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2.3.S DRUG SUBSTANCE [mRNA-1273.815 LNP-B]

2.3.S.1 General Information

This product is an mRNA-lipid complex [lipid nanoparticle (LNP)] dispersion containing CX-038839 mRNA that encodes for the prefusion stabilized Spike protein of the SARS-CoV-2 XBB.1.5 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 (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-1273.815
Drug Product name:	mRNA-1273
Synonymous name:	mRNA-1273.815 Lipid Nanoparticle (LNP), mRNA-1273.815 LNP - B

2.3.S.1.2 Structure

mRNA-1273.815 Lipid Nanoparticle (LNP) - B CCI [redacted] The molecular sequence of CX-038839is provided in Section 3.2.S.1.2 {CX-038839}CCI [redacted]

2.3.S.1.3 General Properties

General properties of mRNA-1273.815 LNP – B are listed in Table 1.

Table 1: General Properties of mRNA-1273.815 LNP-B

Description	mRNA-1273.815 LNP- B has a total RNA content of CCI and a total lipid content of CCI. The mRNA-1273.815 LNP-B is stored in CCI.
Appearance	White to off-white LNP dispersion. The mRNA-1273.815 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-1273.815 LNP-B are listed in Table 2 and Table 3.

Table 2: European Facilities and Responsibilities for Manufacture and Testing of the mRNA-1273.815 LNP-B

Facility	Address	Responsibility
Lonza AG	Lonzastrasse 3930 Visp Switzerland	• Manufacture of mRNA-1273.815 LNP- B (200 g Scale) • Quality control testing (excluding identity testing and in vitro translation testing)
Microsynth AG	Schützenstrasse 15 9436 Balgach Switzerland	• Quality control testing for identity
Eurofins Biopharma	Clogherane, Dungarven Co. Waterfold Ireland	• Quality control testing (excluding identity testing)
Laboratorios Farmacéuticos ROVI, S.A.	Avda. de la Ilustración 110 - Parque Tecnológico de Ciencias de la Salud 18016 Granada Spain	• Manufacture of mRNA-1273.815 LNP- B (200 g Scale) • Quality control testing (except identity and in vitro translation testing)
Rovi Pharma Industrial Services, S.A.	Via Complutense, 140 Alcala de Henares 28805 Madrid Spain	• Quality control testing for identity and in vitro translation
Moderna Biotech Spain S.L.	C/ Julián Camarillo n°31 28037 Madrid Spain	• Release and stability testing (all methods excluding Bioburden)

Table 3: US Facilities and Responsibilities for Manufacture and Testing of the mRNA 1273.815 LNP-B

Facility	Address	Responsibility
ModernaTX, Inc.	One Moderna Way Norwood, MA 02062 USA	• Manufacture of mRNA-1273.815 LNP-B (200g Scale) • Quality control testing (excluding bacterial endotoxin testing)
ModernaTX, Inc. (Quality Control Laboratory Annex)	210 Rustcraft Road Dedham, MA 02026 USA	• Quality control testing (excluding bacterial endotoxin and in vitro translation testing)
Associates of Cape Cod, Inc.	124 Bernard E. St. Jean Drive East Falmouth, MA 02536 USA	• Bacterial endotoxin testing

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

mRNA-1273.815 LNP-B is produced in a 200 g nominal batch size, according to the same manufacturing process described for mRNA-1273 LNP-B.

Table 4: mRNA-1273.815 Lipid Nanoparticle Item Numbers

mRNA-1273 LNP name	Item Number	Nominal Batch Size	Manufacturing Site
mRNA-1273.815 LNP-B	50186	200 g	ModernaTX, Inc. (Norwood, MA, USA)
mRNA-1273.815 LNP-B	50181	200 g	Lonza AG (Lonza Visp) (Visp, Switzerland)
mRNA-1273.815 LNP-B	50198 [a] 50199 [b]	200 g	Laboratorios Farmacéuticos ROVI, S.A. (Granada,Spain)

CCI [redacted]

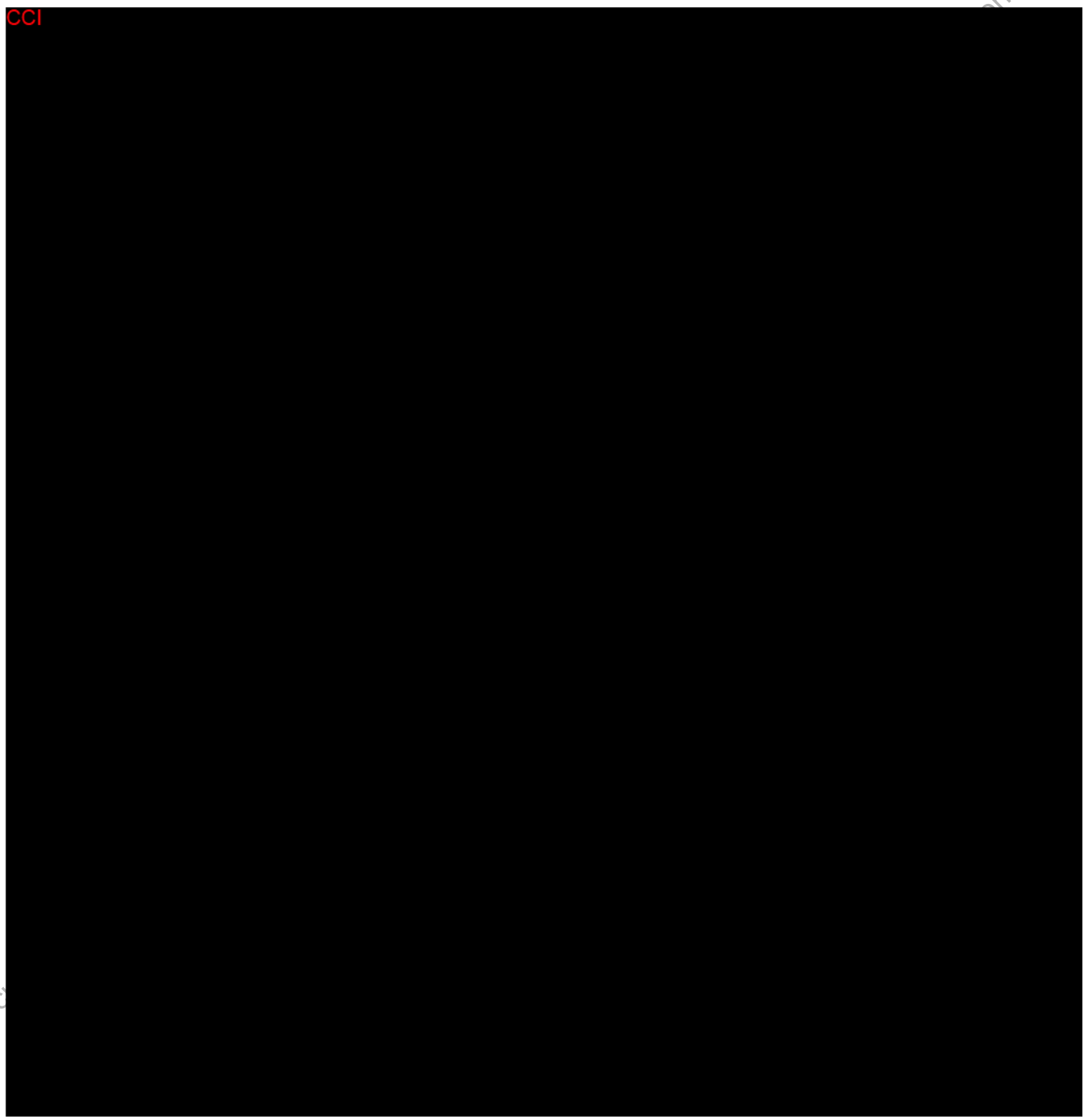
The purpose of the manufacturing process is to encapsulate mRNA within CCI [redacted] LNP, which provides biological functionality including enabling cellular uptake and endosomal escape, and to add components to stabilize the dispersion of mRNA-loaded LNPs.

The mRNA-1273.815 LNP-B manufacturing process includes encapsulation via mixing, neutralization, CCI [redacted], clarification, fill, freezing, and storage as shown in Figure 1. CCI [redacted]; the resulting mRNA-1273.815 LNP-B

dispersion is filled into bags (Section 3.2.S.6 {mRNA-1273.815 LNP-B}) for frozen storage between -60°C to -90°C until the fill/finish operation for mRNA-1273 Drug 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

Raw materials used in the manufacturing process of mRNA-1273.815 LNP-B are the same as those used in the manufacturing process of the other previous LNPs.

Descriptions of the control of materials used in the manufacture of the mRNA-1273 LNP and mRNA-1273 LNP – B are discussed in Section 3.2.S.2.3 {mRNA-1273 LNP - B}.

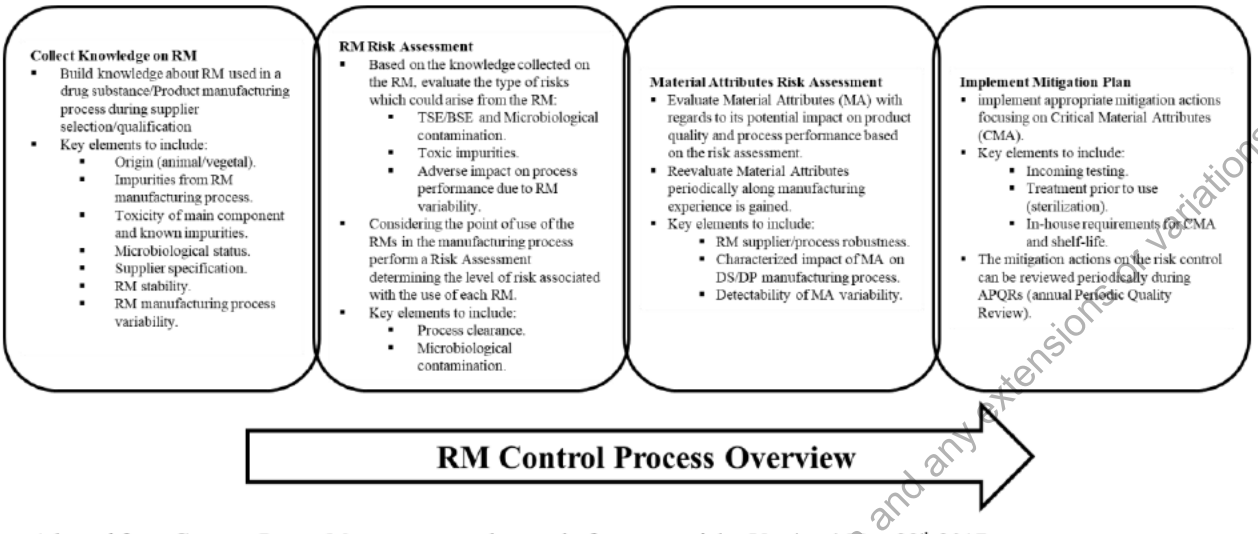
All the raw materials used for both mRNA-1273 LNP and mRNA-1273 LNP-B are similar. The only difference regarding the materials used for manufacture of both products is that the mRNA-1273 LNP CCI [redacted]

Raw Materials

Raw materials used in the production of mRNA-1273 LNP are categorized as compendial or non-compendial. Raw materials are supplied from approved vendors or suppliers and are released prior to use per controlled incoming material specifications and cGMP guidelines. At a minimum, all raw materials are confirmed to conform with CoAs or Certificates of Compliance, which includes verification of BSE/TSE safety. In addition, all non-compendial raw materials are tested for identification or other material attributes. Specifications for non-compendial materials are provided.

All incoming raw materials are stored in a GMP warehouse. An overview of the RM control process is provided in Figure 2. In instances of material transfer within the global manufacturing network, raw materials initially received at a manufacturing site and released may be transferred to another manufacturing site and received as released goods for manufacturing based on a risk-based approach that will managed through the Quality Management System accordingly.

Figure 2: Raw Material Control Process Overview



Adapted from Concept Paper: Management and control of raw materials. Version 1 Nov 29th 2017

More detailed information on the control of raw materials used in the manufacturing process of mRNA-1273.815 LNP-B is provided in Section 3.2.S.2.3 {mRNA-1273 LNP}.

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

During the mRNA-1273.815 LNP-B manufacturing process, in-process tests are performed to provide control over the inputs to the process.

The control strategy applied to the mRNA-1273.815 LNP-B material is identical to the control strategy applied to the mRNA-1273.529 LNP-B and is summarized below.

Critical Process Parameters

Critical process parameters (CPPs) and their proven acceptable range (PARs) for the mRNA-1273.815 LNP-B manufacturing process are provided in **Table 5**. Excursions outside of these established ranges are reported, investigated, and assessed by the Quality Unit per established standard operating procedures.

Table 5: mRNA-1273.815 LNP-B Critical Process Parameters

Step	CPP	Target	PAR	Rationale
CCI [redacted] CCI				

Microbial Control

The mRNA-1273.815 LNP-B manufacturing process is carried out in a Grade C manufacturing area. CCI [redacted] Manufacturing controls specifically intended for microbial control of the mRNA-1273.815 LNP-B manufacturing process are listed in Section 3.2.S.2.4 {mRNA-1273.815 LNP-B}. Note that additional microbial controls may be present. Any deviations incurred in the implementation of these microbial controls are assessed for product quality impact.

In-Process Holds

Process intermediate hold conditions are provided in respective Section 3.2.S.2.2 Description of Manufacturing Process and Process Controls: 3.2.S.2.2 Description of Manufacturing Process and Process Controls {mRNA-1273 LNP – Lonza Visp}, 3.2.S.2.2 Description of Manufacturing Process and Process Controls {mRNA-1273 LNP – Rovi Granada}, 3.2.S.2.2 Description of Manufacturing Process and Process Controls {mRNA-1273 LNP – US}, 3.2.S.2.2 Description of Manufacturing Process and Process Controls {mRNA-1273 LNP – B}.

Resin and Membrane Re-use

No resins or membranes are used in the mRNA-1273 LNPs manufacturing process.

Critical In-process Controls Testing

There are no critical in-process control tests required during mRNA-1273 LNPs manufacturing.

2.3.S.2.5 Process Validation and/or Evaluation

Process validation for mRNA-1273 LNP – 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-1273.815 LNP-B} for control strategy and Section 3.2.S.2.6. {mRNA-1273.815 LNP-B} for process development. PPQ (Phase 2) and CPV (Phase 3) are discussed in Section 3.2.S.2.5 {mRNA-1273 LNP-B}.

For mRNA-1273.815 LNP-B, the only process change is the change in mRNA sequence. One confirmatory PPQ verification lot per site was performed to demonstrate process consistency. Moderna has successfully completed PPQ verification of the mRNA-1273.815 LNP-B manufacturing process 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.

The commercial control strategy (Section 3.2.S.2.4 {mRNA-1273.815 LNP-B}) defines critical quality attributes (CQAs) and identifies 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.

Validation results are presented in Section 3.2.S.2.5 {mRNA-1273.815 LNP – B}.

Based on the outcome of the PPQ exercise, the mRNA-1273.815 LNP - B manufacturing process has been successfully validated at the 200 g scale at ModernaTX Norwood, Lonza Visp and Rovi Granada. More complete information on process validation is provided in Section 3.2.S.2.5 {mRNA-1273.815 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 LNP}.

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-1273.815 LNP-B.

Subsequent process characterization beyond that described in Section 3.2.S.2.6 {mRNA-1273 LNP} was performed for mRNA-1273.815 LNP-B (XBB.1.5), 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 LNP-B} and Section 3.2.S.2.4 {mRNA 1273.815 LNP-B}.

The comparability demonstration, including evaluation of process change impact on critical quality attributes, is included in Section 3.2.S.2.6.3 {mRNA-1273.815 LNP-B}.

The mRNA-1273.815 LNP-B (Omicron XBB.1.5) manufacturing process was successfully established at ModernaTX (Norwood, MA), Lonza (Visp, Switzerland) and Rovi (Granada, Spain) at a 200 g RNA scale. A process performance qualification (PPQ) verification batch for each manufacturing site was manufactured according to the Process Validation Master Plan and comparability was assessed against the expected ranges per DPAD-PRO-0797. More details are provided in Section 3.2.S.2.6 {mRNA-1273.815 LNP-B}.

2.3.S.3 Characterisation

2.3.S.3.1 Elucidation of Structure and Other Characteristics

As the mRNA-1273.815 LNP-B has been established as comparable to the prototype mRNA-1273 LNP-B (refer to Section 2.3.S.2.6 {mRNA-1273.815 LNP-B) and uses the same manufacturing process as the prototype mRNA-1273 LNP-B at the 200 g nominal batch size, the impurity profile will be consistent across both LNPs.

The set of analytical tests employed for the extended characterization of the mRNA-1273 LNP is detailed in Table 6. The selection of these assays was intended to complement and, in some cases, be orthogonal to the analytical data as part of lot release.

CCI

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

The lipid nanoparticle formulation for mRNA-1273.815 LNP-B is consistent with the formulation used for the prototype mRNA-1273 LNP-B. The manufacturing process for mRNA-1273.815 LNP-B is also consistent with the manufacturing process for the original prototype, mRNA-1273 LNP at the 200 g nominal batch size. Therefore, any product- or process-related impurities present in mRNA-1273.815 LNP-B would be consistent with the impurities present in the prototype mRNA-1273 LNP-B. Please refer to Section 3.2.S.3.2 {mRNA-1273.815 LNP-B} for more information.

Product-Related Impurities

Product-related impurities are molecular variants arising during manufacture or storage with properties different from those of the desired product with respect to activity, efficacy, and safety. Due to the unique mRNA 1273 LNP production process and complex molecular characteristics of the mRNA and the lipids, the mRNA-1273 LNP can also include several molecular entities or variants. These variants are formed during the manufacturing process and/or storage and have properties comparable to the desired product; therefore, they are considered product-related substances and not impurities.

Characterization of mRNA-1273 LNP identified the presence of minor amounts of product variants and degradants derived from mRNA-1273 LNP covalently linking to lipid impurities and

degradants. These adducts render mRNA inactive and thus affect the potency of the mRNA 1273 LNP. The presence, impact, and ability of the process to control such impurities are discussed. The particulate matter was demonstrated to be product-related and having no impact on the overall characteristics for the SM-102 formulated RNA, as assessed by USP <788> Method 2.

More detailed information is provided in Section 3.2.S.3.2 {mRNA-1273 LNP}.

Process-Related Impurities

There are no process-related impurities introduced to or generated during the mRNA-1273 LNP manufacturing process that are not already described in Section 3.2.S.3.2 {CX-024414} [redacted]

2.3.S.4 Control of the Drug Substance

2.3.S.4.1 Specification

The specification for mRNA-1273.815 LNP-B is described in Table 7.

Table 7: Specification for mRNA-1273.815 LNP – B

Test	Analytical Method	Acceptance Criteria
Appearance	Visual USP <631>, USP<790>, Ph. Eur. 2.2.2, 2.9.20 (SOP-0278 ModernaTX, Inc., Rovi) (CHVI-101557 Lonza AG)	White to off-white dispersion. May contain visible, white or translucent product-related particulates.
Identity	Reverse Transcription/Sanger Sequencing (SOP-1337 ModernaTX, Inc., Microsynth AG, Rovi)	Sequence matches description
Total RNA content	AEX-HPLC (SOP-0999 ModernaTX, Inc., Rovi) (GROUP-107933 Lonza AG)	[redacted]
Purity	RP-IP- HPLC (SOP-1142 ModernaTX, Inc.) (GROUP-116855 Lonza AG) (RGR-PNT-L2-611 Rovi)	
Product-related impurities		
% RNA encapsulation	Absorbance Assay (SOP-1000 ModernaTX, Inc., Rovi) (GROUP-108245 Lonza AG)	
Mean particle size	Dynamic Light Scattering (SOP-0998 ModernaTX, Inc., Rovi) (GROUP-109237 Lonza AG)	
Polydispersity		
Lipid identification		
SM-102	HPLC-CAD (SOP-1001 ModernaTX, Inc., Rovi) (GROUP-107937 Lonza AG)	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., Rovi) (GROUP-107937 Lonza AG)	[redacted]
Cholesterol		
DSPC		

Test	Analytical Method	Acceptance Criteria
PEG2000-DMG		CCI
Lipid impurities	HPLC-CAD (SOP-1001 ModernaTX, Inc., Rovi) (GROUP-107937 Lonza AG)	Individual impurities: CCI Total impurities:
In Vitro Translation	Methionine labelling (SOP-0937 Moderna Tx, Inc., Rovi) Eurofins Biopharma SOP-0937)	CCI
pH	USP <791>, Ph. Eur. 2.2.3 (SOP-0288 ModernaTX, Inc., Rovi) (CHVI-82391 Lonza AG)	
Osmolality	USP <785>, Ph. Eur. 2.2.35 (SOP-0279 ModernaTX, Inc., Rovi) (CHVI-50752 Lonza AG)	
Bacterial endotoxin	USP <85>, EP 2.6.14 (M-CTS-CS-0929 Associates of Cape Cod) (CHVI-6303 Lonza AG) (RGR-PNT-L2-556 Rovi)	
Bioburden	USP <61>, EP 2.6.12 (SOP-0480 ModernaTX, Inc.) (CHVI-8889 Lonza AG) (RGR-PNT-L2-526 Rovi)	

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 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-1273.815 LNP-B and the prototype mRNA-1273 LNPs 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-1273.815 LNP-B identity method is provided in Section 3.2.S.4.2 {mRNA-1273.815 LNP-B}.

2.3.S.4.3 Validation of Analytical Procedures

The analytical methods used for release testing of the prototype mRNA-1273 LNPs and mRNA-1273.815 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-1273.815 LNP-B is provided in Section 3.2.S.4.3 {mRNA-1273.815 LNP-B}.

2.3.S.4.4 Batch Analyses

The mRNA-1273.815 LNP-B GMP lots are intended for further manufacturing into mRNA-1273.815 Drug Product lots. Batch analysis data is generated for mRNA-1273.815 LNP-B according to an approved specification and is presented in Section 3.2.S.4.4 {mRNA-1273.815 LNP-B}.

2.3.S.4.5 Justification of Specification

The Justification of specification is described in Section {mRNA-1273 LNP} for all methods except for Identity by reverse transcription Sanger sequencing for the RNA region of interest, which is described in Section 3.2.S.4.5 {mRNA-1273.529 LNP- B}. This test method can unambiguously distinguish prototype and variant mRNAs used in the manufacture of monovalent and bivalent mRNA-1273 drug products.

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 CQA 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.

Table 8 summarizes the CQAs and the corresponding justifications for the mRNA 1273 LNP (prototype and associated variant LNPs) based on risk assessment performed and process and product characterization knowledge gained for mRNA-1273 and general SM-102 lipid formulated drug product with other mRNAs.

Table 8: Critical Quality Attribute Assessment for mRNA-1273.815 LNP-B

Quality Attribute	Classification	Justification
Appearance	CQA	CCI [redacted]
Identity (mRNA)	CQA	
Identity (Lipids)	CQA	
pH	CQA	
Osmolality	CQA	
Bacterial Endotoxins	CQA	
Bioburden	CQA	

Quality Attribute	Classification	Justification
RNA Content	CQA	CCI [redacted]
RNA Purity	CQA	
RNA Impurities (Product-related)	CQA	
% RNA Encapsulation	CQA	
Particle Size	CQA	
Polydispersity	CQA	
Lipids Content	CQA	
Impurities (Lipid-related)	CQA	
In Vitro Translation (IVT)	CQA	

CCI [redacted]

The rationale for the establishment and justification of the release specification is provided in Section 3.2.S.4.5 {mRNA-1273 LNP-B} and Section 3.2.S.4.5 {mRNA-1273.529 LNP- B}.

2.3.S.5 Reference Standards or Materials

The reference standard for the mRNA-1273.815 Lipid Nanoparticle (LNP) – B is the same as for the prototype mRNA-1273 LNP. For information on the reference standard refer to Section 3.2.S.5 {mRNA-1273 LNP}.

2.3.S.6 Container Closure System

The container closure system for mRNA-1273.815 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}.

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-1273.815 LNP-B material stored in the commercial container closure defined in Section 3.2.S.6 {mRNA-1273.815 LNP-B}, 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-1273.815 LNP-B.

The product quality attribute expected to change 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 protein expression. Direct measure of mRNA degradation utilizing the mRNA purity assay by RP-IP-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 CX-024414 and CX-038839 mRNA have approximately the same overall length (~4,000 nt), a similar rate of degradation is expected across these mRNA-1273 LNP and mRNA-1273.815 LNP-B.

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.

The shelf life is justified from the purity analysis including purity degradation rates at different temperatures, which is described in detail in Section 3.2.S.7.1.1 {mRNA-1273.529 LNP-B}.

mRNA-1273.815 LNP-B Scale B PPQ verification lots manufactured using the process described in Section 3.2.S.2.2 {mRNA-1273.815 LNP-B}, were placed on stability studies.

Stability samples are stored in a scaled-down container closure system (50-mL CCI 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-1273.815 LNP-B}. The data from the stability studies are presented in Section 3.2.S.7.3 {mRNA-1273.815 LNP-B}.

Table 9: mRNA-1273.815 LNP-B Supporting Stability Program Lots

Lot	Product	Purpose	Manufacturing Site	Lot Size	Fill Volume	Container Closure	Conditions	
							Temperature [a]	Duration
DH-78330.2	mRNA-1273.815 LNP – B	Development	ModernaTX (Norwood, MA)	CCI	6.0 mL	50 mL CCI Bag	-70°C (-90°C to -60°C)	48 months
							5°C (2°C to 8°C)	6 months
							25°C (20°C to 30°C)	3 months

Table 10: mRNA-1273.815 LNP-B Registration Stability Program Lots

Lot	Product	Purpose	Manufacturing Site	Lot Size	Fill Volume	Scale	Process Train	Container Closure	Conditions	
									Temperature	Duration
5018623001	mRNA-1273.815 LNP - B	PPQ Comparability	ModernaTX (Norwood, MA)	200 g	15 mL	B	1	50 mL CCI bag	-70°C±10°C	36 months
									5 ± 3°C	2 months
5018123001 (Lonza lot 1114001)	mRNA-1273.815 LNP - B	PPQ Comparability	Lonza Visp, Switzerland	200 g	30 mL	B	11	50 mL CCI bag	-70°C±10°C	36 months
									5 ± 3°C	2 months
5019823001 (Rovi lot 1148100123)	mRNA-1273.815 LNP - B	PPQ Comparability	Rovi Granada, Spain	200 g	30 mL	B	10	50 mL CCI bag	-70°C±10°C	36 months
									5°C ± 3°C	2 months

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-1273.815 LNP-B}.

2.3.S.7.3 Stability Data

All stability data available are provided in Section 3.2.S.7.3 {mRNA-1273.815 LNP-B}.