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2.3.S DRUG SUBSTANCE [mRNA-1273.529 LNP-B]

2.3.S.1 General Information

This product is an mRNA-lipid complex [lipid nanoparticle (LNP)] dispersion containing CX-031302 mRNA that encodes for the prefusion stabilized Spike protein of the SARS-CoV-2 B.1.1.529 Omicron Variant. The LNP is composed of the following four lipid components:

- Cholesterol,
- SM-102 (a custom-manufactured ionizable lipid),
- DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine), and
- PEG2000-DMG (1monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000).

2.3.S.1.1 Nomenclature

International Non-proprietary Name (INN):	N/A
Proprietary name:	N/A
Company product codes:	mRNA-1273.529
Drug Product name:	mRNA-1273
Synonymous name:	mRNA-1273.529 Lipid Nanoparticle (LNP), mRNA-1273.529 LNP-B

2.3.S.1.2 Structure

mRNA-1273.529 Lipid Nanoparticle (LNP) – B CCI [redacted]. The molecular sequence of CX-031302 is provided in Section 3.2.S.1.2 {CX-031302} CCI [redacted]

2.3.S.1.3 General Properties

The general properties of mRNA-1273.529 Lipid Nanoparticle (LNP) – B are summarized in Table 1.

Table 1: General Properties of mRNA1273.529 Lipid Nanoparticle - B

Description	mRNA-1273.529 LNP - B has a total RNA content of CCI and a total lipid content of CCI. The mRNA-1273.529 LNP is stored in CCI
Appearance	White to off-white LNP dispersion. The mRNA-1273.529 LNP – B may contain visible, white or translucent product-related particulates.
pH	CCI
Osmolality	CCI
Density	CCI
Particle Size	CCI

2.3.S.2 Manufacture

2.3.S.2.1 Manufacturer(s)

The name and address for the manufacturing and testing facilities of mRNA-1273 Lipid Nanoparticle (LNP)s-B are listed in Section 3.2.S.2.1 {mRNA-1273 LNP-B}.

2.3.S.2.2 Description of Manufacturing Process and Process Controls

The mRNA-1273.529 LNP-B is produced in a 200 g nominal batch size, according to the same manufacturing process described for mRNA-1273 LNP-B, as described in Section 3.2.S.2.2 {mRNA-1273 LNP - B}.

2.3.S.2.3 Control of Materials

Raw Materials

Reference is made to the descriptions of the control of materials used in the manufacture of the mRNA-1273 Lipid Nanoparticle (LNP) and mRNA-1273 LNP – B as discussed in Section 3.2.S.2.3 (Raw Materials) {mRNA-1273 LNP - B}.

Materials or Starting Materials of Biological Origin

There are no materials or starting materials of animal or human origin used in the manufacture of mRNA-1273 LNP.

2.3.S.2.4 Controls of Critical Steps and Intermediates

The manufacturing process and process controls for the mRNA-1273.529 LNP-B are identical to the ones in place for the mRNA-1273 LNP, as described in Section 3.2.S.2.4 {mRNA-1273 LNP.

2.3.S.2.5 Process Validation and/or Evaluation

Process validation for mRNA-1273 lipid nanoparticles (LNPs) – B is performed in compliance with European Medicines Agency (EMA), United States Food and Drug Administration (FDA), International Council for Harmonization (ICH), and international regulatory expectations. Process

validation comprises Process Design (Phase 1), Process Performance Qualification (PPQ; Phase 2), and Continued Process Verification (CPV; Phase 3). The elements of Process Design (Phase 1) are described in Section 3.2.S.2.4 {mRNA-1273 LNPs} for control strategy and Section 3.2.S.2.6.1 {mRNA-1273 LNPs} for process development. PPQ (Phase 2) and CPV (Phase 3) are discussed in Section 3.2.S.2.5 {mRNA-1273.529 LNPs-B}. All material referenced in these sections is mRNA-1273 LNP-B CCI [redacted]

For mRNA-1273 LNPs-B variant processes that use a manufacturing process and control strategy equivalent (equivalent excepting for mRNA sequence specific control elements) to the prototype mRNA-1273 process, one confirmatory PPQ verification lot was performed to demonstrate process consistency per site per the requirements specified in the Process Validation Master Plan. Moderna has successfully completed PPQ verification of the mRNA-1273 variant manufacturing process in Module M kit 5 at Lonza Visp as a means of demonstrating that the commercial-scale manufacturing process is capable of consistently delivering quality product. The PPQ verification has generated data at commercial scale to support and complement concurrent laboratory-scale studies.

Three additional kits, Kit 11, 12 and 13, have been introduced for manufacturing mRNA- 1273.529 LNP-B at Lonza Visp. To verify the new kits, one PPQ verification batch (128001) was produced at the 200 g scale. An assessment of the results for process parameters, in-process controls and release results against the defined acceptance criteria was performed. In addition, the results were compared to the data from the previous PPQ batches which have been validated for the mRNA-1273 LNP-B, CCI [redacted] process in Kit 11 (116001, 116002, 116003) and Kit 12 (126001). The batch 128001 is also compared to the data from the PPQ verification batch 58001 (mRNA-1273.529 LNP-B, CCI [redacted]) produced in Module M Kit 5. Both batches have been manufactured using the CX-031302 mRNA material from batch 57001. The validation results are provided in Section 3.2.S.2.5 {mRNA-1273.529 LNPs-B}.

The commercial control strategy (Section 3.2.S.2.4 {mRNA-1273 LNPs}) defines critical quality attributes (CQAs) and identifies critical process parameters (CPPs). The commercial control strategy is the basis of the defined acceptance criteria for PPQ verification and no further revision to the commercial control strategy was deemed necessary following PPQ verification.

Validation results are presented in Section 3.2.S.2.5.1 {mRNA-1273.529 LNPs – B}. The CPV Plan is described in Section 3.2.S.2.5.1.2.3 {mRNA-1273.529 LNPs – B}.

Based on the outcome of the PPQ exercise, the mRNA-1273 LNPs - B manufacturing process has been successfully validated at the 200 g scale at Moderna Norwood, Lonza Visp and Rovi Granada. More complete information on process validation is provided in Section 3.2.S.2.5 {mRNA-1273.529 LNPs - B}.

2.3.S.2.6 Manufacturing Process Development

The mRNA-1273.529 Lipid Nanoparticle (LNP) is CCI [redacted] filled into single-use, disposable bags (described in Section 3.2.S.6 {mRNA-1273 LNPs}).

The development of additional mRNA-1273 vaccines was initiated in response to the emergence of SARS-CoV-2 variants of concern. Sequences for mRNA-1273 vaccines are designed based upon the S-2P encoding sequence for CX-024414 mRNA. Changes relative to this sequence are made only to incorporate the specific mutations of the variant S protein sequence encoded by the specific mRNA-1273 RNA. The manufacturing process and process and analytical control strategies established for the prototype mRNA-1273 LNP are applied directly to all mRNA-1273 LNPs.

Subsequent process characterization beyond that described in Section 3.2.S.2.6 {mRNA-1273 LNP - Process Characterization} was performed for mRNA-1273 LNPs, with the intent of verifying the applicability of the process description and process control strategy defined in Section 3.2.S.2.2 {mRNA-1273.529 LNPs-B} and Section 3.2.S.2.4 {mRNA-1273.529 LNPs-B}, respectively, to all mRNA-1273 LNPs. Process characterization results are provided in 3.2.S.2.6.1 {mRNA-1273.529 LNPs}.

The comparability demonstration, including evaluation of process change impact on critical quality attributes, is included in Section 3.2.S.2.6.3 {mRNA-1273.529 LNPs}.

The mRNA-1273.529 LNP-B manufacturing process was successfully established at ModernaTX (Norwood, MA, USA), Rovi (Granada, Spain), and Lonza (Visp, Switzerland) at a 200 g mRNA scale to provide commercial material. A process performance qualification (PPQ) batch at ModernaTX, and PPQ verification batches at Rovi and Lonza were manufactured according to the Process Validation Master Plan and comparability was assessed against the expected ranges per DPAD-PRO-0797.

An additional kit 13 has been introduced for manufacturing mRNA- 1273.529 LNP-B at Lonza Visp. The new kit has been verified with one PPQ batch (128001) produced at the 200 g scale. The verification strategy is described in the Validation Protocol CHVI-469874 where an assessment of the in-process controls, process parameters and critical process parameters results versus the defined acceptance criteria was performed. Briefly, batch 128001 results were verified by comparison to the data from the previous PPQ batches which have been validated for the mRNA-1273 LNP-B, CCI [redacted] process in Kit 11 (116001, 116002, 116003) and Kit 12 (126001) verifying that this process change did not impact process consistency. The batch 128001 was also compared to the data from the PPQ verification batch 58001 (mRNA-1273.529 LNP-B) produced

in Module M Kit 5 using the CCI [redacted] process, demonstrating process consistency across kits. Batch data from mRNA-1273.529 LNP-B are provided in Section 3.2.S.4.4 {mRNA-1273.529 LNPs-B} and confirm consistency.

More details are provided in Section 3.2.S.2.6 {mRNA-1273.529 LNPs}.

2.3.S.3 Characterisation

2.3.S.3.1 Elucidation of Structure and Other Characteristics

A discussion of the methods and results of the characterization studies is provided in Section 3.2.S.3.1 {mRNA-1273 LNP}.

2.3.S.3.2 Impurities

A discussion of the impurities is presented in Section 3.2.S.3.2 {mRNA-1273 LNP}.

2.3.S.4 Control of the Drug Substance

2.3.S.4.1 Specification

The specifications are presented in Section 3.2.S.4.1 {mRNA-1273 LNP-B}.

2.3.S.4.2 Analytical Procedures

The proposed drug substance specification has been designed to ensure safety and quality of the product, with the objective of patient safety. Acceptance criteria for tests for appearance, identity, strength, purity, impurities and microbiological quality of mRNA-1273 LNPs were established based on compliance with regulations, guidances and compendial methods, and are justified based on characterization studies, the manufacturing process, available batch analyses data, and stability results using validated analytical methods.

The analytical methods used for release testing of mRNA-1273.529 LNPs and the prototype mRNA-1273 LNP are identical with the exception of the identity method, since this is the only method that is sequence-specific. For descriptions of the common methods please refer to Section 3.2.S.4.2 {mRNA-1273 LNP}. A description of the mRNA-1273.529 LNPs identity method is provided in Section 3.2.S.4.2 {mRNA-1273.529 LNPs-B}.

2.3.S.4.3 Validation of Analytical Procedures

The analytical procedures used for testing mRNA-1273 LNP have been validated by ModernaTX, Inc. at the Norwood, MA Quality Control (QC) Laboratory. The analytical methods were subsequently transferred to ModernaTX, Inc. QC laboratory (Dedham, MA), Lonza AG (Visp, Switzerland), and Rovi (Granada, Spain).

The analytical procedures for testing of the mRNA-1273 LNP were confirmed as suitable for their intended use through method validation experiments. A summary of the validation parameters provided in Section 3.2.S.4.3 {mRNA-1273.529 LNPs}.

The analytical methods used for release testing of mRNA-1273 LNP – B and mRNA-1273.529 LNP - B are identical with the exception of the identity method, since this is the only method which

is sequence-specific. For information on validation of common methods, please refer to Section 3.2.S.4.3 {mRNA-1273 LNP}. A validation summary of the identity testing method for mRNA-1273.529 LNP – B is provided in Section 3.2.S.4.3 {mRNA-1273.529 LNPs-B}.

2.3.S.4.4 Batch Analyses

The mRNA-1273 Lipid Nanoparticle (LNPs) lots are intended for further manufacturing into mRNA-1273 Drug Product lots. Batch analysis data is generated for mRNA-1273 Lipid Nanoparticle (LNPs) according to an approved specification and is presented in Section 3.2.S.4.4 {mRNA-1273.529 LNPs-B}.

2.3.S.4.5 Justification of Specification

Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities. Specifications are chosen to confirm the quality of the mRNA 1273 LNP and mRNA-1273 LNP – B rather than to establish full characterization and should focus on those characteristics found to be useful in ensuring the safety and efficacy of the mRNA-1273 LNP (ICH Q6B and Q11).

A Critical Quality Attribute is defined as a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality per ICH Q8(R2) - Pharmaceutical Development.

The rationale for the establishment and justification of the release specification is provided in Section 3.2.S.4.5 {mRNA-1273 LNP-B}. CCI [redacted]

2.3.S.5 Reference Standards or Materials

For information on the reference standard refer to Section 3.2.S.5 {mRNA-1273 LNP}.

2.3.S.6 Container Closure System

For information regarding the container closure system please refer to Section 3.2.S.6 {mRNA-1273 LNP}.

2.3.S.7 Stability

2.3.S.7.1 Stability Summary and Conclusions

The mRNA-1273 Lipid Nanoparticle (LNP) registration stability program was executed according to ICH Q1A (R2*), Stability Testing of new Drug Substances and Products, and ICH Q5C, Stability Testing of Biotechnological/Biological Products*. An initial shelf life of 12 months is proposed for mRNA-1273 LNP material stored in the commercial container closure defined in Section 3.2.S.6 {mRNA-1273 LNP}, when stored at the recommended long-term storage condition of -60°C to -90°C.

The properties of mRNA-loaded lipid nanoparticles with respect to the attributes that affect

product potency has been systematically and thoroughly assessed. These attributes include the quantity of mRNA delivered; the fidelity of the mRNA sequence, including cap, tail, and open reading frame; the integrity of the mRNA; and various biophysical attributes of the lipid nanoparticles, particularly including the state of mRNA encapsulation and the size distribution of the particles. Direct measurements of those attributes of greatest significance have been established and has included those assays in the routine release panel for mRNA-1273 prototype and variant LNPs. The stability of mRNA-1273 variant LNPs will be evaluated against a broad set of stability data and modelling encompassing both prototype registration lots and additional variant RNAs associated with the mRNA-1273 program (Table 2 and Table 3).

The product quality attribute expected to vary during the manufacturing and distribution of the product is mRNA integrity as assessed by mRNA purity. The degradation of mRNA in the product has been extensively studied by applying a sensitive chromatographic assay to assess the formation of RNA degradants. The principal routes of degradation are hydrolytic chain scission, which is measured by the species which elute prior to the main peak (RNA fragments); and the formation of covalent adducts between the RNA and degradants of the cationic lipid, which are relatively hydrophobic and elute after the main peak (RNA-lipid adduct). There is a strong quantitative correlation between RNA degradation as measured directly and the resulting protein levels. Direct measure of mRNA degradation utilizing the mRNA purity assay by RP-HPLC is precise, accurate, and the most stability-indicating measure of product activity.

The degradation rates can be determined from the purity analysis over different stability timepoints. Based on the stochastic nature of the degradation mechanism, there is a dependence on the rate of degradation on RNA size (length). Since mRNA-1273 prototype and variant RNAs have approximately the same overall length (~4,000 nt), a similar rate of degradation is expected across these mRNA-1273 and mRNA-1273.529 LNP.

The stability profiles for all the stability-indicating attributes are being evaluated and monitored, but purity is the primary determinant of shelf-life, since it is the most stability-indicating attribute. Degradation rates for purity at each temperature of interest (-60°C to -90°C and 5 ± 3°C) are reported in Section 3.2.S.7.1.1 {mRNA-1273 LNPs}.

The shelf life is justified from the purity modelling analysis. Stability and characterization studies designed to evaluate product stability under various stressed conditions (freeze/thaw) have been performed. The mRNA-1273 LNP lots used in the purity modelling analysis (Table 2) used a development process and the Scale B process (Section 3.2.S.2.6 {mRNA-1273 LNPs}). Modelling analysis also included additional lots not listed that were manufactured outside the United States as part of Moderna's global network. The purity modelling results are provided in Section 3.2.S.7.1.1 {mRNA-1273 LNPs} and the purity data from these studies are presented in Section 3.2.S.7.3 {mRNA-1273.529 LNPs}.

Registration lots, Scale B Process Performance Qualification (PPQ) lots manufactured using the process described in Section 3.2.S.2.2 {mRNA-1273 LNPs-B}, were also placed on stability

studies (Table 3). The data from these studies are presented in Section 3.2.S.7.3 {mRNA-1273.529 LNPs} and protocols are provided in Section 3.2.S.7.1.2 {mRNA-1273 LNPs}.

Stability samples were stored in a scaled-down container closure system (50-mL Aramus bag). The scaled down bag is representative of the storage container used for commercial manufacture with the same product contact surfaces. Based on the sample volume and size of the scaled-down container, the surface area:volume ratio is considered worst case in the stability studies. Samples stored at the recommended condition of -60°C to -90°C are evaluated against the specification current at the time of testing. Samples stored at alternate storage conditions use the specification as a reference point to characterize stability trends at that condition.

Stability protocols are described in Section 3.2.S.7.1 {mRNA-1273.529 LNPs-B}. The data from the stability studies are presented in Section 3.2.S.7.3 {mRNA-1273.529 LNPs-B}.

Table 2: Additional mRNA-1273 LNP Stability Modelling Lots

Lot	Product	Purpose	Manufacturing Site	Lot Size	Fill Volume (mL)	Container Closure	Conditions		Status
							Temperature	Duration	
DH-06191.1	mRNA-1273.351	Development	ModernaTX	CCI	6 mL	50 mL Aramus Bag	-60°C to -90°C	9 months	Completed
							5°C ± 3°C	1 month	Completed
DH-06191.2	mRNA-1273.211	Development	ModernaTX	CCI	6 mL	50 mL Aramus Bag	-60°C to -90°C	9 months	Completed
							5°C ± 3°C	1 month	Completed
5011122003	mRNA-1273.529	PPQ Comparability	ModernaTX	200 g	15 mL	50 mL Aramus Bag	-60°C to -90°C	36 months	Ongoing
							5°C ± 3°C	2 months	Completed

Abbreviations: PPQ = process performance qualification

Table 3: mRNA-1273 LNP Registration Stability Program Lots

Lot	Product	Purpose	Manufacturing Site	Lot Size	Fill Volume (mL)	Scale	Process Train	Container Closure	Conditions	
									Temperature	Duration
5011122003	mRNA-1273.529 LNP-B	Stability[a]	ModernaTX (Norwood, MA)	200 g	15	B	8	50 mL Aramus bag	-60°C to -90°C	36 months
									5°C ± 3°C	2 months
5011522001	mRNA-1273.529 LNP-B	PPQ Comparability	Rovi (Granada, Spain)	200 g	40	B	10	50 mL Aramus bag	-60°C to -90°C	36 months
									5°C ± 3°C	3 months
5011422001	mRNA-1273.529 LNP-B	PPQ Comparability	Lonza (Visp, Switzerland)	200 g	30	B	5	50 mL Aramus bag	-80°C ± 10°C	36 months
									5°C ± 3°C	2 months
5012222002	mRNA-1273.529 LNP-B	PPQ Comparability	Lonza (Visp, Switzerland)	200 g	30	B	12	50 mL Aramus bag	-80°C ± 10°C	36 months
									5°C ± 3°C	2 months

Abbreviations: PPQ = process performance qualification

[a] Lot 5011122003 was manufactured using the identical process as the PPQ verification batch 5011122001.

2.3.S.7.2 Post-Approval Stability Protocol and Stability Commitment

For information on post-approval stability, please refer to Section 3.2.S.7.2 {mRNA-1273 LNP}.

2.3.S.7.3 Stability Data

All stability data available are provided in Section 3.2.S.7.3 {mRNA-1273.529 LNPs-B}.