endpoints: efficacy of mRNA-1273 in the prevention of severe COVID-19 as defined by one of the following criteria: respiratory rate of 30 or more breaths per minute; heart rate at or exceeding 125 beats per minute; oxygen saturation at 93% or less while the participant was breathing ambient air at sea level or a ratio of the partial pressure of oxygen to the fraction of inspired oxygen below 300 mm Hg; respiratory failure; acute respiratory distress syndrome; evidence of shock (systolic blood pressure <90 mm Hg, diastolic blood pressure <60 mm Hg, or a need for vasopressors); clinically significant acute renal, hepatic, or neurologic dysfunction; admission to an ICU; or death.

Primary Immunogenicity endpoints:

From mRNA-1273-201:

- Immunogenicity of mRNA-1273 by measure of specific binding antibody levels (primary)
- Immunogenicity of mRNA-1273 by measure of specific neutralizing antibody levels

From P20-0003:

- Immunogenicity of mRNA 1273 measured by IgG ELISA to SARS-CoV-2 spike protein

Evidence of Efficacy and Effectiveness is authorized indications:

To meet the regulatory agencies' requirement of a median follow-up duration of at least 2 months after completion of the two-dose regimen, a second analysis was performed, with an efficacy data cut-off date of 21 Nov 2020. This second analysis is considered the primary analysis of efficacy, with a total of 196 adjudicated COVID-19 cases in the per-protocol population, which exceeds the target total number of cases (151) specified in the protocol. This was an increase from the 95 cases observed at the first interim analysis data cut-off on 11 Nov 2020. After Day 1 and through 25 Nov 2020, a total of 269 COVID-19 cases were identified, with an incidence of 79.7 cases per 1,000 person-years (95% CI, 70.5 to 89.9) among participants in the placebo group with no evidence of previous SARS-CoV-2 infection. For the primary analysis, 196 cases of COVID-19 were diagnosed: 11 cases in the vaccine group (3.3 per 1,000 person-years; 95% CI, 1.7 to 6.0) and 185 cases in the placebo group (56.5 per 1,000 person-years; 95% CI, 48.7 to 65.3), indicating 94.1% efficacy of the mRNA-1273 vaccine (95% CI, 89.3 to 96.8%; P<0.001) for the prevention of symptomatic SARS-CoV-2 infection as compared with placebo.

17.2. Newly Identified Information on Efficacy and Effectiveness

The following information concerning efficacy/effectiveness of SPIKEVAX in active immunizations to prevent COVID-19 caused by SARS-CoV-2 became available during the reporting period:

Efficacy in children 6 through 11 years of age

The pediatric study is an ongoing Phase 2/3 randomized, placebo-controlled, observer-blind, clinical trial to evaluate the safety, reactogenicity, and effectiveness of the Moderna COVID-19 vaccine in children ages 6 through 11 years in the United States and Canada (NCT04796896). Participants with a known history of SARS-CoV-2 infection were excluded from the study. A total of 4,011 participants were randomized 3:1 to receive 2 doses of the Moderna COVID-19 Vaccine or saline placebo 1 month apart. Participants will be followed for effectiveness and safety until 1-year after the second dose.

A descriptive efficacy analysis evaluating confirmed COVID-19 cases accrued up to the data cut-off date of October 6, 2021 was performed in 3,556 participants who received two doses (0.25 mL at 0 and 1 month) of either the Moderna COVID-19 Vaccine (n=2,678) or placebo (n=878) and had a negative baseline SARS-CoV-2 status (referred to as the modified Intent-to-Treat Set [164]). Between participants who received the Moderna COVID-19 Vaccine and those who received placebo, there were no notable differences in demographics.

The median length of follow-up for efficacy for participants in the study was 50 days post Dose 1.

The efficacy information in children 6 through 11 years of age is presented in Table 17.4.

Table 17.4 Efficacy analysis: COVID-19 and SARS-CoV-2 infections in participants 6 through 11 years of age starting 14 days after dose 1 – modified intent-to-treat set

	Moderna COVID-19 Vaccine N=2,672		Placebo N=877		% Vaccine Efficacy (95% CI)*
	Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	
COVID-19 Cases - Definition 1[a]	0	0	13	152.027	100.0 (89.3, NE)
COVID-19 Cases - Definition 2[b]	3	11.399	14	163.810	93.0 (75.1, 98.7)
SARS-CoV-2 Infections (regardless of symptoms)[c]	16	60.958	26	306.853	80.1 (61.5, 90.0)

	Moderna COVID-19 Vaccine N=2,672		Placebo N=877		% Vaccine Efficacy (95% CI)*
	Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	Cases (n)	Incidence Rate of COVID-19 per 1,000 Person-Years	
Asymptomatic SARS-CoV-2 Infections[d]	13	49.529	12	141.625	65.0 (16.1, 85.3)

N = Number of participants at risk at 14 days after Dose 1 for specific efficacy endpoint.
NE = Not estimable
* Vaccine efficacy defined as 1 — ratio of incidence rate (Moderna COVID-19 Vaccine vs. placebo). The 95% CI of the ratio is calculated using the exact method conditional upon the total number of cases, adjusting for person-years.
a Participant must have experienced at least two of the following systemic symptoms: fever (≥38°C / ≥100.4°F), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s); or the participant must have experienced at least one of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, or clinical or radiographical evidence of pneumonia; and the participant must have at least one NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS- CoV-2 by RT-PCR.
b Presence of at least one symptom from a list of COVID-19 symptoms and a positive NP swab or saliva sample for SARS-CoV-2 by RT-PCR. Listed symptoms were fever (temperature >38°C / ≥100.4°F), or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle aches, or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea, or vomiting or diarrhea.
c A combination of COVID-19 and asymptomatic SARS-CoV-2 infection for participants with negative SARS-CoV-2 status at baseline: binding antibody against SARS-CoV-2 nucleocapsid protein negative at Day 1 that becomes positive post-baseline, or positive RT-PCR test post-baseline.
d Absence of symptoms and infections as detected by RT-PCR or serology tests: absent of COVID-19 symptoms and at least 1 of the following: binding antibody level against SARS-CoV-2 nucleocapsid protein negative at Day 1 that becomes positive post-baseline, or positive RT-PCR test post-baseline at scheduled or unscheduled/illness visits.

Immunogenicity in children 6 through 11 years of age

An analysis evaluating SARS-CoV-2 50% neutralizing titers and seroresponse rates 28 days after Dose 2 was conducted in subset of children aged 6 through 11 (n=134) in the pediatric study and in participants aged 18 through 25 (n=296) in the adult study (NCT04796896). Subjects had no immunologic or virologic evidence of prior SARS-CoV-2 infection at baseline. The GMR of the neutralizing antibody titers in children 6 through 11 years of age compared to the 18- to 25-year-olds was 1.5 (95% CI: 1.3, 1.8). The difference in seroresponse rate was 0.6% (95% CI: -2.8, 2.8). Non-inferiority criteria (lower bound of the 95% CI for GMR > 0.67 and lower bound of the 95% CI of the seroresponse rate difference > -10%) were met.

Immunogenicity in booster dose participants

mRNA-1273-P201is an ongoing Phase 2, randomized, observer-blind, placebo-controlled, dose-confirmation study to evaluate the safety, reactogenicity, and immunogenicity of the Moderna COVID-19 Vaccine in participants 18 years of age and older (NCT04405076). In this study, 198 participants received two doses (0.5 mL 1 month apart) of the Moderna COVID-19 Vaccine primary series. In an open-label phase, 149 of those participants (Per-Protocol Set) received a single booster dose (0.25 mL) at least 6 months after receiving the second dose in the primary

series. A single booster dose (0.25 mL) was shown to be immunogenic at Day 29 post-booster dose and non-inferior to Day 57 immunogenicity of the primary series (two doses of 0.5 mL 1 month apart) in a subset of participants 18 years of age and older in mRNA-1273-P301.

Immunogenicity of a booster dose following primary vaccination with another authorized or approved COVID-19 vaccine in adults 18 years of age and older

Effectiveness of a Moderna COVID-19 Vaccine (0.25 mL) booster dose in individuals who completed primary vaccination with another authorized or approved COVID-19 Vaccine (heterologous booster dose) is inferred from immunogenicity data supporting effectiveness of a Moderna COVID-19 Vaccine (0.25 mL) booster dose administered following completion of a Moderna COVID-19 Vaccine primary series and from immunogenicity data from an independent Phase 1/2 open-label clinical trial (NCT04889209) conducted in the United States that evaluated a heterologous booster dose (0.5 mL) of the Moderna COVID-19 Vaccine. In this study, adults who had completed primary vaccination with a Moderna COVID-19 Vaccine 2-dose series (N=151), a Janssen COVID-19 Vaccine single dose (N=156), or a Pfizer-BioNTech COVID-19 Vaccine 2-dose series (N=151) at least 12 weeks prior to enrolment and who reported no history of SARS-CoV-2 infection were randomized 1:1:1 to receive a booster dose of one of three vaccines: Moderna COVID-19 Vaccine, Janssen COVID-19 Vaccine, or Pfizer-BioNTech COVID-19 Vaccine. Neutralizing antibody titers, as measured by a pseudovirus neutralization assay using a lentivirus expressing the SARS-CoV-2 Spike protein with D614G mutation, were assessed on Day 1 prior to administration of the booster dose and on Day 15 after the booster dose. A booster response to the Moderna COVID-19 Vaccine (0.5 mL) was demonstrated regardless of primary vaccination.

Immunogenicity in adult participants against the B.1.617.2 (Delta) variant

Serum samples were obtained from participants in mRNA-1273-P201 (Part B) pre-booster and on Day 29 post-booster. Results of the pseudovirion neutralization assay (PsVNA) against the B.1.617.2 (Delta) variant showed that administration of the Moderna COVID-19 Vaccine booster (50 mcg) induced an 18-fold rise in neutralizing titers against the Delta variant compared with pre-booster levels (Geometric mean fold rise (GMFR) = 18.97; 95% CI, 16.72, 21.53; overall group, n = 295).

In the overall mRNA-1273-P201 (Part B) group (n = 293), the pre-booster neutralizing antibodies (nAb) Geometric mean titer (GMT) for the Delta variant was 42.27 (95% CI: 37.19, 48.04; n = 293) and 28 days post-booster, the GMT was 803.51 (95% CI: 731.42, 882.70; n = 295). Over 90% of booster recipients in the overall group (92.2%; 95% CI: 88.5, 95.0%; n = 293) met the definition of a seroresponse for the Delta variant (using a 4-fold increase from pre-booster baseline).

Administration of the 50-µg mRNA-1273 prototype booster resulted in robust increases in nAb responses against the Delta variant regardless of the priming dose. Participants primed with 50 µg had a GMFR of 20.89 (95% CI: 17.54, 24.87); those primed with 100 µg had a GMFR of 17.28 (95% CI: 14.38, 20.77), showing the consistency in responses regardless of priming dose.

Additional analyses of Delta variant nAb GMT by age group have been conducted. nAb responses in older adults are numerically similar to those observed in the younger groups (749.94 vs. 822.98).

The GMFR (Day 29 post-booster: pre-booster) achieved by Moderna COVID-19 Vaccine booster, measured by the Delta pseudovirus assay (18.97; 95% CI: 16.72, 21.53), points to the ability of the prototype vaccine booster to enhance a breadth of nAb responses, including against the highly transmissible Delta variant. Just as the Moderna COVID-19 Vaccine booster generated enhanced nAb levels against the original strain (GMFR 15.06 [95% CI: 13.43, 16,89]), it also was able to broaden, and increase nAb levels against Delta variant.

Immunogenicity in children against the B.1.617.2 (Delta) variant

Additional data on the immunogenicity of the Moderna COVID-19 Vaccine against the Delta variant comes from pediatric study. Serum samples were obtained at baseline and on Day 57 from participants 6 to <12 years of age.

In the per-protocol immunogenicity subset (n=134), the baseline nAb GMT against Delta (measured by PsVNA ID50) in children 6 years to < 12 years old was below the LLOQ; 28 days after 2 doses of 50 mcg of the Moderna COVID-19 Vaccine, serum nAb GMT was 756.46 (95% CI: 650.99, 878.77). Furthermore, 99.3% of children met the definition of seroresponse against the Delta variant. The GMFR from baseline to D57 was 81.77 (95% CI: 70.38, 95.00) for the Delta variant.

17.3. Characterization of Benefits

An efficacy analysis was performed in mRNA-1273-P204, an ongoing Phase 2/3 randomized, placebo-controlled, observer-blind, clinical trial to evaluate the safety, reactogenicity, and effectiveness of the Moderna COVID-19 Vaccine in children ages 6 through 11 years in the US and Canada (NCT04796896).

In mRNA-1273-P204, the immunogenicity of the mRNA-1273 vaccine in children 6 through 11 years of age was evaluated: An analysis was conducted of SARS-CoV-2 50% neutralizing titers and seroresponse rates 28 days after Dose 2 in a subset of children aged 6 through 11 in mRNA-1273-P204 and in participants aged 18 through 25 in in the adult study (NCT04796896) who had no immunologic or virologic evidence of prior COVID-19 at baseline. Noninferior immune responses and seroresponse rates were demonstrated in comparison children 6 to 11 years

of age to participants aged 18 to 25 years enrolled in the ongoing Phase 3 efficacy study (Study mRNA-1273-P301).

An efficacy analysis was performed in mRNA-1273-P201, an ongoing Phase 2, randomized, observer-blind, placebo-controlled, dose-confirmation study to evaluate the safety, reactogenicity, and immunogenicity of the Moderna COVID-19 Vaccine in participants 18 years of age and older (NCT04405076). A single booster dose was shown to be immunogenic in a subset of participants 18 years of age and older.

Moderna COVID-19 Vaccine booster response was demonstrated in individuals who completed primary vaccination with another authorized or approved COVID-19 Vaccine in participants 18 years of age and older.

Administration of the 50-µg mRNA-1273 prototype booster resulted in robust increases in nAb responses in adult participants against the Delta variant regardless of the priming dose.

Immunogenicity data of the Moderna COVID-19 Vaccine against the Delta variant in pediatric study showed 99.3% of children met the definition of seroresponse against the Delta variant B.1.617.2.

18. INTEGRATED BENEFIT-RISK ANALYSIS FOR AUTHORISED INDICATIONS

18.1. Benefit-Risk Context – Medical Need and Important Alternatives

As of 27 Dec 2021, approximately 290,469,670 confirmed cases and 5,442,452 deaths have been attributed to the COVID-19 pandemic globally [236]. Widespread community transmission of SARS-CoV-2 has been reported in all WHO regions [237], [238]; with 30.8% of global mortality from SARS-CoV-2 reported from the European Region [239]. As of 31 Dec 2021, an estimated 827,274,740 doses had been distributed; 466,804,529 doses are estimated to have been administered. SPIKEVAX is approved and/or authorized in numerous countries throughout the world for adults (≥18 years age) and adolescents (12 to < 18 years of age) as a two dose primary series, while approvals and/or authorizations for third doses in special populations (e.g., immunocompromised) and/or as a booster dose in certain individuals at higher risk of severe COVID-19 continue to expand.

Multiple studies from the US and other countries have demonstrated high effectiveness of a 2-dose COVID-19 mRNA vaccination series against SARS-CoV-2 infection (including both symptomatic and asymptomatic infections) caused by the original and variant strains and sequelae including severe disease, hospitalization, and death. Robust effectiveness for mRNA vaccines has been demonstrated not only against the original virus strain but also multiple VOCs. Studies from Qatar have demonstrated high effectiveness against documented infection with Alpha (B.1.1.7) and Beta

(B.1.351) variants ≥14 days after receiving the Pfizer-BioNTech vaccine (90% and 75%, respectively) and the Moderna vaccine (100% and 96%, respectively); importantly, both vaccines were 96-100% effective against severe, critical, or fatal disease, regardless of strain [240], [241].

Real-world evidence, however, also suggests that by 6 months following receipt of EUA vaccine regimens (or natural infection), waning immunity may occur [242]. Such decline in immunity may contribute to reinfection or breakthrough infections against the original strain (D614G; Wuhan-Hu-1 isolate) or VOCs, such as Alpha, Beta, Gamma, and Delta, and VOIs [243]. Data from the Mayo Clinic indicate that observed VE for both authorized mRNA vaccines declined over time against infection with the Delta variant. This observational study showed that between January and July 2021, VE against SARS-CoV-2 infection for each vaccine was 86% (95% CI: 81%, 90.6%; Moderna [mRNA-1273]) and 76% (95% CI: 69%, 81%; Pfizer/BioNTech [BNT1652b2]). In July, however, when B.1.617.2 (Delta) became the dominant circulating variant, effectiveness dropped to 76% for mRNA-1273 (95% CI: 58%, 87%) and 42% for BNT1652b2 (95% CI: 13%, 62%) [244]. Another study from New York state suggests that age-adjusted VE against new COVID-19 diagnoses declined from 92 to 80% [245].

Given the potential for waning immunity from the primary series and the emergence of SARS-CoV-2 variants with increased transmissibility and ability to partially escape immunity a single 50 µg booster administered at least 6-months after the primary series of SPIKEVAX (2 doses of 100 µg) boosts circulating nAb titers against the original strain and against critical VOC.

Since the beginning of the COVID-19 pandemic, severe disease and deaths associated with COVID-19 have occurred more frequently in adults [246], [247], [248]; however, COVID-19 can also lead to severe outcomes in children and adolescents [249], [250]. From the start of the pandemic to Dec 2021, approximately 3.3 million cases of COVID-19 have been reported among children 5 to 9 years of age and approximately 4.8 million cases have been reported among children 10 to 14 years of age in 105 countries [251]. In the US, due to COVID-19, an excess of 4,155 hospitalizations among children 5 years to 17 years of age have been observed through 31 Dec 2021 with 27.5% requiring intensive care unit interventions [248].

While the burden of COVID-19 disease has largely affected adult populations, changes in social policy, individual behavior, and viral dynamics are moving the burden of disease into younger age groups. Schools have opened for in-person learning, and many children have returned to early educational programs and kindergartens. The opening of these institutions is occurring at the same time as relaxed mask mandates and an increase in the number of cases caused by the highly transmissible B.1.617.2 Delta variant of SARS-CoV-2 [252]. An evaluation of case trends, by age, demonstrates a rapid change in demographics when comparing the winter 2020-2021 COVID-19 wave to the current Delta wave in the US. Before the Delta wave, persons 17 years of age and

younger comprised the lowest weekly cases and death rates per 100,000 population; however, in the current Delta wave, adolescents 12 to 17 years of age have the highest case rates, followed closely by children 5 years to 11 years of age [253].

A distinctive manifestation of SARS-Co-V-2 in children and adolescents is development of a life-threatening hyperinflammatory state 4 to 6 weeks after infection with primary COVID-19. Termed multisystem inflammatory syndrome in children (MIS-C) [254], this often presents with persistent fever, laboratory evidence of inflammation and cardiac damage, and, in severe cases, hypotension and shock [255]. Additionally, a large cohort study found that children under 16 years of age with COVID-19 are at 37 times higher risk of myocarditis than the uninfected age and gender-matched control population [47]. There is also evidence of chronic sequelae known as "long-COVID-19" in children even after mild infection; this includes fatigue, muscle and joint pain, insomnia, respiratory problems, and palpitations that may be seen up to 6-months after infection [256]. More than 5217 cases and 46 deaths meeting case definition of MIS-C have been reported in the US [257].

A recent paper published by the US CDC using data from the Coronavirus Disease 2019–Associated Hospitalization Surveillance Network (COVID-NET) reported on indicators of severe COVID-19 among children and adolescents [258]. COVID-NET is a database of COVID-19–associated hospitalizations in 99 counties across 14 states, and the study described pediatric hospitalization from 01 Mar 2020 through 14 Aug 2021. During 01 Mar 2020 to 14 Aug 2021, the cumulative incidence of COVID 19–associated hospitalizations was 49.7 per 100,000 children and adolescents. COVID-NET reported hospitalization rates were highest among children 0 to 4 years of age (69.2 per 100,000 children) followed by adolescents 12 to 17 years of age (63.7 per 100,000 children) and children 5 years to 11 years of age (24.0 per 100,000 children). The lowest weekly hospitalization rates in 2021 were observed during the weeks ending 12 June 2021 to 03 July 2021 (0.3 per 100,000 children and adolescents each week). In the following 6-week period after the Delta variant became predominant, rates rose each week to 1.4 per 100,000 children during the week ending 14 Aug 2021, which was 4.7 times the rate during the week ending 26 Jun 2021 and approached the peak hospitalization rate of 1.5 per 100,000 children observed during the week ending 09 Jan 2021.

Since Mar 2020, approximately 1 in 4 hospitalized children and adolescents with COVID-19 has required intensive care, although the proportions with indicators of severe disease during the period when the Delta variant predominated were generally similar compared with those earlier in the pandemic. The authors of studies of MIS-C and "long-COVID" in children report the observed indicators (insomnia [18.6%], respiratory symptoms [including pain and chest tightness] [14.7%], nasal congestion [12.4%], fatigue [10.8%], muscle [10.1%] and joint pain [6.9%], and

concentration difficulties [10.1%]) of severe COVID 19 among children and adolescents, as well as the potential for serious longer-term sequelae (e.g., MIS-C) [259], [260], and underscore the importance of implementing multipronged preventive measures to reduce severe COVID-19 disease, including nonpharmaceutical interventions and vaccination among eligible age groups.

COVID-NET data indicate that vaccination was highly effective in preventing COVID-19–associated hospitalizations in adolescents [258]. Among adolescents 12 to 17 years of age, the only pediatric age group for whom a COVID-19 vaccine is currently approved, hospitalization rates were approximately 10 times higher in unvaccinated compared with fully vaccinated adolescents, indicating that vaccines were highly effective at preventing serious COVID-19 illness in this age group during a period when the Delta variant predominated. As of 31 Jul 2021, 32% of US adolescents had completed a COVID-19 vaccination series [261]; increasing vaccination coverage among adolescents, as well as expanding eligibility for COVID-19 vaccination to younger age groups if approved and recommended, is expected to reduce severe COVID-19–associated outcomes among children and adolescents

18.2. Benefit-Risk Analysis Evaluation

There is an established safety profile of 2 doses of 100 µg of SPIKEVAX primary series, from data in clinical studies and post licensure data with 827,274,740 doses of SPIKEVAX distributed; 466,804,529 doses are estimated to have been administered globally as of 31 Dec 2021. Further, booster safety has been demonstrated in adults including young adults (18 to < 25 years) in clinical studies and post authorization settings, where approximately 73.9 million adults and 6.7 young adults 18 to <25 years have received a third dose.

The safety of a 50-µg booster in adults, in clinical trials and post-authorization shows a trend toward lower reactogenicity than Post-Dose 2. A review of spontaneous post-authorization AE reports showed no AESI, were reported at higher rates in 18- to 25-year-old booster recipients when compared to the population-based expected rates (including myocarditis) (Safety Summary Report #11).

Based on the successful immunobridging, the VE of SPIKEVAX in children 6 years to <12 years of age is expected to match the VE observed in the pivotal P301 study in adults, where VE was 94.1%. Study P204, Part 2 was conducted at a time when the Delta variant was the predominant circulating COVID-19 variant, and VE in the mITT1 population was demonstrated.

Observational data on the effectiveness of SPIKEVAX against variants of concern, including the highly transmittable Delta variant [262], also support that SPIKEVAX would be similarly expected to provide protection for children against cases and hospitalizations due to the Delta variant.

In P204, there has been no emergent safety concerns in children 6 years to < 12 years old, and the AE profile of SPIKEVAX consists primarily of grade 1 to grade 2 reactogenicity AE lasting 2 to 3 days. Overall, both local and systemic reactogenicity AE was generally consistent for SPIKEVAX in children 6 years to < 12 years of age and in the young adult (18 to 25 years of age) population in the mRNA-1273-P301 study. Vaccination with SPIKEVAX generally resulted in transient local injection site and systemic reactions. Review of unsolicited AEs did not reveal any new safety signals and no SAEs during the study were assessed by the Investigator as related to SPIKEVAX. There were no deaths reported. The overall safety profile observed in this study was generally consistent with the known safety profile to date observed in other studies of SPIKEVAX.

A cumulative review of post-authorization safety data received as of 31 Dec2021 showed that events of myocarditis and pericarditis continues to primarily occur in young adult males shortly after the second dose of the vaccine with a TTO less than 7 days. A large proportion of the myocarditis and pericarditis events received were reported as either resolved or resolving including 7 events reported as resolved with sequelae.

Evaluation of the data of those patients receiving a booster continues to be consistent with the known safety profile of SPIKEVAX, as well as for reports of myocarditis and pericarditis in adolescents 12 to 17 years of age. There have been no fatal reports in adolescents due to myocarditis or pericarditis and no cases of myocarditis reported in adolescents 12 to 17-years of age after a third/booster dose of SPIKEVAX. For those case reports for which diagnostic results information is available, including several literature articles and case reviews that have been published, clinical presentation seems to be consistent with the majority of patients having normal ventricular systolic function on echocardiogram, with many have abnormal findings suggestive of myocarditis on cardiac MRI in the setting of elevated troponin and electrocardiographic changes; the presentation of the myocarditis is usually characterized by a mild illness with rapid resolution of symptoms within few days in most patients [263].

These risks, considered manageable, have been described in product labels with their respective risk factors, with appropriate risk minimization measures. They also have been communicated to patients and caregivers in patient leaflets to be alert to signs and symptoms requiring medical attention. ModernaTX, Inc. also have an RMP with ongoing studies to continue characterizing these important identified risks.

Based on the data presented in this PBRER, SPIKEVAX administered as two 100 µg doses given 28 days apart or as a third 100 µg dose for immunocompromised individuals, including a 50 µg booster dose at least 6 months after primary vaccination against SARS-COV-2 is a highly effective vaccine and capable of restoring nAbs, particularly against emerging VOCs in order to help contain the pandemic with an acceptable safety profile for the prevention of COVID-19 in individuals

6 years of age and older. Considering the ongoing public health emergency due to SARS-CoV-2, the available safety and efficacy data from the 8 clinical studies presented herein, and the ongoing post-authorization surveillance, ModernaTX, Inc. considers that the known and potential benefits outweigh the known and potential risks for SPIKEVAX.

Risks associated with SPIKEVAX are considered adequately managed with the product labels. An RMP is in place with ongoing studies including the continuation of the ongoing pivotal trial, Study mRNA-1273 P301, and other observational studies to further characterize important risks as well as the identified uncertainties (i.e., use in pregnancy, long-term safety, use in immunocompromised or frail individuals). Routine pharmacovigilance will monitor for potential new ARs.

Because the purpose of vaccination is different from that of treatment of infection, the focus of this section is on vaccines only. In addition to many vaccines that remain under development, several vaccines against COVID-19 are currently available for use under various regulatory provisions in countries around the world, as follows:

- mRNA-based vaccines: Pfizer/BioNTech Comirnaty (BNT162b2); Moderna COVID-19 Vaccine (SPIKEVAX; the subject of this application)
- Viral vector, non-replicating: Adenovirus vaccine: AstraZeneca (Vaxzevria/Covishield); Janssen Vaccines (Johnson & Johnson) (JNJ-78436735; Ad26.COV2.S)
- Recombinant adenovirus vaccines: Gamaleya Research Institute, Acellena Contract Drug Research and Development Sputnik V (rAd26 and rAd5); Gamaleya Research Institute, Acellena Contract Drug Research and Development Sputnik Light (rAd26); CanSino Biologics Convidicea (PakVac, Ad5-nCov)
- Inactivated vaccines: Sinovac (CoronaVac); Beijing Institute of Biological Products (BBIBP-CorV); Bharat Biotech ICMR, Ocugen, ViroVax (Covaxin); Wuhan Institute of Biological Products, China National Pharmaceutical Group (WIBP-CorV); Chumakov Federal Scientific Center for Research and Development of Immune and Biological Products (CoviVac); Research Institute for Biological Safety Problems (QazVac); Minhai Biotechnology Co, Kangtai Biological Products Co. Ltd. (Unnamed vaccine candidate); Shifa Pharmed Industrial Group (CovIran Barekat); Chinese Academy of Medical Sciences, Institute of Medical Biology (Unnamed vaccine candidate)
- Peptide vaccine: Federal Budgetary Research Institution State Research Center of Virology and Biotechnology (EpiVacCorona)
- Recombinant vaccine: Anhui Zhifei Longcom Biopharmaceutical, Institute of

Microbiology of the Chinese Academy of Sciences (ZF2001)

- Protein subunit vaccine: Center for Genetic and Engineering Biotechnology (Abdala); Medigen Vaccine Biologics, Dynavax (MVC-COV1901)
- Conjugate vaccine: Finlay Institute of Vaccines, Pasteur Institute (Soberana 02).

Table 18-1. Benefit-Risk Evaluation Table

Decision Factors	Evidence/ Uncertainties	Conclusions
Analysis of Condition/ Disease	An outbreak of cCOVID-19 caused by SARS-CoV-2 began in Wuhan, Hubei Province, China in Dec 2019, and the disease quickly spread globally. The WHO declared COVID-19 a Public Health Emergency of International Concern on 30 Jan 2020 and declared COVID-19 a pandemic on 11 Mar 2020. Of major public health concern is whether immunity to early pandemic strains, developed via vaccination (or natural infection), confers protection against newly circulating variants. Children and adolescents are as susceptible to infection with SARS-CoV-2 as adults but develop symptomatic COVID-19 primary infection at significantly lesser rates and rarely develop severe disease. It also became clear that a fraction of children develops a life-threatening hyperinflammatory state 4–6 weeks after infection with primary COVID-19 termed Multisystem Inflammatory Syndrome in Children (MIS-C)	• COVID-19 disease is a pandemic and a public health emergency. • Evidence suggests that immunity against COVID-19 is waning worldwide and may contribute to reinfection or breakthrough infections from the original virus strain or escape variants. • Children and adolescents are as susceptible to infection with SARS-CoV-2 as adults but develop symptomatic COVID-19 primary infection at significantly lesser rates and rarely develop severe disease.
Medical Need for Treatment of Condition/ Disease	As of 27 Dec2021, approximately 290,469,670 confirmed cases and 5,442,452 deaths have been attributed to the COVID-19 pandemic globally (WHO 2022d). Widespread community transmission of SARS-CoV-2 has been reported in all WHO regions (WHO 2022a and WHO 2022b). Since the beginning of the COVID-19 pandemic, severe disease and deaths associated with COVID-19 have occurred more frequently in adults [246], [247], [248]; however, COVID-19 can also lead to severe outcomes in children and adolescents [249], [250]. From the start of the pandemic to Dec 2021, approximately 3.3 million cases of COVID-19 have been reported among children 5 to 9 years of age and approximately 4.8 million cases have been reported among children 10 to 14 years of age in 105 countries [251]. In the US, due to COVID-19, an excess of 4,155 hospitalizations among children 5 years to 17 years of age have been observed through 31 Dec 2021 with 27.5% requiring intensive care unit interventions [248].	Since Dec 2020, SPIKEVAX and other COVID-19 vaccines have been available under EUA and conditional approvals worldwide. As of 31 Dec 2021, an estimated 827,274,740 doses of SPIKEVAX have been distributed; 466,804,529 doses are estimated to have been administered for use in adults (≥18 years age) and adolescents (12 to < 18 years of age) as a two dose primary series, while approvals and/or authorizations for third doses in special populations (e.g., immunocompromised) and/or as a booster dose in certain individuals at higher

Decision Factors	Evidence/ Uncertainties	Conclusions
	Comparison of apparent case fatality rates from early in the pandemic (acknowledging the limitations of such data) showed that the risk of death from COVID-19 was higher among the elderly and among individuals with certain pre-existing health conditions. Among all fatal cases, 75% had one of the listed pre-existing conditions. The most common was cardiac disorder, diabetes, and cancer malignancy. Two thirds (67.8%) of all severe hospitalizations were in patients with one of the listed pre-existing conditions.	risk of severe COVID-19 continue to expand.
Key Benefits	The efficacy of SPIKEVAX to prevent COVID-19 has been confirmed in adults 18 years and older in Study mRNA-1273 P301. Analysis of the 04 May 2021 dataset showed that SPIKEVAX 100 µg was 98.2% effective in preventing severe COVID-19. Subgroup analyses of VE to prevent severe COVID-19 showed consistent high efficacy in subgroups of participants with 1 risk factor, at least 2 risk factors, chronic lung disease, significant cardiac disease, severe obesity, diabetes, liver disease, and HIV infection. Additionally, SPIKEVAX was effective in preventing COVID-19 regardless of prior SARS-CoV-2 infection for cases starting 14 days after the second dose of SPIKEVAX (VE of 92.8% based on HR). Multiple studies from the US and other countries have demonstrated high effectiveness of a 2 dose COVID-19 mRNA vaccination series against SARS-CoV-2 infection (including both symptomatic and asymptomatic infections) caused by the original and variant strains and sequelae including severe disease, hospitalization, and death. Real-world effectiveness studies report COVID-19 mRNA vaccine effectiveness ranging from 86-89% for SARS-CoV-2 infection, 65-92% for asymptomatic infections, 85 to 97% for symptomatic disease, 87 to 98% for hospitalization or severe disease, and 97% effectiveness against death depending on the population studied and geographic region. Data from both P201 Part A and P301 Part A support persistence of immunogenicity and effectiveness through at least 6 months. Results from the P301 final blinded analysis were consistent with results of the interim and primary analyses, confirming persistence of high rates of efficacy over a median of 5.3-month blinded observation period. Administration of a booster dose of SPIKEVAX of 50 µg at least 6 months after administration of the second of 2 doses of the primary series greatly enhanced immune responses compared to pre-boost	• The efficacy of SPIKEVAX to prevent COVID-19 has been confirmed in adults 18 years and older in Study mRNA-1273 P301. • Demonstration of SPIKEVAX capacity to greatly enhanced immune responses compared to pre-boost levels after the administration of a booster dose of 50 µg at least 6 months after administration of the second of 2 doses of the SPIKEVAX primary series has been confirmed in Study mRNA-1273 P201 Part A, Part B, and P301, as well as Study DMID 21-0012.

Decision Factors	Evidence/ Uncertainties	Conclusions
	levels showing within 2 weeks nAb responses against these variants a 32- to 44-fold rise compared to the pre-booster titers.	
Key Risks	The safety of SPIKEVAX in controlled clinical studies is based largely on data from Study mRNA-1273 P301, which was a 2-part Phase 3 study: • Part A, the blinded Phase was a randomized, stratified, observer-blind, placebo-controlled study to evaluate the efficacy, safety, and immunogenicity of mRNA-1273 SARS-CoV-2 vaccine compared to placebo in adults 18 years of age and older who have no known history of SARS CoV-2 infection. • Part B, the open-label observational Phase was designed to offer participants who received placebo in Part A of this study and who met EUA eligibility an option to request 2 doses of mRNA-1273 vaccine and remain on study. Cumulatively, 48,823 subjects have been exposed to either mRNA-1273, mRNA-1273.351, mRNA-1273.211, mRNA-1273.213, mRNA-1273.617.2, and/or placebo in the mRNA clinical development program sponsored by ModernaTX, Inc (the 48,823 does not represent unique subjects). Of the 48,823 subjects, 36,181 subjects were exposed to mRNA-1273 and the remaining 12,642 subjects were exposed to mRNA-1273 and/or mRNA-1273.351, mRNA-1273.211, mRNA-1273.213, mRNA 1273.617.2, or placebo. Cumulatively 645 subjects were exposed to mRNA-1273 in clinical trials sponsored by DMID, 1,533 subjects were exposed to mRNA 1273 in clinical trial sponsored by GSK and 104 subjects were exposed to mRNA 1273 in clinical trial sponsored by Sanofi. The exposure data from Investigator sponsored studies is unavailable. The type, incidence, and severity of ARs and TEAEs reported with SPIKEVAX in clinical trials were consistent with the clinical trial data previously submitted in support of authorization. No unexpected safety findings were identified. Solicited local and systemic ARs were more common in participants who received mRNA 1273 compared with those who received placebo after both the first and second doses. While the severity of solicited symptoms increased after the second mRNA-1273 dose, relative to the first dose, the majority of ARs were mild-to-moderate in severity. The most common solicited local AR was pain, and the most commonly reported solicited systemic ARs were fatigue, headache, myalgia, and arthralgia. The majority of the solicited local and systemic ARs occurred within the first 2 days after administration	In the ongoing clinical trials for SPIKEVAX the most common solicited local AR was pain, and the most commonly reported solicited systemic ARs were fatigue, headache, myalgia, and arthralgia. The majority of the solicited local and systemic ARs occurred within the first 2 days after administration of mRNA 1273 and generally persisted for 1 to 3 days. Overall, in the Phase 1/2/3 ongoing clinical trials no new clinically significant abnormalities or new safety risks were identified beyond those already included in the CCDS/ IB. Anaphylaxis has been reported in individuals who have received the Moderna COVID-19 Vaccine. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine. Since July 2021, myocarditis and pericarditis have been considered as undesirable effects that may occur following vaccination against COVID-19 with a messenger RNA vaccine, especially in young men. Available data suggest that the course of myocarditis and pericarditis following vaccination is typically milder than viral myocarditis or pericarditis and is self-limited. The clinical course of cases of myocarditis and pericarditis appears generally favorable;

Decision Factors	Evidence/ Uncertainties	Conclusions
	of mRNA 1273 and generally persisted for 1 to 3 days. In the mRNA-1273 group, pain was the most common grade 3 solicited local AR, and grade 3 pain was more common after the second injection than after the first. Fatigue and headache were the most commonly reported grade 3 systemic ARs in the SPIKEVAX group after the first injection and second injection. The local and systemic ARs are considered risks with minimal and temporary clinical impact. Hypersensitivity events were more common among SPIKEVAX participants than placebo participants, however, most imbalance was due to injection site urticaria and rashes. In Study mRNA-1273 P301, anaphylaxis, a potentially life-threatening hypersensitivity reaction that can occur after any vaccination was not reported within 30 minutes after injection with SPIKEVAX. No cases of myocarditis have been reported in any of the ongoing studies for SPIKEVAX. Pericarditis was reported in 5 participants, 2 each in the SPIKEVAX and placebo groups during Part A, with 1 female and 1 male participant in each group having an SAE of pericarditis reported, and 1 male participant in Part B. There was no evidence of an increased risk of pericarditis in the SPIKEVAX group. In addition, the careful review of symptoms suggestive of myocarditis did not identify a concern. A cumulative review of post-authorization safety data received as of 31 Dec 2021 showed that events of myocarditis and pericarditis continues to primarily occur in young adult males shortly after the second dose of the vaccine with a TTO less than 7 days. A large proportion of the myocarditis and pericarditis events received were reported as either resolved or resolving including 7 events reported as resolved with sequelae. Evaluation of the data of those patients receiving a booster continues to be consistent with the known safety profile of SPIKEVAX, as well as for reports of myocarditis and pericarditis in adolescents 12 to 17 years of age. There have been no fatal reports in adolescents due to myocarditis or pericarditis and no cases of myocarditis reported in adolescents 12 to 17 years of age after a third/booster dose of SPIKEVAX.	those individuals who are hospitalized have lengths of stay of around 2 to 4 days on average. Analysis of post-authorization safety data has shown that this identified risk of myocarditis and pericarditis is generally within 7 days following vaccination against COVID-19 with an mRNA vaccine in people aged 12 to 40 years, particularly young people under 30 years old. However, the number of cases attributable to vaccines appears to be very rare in relation to the number of doses administered. To date, based on the data from ongoing trials, and post-authorization safety information, the general safety profile of SPIKEVAX continues to appear well tolerated and with an acceptable safety profile.

19. CONCLUSIONS AND ACTIONS

Overall, the new evidence on efficacy and effectiveness obtained during the current reporting period supports the findings from previous studies which formed the basis of the benefit profile for SPIKEVAX described in the RSI. The cumulative evidence on the safety and efficacy for SPIKEVAX fully supports the indication described in the RSI, authorized as a suspension for injection for active immunizations to prevent COVID-19 caused by SARS-CoV-2 in individuals 6 years of age and older.

Clinical trial data and the results of the post-authorization NIS conducted to date support the positive safety and efficacy profile of mRNA-1273.

The ongoing review of ModernaTX, Inc's global safety database supports the current listed AEs.

During the reporting period, requests related to the topics "Dizziness", "Neuralgic amyotrophy", "Erythema Multiforme", "Glomerulonephritis and nephrotic syndrome", "Serious Hypertension", "Multisystem Inflammatory syndrome", "Capillary Leak Syndrome" and "Cerebral Venous Sinus Thrombosis" were received from HAs or regulatory bodies and these were all considered as validated signals. In addition to these signals, "Myelitis Transverse" was triggered following review of a literature article. Of these 9 signals, 1 signal "Dizziness" was closed and categorized as an identified risk (not important). The remaining 8 signals were closed and refuted during the reporting period. Finally, a new signal for myocarditis and pericarditis was opened to further characterize the risks' frequency from "Unknown" to "Very rare" for both myocarditis and pericarditis.

The signal of "Autoimmune Hepatitis" was validated during the review period following a regulatory authority request, however it was refuted following assessment after DLP of this report (closed on 19 Jan 2022).

During the reporting period SPIKEVAX risk management plan was updated to RMP v2.1 to include myocarditis and pericarditis as new important identified risks and was submitted to EMA on 19 Jul 2021. Consequently, the IB and ICFs for all ongoing studies have also been updated to include the information on myocarditis and pericarditis after receipt of SPIKEVAX. Additionally, a joint Direct Healthcare Professional Communication related to the risks of myocarditis and pericarditis was disseminated on 19 July 2021 by ModernaTX, Inc. and Pfizer/BioNtech to general practitioners, cardiologists, specialists in emergency medicine, and vaccination centres in all EEA countries. A similar joint direct healthcare professional communication agreed with Swissmedic was disseminated in Switzerland on 12 Aug 2021.

In addition, there have been updates to the RMP versions (v2.2 dated 16 Aug 2021 through v2.3 dated 28 Oct 2021) with no additional changes to the list of safety concerns.

At the time of the DLP of this PBRER, the following important identified and important potential risks are being closely monitored as per SPIKEVAX RMP v2.3 dated 28 Oct 2021:

Important identified risks

- Anaphylaxis
- Myocarditis
- Pericarditis

Important potential risks

- Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD)

Missing information

- Use in pregnancy and while breastfeeding
- Long-term safety
- Use in immunocompromised subjects
- Interaction with other vaccines
- Use in frail subjects with unstable health conditions and co-morbidities (e.g., chronic obstructive pulmonary disease (COPD), diabetes, chronic neurological disease, cardiovascular disorders)
- Use in subjects with autoimmune or inflammatory disorders

On 29 Oct 2021, following PRAC discussion on the signal of multisystem inflammatory syndrome (MIS) (EPITT 19732) and as per the assessment reports, PRAC recommended that a follow-up questionnaire should be implemented for all MIS cases. The MAH for all authorized COVID-19 vaccines were requested to prepare and implement a targeted questionnaire in order to follow up cases of MIS.

On 17 Dec 2021, the CHMP has requested to the MAH a review of all available evidence on vaccination in pregnant women and breastfeeding that must be provided as a LEG (EMEA/H/C/005791/LEG/055) in order to critically discuss the need to update SPIKEVAX product information. As a result, after the DLP of this report section 4.6 of the SmPC has been updated accordingly.

Analysis of the data contained within this report supports the adequacy of the current RSI (CCDS v11.0 dated 10 Dec 2021) for SPIKEVAX. Examination of the data contained within this report supports the conclusion that the overall benefit-risk balance for SPIKEVAX continues to be positive.

The data included in this PBRER does not indicate any unfavorable change in the benefit-risk profile of SPIKEVAX.

The safety profile of SPIKEVAX is closely monitored on a continuous basis. Based on the cumulative evidence, the benefit-risk profile of SPIKEVAX remains positive.