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2.3.S DRUG SUBSTANCE [mRNA-1273.251 LNP-B]

2.3.S.1 GENERAL INFORMATION

This product is an mRNA-lipid complex [lipid nanoparticle (LNP)] dispersion containing CX-051869 mRNA that encodes for the pre-fusion stabilized Spike protein of the SARS-CoV-2 LP.8.1 variant.

The LNP is composed of the following four lipid components:

- Cholesterol,
- SM102 (a custom-manufactured ionizable lipid),
- DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine)
- PEG2000-DMG (1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol).

2.3.S.1.1 Nomenclature

Generic name:	N/A
CAS Registry Number® (CAS RN):	3074514-60-3
CA Index Name:	RNA (recombinant 5'-(m7G-(5'→5')-ppp-Gm)-capped all uridine→N1- methylpseudouridine-substituted severe acute respiratory syndrome coronavirus 2 pre-fusion spike glycoprotein [981-proline, 982-proline] LP.8.1 variant plus 5'- and 3'-untranslated flanking region-containing poly(A)-tailed messenger CX-051869), inner salt
Synonyms:	mRNA-1273.251 Lipid Nanoparticle (LNP), mRNA-1273.251 LNP - B
Product code:	mRNA-1273.251
Established names:	N/A

2.3.S.1.2 Structure

mRNA-1273 Lipid Nanoparticle (LNP) - B CCI [redacted] which protects the mRNA from nucleolytic degradation in biological fluids. Additionally, encapsulation of the RNA in a lipid particle of appropriate composition is critical to cellular uptake of the nanoparticle, endosomal escape, and ultimately productive cytosolic display of the mRNA

such that protein translation may occur as detailed in Section 3.2.S.1.2 {mRNA-1273 RNA LNP-B}.

2.3.S.1.3 General Properties

General properties of mRNA-1273.251 LNP are shown in Section 3.2.S.1.3 LP.8.1 {mRNA-1273.251 LNP - B} and listed in Table 1.

Table 1: General Properties of mRNA-1273.251 LNP-B

Description	mRNA-1273.251 LNP has a nominal total lipid content of CCI and a total mRNA content of CCI The mRNA-1273.251 LNP is stored in C CI
Appearance	White to off-white dispersion. May contain visible, white or translucent product-related particulates.
pH	CCI
Osmolality	
Density	
Particle Size	

2.3.S.2 MANUFACTURE

2.3.S.2.1 Manufacturer(s)

The name and address for the manufacturing and testing facilities of mRNA-1273.251 LNP-B are listed in Table 2.

Table 2 Facilities and Responsibilities for Manufacture and Testing of the mRNA-1273.251 LNP-B

Facility	Address	Responsibility
ModernaTX, Inc.	One Moderna Way Norwood, MA 02062 USA	• Manufacture of mRNA-1273 LNP-B (200 g Scale) • Quality control testing (excluding bacterial endotoxin testing)
CCI		

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

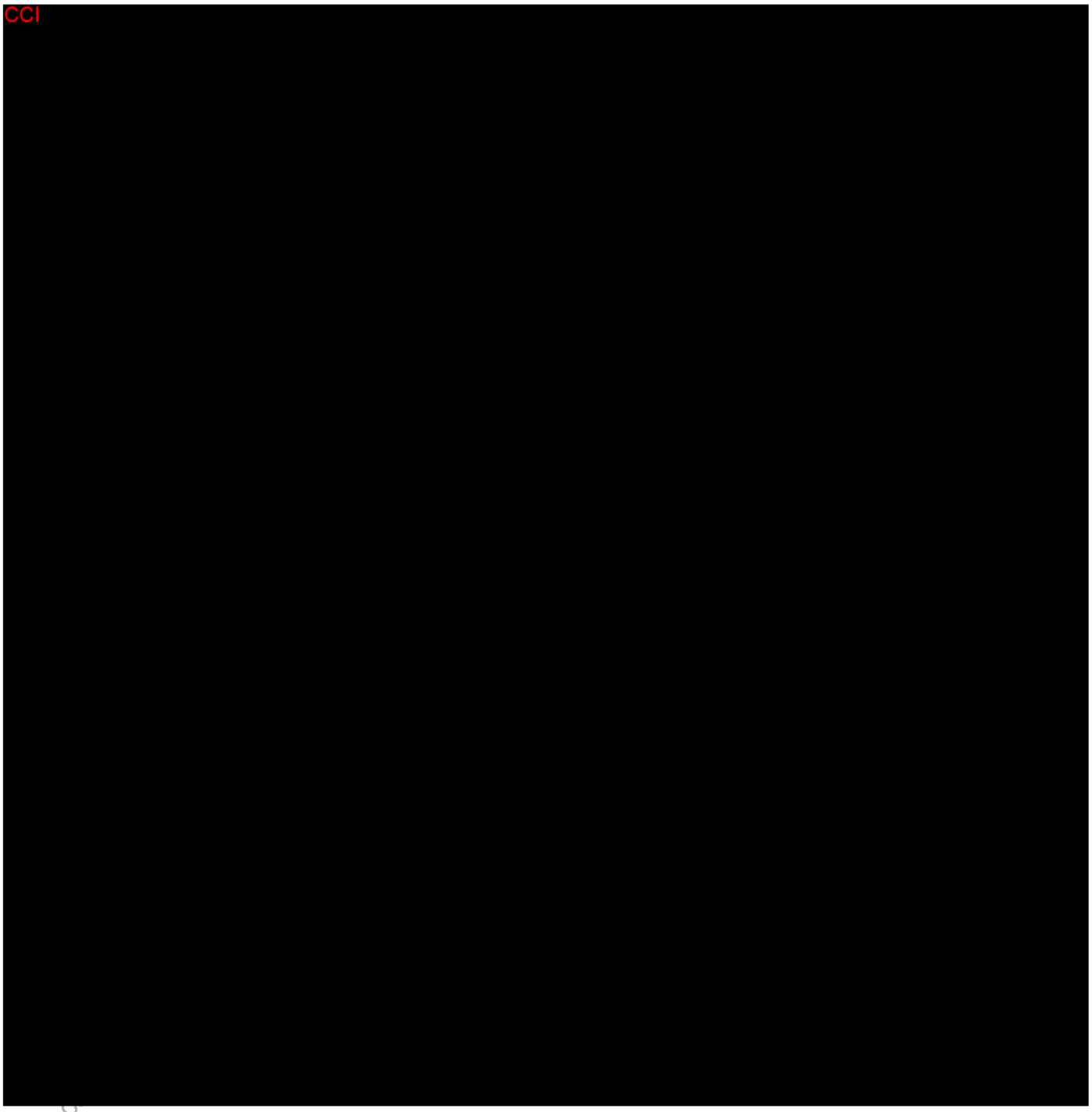
mRNA-1273 LNP-B is produced in a 200 g nominal batch size. The purpose of the mRNA-1273 LNP manufacturing process is to encapsulate mRNA CCI [redacted], which provides biological functionality including enabling cellular uptake and endosomal escape, and to add components to stabilize the dispersion of RNA-loaded LNPs.

The mRNA-1273 LNP manufacturing process includes encapsulation via mixing, neutralization, PEG2000-DMG addition, clarification, fill, freezing, and storage as shown in Figure 1.

CCI [redacted] the resulting mRNA-1273 LNP-B dispersion is filled into bags for frozen storage between -60°C to -90°C until the fill/finish operation for mRNA-1273Drug Product.

Detailed description of the manufacturing process including in-process controls and process parameters is provided in Section 3.2.S.2.2 {mRNA-1273 LNP-B}.

CCI



2.3.S.2.3 Control of Materials

The control of raw materials used in the manufacturing process of mRNA-1273 LNP-B is described in Section 3.2.S.2.3) {mRNA-1273 LNP-B}.

Raw materials are received from qualified suppliers. The supplier qualification process demonstrates the supplier has an effective and acceptable Quality Management System in place as described.

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

2.3.S.2.4 Controls of Critical Steps and Intermediates

The process control strategy and methods for critical in-process controls testing for the mRNA-1273 manufacturing process are identical to the ones established. Please refer to Section 3.2.S.2.4 {mRNA-1273 LNP}.

2.3.S.2.5 Process Validation and/or Evaluation

Moderna has successfully completed process verification of the for the successive mRNA-1273 LNP variants as a means of demonstrating that the commercial-scale manufacturing process platform is capable of consistently delivering quality product. The PPQ verification has generated data at commercial scale to support and complement concurrent laboratory-scale studies. One confirmatory PPQ verification lot was performed per variant to demonstrate process consistency per site per the requirements specified in the Process Validation Master Plan.

The commercial control strategy defines critical quality attributes (CQAs) and identifies critical process parameters (CPPs) and critical in-process controls (CIPCs) for the manufacturing process. The commercial control strategy is the basis of the defined acceptance criteria for PPQ verification.

More complete information on process validation is provided in Section 3.2.S.2.5 {mRNA-1273.251 LNP-B}.

2.3.S.2.6 Manufacturing Process Development

In accordance with ICH Q9, a systematic assessment of the potential risk to product quality of the prototype mRNA-1273 vaccine was performed with respect to the manufacturing process, as described in Section 3.2.S.2.6 {mRNA-1273.251 LNP-B}.

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-B are applied directly to mRNA-1273.251 LNP-B.

Subsequent process performance verification was performed for mRNA-1273.251 LNP-B (LP.8.1), with the intent of verifying the applicability of the process description and process control strategy.

The comparability demonstration for this variant is included.

The mRNA-1273.251 LNP-B (LP.8.1) manufacturing process was successfully established at ModernaTX (Norwood, MA) at a 200 g RNA scale. A process performance qualification (PPQ) verification batch and comparability was assessed.

2.3.S.3 CHARACTERISATION

2.3.S.3.1 Elucidation of Structure and Other Characteristics

The structure and physicochemical properties were verified to be comparable to the prototype mRNA-1273 LNP-B (refer to Section 2.3.S.2.6 {mRNA-1273 LNP-B)

2.3.S.3.2 Impurities

The lipid nanoparticle formulation and manufacturing process for mRNA-1273 LNP-B are consistent with the prototype mRNA-1273 LNP at the 200 g nominal batch size. Therefore, any product- or process-related impurities are expected to be consistent. Please refer to Section 3.2.S.3.2 {mRNA-1273 LNP-B} for more information.

2.3.S.4 CONTROL OF THE DRUG SUBSTANCE

2.3.S.4.1 Specification

The specification for mRNA-1273.251 LNP-B is described in Table 3.

Table 3: Specification for mRNA-1273.251 LNP – B

Test	Analytical Method	Acceptance Criteria
Appearance	Visual USP <631>, USP<790>, Ph. Eur. 2.2.2, Ph. Eur. 2.9.20 (SOP-0278 ModernaTX, Inc., CCI)	White to off-white dispersion. May contain visible, white or translucent product-related particulates.
Identity	Reverse Transcription/Sanger Sequencing (SOP-1337 ModernaTX, Inc., CCI)	Sequence matches description
Total RNA content	AEX-HPLC (SOP-0999 ModernaTX, Inc., CCI)	CCI
Purity	RP-IP- HPLC (SOP-1142 ModernaTX, Inc.) (RGR-PNT-L2-611 CCI)	
Product-related impurities		

Test	Analytical Method	Acceptance Criteria
% RNA encapsulation	Absorbance Assay (SOP-1000 ModernaTX, Inc., CCI)	CCI
Particle size	Dynamic Light Scattering (SOP-0998 ModernaTX, Inc., CCI)	
Polydispersity		
Lipid identification		
SM-102	HPLC-CAD (SOP-1001 ModernaTX, Inc., CCI)	Matches RT of Standard
Cholesterol		Matches RT of Standard
DSPC		Matches RT of Standard
PEG2000-DMG		Matches RT of Standard
Lipid content		
SM-102	HPLC-CAD (SOP-1001 ModernaTX, Inc., CCI)	CCI
Cholesterol		
DSPC		
PEG2000-DMG		
Lipid impurities	HPLC-CAD (SOP-1001 ModernaTX, Inc., CCI)	Individual impurities: Report % area and RRT Total impurities: CCI
In Vitro Translation	Methionine labelling (SOP-0937 Moderna Tx, Inc., CCI) CCI rma SOP-0937)	CCI
pH	USP <791>, Ph. Eur. 2.2.3 (SOP-0288 ModernaTX, Inc., CCI)	
Osmolality	USP <785>, Ph. Eur. 2.2.35 (SOP-0279 ModernaTX, Inc., CCI)	
Bacterial endotoxin	USP <85>, EP 2.6.14 (M-CTS-CS-0929 CCI) (RGR-PNT-L2-556 CCI)	
Bioburden	USP <61>, EP 2.6.12 (SOP-0480 ModernaTX, Inc.) (RGR-PNT-L2-526 CCI)	

Abbreviations: HPLC = High performance liquid chromatography; HPLC-CAD = High performance liquid chromatography charged aerosol detector; LNP = lipid nanoparticle; RP-IP-HPLC = reverse-phase ion pair high-performance liquid chromatography; RT = retention time; RRT = relative retention time; TAMC = total aerobic microbial count; TYMC = total combined yeasts/molds count

2.3.S.4.2 Analytical Procedures

The analytical methods used for the release and stability testing of mRNA-1273.251 LNP-B, are described in Section 3.2.S.4.2 LP.8.1 {mRNA-1273.251 LNP-B}.

2.3.S.4.3 Validation of Analytical Procedures

The analytical procedures used are identical with the exception of the identity method, since this is the only method that is sequence specific. For information on validation of common methods and the validation summary of the identity testing method please refer to Section Section 3.2.S.4.3 LP.8.1{mRNA-1273.251 LNP-B}.

2.3.S.4.4 Batch Analyses

The mRNA-1273.251 LNP-B lots are intended for further manufacturing into mRNA-1273.251

Drug Product lots. Batch analysis data is generated for mRNA-1273.251 LNP-B according to approved specification and is presented in Section 3.2.S.4.4 LP.8.1 {mRNA-1273.251 LNP-B}.

2.3.S.4.5 Justification of Specification

The Justification of specification described in Section 3.2.S.4.5 {mRNA-1273 LNP-B} is applicable for mRNA-1273 LNP-B, including the current variant.

2.3.S.5 REFERENCE STANDARDS OR MATERIALS

A two-tiered reference material program has been established in accordance with ICH Q6B, Specification:

It consists of one in-house primary reference material CCI [redacted] allows for consistent bridging across working reference materials. Appropriate procedural controls are in place to define the qualification of the PRM. The procedural controls also define the qualification of CCI [redacted].

Qualification of CCI [redacted] will be performed per the pre-established qualification protocol including release and extended characterization testing are described in Section 3.2.S.5 LP.8.1{mRNA-1273.251 RNA}.

2.3.S.6 CONTAINER CLOSURE SYSTEM

The container closure system for mRNA-1273 LNP – B at the 200g nominal batch size is the same as for the original prototype, mRNA-1273 LNP. For information regarding the container closure system please refer to Section 3.2.S.6 {mRNA-1273 LNP-B}.

2.3.S.7 STABILITY

2.3.S.7.1 Stability Summary and Conclusions

The mRNA-1273 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. A shelf life of 12 months is proposed for mRNA-1273 LNP and mRNA-1273.251 LNP-B material stored in the commercial container closure defined, 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 LNP and mRNA-1273.251 LNP-B.

The product quality attribute expected to change during the manufacturing and distribution of the product mRNA purity.

The shelf-life is justified from the purity statistical model described. These and stability protocols are provided in Section 3.2.S.7.1 {mRNA-1273.251 LNP-B}.

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-B}.

2.3.S.7.3 Stability Data

Stability data available are provided in Section 3.2.S.7.3 LP.8.1 {mRNA-1273.251 LNP-B}.