

**CBER CMC BLA  
Review Memorandum**

**BLA STN 125796**

**MRESVIA**

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1. **BLA#:** STN 125796/0

2. **ModernaTX, Ind., License #2256**

3. **PRODUCT NAME/PRODUCT TYPE**

Non-proprietary name: Respiratory Syncytial Virus Vaccine (mRNA-1345)

Proprietary name: MRESVIA

4. **GENERAL DESCRIPTION OF THE FINAL PRODUCT**

MRESVIA is a vaccine that consists of lipid nanoparticles (LNPs) that encapsulate linear mRNA (mRNA-1345) provided as a single-dose, preservative-free, white to off-white, liquid suspension in a prefilled, sterile, 1 mL cyclic olefin copolymer (COC) syringe with plastic tip cap and fluoropolymer-coated, halobutyl plunger stopper. The mRNA encodes the nucleotide sequence for the respiratory syncytial virus (RSV) fusion protein engineered to contain mutations that stabilize the protein antigen in the prefusion conformation when expressed *de novo* following immunization and translation *in vivo*.

(b) (4)

The lipid nanoparticle contains four lipids: SM-102 (a custom-manufactured ionizable lipid); PEG-2000-DMG, cholesterol, and 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) that encapsulate, protect, and facilitate mRNA uptake by cells after administration. The vaccine is administered intramuscularly as 0.5mL targeted to contain ~50mcg of mRNA-1345 per dose in 20mM Tris buffer (composed of Tromethamine and Tromethamine-HCl), 87g/L sucrose, and (b) (4) mM acetate at (b) (4). The vaccine is indicated for active immunization of adults 60 years of age and older for the prevention of lower respiratory tract disease (LRTD) due to RSV.

5. **MAJOR MILESTONES**

Date of submission Part 1:	June 28, 2023 (Module 3 and Module 4)
Date of submission Part 2:	September 12, 2023, (Module 5)
Filing date:	November 9, 2023
Midcycle meeting:	December 27, 2023
Midcycle communication:	January 3, 2024
Late cycle meeting:	February 26, 2024
Late cycle communication:	March 11, 2024
VRBPAC	Meeting not required.
ADD:	May 31, 2024,

6. **CMC/QUALITY REVIEW TEAM**

Reviewer/Affiliation	Section/Subject Matter
Judy Beeler/OVRR/DVP	Module 3 all sections except those pertaining to assay validation 32S DS: RNA-100-AR02

Reviewer/Affiliation	Section/Subject Matter
	32S DS: SM-102 32S DS: mPEG2000-DMG 32S DS: (b) (4) 32S DS: LNP-100-AR02 32P DP: mRNA-1345 Appendices
R. Lynne Crim/OVRR/DVP	Module 4: Non-clinical pharmacology testing Module 5: Clinical assays for RSV
Alena Dabrazhynetskaya/OVRR/DVP	Module 3: The platform approach to review of quality assays and method validation reports for (b) (4) tests are summarized in the Introduction. Information pertaining to individual test methods are described in the following sections: 32S DS: RNA-100-AR02 32S DS: (b) (4) 32S DS: LNP-100-AR02 32P DP: mRNA-1345
Andrea Gray CBER/ORO/DROP/RPB	Module 3: DP: Review of prefilled syringe and device verification report; see separate review memo.

**7. INTER-CENTER CONSULTS REQUESTED:** None

**8. SUBMISSION(S) REVIEWED**

Date Received	Submission	Comments/ Status
6/28/2023	STN 125796/0	Original submission Module 3 and 4
11/13/2023	STN 125796/9	Responses to CMC IR #5; Comments on Module 3, RNA-100-AR02 DS, SM-102 DS, PEG2000-DMG DS and (b) (4)
1/24/24	STN125796/23	Response to IR#15 Clarification of testing responsibilities and analytical methods (AD)
2/22/24	STN 125796/35	Response to IR#25 Method transfer validation report. (AD)
2/28/2024	STN 125769/39	Responses to CMC IR #23; comments on Module 3, DS LNP-100-AR02 and mRNA1345 DP.
3/19/2024	STN 125796/49	Response to CMC IR Q19 in IR #23: PVR-DP-11094 Version 3.0
4/5/2024	STN 125796/54	Response to CMC IR # 35 Comments on Module 3

**9. Referenced REGULATORY SUBMISSIONS**

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
IND 23342	ModernaTX, Inc.	mRNA-1345	NA	IND for mRNA-1345
MF (b) (4)	(b) (4)	(b) (4) Pre-fillable Syringes	Yes	Permission to cross-reference CDER MF. See section 32P7. No need to review DMF since information pertinent to the PFS is included in the BLA.
MF (b) (4)	(b) (4)	1,2 distearoyal- sn-glycero-3-phosphocholine (DSPC)	Yes	Permission to cross reference MF; No need to review MF since information pertinent to DSPC is included in the BLA.
MF (b) (4)	(b) (4)	Elastomeric Formulations, Coating and Films. Piston plunger (b) (4) gray	Yes	Permission to cross reference file section 32P7. No need to review DMF since information pertinent to the plunger is included in the BLA.
Type III DMF MF (b) (4)	(b) (4)	(b) (4) syringe	Yes	Permission to cross-reference MF. No need to review DMF since information pertinent to the PFS is included in the BLA.

**10. REVIEWER SUMMARY AND RECOMMENDATION****A. EXECUTIVE SUMMARY**

This review encompasses all CMC-related information in Module 3 of BLA 125796 and additional information submitted in multiple BLA amendments. The memo also summarizes the review of non-clinical pharmacology studies that support vaccine effectiveness and assess risk for enhanced disease (Module 4) and the review of the validation of clinical assays supporting case confirmation testing for clinical efficacy and immunogenicity endpoints (Module 5).

***Chemistry, Manufacturing, and Controls***


MRESVIA (code, mRNA-1345) is a nucleoside modified messenger RNA (mRNA)-based vaccine indicated for active immunization for the prevention of lower respiratory tract disease caused by Respiratory Syncytial Virus (RSV) in individuals 60 years of age and older.

The manufacturing process for the DS consists of (b) (4) main steps: (b) (4)

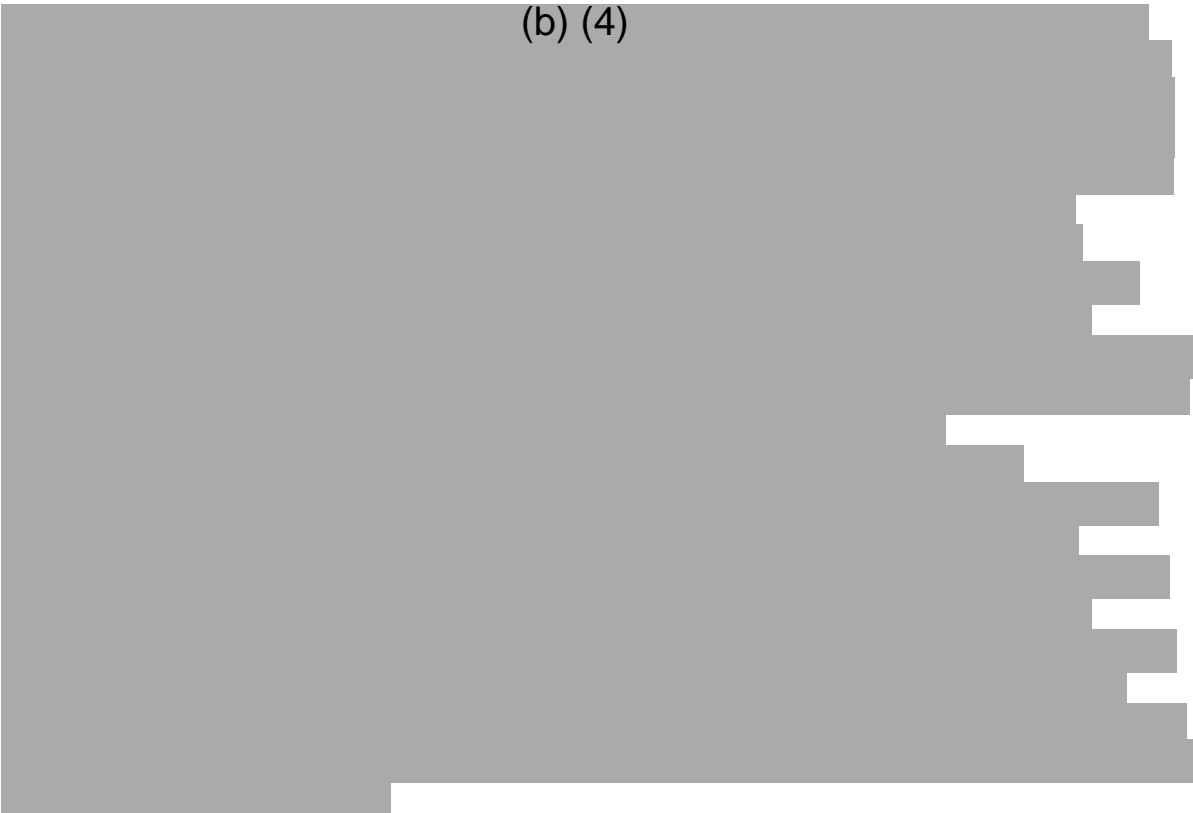
The DP (mRNA-1345) is manufactured by adjusting the concentration of the LNP-100-AR02 to the target RNA dose and formulation with a cryoprotectant, followed by sterile filtration, filling into syringes, labeling and packaging. To support the BLA, process performance qualification (PPQ) data and results of in-process, release, extended-characterization, and stability testing for (b) (4) DP mRNA-1345 (b) (4) lots were provided for each manufacturing facility.

The MRESVIA manufacturing process went through several process upgrades during product development to align the formulation with that intended for commercial production and to increase scale to achieve capacity.

(b) (4)



(b) (4)



Manufacture of the DP went through (b) (4) process upgrades. Changes included (b) (4)



(b) (4). The commercial process was moved to the (b) (4) facility and includes two options for packaging and labeling activities. In Process Flow 1, following filling and visual inspection, the PFS are moved to (b) (4) for a (b) (4) before being returned to (b) (4) for assembly, labeling and packaging activities. In contrast, using Process Flow 2, following visual inspection, the PFS are assembled, labeled, and packaged immediately before transfer to (b) (4) for (b) (4) and long-term, storage. Analytical comparability of the DP showed that clinical lots (manufactured at ModernaTX) and commercial lots (manufactured at (b) (4)) were similar. MRESVIA lots were compared to the acceptance criteria set using (b) (4) SPIKEVAX lots. This analysis demonstrated that the two products were similar in quality.

The date of manufacture for MRESVIA is defined as the date of labeling and packaging of PFS.

The analytical procedures developed and used for release and stability testing of intermediates, (b) (4) DP include tests to ensure vaccine safety, identity, purity, quality, and potency. These methods are identical to the methods used to release SPIKEVAX and are performed according to standard operating procedures (SOPs). Accordingly, a platform approach was used to validate sequence agnostic test methods for quality control and release of the MRESVIA (b) (4) DP. This summary, shown in the Introduction to Module 3, verifies that each method was adequately validated at all sites proposed for the release and stability testing through analytical method validation or by a method transfer protocol. Validation results demonstrated acceptable precision, accuracy, sensitivity, specificity, and reproducibility indicating the assays are suitable for product quality control.

### ***Non-clinical Pharmacology Studies***

Non-clinical testing in mice and cotton rats demonstrated that MRESVIA was immunogenic, that immunity following immunization protected lungs against a live RSV challenge and was not associated with enhanced disease.

### ***Clinical Assays***

The FDA-cleared, CE-marked (b) (4) kit test was used for RSV clinical case confirmation in Phase 3 trial mRNA-1345-P301. Testing was performed in (b) (4) in the USA, the Netherlands, and Singapore. (b) (4) assays were performed at (b) (4) in the Netherlands. (b) (4) assays are used to measure anti-RSV-preF and -post F IgG responses in serum at (b) (4) in (b) (4). The (b) (4) assays and (b) (4) assays are validated and suitable for their intended purposes. An (b) (4) assay uses (b) (4) to measure (b) (4) and is performed in Moderna Research Laboratories in (b) (4).

**B. RECOMMENDATION**

**I. We recommend APPROVAL.**

**II. COMPLETE RESPONSE (CR): No CMC deficiencies noted.**

**III. SIGNATURE BLOCK**

<b>Reviewer/Title/Affiliation</b>	<b>Signature and Date</b>
Judy Beeler/Medical Officer/LPRVD/DVP/OVRR	
R. Lynne Crim/Biologist/LPRVD/DVP/OVRR	
Alena Dabrazhynetskaya/LDNAV/DVP/OVRR	
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Sara Gagneten/Biologist/IOD/DVP	
Robin Levis/Deputy Director/DVP/OVRR	
Jerry Weir/Director/DVP/OVRR	

# Abbreviations

µg Microgram

(b) (4)

APS Aseptic Process Simulations

ATP Adenosine-5'-triphosphate

C Characterization

(b) (4)

CCS Container Closure System

CFU Colony Forming Unit

CIPC Critical In-process Control

CoA Certificate of Analysis

CPA Critical Process Attribute

CPD Cumulative Process Duration

CPP Critical Process Parameter

CPV Continuous Process Verification

CQA Critical Quality Attribute

CRT Controlled Room Temperature

CS Calibration Standard

(b) (4)

(b) (4)

CV Coefficient of variation

(b) (4)

(b) (4)

DNA Deoxyribonucleic acid

DP Drug Product

DS Drug Substance

DTT Dithiothreitol

(b) (4)

(b) (4)

(b) (4)

EOPC End of production cell

EOSL End of shelf life

(b) (4)

EUA Emergency Use Authorization

(b) (4)

FC Final container

(b) (4)

GCV Geometric coefficient of variation

GMC Geometric mean concentration

GMP Good Manufacturing Practice

(b) (4)

HCP Host Cell Protein

HDPE High density polyethylene

Hg Mercury

(b) (4)

(b) (4)

(b) (4)

IC Internal control

(b) (4)

(b) (4)

IPA Isopropyl alcohol

IPC In-process Control

(b) (4)

(b) (4)

(b) (4)

(b) (4)

LLOD Lower Limit of Detection

LLOQ Lower Limit of Quantitation

LNP Lipid Nanoparticle

LOB Limit of blank

LOQ Limit of Quantitation

LRF Log Reduction Factor

LRTD Lower respiratory tract disease

(b) (4)

(b) (4)

(b) (4)

MCB Master Cell Bank

mg Milligram

(b) (4)

MVR Method Validation Report

NA Not Applicable

Nab Neutralizing antibody.

(b) (4)

NLT Not less than

NMT Not more than

(b) (4)

(b) (4)

PAR Proven Acceptable Ranges

(b) (4)

PCR Polymerase chain reaction

PDE Permissible Daily Exposure

(b) (4)

(b) (4)

(b) (4)

PE Process evaluation

(b) (4)

(b) (4)

PM Process monitoring

(b) (4)

PPQ Process Performance Qualification

PVU Personal Vaccine Unit

QC Quality Control

QD Quality Decision

QR Quality Release

RNA Ribonucleic acid

ROI Region of Interest

(b) (4)

(b) (4)

(b) (4)

(b) (4)

RSD Relative Standard Deviation

RT-qPCR Quantitative Reverse Transcription-Polymerase

Chain Reaction

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

SST System Suitability Tests

(b) (4)

SUM Single use mixing

(b) (4)

TAR Target Acceptable Range

(b) (4)

TCS Temperature cycling studies

(b) (4)

(b) (4)

(b) (4)

(b) (4)

TOR Time Out of Refrigeration

TRA Technical Risk Assessment

(b) (4)

TSE Transmissible Spongiform Encephalopathy

ULOQ Upper Limit of Quantitation

(b) (4)

(b) (4)

(b) (4)

WCB Working Cell Bank

WFI Water for injection



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### **Module 3**

#### **INTRODUCTION**

This BLA submission for MRESVIA contains information pertaining to the manufacture of five Drug Substance intermediates including RNA-100-AR02, SM-102, PEG2000-DMG, (b) (4), and LNP-100-AR02. **AR02** is the product code designated for mRNA-1345 containing the nucleotide sequence for RSVpreF protein with the (b) (4). **100** is the code for the vaccine manufacturing process used to produce the RNA DS intermediate, (b) (4), and the lipid nanoparticle (LNP), that is a combination of the two intermediates.

The Drug Product is referred to by the simple name "mRNA-1345 DP" and/or by RNA-100 process names UDP-100-AR02 and LDP-100-AR02, for the unlabeled and labeled Drug Product, respectively. Manufacturing sites used during development and for commercial production are shown in **Table 1** below.

**Table 1. Manufacturing Sites used for *Clinical Lots (in italics)* and Commercial Product (bolded):**

Component/ Starting Material	Site 1	Site 2	Site 3	Site 4
(b) (4)	(b) (4)			
DS: RNA-100-AR02	<b>ModernaTX</b> , (b) (4)			
DS: SM-102	(b) (4)	(b) (4)		
DS: PEG2000-DMG	(b) (4)	(b) (4)	(b) (4)	(b) (4)
DS: (b) (4)	<b>ModernaTX</b> , (b) (4)	(b) (4)		
DS: LNP-100-AR02	<b>ModernaTX</b> , (b) (4)	(b) (4)	(b) (4)	
UDP-100-AR02	(b) (4)	(b) (4)	(b) (4)	
LDP-100-AR02	(b) (4)	(b) (4)	(b) (4)	

### Platform Validation of the Manufacturing Process

ModernaTX manufactures all mRNA vaccines according to the 100 process, using similar process steps, equipment, materials, with similar or identical in-process parameters, proven acceptable ranges and with common release specifications for attributes that are not dependent on RNA sequence or length. Accordingly, ModernaTX proposes to use a platform validation approach to support manufacture of vaccine-100 products based on process performance qualification of (b) (4) lots of (b) (4) RNA vaccine per manufacturing site followed by process performance qualification for (b) (4) lot for each new RNA vaccine per manufacturing site. This platform approach to process validation was introduced to support the manufacture of MRESVIA RNA-100-AR02 DS at ModernaTX, (b) (4); manufacture of (b) (4) at the (b) (4) facility in (b) (4); manufacture of LNP-100-AR02 at (b) (4); and manufacture of the DP at (b) (4) in (b) (4). The details of the individual process performance qualification for MRESVIA at each manufacturing stage are reviewed in each related section of Module 3. Terms of reference and nomenclature for the commercial mRNA-1345 vaccine-100 process are shown in **Table 2** below:

**Table 2. Terms of Reference for Intermediates, Drug Substance, and Drug Product.**

(b) (4)
---------

### Platform Validation of Analytical Procedures

Likewise, ModernaTX uses a common set of release assays to evaluate and monitor critical quality attributes (CQA) at each stage of the manufacturing process. Since many attributes are independent of RNA sequence, the methods used to assess these CQAs are considered RNA agnostic and validation does not require a reassessment for each new RNA tested. Accordingly, a platform approach was applied for validation of assays known to be RNA agnostic. Methods validated at one site were transferred to other testing sites using a Method Transfer Study described in individual Method Transfer

Reports. Evaluation of CQAs that are dependent on (b) (4)

(b) (4) were validated for each new RNA. In summary, RNA agnostic methods were validated using mRNA-1273 under the platform approach and RNA sequence dependent assays for MRESVIA were validated using mRNA-1345; a summary of the approach used for each assay is given below.

This section covers the quality-control tests performed on the following mRNA-1345 materials:

- RNA-100-AR02,
- (b) (4)
- LNP-100-AR02, and
- mRNA-1345 DP or UDP-100-AR02 and LDP-100-AR02.

All (b) (4) and (b) (4) quality-control methods for in-process, release and stability testing of mRNA-1345 materials are performed in the qualified QC laboratories as referred in **Tables 6, 64, 93, and 113** of this memo.

ModernaTX utilizes a platform approach for the quality testing of different mRNA products with similar composition and biochemical characteristics. This platform approach applies to methods that do not have to be significantly changed when used to test different mRNA products, that is, operating conditions, system suitability and reporting of results are the same or only slightly adjusted. The platform analytical methods were performed consistently for multiple mRNA vaccines in ModernaTX's infectious-disease portfolio, including commercial, clinical, and investigational products. These procedures were utilized for analytical testing of GMP and registration (PPQ) lots of RNA-100-AR02 (RNA), (b) (4), LNP-100-AR02 (DS), and mRNA-1345 DP (DP) (UDP-100-AR02 and LDP-100-AR02) and will continue to be used for testing all future commercial scale lots.

The use of platform methods for mRNA-1345 testing was verified based on a combination of method-validation data obtained using both mRNA-1273 (SPIKEVAX) and mRNA-1345 (MRESVIA) materials. These two vaccines share common manufacturing processes and process controls, and comparison of the RNA, (b) (4), LNP DS, and DP characteristics revealed compositional, biochemical, and biophysical consistency of mRNA-1345 and mRNA-1273. Since the primary differences between these two vaccines are the mRNA length ((b) (4) nt for mRNA-1273 and (b) (4) nt for mRNA-1345) and mRNA sequence, the mRNA-1345-specific validations were performed only for those methods for which the product-specific parameters must be confirmed.

The necessity of product-specific validation for each platform method performed on RNA, (b) (4), LNP DS, and DP release was additionally confirmed based on product-specific reference material or assay-control materials. Reference materials served as a comparator against which the test sample results are calculated, while assay controls were used to assess system performance parameters and assay validity criteria. **Table 3** below provides a summary of the platform-analytical methods identified as sequence agnostic or sequence specific.

**Table 3. Summary of Platform Analytical Methods Used for Testing the (b) (4) DP**

Test Method	RNA agnostic vs. RNA specific assays	ModernaTX SOP#	(b) (4)	Product Specific Reference Material	Product Specific Assay Control	Product Agnostic Assay Control
Identity by (b) (4)	Specific	1019	(b) (4)	X		X
Identity by (b) (4)	Specific	1337		X		X
(b) (4)	Agnostic	0995				X
Total RNA Content by (b) (4)	Agnostic	0999		X		
(b) (4)	Agnostic	0997				X
(b) (4)	Agnostic	0994				X
(b) (4) by (b) (4)	Agnostic	1000				X
mRNA Purity/Impurities by (b) (4)	Specific	1142			X	
Lipid Identity/Content /Impurities by (b) (4)	Agnostic	1001				X
(b) (4) by (b) (4)	Agnostic	0998				X
(b) (4)	Specific	0937				X

√ - Release test method used for specific mRNA-1345 material testing;

(b) (4)

**Note:** The Lipid Identity/Content/Impurities by (b) (4) (SOP-1001) and (b) (4) by (b) (4) (SOP-0998) methods used for the (b) (4) DP testing are not affected by mRNA-1345-specific materials and, therefore, are not covered in this memo. Tests for lipid identity, content and impurities that are common for to the release of (b) (4) DP are described below. The description of additional analytical procedures developed for testing (b) (4) critical quality attributes and details on the validation can be found in the BLA 125752 CMC review memos from DVP and DBSQC reviewers.

Prior to implementation, all (b) (4) analytical procedures validated using mRNA-1273 material testing and revised for testing mRNA-1345 were additionally assessed to confirm their compliance with the quality-management system. Based on the assessment, no significant updates were made to these methods, and no impact on method performance or validation was identified.

The status of each platform-analytical method validation across the QC facilities qualified for the mRNA-1345 materials is presented in **Table 4**.

**Table 4. Summary of Platform Analytical Methods Validation for Release and Stability Testing of mRNA-1345 materials.**

Test Method	(b) (4)	mRNA-1345 DP	ModernaTX	(b) (4)	(b) (4)	(b) (4)
Identity by (b) (4)	(b) (4)		QC-MVR-0057	N/A	N/A	N/A
Identity by (b) (4)		√	QC-MVR-0058	N/A	N/A	AST-CMO-0391

# RSV-preF vaccine, mRNA-1345, MRESVIA

Test Method	(b) (4)	mRNA-1345 DP	ModernaTX	(b) (4)	(b) (4)	(b) (4)
Total RNA content by (b) (4) (SOP-0995)	(b) (4)		QC-MVR-0003	MQR-0358	N/A	N/A
Total RNA content by (b) (4) (SOP-0999)	(b) (4)	√	QC-MVR-0008	N/A	AST-CMO-0049	EXT-1505
(b) (4)	(b) (4)		(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)		(b) (4)	(b) (4)	(b) (4)	(b) (4)
RNA purity/Product-related Impurities by (b) (4) (SOP-1142)	(b) (4)	√	QC-MVR-0025 QC-MVR-0061	QC-MVR-0025 v2	AST-CMO-0441	AST-CMO-0142
Lipid Identity/ Content/ Impurities by (b) (4) (SOP-1001)	(b) (4)		QC-MVR-0010	MQR-281	AST-CMO-0056	EXT-1506
(b) (4)	(b) (4)		(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	√	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	√	(b) (4)	(b) (4)	(b) (4)	(b) (4)

N/A – the test is not performed at the testing site;

ROI – Region of Interest;

Validation of (b) (4) analytical procedures and verification of (b) (4) analytical procedures (e.g., (b) (4), extractable volume, (b) (4) endotoxin, bioburden, sterility, and container-closure integrity) for release testing of mRNA-1345 materials were performed at the appropriate testing sites. **The description of (b) (4) and (b) (4) analytical procedures developed for testing mRNA-1273 products and details on their validation or verification can be found in the BLA 125752 CMC review memos from DVP and DBSQC reviewers.** The current memo covers method-validation results for (b) (4) methods used for mRNA-1345 materials and qualification data for method transfer to the additional testing sites.




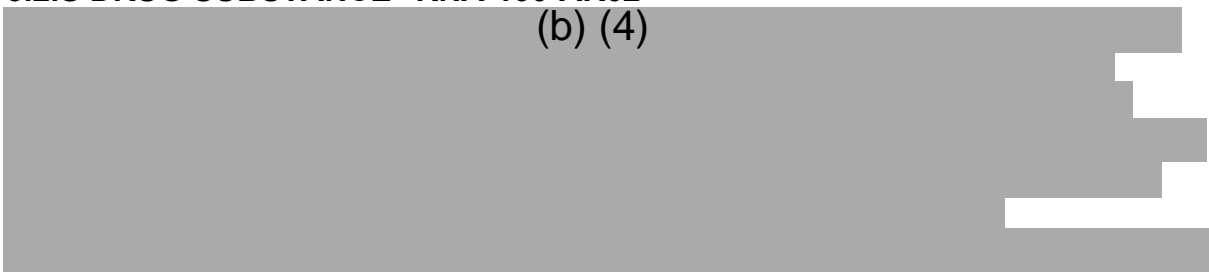
Validations of the following (b) (4) assays are described under the section for DS intermediate RNA-100-AR02, 3.2.S.4.2, Analytical Procedures and 3.2.S.4.3, Validation of Analytical Procedures: (b) (4)

. Validation of the assays used to evaluate (b) (4) are described under the section for DS intermediate (b) (4), 3.2.S.4.2, Analytical Procedures and 3.2.S.4.3, Validation of Analytical Procedures. Validation of all other assays are described under the section for DS LNP-100-AR02, 3.2.S.4.2, Analytical Procedures and 3.2.S.4.3, Validation of Analytical Procedures. The results provided in the submission confirm that all analytical methods used for in-process, release and stability testing across the qualified QC facilities are suitable for testing (b) (4) and UDP- and LDP-100-AR02 DP materials.



**3.2.S DRUG SUBSTANCE<sup>1</sup> RNA-100-AR02**

(b) (4)



148 pages have been determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

### 3.2.P DRUG PRODUCT<sup>5</sup> mRNA-1345

#### 3.2.P.1 Description and Composition of the Drug Product

mRNA-1345 Drug Product (DP) is a white to off-white suspension of nanoparticles composed of four lipids: SM-102, (a custom, ionizable lipid), cholesterol, DSPC (1,2 distearoyl-sn-glycero-3-phosphocholine) and PEG2000-DMG (1,2-dimyristoyl-rac-glycerol-3-methoxypolyethylene glycerol 2000) that protect and deliver mRNA that encodes for the RSV-F protein stabilized in the prefusion conformation in a 20 mM Tris buffer containing 87 g/L sucrose as a cryoprotectant and (b) (4) mM acetate buffer at (b) (4)

(b) (4). mRNA-1345 DP is supplied as sterile, single-dose, ready-to-use liquid solution in a 1mL prefilled syringe for IM injection. Each prefilled syringe contains approximately (b) (4)mL to ensure delivery of a 0.5mL dose containing 50 mcg of mRNA with approximately 1 mg of total lipids. DP composition per mL and per unit dose and properties of the prefilled syringe are shown in **Tables 105** and **106** below.

**Table 105. mRNA-1345 DP Composition (50mcg RNA per Dose)**

Component	Grade	Function	Unit formula mg/mL	Unit Formula mg/dose (0.5mL)
RNA-100- AR02	Custom	Encodes of RSVpreF protein	0.10	0.050
SM-102	Custom (b) (4)	Component of LNP	(b) (4)	(b) (4)
Cholesterol	(b) (4)	Component of LNP	(b) (4)	(b) (4)
DSPC	(b) (4)	Component of LNP	(b) (4)	(b) (4)
PEG2000-DMG	Custom (b) (4)	Component of LNP	(b) (4)	(b) (4)
Tris /Tromethamine	(b) (4)	Component of Tris buffer	0.50	0.25
Tris HCL	Non-compendial	Component of Tris buffer	2.5	1.2
Acetic Acid ((b) (4))	(b) (4)	Components from acetate buffer in RNA and LNP	0.043	0.021
Sodium acetate trihydrate	(b) (4)	Components from acetate buffer in RNA and LNP	0.20	0.10
Sucrose	(b) (4)	Cryoprotection	87	44
WFI	(b) (4)	Diluent	a.s. to 1.0mL	a.s. to 0.5mL

**Abbreviations:** DSPC, 1,2-distearoyl-sn-glycero-3-phosphocholine; PEG2000-DMG, 1,2-dimyristoyl-rac-3-methoxypropylglycerol-2000; LNP, lipid nanoparticle, (b) (4) WFI, water for injection, q.s. quantum sufficient, mL, milliliter, mg, milligram.

**Table 106. mRNA-1345 DP in Prefilled Syringes**

RNA dose	50 mcg RNA
Syringe	1 mL cyclic olefin copolymer, COC, barrel with halo-butyl rubber tip-cap in a rigid plastic cover.
Plunger rod	Polypropylene 1mL long
Plunger/stopper	Halo-butyl rubber plunger with fluoropolymer coating on product contact surface
Dose/syringe	Single dose, 0.5mL
Long term storage	-40°C to -15°C
Needle	<i>Not supplied by ModernaTX; appropriately sized luer-lock needle supplied by the health care provider at the time of administration</i>

**Abbreviations:** DP, Drug Product; mcg, microgram; mL, milliliter.

### 3.2.P.2 Pharmaceutical Development of mRNA-1345 DP

### 3.2.P.2.1 Components of the Drug Product

### 3.2.P.2.1.1 Drug Substance

(b) (4)

(b) (4)

**3.2.P.2.1.2 Excipients**

Excipients include Tris buffer and sucrose.

**Tris buffer** is composed of tromethamine and Tris HCl and is used to (b) (4)

(b) (4). Tris buffer has adequate buffering capacity and maintains the (b) (4) over a wide range of temperatures optimizing product stability. **Sucrose** is used as a cryoprotectant.

**3.2.P.2.2 Drug Product mRNA-1345****3.2.P.2.2.1 Formulation Development**

The manufacture of the DP has been through (b) (4) process upgrades from (b) (4) Generation, through (b) (4) Generation to the Commercial process. Formulation adjustments were minor as described in Section 3.2.P.2.3 below and summarized in **Table 107** below.

**Table 107. Comparison of Clinical and Commercial DP Formulations**

Component	Commercial mg/mL/[mM]
RNA-100-AR01	-
RNA-100-AR02	0.10
SM102	(b) (4)
Cholesterol	(b) (4)
DSPC	(b) (4)
PEG2000-DMG	(b) (4)
Tromethamine (Tris)	0.50 / [4.2]
Tris HCl	2.5 / [16]
Acetic Acid	0.043 / [0.71]
Sodium acetate trihydrate	0.20 / [1.4]
DTPA	NA
Sucrose	87
Water for injection	q.s. to 1 mL

**Abbreviations:** DSPC, 1,2-distearoyl-sn-glycero-3-phosphocholine; PEG2000-DMG, 1,2-dimyristoyl-rac-3-methoxypropyl ethylene glycol-2000. DP, Drug Product; mg, milligram; mL, milliliter; mM, millimolar; DTPA, diethylenetriaminepentaacetic acid; q.s., quantum sufficient, Gen, generation as in manufacturing generation or epoch, NA, not applicable.

**Reviewer's assessment:** Changes in formulation noted between (b) (4) Generation lots used in the Phase 3 clinical trial versus commercial lots are minor; it is reasonable to conclude that the formulations are comparable and that the formulation and testing of the (b) (4) generation clinical lots in the Phase 3 clinical trial support the use of the commercial lots intended for release.

**Developmental Stability Studies:**

**Container Comparability. Study design:** These studies compared stability of the DP at the intended long term storage condition (-25°C to -15°C) and under accelerated conditions (at 2°C to 8°C and 23°C to (b) (4) °C) after dispensing into (b) (4), cyclic olefin copolymer (COC) prefilled syringes (PFSs) or (b) (4). Testing also included routine quiescent storage, exposure to light, and stress during transport. The following known stability-indicating parameters were assessed at each time point tested: mRNA

purity (by (b) (4)), (b) (4) by (b) (4), (b) (4) by (b) (4), total lipid impurities (by (b) (4)) and (b) (4) at T0 and at 3, 6, 9 and 12 months or as noted below. For setting DP expiry, the greatest mRNA purity degradation rate was used. *Results:* No clear trend was observed in any of the stability indicating attributes (including mRNA purity, (b) (4), (b) (4), and total lipid impurities) based on testing (b) (4) lots ((b) (4) COC-PFS (b) (4)). Based on these data, stability data from (b) (4) can be considered supportive of stability of the DP in COC-PFS.

**ICH Q1B Photostability Study:** This study was performed to assess the impact of light conditions encountered during manufacture and handling on DP quality. *Study design:*

(b) (4)

**Stability during transport:** Review of the transport study is deferred to DMPQ.

*Study design:* Briefly, mRNA-1345 DP (0.1mgRNA/mL) in COC PFS were packed in cardboard cartons with booklets and loaded into a shipper box. Syringes in cartons had greater freedom of movement than PFS packed into blister packs. Cartons were not secured in the shipper box to examine a worst-case scenario. PFS were shipped frozen (-25°C to -15°C) (b) (4) and subjected to shipping simulation per (b) (4). Stability indicating attributes of stress (including (b) (4)) of the shipped DP were compared to attributes obtained for PFS of the same lot that were not shipped. Other attributes that were evaluated included mRNA purity, lipid content, lipid impurities, and subvisible particle counts. *Results:* Shipping using the defined transport conditions had no major impact on the quality attributes tested irrespective of whether the DP was shipped frozen (b) (4).

### Overages mRNA-1345 DP

No overages are applied for mRNA-1345 DP in PFS.

An overfill is applied to ensure delivery of the 0.5mL dose from the PFS with needle attached. Target fill volume for the COC PFS is (b) (4) mL per syringe.

Individual filled syringes are (b) (4) and must meet (b) (4) specification as a (b) (4) per syringe; this provides (b) (4) assurance that the target fill volume was achieved.

### Physicochemical and Biological Properties of mRNA-1345 DP

Relevant physical properties of the mRNA-1345 DP are listed below:

(b) (4)

***A comment was sent to the applicant in IR#5 on October 30, 2023: With respect to the section describing manufacture of mRNA-1345 DP: In Section 3.2.P.2.2.3 Physiochemical and Biological Properties, please provide the density of the DP since syringe overfill is monitored by weight while DP potency is stated in micrograms. We note that in Section 3.2.P.3.5., the summary report from (b) (4) for filling DP into prefilled syringes describes a (b) (4) in Section 4.4.1 of the document (page 23 of 41). However please include the density of the DP in Section 3.2.P.2.2.3, Table 10, describing Physical and Biological Properties of the DP.***

***On November 13, 2023, the applicant provided a response to item #22 in IR#5 in amendment 9, (SN10): The (b) (4) of the DP is (b) (4) and this DP property was included in Table 10 as requested.***

### 3.2.P.2.3 Manufacturing Process Development for mRNA-1345 DP

#### Manufacturing History:

The manufacture of the DP has been through (b) (4) process upgrades from (b) (4) to the Commercial process.

Additionally, a few small lots were manufactured to supply clinical trial material using the (b) (4) manufacturing processes. A synopsis of process development is given below:

(b) (4)

(b) (4)

**Commercial Scale:** Commercial manufacture occurs at a scale of (b) (4) using LNP ((b) (4)), to formulate vaccine at 0.10 mg RNA/mL with (b) (4) mL dispensed per 1mL COC-prefilled syringe (PFS). Due to the (b) (4) in scale the following (b) (4) adjustments were made to accommodate (b) (4) volumes with longer processing times and use of the PFS presentation: (b) (4)

DP lots manufactured for PPQ and comparability (discussed below) along with batch genealogy information about the DS intermediates used to formulate each DP lot are summarized in a table in **Appendix 8A**.

(b) (4)

**A comment was sent to the applicant in IR #23 on February 14, 2024:** With respect to section 3.2.P.2 Manufacturing Process Development {Manufacturing History}, Table 1, Manufacturing Site and Part Numbers for DP Processes, in addition to the nominal batch size in (b) (4), please provide the number of final syringes filled per batch for each batch size listed.

**On February 28, 2024, the applicant provided a response to item #9 IN IR#23 in**



**amendment 39, (SN40):** The applicant updated Table 1, Manufacturing Site and Part Numbers for DP Processes as requested to show the number of containers filled per batch and target batch size. I reviewed the information in the updated BLA. **Table 108** below was updated to contain the data for number of containers per batch. The response is acceptable.

**A comment was sent to the applicant in IR #23 on February 14, 2024:** With respect to section 3.2.P.2 Manufacturing Process Development {Manufacturing History}, please update Table 2, Development Manufacturing History -Development mRNA -1345 DP to include the manufacturing process (i.e., (b) (4) versus Commercial, (b) (4)) and batch size for each of the (b) (4) lots listed.

**On February 28, 2024, the applicant provided a response to item #10 in IR#23 in amendment 39, (SN40):** Table 2 in Section 3.2.P.2 Manufacturing process Development (Manufacturing History) was updated with the information as requested. I reviewed the updated table that now shows information for (b) (4) commercial development lots. All development lots were small, ranging in size from (b) (4) and used to support stability under long term and accelerated conditions.

**A comment was sent to the applicant in IR #23 on February 14, 2024:** With respect to section 3.2.P.2 Manufacturing Process Development {Manufacturing History}, Table 3, Clinical Development Manufacturing History - Clinical mRNA-1345 DP, we note that both (b) (4) Generation DP Lot (b) (4) and (b) (4) Generation DP Lot (b) (4) were used in Phase 3 Clinical Trial, mRNA-1345-P301, while (b) (4) other (b) (4) Generation lots, Lots (b) (4), were designated for use in “other clinical trials”. In contrast, the response to Item 22 in IR #6 (received on November 22, 2023) indicated that (b) (4) lots were used in Clinical Trial mRNA-1345-P301 including lots (b) (4). Please clarify the apparent discrepancy in the clinical lots used in study mRNA-1345-P301.

**On February 28, 2024, the applicant provided a response to item #11 in IR#23 in amendment 39, (SN40):** The applicant clarified that only Lots (b) (4) were used to dose participants in Clinical Trial mRNA-1345-P301 for the clinical data presented in this BLA. Lot (b) (4) was used for an extension of the P301 study in South Korea. Lot (b) (4) is being used for Part B of P301 for the 24month re-vaccination. The response is acceptable.

**Comparability of Commercial versus Clinical mRNA-1345 DP lots:** Table 108 below summarizes the comparison of the manufacture of mRNA-1345 DP across the manufacturing epochs and includes information about small-scale manufacture at the (b) (4) scale. Table 109 below provides a comparison of the process changes with product development.

**Table 108. Summary Across (b) (4) and Commercial Manufacturing Processes with Clinical, PPQ, and Registration Lots.**

	(b) (4)	Commercial	(b) (4)
Manufacturing site		(b) (4)	
Nominal Batch size (b) (4)		(b) (4)	
Number of containers filled per Batch		(b) (4) PFS (b) (4) PFS	
Nominal RNA input (b) (4)		(b) (4)	
Primary container		1mL COC PFS, halobutyl plunger stopper with fluoropolymer coating on product facing surface, plastic plunger rod	
Volume or weight per unit		(b) (4) mL	
mg/mL		0.10 mg/mL	
Part number UDP		(b) (4)	
Clinical DP Lots  (*Clinical Trial code number)		NA	
PPQ and Registration UDP DP Lots		(b) (4)	

Abbreviations: PVU, personal vaccine unit; (b) (4); mL, milliliter, mg, milligram; (b) (4); PFS, prefilled syringe, COC, ccylc olefin copolymer, UDP, unlabeled drug product; DP, Drug Product, (b) (4); PPQ, process performance qualification.

(b) (4)

One page has been determined to be not releasable: (b)(4)

(b) (4)

**Comparability Assessment:** Analytical comparability of mRNA-1345 DP lots manufactured at the commercial scale was demonstrated versus DP lots used to supply Clinical Trial mRNA-1345-P101 and -P301 to ensure that the intended commercial process produces vaccine consistent with the materials evaluated during clinical development. The following strategy was used to show that the processes used to produce commercial mRNA-1345 lots (post-change) did not impact the quality attributes of mRNA-1345 DP manufactured using the (b) (4) generation processes and used in the clinical studies (pre-change):

1. Comparability based on specifications in place at the time of release of commercial lots.
2. Comparability based on historical mRNA-1273 DP (SPIKEVAX) criteria were set using data accrued from (b) (4) mRNA-1273 development and GMP (including clinical, PPQ and commercial) lots established by calculating 95% confidence, 99% coverage tolerance intervals. If the tolerance interval was wider than the limit set by the release specification, the tighter specification was used. Comparability assessments based on the tolerance intervals set using mRNA-1273 historical data were used to assess comparability based on (b) (4)
3. Comparability based on stability testing of commercial and clinical mRNA-1345 DP lots: These data are shown in Section 3.2.P.7 Stability Testing.

Comparability analyses were based on data derived from (b) (4) mRNA-1345 DP clinical lots (with (b) (4) used in the Phase 1 trial, (b) (4) lots used in the Phase 3 trial, and (b) (4) lots intended for use future or ongoing clinical studies) compared with data obtained using (b) (4)

commercial PPQ lots manufactured at (b) (4) along with (b) (4) mRNA-1345 development lots (including (b) (4) UDP-100-AR01 and (b) (4) UDP-100-AR02 lots) and the (b) (4) historical mRNA-1273 lots used to set tolerance intervals. Clinical and commercial lots of mRNA-1345 lots are described above in **Table 108** in this section.

**Results of analytical comparability across all clinical lots:** Each of the (b) (4) clinical lots used in Phase 1 (Lot (b) (4) ) or Phase 3 (Lots (b) (4) ) clinical trials met all specifications for release and met all comparability criteria using tolerance intervals calculated from mRNA-1273 lot release data. The (b) (4) clinical lots intended for use in ongoing or future clinical trials (Lots (b) (4) ) also met these same criteria with two exceptions: Lot (b) (4) had an RNA purity of (b) (4) which fell outside of the release specification and tolerance limit of (b) (4); likewise this same lot had (b) (4) particles per container (b) (4) which exceeded the tolerance limit set by the mRNA-1273 historical data but was within the release specification of (b) (4) particles per container. The OOS result for purity for this lot was attributed to extended processing time. The particle count was not a concern since the lot was within the specification for release.

#### **Results of analytical comparability of clinical lots versus commercial mRNA-1345**

**DP lots:** The (b) (4) PPQ DP lots ( (b) (4) ) manufactured at (b) (4) , met all release specifications and all tolerance intervals set using mRNA-1273 historical data. Overall, the deviations seen for the one clinical lot described above had no impact on the comparability assessment of the (b) (4) PPQ lots versus clinical lots since the (b) (4) PPQ lots met all comparability criteria. Analytical comparability data for the (b) (4) clinical lots used or to be used in clinical trials and the (b) (4) PPQ DP lots are summarized in **Appendix 8B** and are shown with the release specifications for the commercial product and comparability criteria set using mRNA1273 historical data.

As part of this analytical comparability assessment, the results for all CQAs for mRNA-1345 (b) (4) commercial DP lots were compared graphically with results for clinical lots and development lots manufactured at ModernaTX using a series of (b) (4) dot-plots with one for each CQA evaluated (data reviewed in the BLA but not reproduced in this memo). Results were plotted against the acceptance criteria for each attribute with upper and lower limits shown for tolerance intervals derived from the mRNA-1273 historical data or showing upper and lower specification limits if release specifications were used for the comparability analysis. All commercial, clinical and development lots met the specifications for release with only two exceptions noted for one lot: RNA content and lipid content for (b) (4) clinical Lot (b) (4) (used in clinical trial mRNA-1345-P301) were not shown on the graphs because this lot was manufactured using different targets for release than the commercial lots, so the limits for these two CQAs do not apply to this lot. All lots also met the comparability criteria set using mRNA-1273 historical data with few exceptions: Development Lot (b) (4) had a (b) (4) of (b) (4) that was within specification for release ( (b) (4) ) but was outside the comparability limit ( (b) (4) ); (b) (4) other lots had (b) (4) that were outside of the tolerance limit of (b) (4) per container but well within the specification set for release (b) (4) per container) including

clinical Lot (b) (4) and (b) (4) development lots including (b) (4). Overall, these data show that the clinical lots manufactured at ModernaTX are comparable to commercial DP lots manufactured at (b) (4).

**A comment were sent to the applicant in IR #23 on February 14, 2024:** With respect to section 3.2.P.2.3 Pharmaceutical Development/Manufacturing Process Development – {Comparability}, we cite Figure 16 that contains the data for (b) (4) measuring (b) (4) and note that the footnote to the table describes (b) (4) lots ((b) (4) (b) (4)) with results that exceeded the comparability limit of (b) (4) measuring (b) (4), set using historical data from mRNA-1273 DP lots. However, the figure shows (b) (4) lots (including (b) (4) clinical lot and (b) (4) development lots) above the upper comparability limit while the footnote only names (b) (4) of the (b) (4) development lots. Please identify the (b) (4) development lot that exceeded the upper limit for particulates in the footnote to the figure as appropriate.

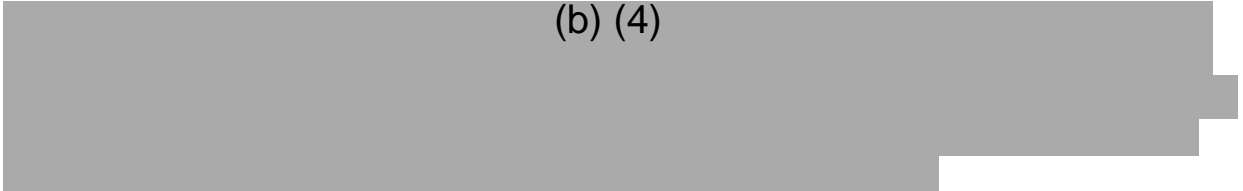
**On February 28, 2024, the applicant provided a response to item #8 in IR#23 in amendment 39, (SN40):** The applicant revised the footnote to figure 16 and identified development lot (b) (4) as the missing lot. To summarize, (b) (4) lots ((b) (4) (b) (4)) had results outside of the comparability limits but within specifications limits for (b) (4) (b) (4) /container) noting also that all commercial lots were within the comparability limits. The response is acceptable.

**Reviewer's assessment:** Analytical comparability of UDP-100-AR02 PPQ lots manufactured at commercial scale at (b) (4) was assessed against the clinical lots used to supply Clinical Trial mRNA-1345-P301 and against additional clinical and development lots. All results conformed to the specifications for release used as comparability acceptance criteria. Likewise, all PPQ lots also met the comparability acceptance criteria set using tolerance intervals determined using historical data from mRNA-1273 lots. The results demonstrate that the commercial scale process at Rovi JC produces UDP-100-AR02 with product quality consistent with the mRNA-1345 clinical lots and that the product quality is also consistent with that of SPIKEVAX.

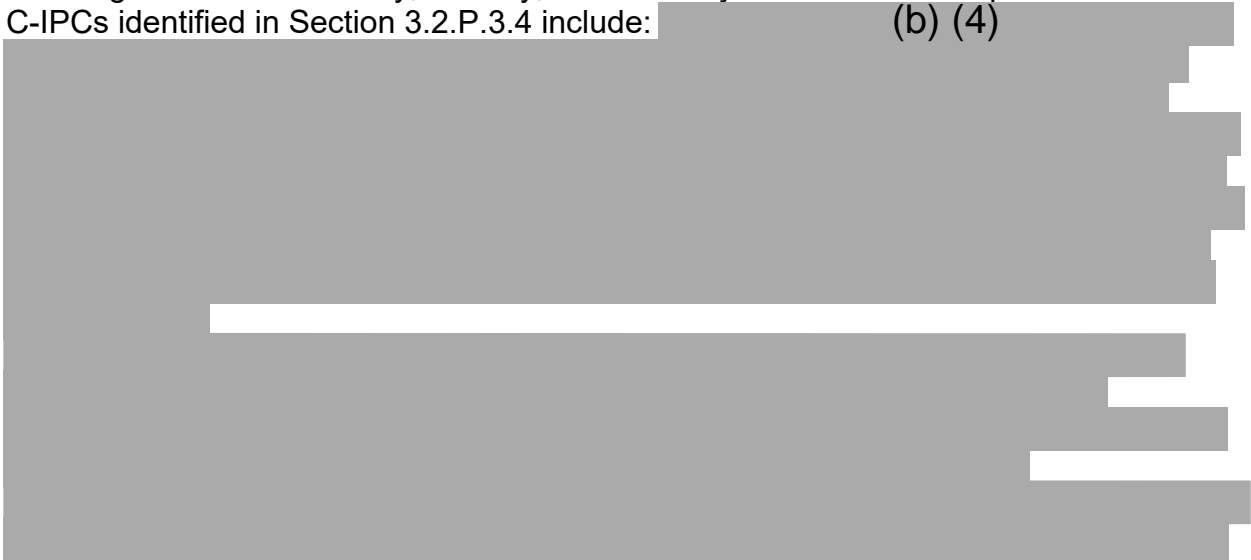
#### **Manufacturing Process Development: Process Characterization.**

(b) (4)

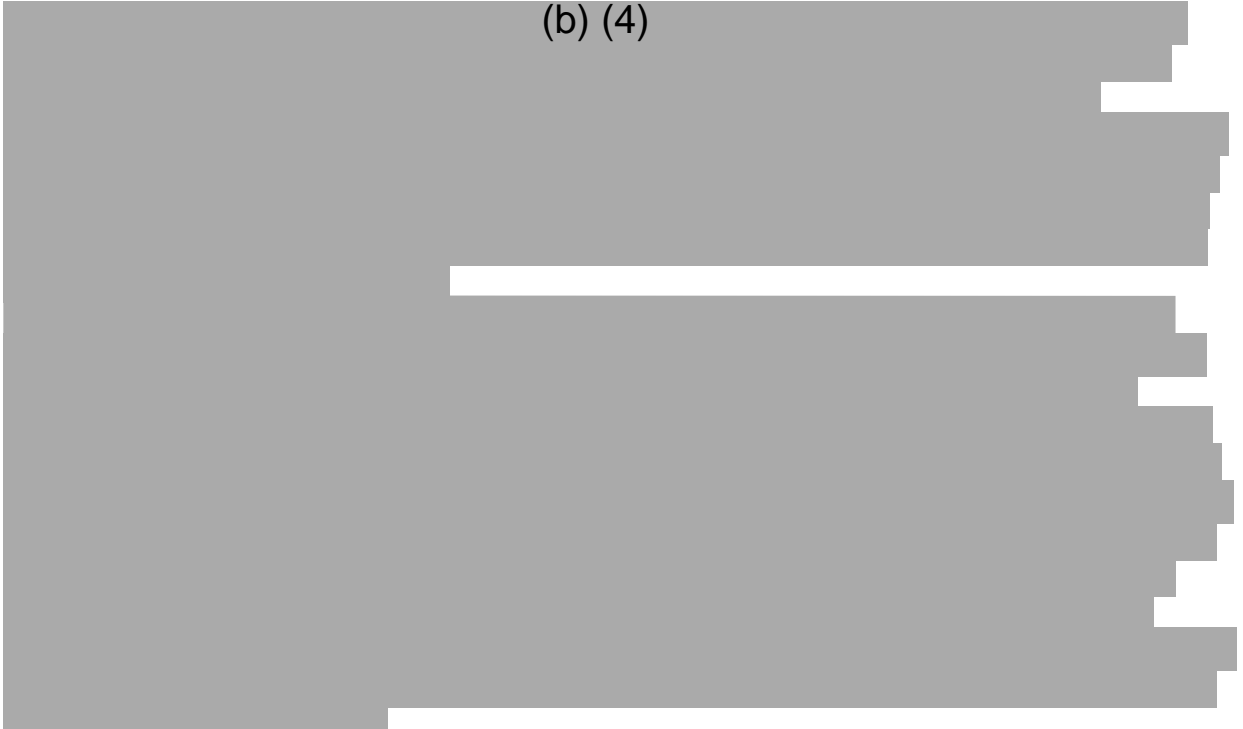
(b) (4)

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**Characterization of C-IPCs:** (b) (4) C-IPCs were identified during manufacture of the DP as being critical to DP safety, efficacy, and/or ability to meet release specifications. The C-IPCs identified in Section 3.2.P.3.4 include: (b) (4)

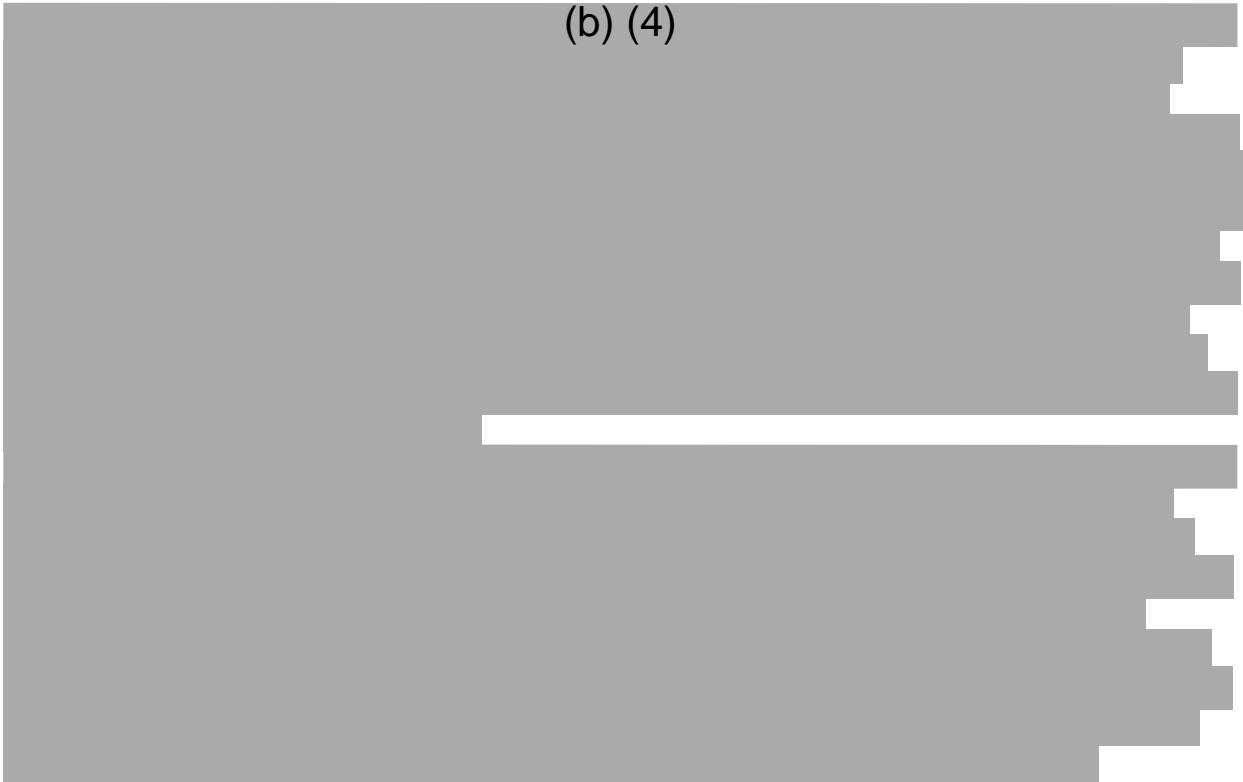
A large rectangular area of the document is redacted with a solid grey fill.

(b) (4)



**Characterization of IPCs (non-critical):** The following parameters are not critical but were characterized to verify the lack of impact on CQAs: Data based on prior knowledge for mRNA-1273 are summarized below. Data acquired at-scale for mRNA-1345 DP lots manufactured at (b) (4) are discussed under Section 3.2.P.3.5 Process Validation.

(b) (4)





2 pages have been determined to be not releasable: (b)(4)

(b) (4)

**A comment was sent to the applicant in IR #23 on February 14, 2024:** With respect to section 3.2.P.2 Pharmaceutical Development {Process Characterization}, in subsection P.2.3.1.2.1 Characterization of the (b) (4) is identified as a Critical Process Parameter (CPP) that requires that the (b) (4). However, this section did not describe any data to support the Proven Acceptable Range (PAR) set for this CPP. Please describe how the CPP was identified and how the PAR was set for manufacture of mRNA-1345 DP. If this is a platform CPP applied to all UDP-100 vaccines, please identify it as such and include the supporting data in this section.

**On February 28, 2024, the applicant provided a response to item #12 in IR#23 in amendment 39, (SN40):** The response indicated that the (b) (4) parameter was set based on process and equipment capability. Capability to meet this range was confirmed during PPQ of mRNA-1345 DP as the (b) (4) met (b) (4) for each batch. I verified the data in the Validation Report, Document # EXT 19309, Section 4.2 Process Parameters and IPCs, page 17/36 that showed that the (b) (4) was (b) (4) for Batch (b) (4) corresponding to ModernaTX DP batch numbers (b) (4).

**Extractables and Leachables Strategy:** The approach used for the risk assessment for extractables and leachables aligns with the (b) (4) guidance and is identical to that described above for DS intermediates including (b) (4) (See Section 3.2.S.2.5 Process Validation and Evaluation, (b) (4) Process Extractables and Leachables) and (b) (4) (See Section 3.2.S.2.5.Process Validation and Evaluation, Section on Validation/Evaluation of Extractables and Leachables). Medium risk consumables are listed in Table 110 below.

(b) (4)

One page has been determined to be not releasable: (b)(4)

in the extractables and leachables study and the results of the *in silico* mutagenicity study. The *in silico* mutagenicity study did not identify any alerts associated with either (b) (4) or with the (b) (4); the estimated TDI for (b) (4) was (b) (4) and the overall estimated amount for the (b) (4) process was (b) (4)

filter may occasionally result in small amounts ((b) (4)) of (b) (4) in the DP that has been reported to be a mild skin irritant but is otherwise not associated with any other known toxicities.

**Container Closure Extractable and Leachable Evaluations:** are discussed under Section 3.2.P.2.4

**Reviewer's assessment:** *This section provides an adequate description of the evolution of the manufacturing process for UDP-100-AR02 from early stages through commercial manufacture at (b) (4). The rationale for significant process changes was well documented for the affected process steps. Comparability assessments indicate the quality attributes of lots used in the Phase 3 clinical trial for efficacy are equivalent to the attributes of the DP lots manufactured at the commercial scale at (b) (4). The control strategy was well characterized and supports the CPPs, C-IPCs and IPCs used during manufacture of the DP. No deficiencies are noted.*

### 3.2.P.2.4 mRNA-1345 DP Container Closure System

The container closure system (CCS) for the DP consists of a prefilled, 1mL-long cyclic olefin copolymer, (COC), syringe with a rigid plastic cover (tip cap) that has an elastomeric lining. The plunger/stopper is made of halobutyl rubber with a fluoropolymer coating and the plunger rod is made of polypropylene. Specifications for each component are reviewed under Section 3.2.P.7 Container Closure System. This section describes the evaluations performed to support functionality, compatibility, stability, container closure integrity, plunger placement, and risk assessment with testing for extractables and leachables.

**Functionality:** Design Verification data were submitted under Section 3.2.R.1.12 that describe the assessment of (b) (4) deliverable volume. These data support the suitability of the PFS for delivery of the intended dose and are also reviewed by bioengineer and device specialist, Dr. Andrea Gray, ORO/DROP/RPB. See a summary of Dr. Gray's review under 3.2.P.7 Container Closure System for details.

**Compatibility:** Compatibility of the CCS was established using stability testing combined with the extractable and leachable profile. Stability testing is reviewed under Section 3.2.P.8 and the extractable and leachables studies are described below.

**Stability:** See section 3.2.P.8 for the review of stability data for DP filled into PFS. These data support the stability of the DP in PFS under the routine storage conditions.

**Container Closure Integrity:** *Study design:* CCI testing was performed using representative prefilled syringes (PFSs) at the intended storage condition and using PFSs filled on the (b) (4) filling line at (b) (4). CCI was assessed using temperatures to reflect routine storage conditions for frozen (-25°C to -15°C) and non-

frozen DP (20°C to 25°C) using (b) (4) methods including (b) (4) analysis to assess integrity as summarized in **Table 111** below. *Results:* Overall, CCI was demonstrated for PFSs with and without plunger rods inserted under routine storage conditions using frozen or non-frozen DP and after (b) (4).

(b) (4)

(b) (4)

(b) (4)

**Extractables and Leachables:** The (b) (4) risk assessment of the PFS indicated that the 1 mL COC syringe barrel and halo-butyl plunger/stopper are high-risk consumables for the DP. Release specifications for each along with a description of the testing to assess extractables and leachables follow below.

**1 mL COC syringe:** The COC polymer container complies with (b) (4) ; the tip cap complies with (b) (4) ; and the (b) (4) used to lubricate the syringe complies with (b) (4) .

**1 mL Halo-butyl rubber plunger/stopper coated with fluoropolymer:** The fluoropolymer used to coat the plunger/stopper is inert and serves to reduce risk for leachables moving from the stopper into the vaccine. The plunger complies with (b) (4) .

*Study design for extractables:* (b) (4)

(b) (4)

(b) (4)

(b) (4)

*Results for 1ml COC syringe:* No leachable compounds were detected above the AET.  
*Results for 1mL fluoropolymer coated halo-butyl rubber stopper/plunger:* No leachable compounds were detected above the AET.

**Reviewer's assessment:** Several extractables were identified when the COC PFS were tested, however, no leachables were detected above the AET of (b) (4) in the simulated leachable study using (b) (4). These data support the safety of the PFS based on the extractable and leachable profiles. The 1mL COC syringe with 1mL plunger stopper is considered suitable for use with the UDP- and LDP-100-AR02.

### 3.2.P.2.5 mRNA-1345 DP Microbiological Attributes

mRNA-1345 DP is manufactured using a conventional aseptic process using sterile filtration prior to filling (b) (4). A microbiological growth promotion study was conducted to evaluate the ability of the DP to promote or hinder growth of common microorganisms over a time frame corresponding to "in-use" time.

**Study design:** (b) (4)

(b) (4)

*Results:* The results

showed that the growth of each microorganism and counts for (b) (4) over the (b) (4) period tested. *Conclusion:* These data indicate that mRNA-1273 DP and by analogy mRNA-1345 DP do not promote the growth of common potential bacterial contaminants over the proposed “in-use” period of (b) (4) at (b) (4). These studies are required to support the use of multi-dose vials but are not required for sterile-single dose presentations for which the risk of contamination is negligible.

### 3.2.P.2.6 mRNA-1345 DP Compatibility

In-use stability studies were performed to mimic handling mRNA-1345 LDP-100-AR02 (0.10mg RNA/mL) at the clinical site using representative materials, representative test articles, and the appropriate preparation procedure for administration. The DP may be thawed in the refrigerator or at room temperature as outlined in **Table 112** below:

**Table 112. DP Administration Thaw Instructions.**

Configuration	Thaw in refrigerator	Thaw Duration (minutes)	Thaw at room temperature	Thaw Duration (minutes)
PFS in blister pack	2°C to 8°C 36°F to 46°F	55	15°C to 25°C 59 F to 77°F	45
Carton	2°C to 8°C 36°F to 46°F	155	15°C to 25°C 59°F to 77°F	140

**Abbreviations:** PFS, prefilled syringe.

*Study design:* This short duration, in-use, hold-time study mimicked handling of the DP at the site of administration using a lot of LDP-100-AR02, (b) (4), representative of commercial production. This study assessed stability of physicochemical properties of the DP in syringes when exposed to (b) (4)

Acceptance criteria for the in-use study aligned with the specifications for release for the commercial DP. *Results of in-use study:* CQAs for DP held in PFS at 25°C (b) (4) for up to 24 hours under (b) (4) were essentially identical to the attributes measured for DP in syringes held under the identical conditions but while (b) (4)

*Conclusion:* These results support the proposed instructions for routine administration.

**A comment was sent to the applicant in IR #23 on February 14, 2024:** In section 3.2.P.2 Compatibility, with respect to the summary given for the in-use study (subsection 3.2.P.2.6.3), please describe whether the prefilled syringes used in the study were thawed in the refrigerator, at room temperature, or if groups of syringes were thawed using each condition. Please indicate the number of syringes tested to obtain the results in Table 3, In-Use Stability Data for Samples Held at 25°C for at Least 24 hours and update this section with this additional information.



**On February 28, 2024, the applicant provided a response to item #13 in IR#23 in amendment 39, (SN40):** In this study, single PFS were thawed at room temperature then held at room temperature under (b) (4) for 24 hours prior to testing. Control and sample groups were treated the same, except that the dark controls were (b) (4). (b) (4) PFS was tested for each DP CQA evaluated. The applicant notes that this section was updated to include the information pertaining to the study design. The study tests the worst-case scenario and covers thawing PFS in the refrigerator at the lower temperature and the 24 hours covers all times reported for dose preparation in the package insert. The response is acceptable.

**Reviewer's assessment:** The information in Section 3.2.P.2.6 Compatibility, is acceptable, and no deficiencies are noted.

### 3.2.P.3 Manufacture of mRNA-1345 DP

#### 3.2.P.3.1 Manufacturer(s)

Drug Product manufacturing and testing are performed at the sites list in **Table 113** below:

**Table 113. mRNA-1345 DP Manufacturers**

Facility	Responsibility
(b) (4) FEI (b) (4) DUNS (b) (4)	UDP Manufacture In process testing: bioburden, endotoxin. Release and stability testing: (endotoxin, sterility, CCIT, (b) (4), extractable volume, particulate matter.) Stability (container closure integrity testing)
(b) (4) FEI (b) (4) DUNS (b) (4)	Distribution
(b) (4)	Distribution
ModernaTX (b) (4) FEI (b) (4) DUNS (b) (4)	Batch Release Combination product development and lifecycle
(b) (4) FEI (b) (4) DUNS (b) (4)	(b) (4) UDP (b) (4) Assembly, labelling, and packaging Release and stability testing (appearance, RNA content, identity, purity and product related impurities, (b) (4) lipid identity /content/purity.
(b) (4)	(b) (4) (UDP and LDP Frozen Storage (b) (4) long term).

\* subcontracted by (b) (4)

**3.2.P.3.2 Batch Formula for mRNA-1345 DP**

The nominal batch size for (b) (4) formulated mRNA-1345 DP is up to (b) (4). Representative batch size composition and formulae are shown in **Table 114** below for batch sizes ranging from (b) (4).

**Table 114. UDP-100-AR02 Drug Product Batch Composition**

Component	Amount per batch at (b) (4)	Amount per batch at (b) (4)
RNA-100-AR02 <sup>a</sup>		
Total lipids <sup>b</sup>		
Tris (Tromethamine)		
Tris HCl		
(b) (4) acetic acid		
Sodium acetate trihydrate		
Sucrose		
Water for injection		

**Abbreviations:** HCL, hydrochloric acid.

<sup>a</sup> Nominal RNA concentration of DS LNP-100-AR02 is (b) (4).

<sup>b</sup> Four lipids, SM-102, cholesterol, DSPC and PEG2000-DMG, are included in the estimate of total lipids. DSPC, 1,2-distearoyl-sn-glycero-3-phosphocholine; PEG2000-DMG, 1,2-dimyristoyl-rac-3-methoxypropylene glycol-2000.

*Reviewer's assessment: The information in sections 3.2.P.3.1 and 3.2.P.3.2 is acceptable and there are no deficiencies noted.*

**3.2.P.3.3 Description of Manufacturing Process for mRNA-1345 DP**

The process used to manufacture mRNA-1345 DP at (b) (4) has two possible process flows shown in the figure **Appendix 8C** copied from the BLA. Briefly, (b) (4)

(b) (4) followed by sterile filtration and aseptic filling of syringes and placement of the plunger/stopper. In the main process flow (Process Flow 1), prefilled syringes (PFS) are shipped at 2°C to 8°C from (b) (4) in (b) (4) in (b) (4) and subjected to a (b) (4) at the (b) (4) facility. (b) (4) PFS are shipped at (b) (4) to -15°C from (b) (4) back to (b) (4) for (b) (4) prior to assembly, labeling, and packaging activities at that site. Packaged PFS are then transferred at 2°C to 8°C back to (b) (4) and subjected to another (b) (4) prior to long term storage at (b) (4) prior to distribution. If the alternative process is used, Process Flow 2, following filling and plunger/stopper placement, the PFS are subjected immediately to assembly, labeling, and packing activities followed by the (b) (4) long-term storage at the (b) (4) facility. As noted above in Section 3.2.P.2.2 Pharmaceutical Development, the total CPD allowed is (b) (4) which excludes the time spent in the (b) (4) and storage. A step-by-step description of each unit operation at (b) (4) (for UDP-100-AR02 manufactured using (b) (4)) and at (b) (4) (or (b) (4), for LDP-100-AR02) is given below:

**Dilution Buffer Preparation:** Dilution buffer (20mM Tris, 87 g/L sucrose, (b) (4)) is used to dilute the (b) (4) to the target RNA concentration of 0.10mg/mL. (b) (4)

(b) (4)

Tris, sucrose, and WFI meet USP requirements prior to use. Tris HCl is a (b) (4) ingredient and requirements met prior to use are presented in Section 3.2.P.4.1.2 Specifications.

(b) (4)

(b) (4)

(b) (4)

**Sterile Filtration:** At (b) (4), sterile filtration takes place in the (b) (4) Filling line, in room (b) (4) in building (b) (4) under Grade (b) (4) at (b) (4). (b) (4)

. The DP undergoes a final sterilizing filtration in-line with filling. A (b) (4) filter i (b) (4) test is performed using (b) (4)

(b) (4)  
 From the (b) (4), the DP is dispensed into syringes through (b) (4) filling needles (b) (4) under (b) (4) unit (b) (4). Plunger stoppers are placed in the filled syringes in grade (b) (4) using mechanical insertion. Filling occurs at (b) (4). A (b) (4) filter (b) (4) test is performed (b) (4) at the (b) (4) of the filtration. Maximum filtration duration is (b) (4) based on validated filter contact time. Deviations noted in (b) (4) are assessed against (b) (4). The (b) (4) filling line is made up of the following equipment: (b) (4)

**Aseptic Filling and Plunger/Stopper Placement:** Ready-to-use (RTU) sterile syringes and RTU plunger/stopper are received sterilized from the vendor and introduced into the Grade (b) (4) filling line within a Grade (b) (4) room. Syringes are debagged and nested syringes in trays are introduced into the Grade (b) (4) filling area where the (b) (4) cover and inner liner are removed from each tray and syringe trays are then introduced into the fill line. The sterile filtered DP in the (b) (4) is filled through the manifold into syringes via needles at a controlled room temperature. RTU-plunger/stoppers are placed immediately after filling in the same Grade (b) (4) area. (b) (4) are monitored periodically and environmental monitoring is performed continuously throughout the filling process.

**Visual Inspection:** All syringes undergo 100% manual or automated visual inspection at controlled room temperature. After inspection, an acceptable quality limit sample set is inspected by a qualified operator. UDP-100-AR02 release samples are taken after visual inspection. Automatic visual inspection at (b) (4) uses the (b) (4) inspection module. This inspects the flange and the presence or absence of the plunger stopper, needle cover, plunger, presence of particles in solution, dosing level, defects, and cracks in the plastic syringe barrel, and identifies cracks between the collar and plunger. Automatic visual inspection was validated according to (b) (4) PQR 09622/1.

**Process Flow 1:** includes the following (b) (4) steps prior to assembly labeling and packaging.

(b) (4)

(b) (4)

**Process Flow 2:** allows for immediate forward processing of the DP without the (b) (4) steps described above.

**Assembly, Labeling and Packaging Activities:** All activities are conducted at CRT of (b) (4). Plunger rods are inserted into each syringe which are then labeled using an automatic labeler. Labeled syringes are placed into thermoformed trays and sealed, then processed into individual blister packages (two PFS per blister) which are packaged into cartons. Variable data and tamper evidence seals are applied to each carton. Cartons are placed into shipping cases. LDP-100-AR02 release samples are taken for release testing after packaging is complete and prior to freezing and must meet the specifications as outlined in Section 3.2.P.5.1, Specifications.

(b) (4)

**Long Term Storage:** Syringes in cases are held at -25°C to -15°C long term.

**Cumulative Process Duration, (CPD):** CPD including time at 2°C to 8°C plus time at 15°C to 25°C is (b) (4); the time out of refrigeration, (TOR. 15°C to 25°C), is limited to (b) (4). Totals do not include the duration of the (b) (4) for Process 1. Total CPD includes the time allowed to transport UDP to the (b) (4) site and back as well as the time required to (b) (4) syringes following (b) (4) for process option 1. (Note: the distance from (b) (4) to (b) (4) is approximately (b) (4).)

**Reprocessing:** The DP is not reprocessed.

**Consumables used in the manufacture of the DP:** Consumables are purchased from approved vendors who sell products meeting current specifications. Packages are inspected upon arrival for physical damage and documentation reviewed including certificate of analysis or conformance, package labeling, packing slips, date of expiry, conformation of shipping temperature and conditions, and verification against purchase order. (b) (4) manages intake and inspection of documents and QA determines the disposition of the material. According to ModernaTX's operating procedures. Root cause investigations by the supplier are defined by protocol should the need arise. Supplier change management occurs under an established program and plan approved by the QA team.

Single-use consumables with direct product contact are listed in **Table 115** below.

(b) (4) filters are certified by the vendor.

**Table 115. Single-use Consumables used During Manufacture of the DP**

Process Step	Consumable	Material of Construction	Method of Sterilization	Meets specifications for use: CoA
(b) (4)				

One page has been determined to be not releasable: (b)(4)

(b) (4)

**Batch scale:** The batch size is defined by the volume of the bulk formulated DP. For this process, the nominal batch size ranges from (b) (4). Batch numbers follow the logic (b) (4) where (b) (4) represents the (b) (4)-digit part of the lot number, (b) (4) represents the year of manufacture and (b) (4) represents a sequential production number. (b) (4) will also assign (b) (4) specific lot numbers using a sequential code between (b) (4) digits long. Sublots manufactured from full lots at (b) (4) are designated by letters e.g., (b) (4).

**The following four comments were sent to the applicant in IR #23 on February 14, 2024:**

**Item #14:** With respect to the manufacture of the DP using Process Flow 1 that includes a (b) (4) for UDP-100-AR02 at (b) (4) for not less than (b) (4) followed by (b) (4), the maximum duration of (b) (4) or storage at each temperature has not been defined. Please describe the maximum duration for the (b) (4) at (b) (4) and for (b) (4) at -20°C (range (b) (4) and provide data to support these storage times.

**On February 28, 2024, the applicant provided a response to item #14 in IR#23 in amendment 39, (SN40):** An internal operational limit of (b) (4) was set for the (b) (4) for UDP-100-AR02 in Process Flow 1. There is negligible impact to product quality when DP is stored at (b) (4). The operational limit of (b) (4) is controlled by the batch record to ensure advancement to (b) (4).

With respect to the duration allowed for (b) (4), a (b) (4) maximum was proposed in response to IR#18 in the response submitted in amendment 24 on January 12, 2024, resulting in updates to Section 3.2.P.3.3 Description of Manufacturing Process and Section 3.2.P.2.3 Manufacturing Process Development. Note: the update included data for (b) (4) of UDP for (b) (4) followed by labeling and packaging activities. LDP characterization showed negligible impact on product quality for either storage duration (at (b) (4)) supporting the proposed UDP (b) (4) of (b) (4) at (b) (4).

**Item #15:** With respect to the manufacture of the DP using Process Flow 1, we note that upon resuming labeling and packaging activities, the PFSs are allowed to (b) (4) for at least (b) (4) but no maximum (b) (4) time is given. Please describe the maximum (b) (4) time allowed for PFS filled at the maximum nominal scale of (b) (4) with

approximately (b) (4) PFSs (as described in the Rovi Validation Report EXT-19309, page 6 of 41).

**On February 28, 2024, the applicant provided a response to item #15 in IR#23 in amendment 39, (SN40):** The sponsor clarified that the (b) (4) time for PFS prior to label and pack activates is included in the total process time out of refrigeration as shown in Table 17 of Section 3.2.P.3.5 which shows the product quality data supporting a total CPD time of (b) (4) and TOR of (b) (4). The response is acceptable.

**Item #16:** With respect to the single-use consumables used during manufacture of the DP shown in Table 14, Drug Product Consumables, please provide representative Certificates of Analysis (CoA) from the vendor, including confirmation of sterilization and TSE/BSE risk requirements.

**On February 28, 2024, the applicant provided a response to item #16 in IR#23 in amendment 39, (SN40):** The applicant provided representative CoAs and BSE/TSE statements for all consumables used in the manufacture of the DP. Consumables delivered to (b) (4) are not sterile upon arrival except for sterilizing filters. Items are (b) (4) sterilized in an (b) (4) at (b) (4) prior to use as described in Section 3.2.A.1 Rovi JC.

**Item #17:** Process 1 includes (b) (4) steps: (b) (4)

- a. Please clarify if (b) (4) steps for labeled and unlabeled DP are performed at (b) (4) and specify where the UDP (b) (4) and LDP long-term storage are located.
- b. Please update sections 3.2.P.3.1 Manufacturers and 3.2.P.3.3 Description of Manufacturing Process and Process Controls, as appropriate, to include the storage locations and description of shipment steps among the various DP manufacturing sites.

**On February 28, 2024, the applicant provided a response to item #17 in IR#23 in amendment 39, (SN40):** (b) (4) steps for (b) (4) and for long term storage are performed at (b) (4). Sections 3.2.P.3.1 and 3.2.P.3.3 were updated to clarify the storage locations and description of shipments among the manufacturing sites. I reviewed the updated sections and verified the changes made to the BLA. The details in the Table shown in section 3.2.P.3.1 Manufacturers in the review memo were revised to show all operations performed at each site. The movement of materials between (b) (4) in (b) (4) and (b) (4) in (b) (4) was similarly updated in the review memo.

**Reviewer's assessment:** The manufacture of the DP is well described and controlled. No major deficiencies are noted.



### 3.2.P.3.4 Controls of Critical Steps and Intermediates for mRNA1345 DP

Critical process parameters (CPPs) with their proven acceptable ranges (PARs) and Critical in-process controls (C-IPCs) and other in-process controls (IPCs) with associated acceptance criteria used to control the manufacture of the DP are summarized in **Table 116** shown below. The (b) (4) CPPs include (b) (4)

(b) (4) C-IPCs and (b) (4)

IPCs are summarized in the table below.

(b) (4)

One page has been determined to be not releasable: (b)(4)

(b) (4)

**Microbial control strategy:** Briefly, the microbial control strategy for the manufacture of UDP-100-AR02 is based on (b) (4)

sterile filtration of the bulk DP just prior to filling. Filtration steps are complemented by qualifying filters (b) (4) filter (b) (4) testing, along with tests for (b) (4)

(b) (4). Filling and plunger/stopper placement operations take place in a Class (b) (4) filling suite with environmental monitoring to prevent contamination and assure integrity of the process. CPPs and C-IPCs assure that the release specifications for the DP are met.

**Reviewer's assessment:** *Control of critical steps and intermediates are acceptable, and no deficiencies are noted.*

### 3.2.P.3.5 Process Validation and/or Evaluation for mRNA-1345 DP

The validation of the UDP-100 process for manufacture of mRNA-1345 DP at (b) (4) consists of the following activities: 1) Process Performance Qualification; 2) Simulated Media Fills; 3) Validation of Sterile Filtration to include (b) (4) testing along with (b) (4) filter (b) (4) tests; 4) Cleaning Validation and 5) Sterilization Validation of Process Contact Parts. Brief descriptions of these studies with results are summarized below.

**Process Performance Qualification (PPQ):** (b) (4) lots of UDP-100-AR02 were manufactured at 50 µg of RNA/dose in prefilled COC syringes per protocol PCP-10614/1 at (b) (4) (hereafter referred to as (b) (4)) using the (b) (4) filling line, following Process (b) (4) of the UDP prior to label and pack activities. The results of this study serve to validate the UDP-100-AR02 and LDP-100-AR02 DP manufacturing processes.

These validation data were initially submitted as *Summary Report of Validation Batches for the Compounding, Filling and Automatic Inspection of mRNA-1345 (UDP-100-AR02) 0.10mg/mL RSV vaccine in 1mL-Long COC Prefilled Syringes (PFS)*, dated 20MAR2023, as document number EXT-19309 (also named (b) (4) Report Code # PVR-11094/ Version 1.0). In response to Item #19 in IR#23 sent to ModernaTX on February 14, 2024 (see details below) an updated version of the report, PVR-11094 Version 3.0, 15MARCH2024, was submitted that contains validation data across the entirety of the DP manufacturing process for (b) (4) lots of LDP-100-AR02 manufactured using Process (b) (4) with (b) (4) for (b) (4) onths prior to (b) (4), packaging, labeling,

including the (b) (4) prior to release testing and long term storage. In response to item #2 in IR#35 sent on 22March2024, the applicant also provided a further revised MVR, PVR-11094, version 4 submitted in amendment 54 on 5APRIL2024 described below.

The PPQ data for the (b) (4) UDP-100-AR02 batches represent the expected range for the nominal bulk formulated volumes and establish the batch size range from a minimum of (b) (4) to a maximum of (b) (4). Validation data reported for the (b) (4) batches include CPPs, C-IPCs, IPCs, and conformance with all process parameters. Additionally, the CQAs for the (b) (4) PPQ lots were satisfactory and met all specifications for release in place at the time of testing. These data are summarized below. PPQ lots executed for the validation of the DP manufacturing process are shown in **Table 117** below.

(b) (4)

Critical process parameters for the (b) (4) PPQ lots were met and are shown in **Table 118** below:

(b) (4)

Critical in-process controls (C-IPCs) assessed during sterile filtration, filling, and plunger placement were within the acceptable range for the (b) (4) PPQ lots as shown in **Table 119** below:

(b) (4)

(b) (4)

During PPQ, microbial control was maintained during (b) (4) and during sterile filtration as shown in **Table 120** below:

(b) (4)

All non-critical in-process controls were within the acceptable range for the (b) (4) PPQ lots manufactured during the validation study as shown in **Table 121** below:

(b) (4)

(b) (4)

All process parameters were met for the (b) (4) UDP-100-AR02 PPQ lots manufactured during the validation study at (b) (4) as shown in **Table 122** below:

(b) (4)

(b) (4)

CQAs for the (b) (4) PPQ lots filled into 1mL syringes and held to meet the maximum processing times for time out of refrigeration (TOR) of (b) (4) and cumulative process duration (at 2°C to 8°C plus time at 15°C to 25°C) of not more than (b) (4) met all specifications for release that were in place at the time of testing as shown in **Table 123** below.

**Table 123. Release Testing\* on PPQ UDP lots (samples collected during visual inspection (b) (4) ) and LDP lots (processed after an (b) (4) with samples collected after labeling and packaging activities and (b) (4) ).**

Test	Specification	(b) (4)
Sterility	No growth	(b) (4)
Endotoxin	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Deliverable volume	(b) (4)	(b) (4)
Appearance	White to off white dispersion. May contain visible white or translucent product related particles.	(b) (4)
RNA content	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)

Test	Specification
(b) (4)	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
Lipid identification	(b) (4)
Lipid Content	SM102: (b) (4)
Lipid Content	Cholesterol (b) (4)
Lipid Content	(b) (4) DSPC
Lipid Content	PEG2000-DMG: (b) (4)
Lipid impurities (individual)	(b) (4)
Lipid impurities (total)	(b) (4)
UDP (b) (4)	
TOR/CPD	
LDP Lot #	
RNA purity (b) (4)	(b) (4)
RNA impurities (b) (4)	(b) (4)
RNA impurities (b) (4)	(b) (4)
CCIT	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)

**Abbreviations:** DSPC, 1,2-distearoyl-sn-glycero-3-phosphocholine; PEG2000-DMG, 1,2-dimyristoyl-rac-3-methoxypropylene glycol-2000; PPQ, process performance qualification; UDP, unlabeled Drug Product; LDP, labeled Drug Product; (b) (4)

DP, drug product; (b) (4)

In another stress test, the TOR was extended to (b) (4) and the total CPD of up to (b) (4); the (b) (4) PPQ lots met all acceptance criteria for release indicating the extended hold times could cover slightly longer processing times for the manufacture of UDP-100-AR02 (data not shown in this report).

Additionally, following CPD times of (b) (4) for (b) (4) UDP-100-AR02 batches (b) (4) respectively, the (b) (4) time following a (b) (4) was extended up to (b) (4) for additional LDP lots (in lieu of (b) (4)); these lots met all acceptance criteria for release after the prolonged (b) (4) at (b) (4) as expected as shown in **Table 124** below.

**Table 124. Testing on PPQ LDP-100-AR02 lots (after (b) (4) and using sample (b) (4) acquired post-label and pack and (b) (4) PVR-11904, Version 3, Table 31).**



Test	Specification
<b>UDP</b> (b) (4)	(b) (4)
<b>Fill UDP</b> TOR CPD	See below
<b>Pack LDP</b> TOR CPD	See below
<b>Total</b> TOR CPD	<b>Total UDP+ LDP</b> (b) (4) TOR (b) (4) CPD
Identity	Same as RS
(b) (4)	(b) (4)
(b) (4)	(b) (4)
RNA purity	(b) (4)
RNA (b) (4)	(b) (4)
RNA (b) (4)	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
RNA content	(b) (4)
Lipid Identification	Each lipid matches (b) (4) of reference
Lipid content	SM102 (b) (4) Cholesterol (b) (4) DSPC (b) (4) PEG2000-DMG (b) (4)
Lipid impurities individual	Each individual impurity is (b) (4)
Lipid impurities total	Total is (b) (4)

(b) (4)

**Abbreviations:** PPQ, process performance qualification; UDP, unlabeled Drug Product; LDP, labeled Drug Product; RS, reference standard; (b) (4)

; CCIT, container closure integrity test.

**Further Validation of Process Option 1 to include Packing and Filling after (b) (4)**  
**of (b) (4)** : PVR-11093 version 3.0 was updated to show Table 36 that includes the results of testing LDP-100-AR02 lots as requested in item 19 in IR#23 sent on February 14, 2024. (b) (4) LDP lots were manufactured from the (b) (4) UDP lots following (b) (4) as follows: UDP-100-AR02 Lot (b) (4) was used to manufacture (b) (4) LDP batches (Lots (b) (4)); UDP-100-AR02 lot (b) (4) was used to manufacture LDP lot (b) (4); and UDP-100-AR02 Lot (b) (4) was used to manufacture LDP lot (b) (4). The results provided for the LDP lots were added to **Table 123** shown above.

**Qualification of Cumulative Process Duration: Study design:** (b) (4)

(b) (4)


. *Results:* Following each CPD challenge test, the (b) (4) batches met all specifications for release in place at the time of testing; results for the initial CPD challenge test are shown in **Table 125** below. These results support the CPD of (b) (4) at 2°C to 8°C that includes up to (b) (4) at 15°C to 25°C.

(b) (4)

**Simulated Media Fills:** The media fill program is used to support and qualify the aseptic manufacturing process using the same equipment, parameters, and materials used for UDP-100-AR02 DP to test maximum hold times, simulate process interventions, and confirm that filled syringes are negative for microbial growth. A summary of the media fill validation is provided below, but the review of this validation is

deferred to DMPQ. *Study design:*


(b) (4)



*Conclusion:* The (b) (4) filling line is qualified for use for filling 1 ml COC syringes during manufacture of UDP-100-AR02 DP.

**Environmental monitoring:** Review of environmental monitoring is deferred to DMPQ.

**Validation of Sterile Filtration:** Sterile filtration of the DP was validated per 21CFR 211.113 and PDA TR 26 Rev 2008, Sterilizing Filtration of Liquids, Section 6.2. (b) (4)



6 pages have been determined to be not releasable: (b)(4)

(b) (4)

**3.2.P.4 Control of Excipients in mRNA-1345 DP****3.2.P.4.1 Specifications and 3.2.P.4.4 Justification of Specifications for Excipients in mRNA-1345 DP**

Excipients are received from qualified suppliers along with Certificates of Analysis and BSE/TSE risk statements, with verification of supplier analytical methods as needed. A full testing panel of (b) (4) unique lots of each excipient is performed by either ModernaTX or a contract laboratory. Excipients may be purchased from multiple suppliers and are qualified for use based on review of the Certificate of Analysis or Certificate of Compliance against the Master Specification list for each material. Any additional in-house testing is based on a risk assessment. Excipients from the FDA BITS-ABC database are shown in **Appendix 2**.

(b) (4) **excipients in the DP** include sucrose, Tris base, sodium acetate trihydrate, and WFI; each raw material meets (b) (4) standards.

The single (b) (4) **excipient** in the DP is Tris (hydroxymethyl) aminomethane hydrochloride (Tris HCl). Tris HCl is purchased from (b) (4) and must meet master specifications using vendor testing as listed in **Table 129** below:

(b) (4)

(b) (4)

### 3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures for excipients

The applicant used a platform approach for assay validation for RNA vaccines manufactured using the “100 process”. The description of (b) (4) analytical procedures developed for testing mRNA-1273 products and details on their validation or verification can be found in the BLA 125752 CMC review memos from DVP and DBSQC reviewers. (b) (4) assays are reviewed by DBSQC. Method-validation results for (b) (4) methods used for UDP and or LDP-100-AR02 and qualification data for method transfer to the additional testing sites are described in other sections of this review memo. Please see RNA-100-AR02 section 3.2.S.4.2 Analytical Procedures and 3.2.S.4.3 Validation of Analytical Procedures for information pertaining to the test for Identity by (b) (4). Please see (b) (4) section 3.2.S.4.2 Analytical Procedures and 3.2.S.4.3 Validation of Analytical Procedures for information pertaining to the tests for Lipid Identity, Content, and Impurities and tests for (b) (4). Please see LNP-100-AR02 section 3.2.S.4.2 Analytical Procedures and 3.2.S.4.3 Validation of Analytical Procedures for information pertaining to the tests for (b) (4) by (b) (4) and the test for (b) (4).

**Reviewer's Conclusion:** Overall, the results provided in the submission confirm that all analytical methods used for in-process, release and stability testing across the qualified QC facilities are suitable for testing UDP and/or LDP-100-AR02 DP materials.

### 3.2.P.4.5 Excipients of Human or Animal Origin

There are no excipients of human or animal origin in the DP.

### 3.2.P.4.6 Novel Excipients

There are no novel excipients in the DP.

**3.2.P.5 Control of Drug Product mRNA-1345****3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s) for mRNA-1345 DP**

mRNA-1345 DP release and shelf-life specifications with acceptance criteria, sampling points, and analytical procedures are summarized in **Table 130** below. These specifications include post-PPQ changes in acceptance criteria for (b) (4), and lipid-related impurities. Justifications for each specification follow the table.

**Table 130. Specifications for mRNA-1345 Drug Product**

Test	Method	Sample	Release Acceptance Criteria	Shelf Life Acceptance Criteria
Appearance	Visual inspection	(b) (4)	White to off- white dispersion; may contain visible white or translucent product- related particulates.	Same
Identity	(b) (4)	(b) (4)	Matches description	NA
Total RNA content			(b) (4)	(b) (4)
mRNA purity				
Product related impurities RNA (b) (4)				
Product related impurities (b) (4)				
(b) (4)				
(b) (4)				
(b) (4)				
(b) (4)				
Lipid Identity SM102				
Lipid Identity Cholesterol				
Lipid Identity DSPC				
Lipid Identity PEG2000-DMG				
Lipid Content SM-102				
Lipid Content Cholesterol				
Lipid Content DSPC				
Lipid Content PEG2000-DMG				
Lipid related impurities				
(b) (4)				
Deliverable volume				
(b) (4)				
(b) (4)				
(b) (4)				
Bacterial endotoxin				
Sterility			No growth	Same
Container Closure Integrity Test			NA	PASS

**Abbreviations:** DSPC, 1,2-distearoyl-sn-glycero-3-phosphcholine; PEG2000-DMG, 1,2-dimyristoyl-rac-3-methoxypolyethylene glycol-2000. LDP, labeled Drug Product; UDP, unlabeled Drug Product; (b) (4)

SOP, standard operating procedure;

(b) (4)

; DP, Drug product,

(b) (4)

**Justification of Specifications:** Specifications for mRNA-1345 DP (UDP-100-AR02 and LDP-100-AR02) were established using (b) (4) for CQAs described in (b) (4) taking into consideration risk assessments, process and product knowledge gained from mRNA-1345 and prior knowledge derived from mRNA-1273 DP. Specifications were also established using clinical experience in setting some limits (such as RNA purity) along with the application of (b) (4) requirements for safety for other attributes. Limits for sequence agnostic attributes were determined using prior knowledge from mRNA-1273 DP. For sequence dependent attributes, acceptance criteria were set to assure consistency with future lots by estimating statistical 95%/99% tolerance intervals approximated by a normal distribution obtained from data accrued across a minimum of (b) (4) mRNA-1345 lots that, in theory, contained 99% of future results with 95% confidence. Limits for (b) (4) are based on the (b) (4) and analytical method capability. Overall, a total of (b) (4) developmental, clinical, PPQ, and registration lots of mRNA-1345 DP were used to set the specifications for release, albeit some lots were excluded from some analyses due to differences in formulation or target specifications in place at the time of manufacture. (b) (4) developmental, PVU, and commercial mRNA-1273 DP lots were used to establish the specifications for release for total RNA and lipid content.

Shelf-life limits for mRNA-1345 DP were set based on mRNA-1345 clinical experience, nonclinical in vivo immunogenicity data, and prior knowledge from mRNA-1273 (using (b) (4) developmental, clinical, and commercial lots). Minimum release limits were then set to assure that the DP meets the shelf-life specification. Justifications for each specification are summarized in **Table 131** below.

(b) (4)



2 pages have been determined to be not releasable: (b)(4)

(b) (4)

**Specification history:** Specifications used to release (b) (4), PPQ/Registration Lots and Commercial lots are compared in **Appendix 8D** along with the rationale for changes.

**A comment was sent to the applicant in IR#23 on February 14, 2024:** *With respect to section 3.2.P.5.6 Justification of Specifications, please describe the statistical approach used to determine the upper and lower acceptance limits for total RNA content by (b) (4) currently set at (b) (4)*

**On February 28, 2024, the applicant provided a response to item #24 in IR#23 in amendment 39, (SN40):** *The specification for RNA content by (b) (4) was set as the target concentration (0.1 mg/mL) (b) (4) to control concentration variability to an acceptable level. The response is acceptable.*

**Reviewer's assessment:** *The description of the specifications for release and stability testing with justifications is complete and no deficiencies are noted.*

### **3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures for mRNA-1345 DP**

The applicant has proposed a platform approach to assay validation for RNA vaccines manufactured using the "100 process". The description of (b) (4) analytical procedures developed for testing mRNA-1273 products and details on their validation or verification can be found in the BLA 125752 CMC review memos from DVP and DBSQC reviewers. The current memo covers method-validation results for (b) (4) methods used for mRNA-1345 materials and qualification data for method transfer to the additional testing sites. Please see the INTRODUCTION to Module 3, pages 5-12, for information pertaining to the review of assay validation and method transfer reports.

**3.2.P.5.4 Batch Analyses for mRNA-1345 DP**

Batch analyses for mRNA-1345 DP included results for (b) (4) lots including (b) (4) clinical lots, PPQ lots manufactured at (b) (4), and (b) (4) additional lots intended for clinical use in future trials. All lots met the specifications for release in place at the time of manufacture. Batch analysis data for mRNA-1345 development lots were placed in the Stability section 3.2.P.7.3. Comparability of lots was discussed under Section 3.2.P.2.3, Manufacturing Process Development for mRNA-1345 DP.

**A comment was sent to the applicant in IR#23 on February 14, 2024:** In section 3.2.P.5.4 Batch Analyses, CoAs were provided for the UDP-100-AR02 PPQ lots manufactured at (b) (4) including lots (b) (4); however, CoAs were not submitted for the corresponding LDP lots. We also note submission of a CoA for clinical lot (b) (4). Please provide the CoAs for each of the (b) (4) mRNA-1345 clinical lots described in the BLA and the CoAs for the (b) (4) PPQ LDP lots.

**On February 28, 2024, the applicant provided a response to item #25 in IR#23 in amendment 39, (SN40):** Section 2.3.P.5.4 Batch Analysis was updated to include two new tables. New Table 2 identifies (b) (4) LDP-100-AR02 COC PFS Commercial Scale Lots manufactured between (b) (4), and (b) (4), at (b) (4) or (b) (4) including lots (b) (4). New Table 4 contains the lot release data for these (b) (4) LDP lots (including identity testing, mRNA purity, (b) (4)). Each lot met the specifications for release. The sponsor also indicated that Certificates of Analysis (CoAs) and Certificates of Testing (CoTs) were attached but these documents were not submitted. Please see IR below.

**A comment was sent to the applicant in IR#35 on March 22, 2024, requesting submission of the missing CoAs and CoTs.** With respect to your response to item 25, pertaining to the CoAs for (b) (4) clinical UDP lots and Certificates of Testing (CoTs) for each respective LDP lot, we note that the CoAs and CoTs were not attached to the submission. Please provide the CoAs for UDP lots (b) (4) and CoTs for LDP lots (b) (4), as intended.

**On April 5, 2024, the applicant provided a response to item #3 in IR#35 in amendment 54 (SN55):** Certificates of Testing (CoTs) for LDP lots (b) (4) were submitted and showed that these lots met the specifications for release including RNA purity and Product-related impurities. Only lots (b) (4) were evaluated for identity and each lot conformed. CoAs for UDP lots (b) (4) (ModernaTX Lot (b) (4)), (b) (4) (ModernaTX Lot (b) (4)) and (b) (4) (ModernaTX Lot (b) (4)) were submitted in the original submission; and each lot met the specifications for release. The response is acceptable.

**Reviewer's assessment:** Batch analyses results demonstrated that the process is adequately controlled for consistent manufacture of DP with attributes that meet the

*criteria needed for release, that clinical lots manufactured at the (b) (4) facility are comparable to commercial lots manufactured at the facility in (b) (4). These data also support the conclusion that the quality of mRNA-1345 DP lots are comparable to the quality of mRNA-1273, SPIKEVAX, lots.*

### **3.2.P.5.5 Characterization of Impurities for mRNA-1345 DP**

The impurity profile of mRNA-1345 DP is the same as the impurity profile of LNP-100-AR02 (discussed in the DS section immediately preceding this section) because no new impurities are formed or introduced during manufacture of the DP. Product-related particulates may form in the DP due to (b) (4) during preparation. (b) (4)

Particulates are controlled as part of release and stability testing as discussed under Section 3.2.P.5.1, Specifications.

### **3.2.P.6 Reference Standards or Materials for mRNA-1345 DP**

The mRNA-1345 RNA reference material is used as a system suitability standard for the following test methods for DP release:

- mRNA purity by (b) (4)
- Total RNA content by (b) (4)
- RNA impurities by (b) (4) can also be identified using this (b) (4), as the (b) (4) of the DP containing (b) (4) shows a (b) (4)
- RNA Reference Standard lots include the following:
  - (b) (4)
  - (b) (4)
  - (b) (4)
  - (b) (4)
- CoAs were provided for each RNA reference standard lot described above.
- Reference standards for lipids SM-102, cholesterol, DSPC, and PEG2000-DMG are used for lipid identity and content testing and are discussed under the DS section for (b) (4).

### **3.2.P.7 mRNA-1345 DP Container Closure System**

The primary container closure system consists of 1 mL COC syringe, 1-mL rubber plunger stopper and a polypropylene plunger rod. Please also see the detailed device review by Dr. Andrea Gray that includes 1) a discussion of device performance and verification testing (deliverable volume, (b) (4)) including performance across the shelf-life and after shipping; 2) a review of the control strategy to ensure that the device meets performance specifications; 3) a review of device biocompatibility (but not extractables and leachables and not CQA's related to DP compatibility); 4) compliance with regulations that define design controls ( 21 CFR 820.30 ) and purchasing controls (21 CFR 820.50).

**Syringe:** The 1 mL syringe with rigid tip cap is a (b) (4) device manufactured by (b) (4) filed under DMF (b) (4). It is composed of high-tech-cyclic olefin copolymers (COC); the raw materials are not of human or animal origin and are not exposed to any human or animal origin materials during manufacture, handling or transportation. COC complies with (b) (4) and carries minimal risk of transmitting the agents associated with TSE/BSE per statements from the manufacturer. Empty, ready-to-use syringe barrels are received sterile in plastic tubs with polypropylene nests and (b) (4) lids. Syringes are siliconized and sterilized by (b) (4) to achieve a sterility level of (b) (4).

Syringes comply with (b) (4)

Specifications for release include (b) (4)

**Tip cap:** The rigid tip cap (part number (b) (4)) is manufactured separately by (b) (4) and does not come in contact with the DP. Shelf-life of empty, sterilized syringes is (b) (4). (b) (4) used as a lubricant is (b) (4) and is qualified per (b) (4). Rubber components are latex free and tested per (b) (4).

**Plunger/Stopper:** The 1-mL long plunger stopper is manufactured by (b) (4), and is received sterilized and ready-to-use. The plunger stopper is made of gray, halobutyl/bromobutyl rubber with a fluorotec coating. The gray rubber (formulation # (b) (4)) and fluorotec coating ((b) (4)) meet the following specifications (b) (4)

(b) (4), and (b) (4). Identity is confirmed by (b) (4) analysis. Materials are not derived from and do not contact materials of human or animal origin. Plungers are sterilized via (b) (4) per (b) (4). The plunger stopper is compliant with (b) (4).

Specifications for release include (b) (4)

**Plunger rod:** The plunger rod is manufactured by (b) (4) in (b) (4). The rod is made of polypropylene and is considered safe with respect to BSE /TSE risk as it complies with section (b) (4). Plunger rods arrive ready to use but are not sterile upon arrival. Plunger rods meet specifications per (b) (4).

**Secondary packaging:** LDP-100-AR02 is labelled, a total of 2 PFS are sealed within a blister, five (5) blisters are packaged in a carton for a total of 10 syringes in a 2x5 configuration. One patient information leaflet (PI) is placed in each secondary carton. Sixteen cartons are placed into a case for a total of 160 PFS per case.

**Two comments (items 26 and 27) were sent to the applicant in IR#23 on February 14, 2024.**

**Item#26:** Documents pertaining to the technical specifications for the plunger stopper (Document QER 122180) and plunger rod (Document QER 12167) were not available at the link provided in the BLA. Please provide the technical specification documents for

these two items as intended.

**On February 28, 2024, the applicant provided a response to item #26 in IR#23 in amendment 39, (SN40):** The technical specification documentation for the syringe and plunger rod, QER 12180 and QER 12167, respectively, were submitted and reviewed. The response is acceptable.

**Item #27:** Please provide the CoA for the plunger rod and information pertaining to rod sterilization prior to insertion into the syringe. If rods are not sterilized prior to use, please update this section to note that this is the practice.

**On February 28, 2024, the applicant provided a response to item #27 in IR#23 in amendment 39, (SN40):** The Certificate of Conformance, EXT-13884, was submitted under Regional Information. The plunger rod is manufactured for ModernaTX by (b) (4) in (b) (4). The plunger rod is not sterile. The response is acceptable.

### 3.2.P.8 mRNA-1345 DP Stability

#### 3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data

The proposed **initial shelf life for mRNA-1345 DP is 18 months** stored in COC prefilled syringes at -40°C to -15°C including up to 30 days at 2°C to 8°C and up to 24 hours at room temperature (15°C to 25°C) to support vaccine administration at the point-of-care site.

The quality attributes assessed during stability testing include all the parameters used for DP release except for RNA identity, lipid identity, deliverable volume, and (b) (4), with sterility testing replaced by CCI testing at some time points. The most sensitive indicator of product stability and potency is the test for mRNA purity by (b) (4) which measures (b) (4)

as well as

(b) (4)

Stability studies measure (b) (4) and these data are used to assess RNA (b) (4). So far, the data demonstrate that RNA (b) (4) occur independent of manufacturing site, scale, process, concentration, and container closure system. The (b) (4) is also expected to be independent of minor changes in RNA sequence (for example, (b) (4))

In contrast, formulations may impact RNA stability and half-life. Accordingly, (b) (4) lot (b) (4) was manufactured as a lyophilized DP using a different formulation than used subsequently and is considered separately and not included in the stability summary tables below. (b) (4) estimates were derived from routine stability testing of developmental, clinical, and commercial DP lots. Based on the available mRNA (b) (4), additional Stability Modeling Studies were performed to assess the lower DP potency (i.e., mRNA purity) limit at release and at expiry.

**Stability data for PPQ/registration lots:** Data are presented for (b) (4) PPQ lots in **Table 132** below. All lots were manufactured at (b) (4).

(b) (4)

**Stability data for clinical lots:** Data for (b) (4) clinical lots including (b) (4) AR01 lots and (b) (4) AR02 lots are summarized in **Table 133** below. Lots were manufactured at ModernaTX, (b) (4) or at (b) (4) as noted in the Table below. Stability data for (b) (4) Generation lot (b) (4), manufactured as a (b) (4) DP using a different formulation, are not included below and only data for liquid frozen DP lots are shown.

**Table 133. Stability Testing Summary for UDP-100-AR01/AR02 Clinical Lots.**

RNA ID	Lot #	DOM	Site	Container	Temperature	Duration Months (m)	Data Available Through LTT	Results Reviewed
(b) (4)	(b) (4)	(b) (4)	ModernaTX	(b) (4)	-25°C to -15°C	(b) (4)	12 m	*SALTT
			Moderna TX		2°C to 8°C		(b) (4)	SALTT
			(b) (4)		-25°C to -15°C		12 m	SALTT
			(b) (4)		2°C to 8°C		(b) (4)	SALTT
			ModernaTX		-25°C to -15°C		6 m	SALTT
			ModernaTX		2°C to 8°C		(b) (4)	SALTT
			ModernaTX		-25°C to -15°C		3 m	SALTT
			ModernaTX		2°C to 8°C		(b) (4)	SALTT
			ModernaTX		-25°C to -15°C		3 m	SALTT
			ModernaTX		2°C to 8°C		(b) (4)	SALTT
			(b) (4)		-25°C to -15°C		T0	MS
			(b) (4)		2°C to 8°C		1 m	SALTT

**Abbreviations:** RNA ID refers to the RNA identification code within the (b) (4); DOM, date of manufacture; m, months; UDP, unlabeled drug product; m, months, \* LTT last timepoint tested. \*SALTT: Stable at last timepoint tested (met specifications for shelf-life as described in Section 3.2.P.5.1, Specifications.) OOS results are cited numerically (OOS1, OOS2, etc.). Results submitted to the BLA were reviewed by this CMC reviewer. \*SALTT: Stable at last timepoint tested (met specifications for shelf-life as described in Section 3.2.P.5.1, Specifications.) OOS results, if noted, are listed numerically. MS: met specification for release.

**Stability data for development lots:** Data are presented for (b) (4) development lots in **Table 134** below. All development lots described below were manufactured at ModernaTX, (b) (4).

(b) (4)



One page has been determined to be not releasable: (b)(4)

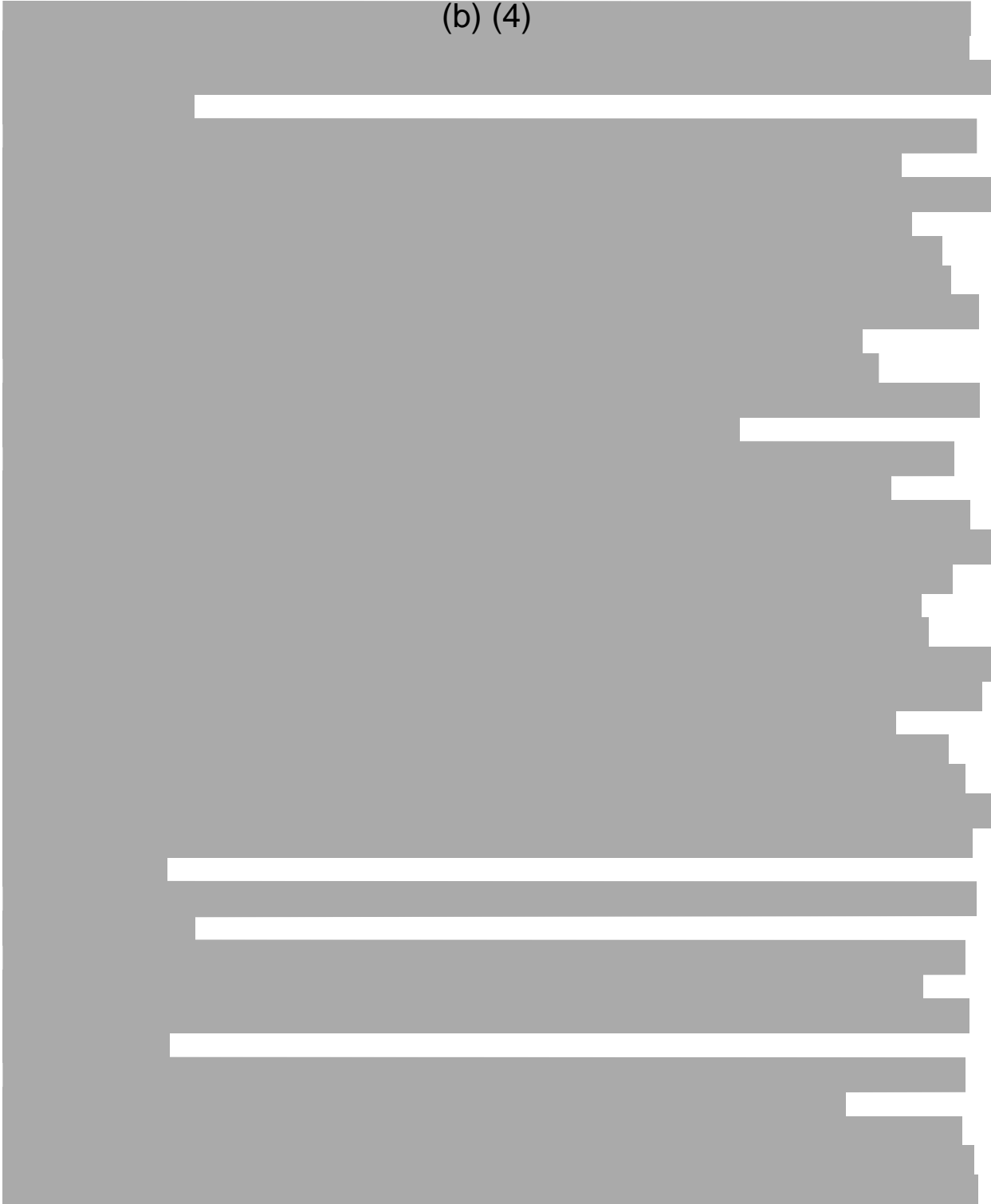
(b) (4)

**Stability Modeling Studies:**

Modeling studies support the intended long-term storage conditions of -40°C to -15°C represented by -25°C to -15°C stability data and confirm that the primary stability indicating attributes is mRNA purity. Significant stability indicating trends were also noted for RNA fragments, RNA (b) (4), and total lipid impurities at -25°C to -15°C and under accelerated conditions at 2°C to 8°C and 23°C to (b) (4)°C, but the degree of change for these attributes does not limit shelf-life. RNA (b) (4) was stability indicating with decreases observed at 2°C to 8°C only. The remaining attributes were not stability indicating with no trends observed at any of the temperatures tested: RNA content, (b) (4), lipid content, (b) (4), bacterial endotoxin, (b) (4), sterility, and container closure integrity.

*Study design:* (b) (4)

(b) (4)



**Minimum Release Limit and Shelf-life:** The shelf-life specification for mRNA purity of (b) (4) is based on clinical results, and in vivo results demonstrating that efficacy and immune responses are not impacted by variation in mRNA purity values above this specification as described in Section 3.2.P.5.6, Justification of Specification. mRNA

purity (b) (4) data was used to compute (i.e., back calculate) the minimum release limit (MRL) for vaccine potency using the formula provided in the (b) (4) guideline on stability evaluation of vaccines, (b) (4), adapted and as shown below:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Based on the modeling data and calculation the estimated MRL for %mRNA purity based on 17 months at -40°C to -15°C, 1 month at 2°C to 8°C and 24 hours at 15°C to 25°C is (b) (4) **The proposed DP release limit is set at an mRNA purity of (b) (4) that exceeds the minimum purity determined by calculation of (b) (4).**

Shelf-life may be extended if the testing results at additional time points in registration and post approval stability protocols follow the stability specifications, if the testing was performed in accordance with the post-approval stability protocol and if these data are submitted in a BLA Annual Report.

**Stability after Photostability Stress:** Discussed under Section 3.2.P.2.2. Based on these studies, a precautionary statement to protect the DP from light is included in the package insert.

**Stability after Freeze-Thaw Stress:** The stability of the DP in COC PFS was evaluated per (b) (4). *Study design:* (b) (4)

(b) (4). *Results:* DP in COC PFS met all acceptance criteria even after (b) (4) cycles at either 2°C to 8°C or 23°C to (b) (4).

**End-to-End Stability Study:** The end-to-end stability studies using both UDP-100-AR02 and LDP-100-AR02 to demonstrate stability at 2°C to 8°C and 23°C to (b) (4) following (b) (4) were initiated, however, data have not yet been submitted to the BLA for review.

*Study design:* There are (b) (4) components for the proposed end-to-end stability study:  
(b) (4)

Please see the IR below regarding the commitment for submission of these data as a product correspondence.

### 3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment

ModernaTX commits to placing a minimum of (b) (4) on stability (b) (4). Samples of UDP-100-AR02 that pass visual inspection will be selected for stability testing. Both UDP and LDP may be sampled for stability testing purposes. (b) (4) of lots on stability are monitored to verify the rate of fall. End-to-end stability testing will consist of samples placed at -25°C to -15°C for 17 months then transferred to 2°C to 8°C for 1 month followed by transfer to 23°C to (b) (4) for 24 hours. The testing protocols at each temperature are shown in **Tables 135, 136 and 137** below:

**Table 135. Stability testing for LDP-100-AR02 (-25°C to -15°C)**

Test Method	Initial	1 M	3 M	6M	9 M	12 M	17 M
Appearance by Visual Inspection	X	X	X	X	X	X	X
(b) (4)	X	X	X	X	X	X	X
mRNA Purity by (b) (4)	X	X	X	X	X	X	X
Product-Related Impurities by (b) (4)	X	X	X	X	X	X	X
(b) (4)	X	X	X	X	X	X	X
(b) (4)	X	X	X	X	X	X	X
(b) (4)	X	N/A	X	N/A	N/A	X	X
(b) (4)	X	N/A	X	N/A	N/A	X	X
Total RNA Content by (b) (4)	X	N/A	X	N/A	N/A	X	X
Lipid Content and Lipid Impurities by (b) (4)	X	X	X	X	X	X	X
Bacterial Endotoxins by (b) (4)	X	N/A	X	N/A	N/A	X	X
(b) (4) by (b) (4)	X	N/A	X	N/A	N/A	X	X
(b) (4)	X	N/A	N/A	N/A	N/A	X	X
(b) (4)	X	N/A	N/A	N/A	N/A	X	X
Container Closure Integrity	X	N/A	N/A	N/A	N/A	X	X
Sterility by (b) (4)	X	N/A	N/A	N/A	N/A	N/A	N/A

**Abbreviations:** X= required per stability protocol; N/A= not required per stability protocol; M, month. LDP, labeled Drug Product; UDP, (b) (4)

**Table 136. Stability testing for LDP-100-AR02 (2°C to 8°C)**

Test Method	Initial test at T0	Test at 1 month
Appearance by Visual Inspection	X	X
(b) (4)	X	X
mRNA Purity by (b) (4)	X	X
Product-Related Impurities by (b) (4)	X	X
(b) (4)	X	X
(b) (4)	X	X
(b) (4)	X	X
(b) (4)	X	X
Total RNA Content by (b) (4)	X	X
Lipid Content and Lipid Impurities by (b) (4)	X	X
Bacterial Endotoxins by (b) (4)	X	X
(b) (4)	X	X
(b) (4)	X	X
(b) (4)	X	X
Container Closure Integrity	X	X
Sterility by (b) (4)	N/A	N/A

**Abbreviations:** X= required per stability protocol; N/A= not required per stability protocol; M, month. LDP, labeled Drug Product; UDP, (b) (4)

**Table 137. Stability testing for LDP-100-AR02 (25°C to (b) (4))**

Test Method	Time Point: 24 hours
Appearance by Visual Inspection	X
(b) (4)	X
mRNA Purity by (b) (4)	X
Product-Related Impurities by (b) (4)	X
(b) (4)	X
(b) (4)	X
(b) (4)	X
(b) (4)	X
Total RNA Content by (b) (4)	X
Lipid Content and Lipid Impurities by (b) (4)	X
Bacterial Endotoxins by (b) (4)	X
Particulate Matter by (b) (4)	X
(b) (4)	X
(b) (4)	X
Container Closure Integrity	X
Sterility by (b) (4)	X

**Abbreviations:** X= required per stability protocol; N/A= not required per stability protocol; M, month. LDP, labeled Drug Product; UDP, (b) (4)

**The following three comments (items 28, 29 and 30) were sent to ModernaTX in IR#23 on February 14, 2024.**

**Item #28:** In section 3.2.P.8.3 Stability Data, Table 49 shows the stability testing results for development lot (b) (4) at 2°C to 8°C; however, the results for appearance at 2 weeks, 1 month, (b) (4) were not provided. Please provide the results for appearance for these timepoints or update the table to include a footnote explaining

the reason for the missing data.

**On February 28, 2024, the applicant provided a response to item #28 in IR#23 in amendment 39, (SN40):** The applicant updated Section 3.2.P.8.3 with all available stability data for the PPQ lots (see response to item #29 below for stability data for the PPQ lots). The data for appearance previously missing for Lot (b) (4) stored at 2°C to 8°C is now supplied. The applicant also notes the re-organization of stability data for commercial and clinical scale lots in the main body of section P.8.3 with data for all development lots now shown as an addendum to this section. The response is acceptable.

**Item #29:** With respect to the three planned end-to-end stability studies described in section 3.2.P.8.1,

- a. Please provide a commitment to submit the final study reports and an estimated date for their submission.
- b. Please provide a commitment to submit the interim stability data from the end-to-end study that will include transfer of samples after 12 and 18 months of storage at -25°C to -15°C and an estimated date for their submission.
- c. The data in items “a” and “b” may be submitted as a product correspondence or as part of a prior approval supplement if used to support implementation of a shelf-life extension of the DP. Please acknowledge.

**On February 28, 2024, the applicant provided a response to item #29 in IR#23 in amendment 39, (SN40):** The applicant commits to providing the final study reports for the end-to-end stability study described in Section 3.2.P.8.1 mRNA-1345 DP with an estimated submission date of September 2025. The applicant commits to submitting an interim study report in June 2024 (for the 12month report) and in December 2024 (for the 18month report). The applicant will submit this information as product correspondence or as part of a prior approval supplement if used to support a shelf-life extension of the DP.

**Item #30:** With respect to the ongoing stability studies for PPQ DP lots (b) (4) covered in section 3.2.P.8.3,

- a. Please provide currently available stability data.
- b. Please provide a commitment to submit the final stability report and an estimated date for submission. The report may be submitted as a product correspondence or as part of a prior approval supplement if used to support implementation of a shelf-life extension of the DP.

**On February 28, 2024, the applicant provided a response to item #30 in IR#23 in amendment 39, (SN40):** The applicant updated Section 3.2.P.8.3 to contain the requested stability data for DP PPQ lots (b) (4) through (b) (4) at (b) (4) to -30°C, -25°C to -15°C and at 2°C to 8°C. I reviewed these data and noted that each of the three PPQ lots remained stable through (b) (4) at each of the three temperature conditions tested. In contrast, each of the (b) (4) lots had values for mRNA purity and RNA fragments that were out of specification after (b) (4) at 23°C to (b) (4) as expected; (b) (4)

(b) (4) by any lot held at 23°C to (b) (4) for (b) (4). The data for labeled DP PPQ lots are still pending. ModernaTX commits to provide updated stability data on the PPQ lots in their annual reports. The response is acceptable.

The applicant also requested a telecon to precede the Late Cycle Meeting on March 11, 2024, to discuss a shelf-life extension to support (b) (4) at 2°C to 8°C. We agreed with the applicant's alternative plan to submit these data for review immediately upon approval of the BLA. While the applicant proposed to submit these data to the BLA "as a CBE-30 immediately upon approval", we recommended that they submit the shelf-life extension request as a PAS (see additional details below).

**On March 22, 2024, the following comment was sent to the applicant in IR#35:**

With respect to your response to item 30.a, pertaining to the updated stability data and commitment to submit final study reports for the (b) (4) DP PPQ lots, we are not able to undertake the review of the additional stability data to modify the storage recommendations to accommodate (b) (4) at 2°C to 8°C at this point in the review cycle. Therefore, please submit a PAS/CBE-30 supplement to support the implementation of this change upon approval of the BLA.

**On April 5, 2024, the applicant provided a response to item 4 in IR#35 in amendment 54 (SN55):**

The response acknowledged that it was not possible for FDA to consider additional stability data at this time to accommodate a change for the storage recommendation to include up to (b) (4) at 2 °C to 8 °C. Given that this change would require a change to the USPI, ModernaTX requested additional feedback to obtain clarity on the reporting category (PAS vs CBE30) for this change. **On April 10, 2024, Dr. Santosh Nanda sent a response to the applicant** informing them that the additional stability data and proposed extension of allowable storage for MRESVIA from (b) (4) at 2°C to 8°C and the request to update the USPI should be submitted as a PAS. ModernaTX acknowledged receipt of this advice.

**Reviewer's Assessment of Section 3.2.P.8:** Ongoing stability testing studies support the proposed initial shelf life for mRNA-1345 DP of 18 months stored in COC prefilled syringes at -40°C to -15°C including up to 30 days at 2°C to 8°C and up to 24 hours at room temperature (15°C to 25°C) albeit end to end stability testing has yet to be performed to verify stability across these temperatures in sequence.

**Inspection request:** Due to the numerous stability studies that are ongoing, I e-mailed an inspection recommendation to Damaris Lopez Rosario, DMPQ, on March 5, 2024, requesting that the DS and DP stability data be reviewed during future inspections of any of the facilities involved with DS and DP manufacture of ModernaTX's RSV vaccine.

## 3.2.A APPENDICES

### 3.2.A.1 Facilities and Equipment:

We defer to DMPQ for review of these materials.



### 3.2.A.2 Adventitious Agents Safety Evaluation

See Sections 3.2.S.2.3 Control of Materials for DS RNA-100-AR02, DS SM102, DS mPEG2000-DMG, DS (b) (4) and DS LNP-100-AR02 and section DP mRNA-1345 Section 3.2.P.4.5. excipients of human and animal origin. No human or animal derived raw materials were used in the manufacture of the DS intermediates or excipients or introduced during manufacture of the DP. All materials with direct product contact were certified to be free of human and animal derived raw materials or they were manufactured using materials (such as tallow) that met (b) (4) criteria and are considered very low risk for BSE/TSE.

**Viral Clearance Studies: Viral clearance studies not applicable to this product.**

### 3.2.A.3 Novel Excipients:

No novel excipients are used in the manufacture of MRESVIA.

## 3.2.R Regional Information (USA)

### 3.2.R.1 Executed Batch Records:

I reviewed the batch records that support the manufacture of UDP-100-AR02 DP lot (b) (4) (b) (4) Lot # (b) (4) ) manufactured at the (b) (4) scale.

The following documents were reviewed:

- RNA-100-AR02 Lot (b) (4) , manufactured at ModernaTX included separate batch records for each manufacturing step including, (b) (4)
- (b) (4) , manufactured at ModernaTX, had separate batch records for each manufacturing step including (b) (4)
- LNP-100-AR02, Lot (b) (4) , manufactured at ModernaTX had separate batch records for each manufacturing step including (b) (4)
- UDP-100-AR02, (b) (4) Lot (b) (4) /ModernaTX Lot (b) (4) had a single batch record for Product Protocol Stages (b) (4)  
(This document was written in Spanish with some translation of the printed text.)

**Reviewer's assessment:** *The Batch records document all raw materials used during each process step. The volume and or quantities of critical materials are listed. All calculations are shown. In-process parameters are described. Time out of refrigeration and time at 2°C to 8°C are listed at each step albeit hold-times for the process overall are not summed in the batch record. Minor deviations are noted. The process is for the most part fully automated; equipment alarms were common and noted. Alarms were not indicative of an equipment malfunction or other underlying problems; most alarms were inactivated after supervisory notification and the process continued without interruption.*

### Method Validation Packages

Validation Reports submitted in support of the manufacturing process at ModernaTX, and (b) (4) for mRNA-1345 DP, LNP-100-AR02, (b) (4) and RNA-100-AR02 and DS intermediates such as SM-102 and PEG2000-DMG manufactured by (b) (4) were reviewed by J. Beeler.

Validation of Analytical Procedures including the assessment of the Platform Approach to Assay Validation for mRNA-100 vaccines were reviewed by A. Dabrazhynetskaya, DVP, and reviewers in DBSQC.

**Combination Products:** MRESVIA is a combination product that consists of the biological DP mRNA-1345 filled into a device, a 1mL COC syringe, for administration intramuscularly. Please see the review by Dr. Andrea Gray for details concerning the PFS device design, history, verification testing and risk analysis studies.

### **3.2.R.2 Comparability Protocols:**

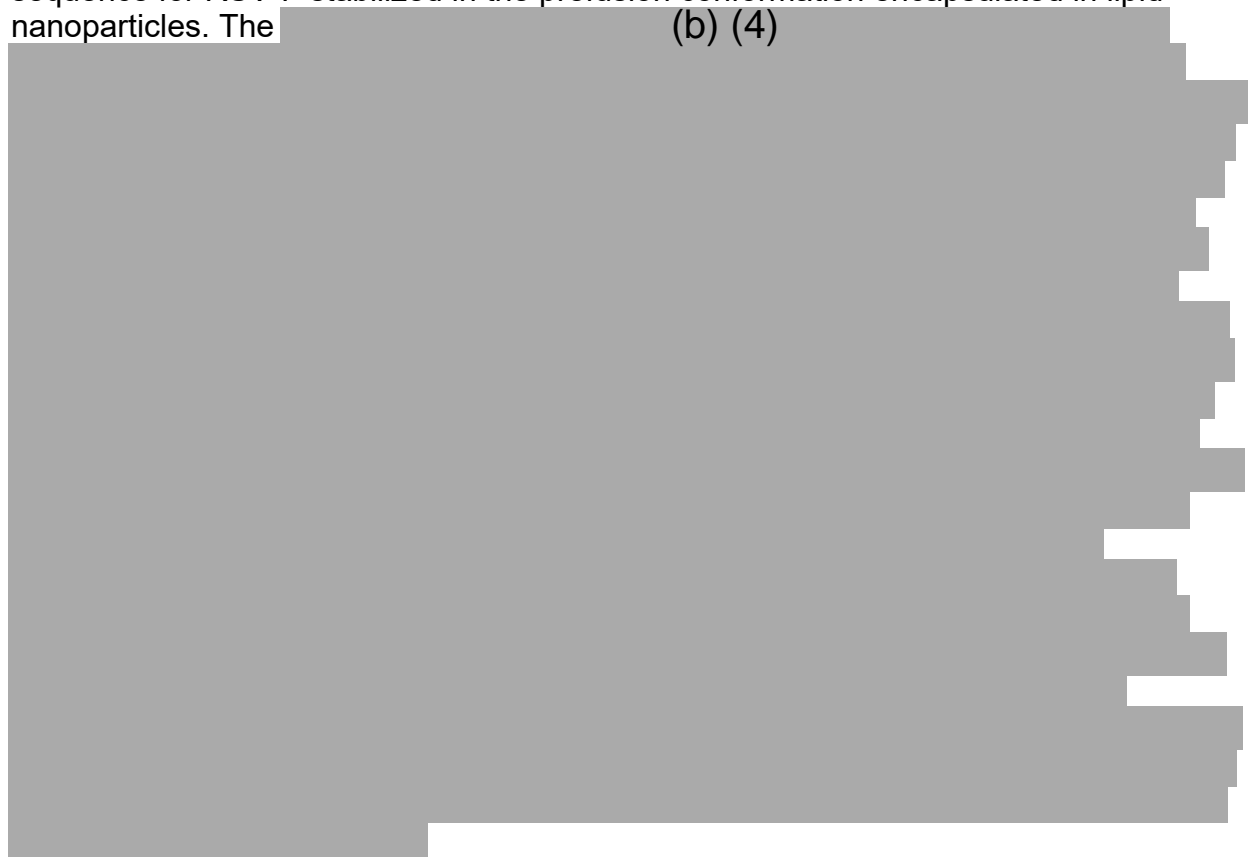
Not applicable to this application.

### **Other eCTD Modules**

#### **Module 1**

### **3.2.R.3 Environmental Assessment or Claim of Categorical Exclusion**

The applicant has requested a categorical exclusion from the Environmental Assessment pursuant to 21CFR25.31(c). MRESVIA consists of mRNA encoding the sequence for RSV-F stabilized in the prefusion conformation encapsulated in lipid nanoparticles. The (b) (4)



The LNP vaccine is administered intramuscularly as 0.5mL targeted to contain ~50mcg of mRNA-1345 and ~ 1mg of total lipid per dose in 20mM Tris buffer (composed of Tromethamine and Tromethamine-HCl), 87g/L sucrose, and (b) (4) mM acetate at pH (b) (4). The vaccine is indicated for active immunization of adults 60 years of age and older for the prevention of lower respiratory tract disease (LRTD) due to RSV.

The RSV-prefusion protein exists, albeit transiently, in nature on the virus and in virus infected cells. Total lipids (1.02 mg/dose) and cholesterol ((b) (4)) mg/dose) in the lipid nanoparticle are a small fraction of the allowable daily intake of lipids and fats for adults (~200-300 mg total depending on health status). Lipids are metabolized and/or excreted in bile into the digestive tract. mRNA encoding the RSV-F protein is not infectious and has a half-life of about three days in vivo following vaccine administration and is degraded by RNase in vivo. The concentration or distribution of MRESVIA RNA and/or the associated lipids, metabolites and degradation products do not significantly impact the environment and therefore do not require an environmental assessment.

### 3.2.R.4 Reference Product Designation Request

The applicant requested reference product exclusivity since there are currently no other licensed mRNA vaccines that are structurally related to MRESVIA. The CMC reviewer recommended that the request be granted with a period of exclusivity of 12 years. On March 26, 2024, the request was reviewed by the ADRAM committee, and they agreed to grant the request.

**Reviewer's assessment:** *Reference product exclusivity is recommended.*

Receipt date: September 12, 2023

CMC review completed: November 17, 2023

DVRPA review completed: December 21, 2023

ADRAM meeting: March 26, 2024

### 3.2.R.5 Labeling Review

The CMC-related information in the Full Prescribing Information (PI) and carton and container labels were reviewed and input was provided to the DVRPA review team.

## 4.0 Non-Clinical Studies

This section summarizes the four non-clinical studies covering the immunogenicity, safety, efficacy, bio-distribution and metabolic profile of the RSV mRNA-1345 vaccine. mRNA-1345 encodes the RSV F glycoprotein stabilized in the prefusion conformation. Most non-clinical studies were conducted using the (b) (4) of the mRNA ((b) (4)) which (b) (4) the mRNA used for manufacture of the commercial product under BLA review ( (b) (4) ). As explained in Module 3, (b) (4)

Please see the review by Dr. Nabil-Al-Humadi for toxicology studies.

The study reports submitted to the BLA are shown in **Table 138** below along with a reference to previous submissions to IND 23342 or (b) (4) as applicable. Since the

identity of the lots used for each specific non-clinical study was not clear, a comment was sent to the applicant:

**On February 14, 2024, the following comment was sent in IR #23 (comment #31):** With respect to the clinical data submitted in Module 4, please provide a list of all mRNA DP lots used in the non-clinical studies.

**On February 28, 2024, the applicant provided a response in amendment 39 (sequence 40):** DP lots DHM-45266, DH-10855.1 and DHM-72202 were used in non-clinical studies. The applicant provided an updated Table 2, Development Manufacturing History-Development mRNA-1345 DP, in Section 3.2.P.2.3 Manufacturing Process Development {Manufacturing History} identifying the lots used in the non-clinical studies. However, Table 2 was not found to be completely accurate since several DP lots used in non-clinical studies were not listed.

**A follow-up comment was sent to the applicant on March 22, 2024 in IR # 35:** We requested further clarification of all lots used in non-clinical studies.

**On April 5, 2024, the applicant provided a response in amendment 54 (sequence 55):** All mRNA-1345 DP lots used in non-clinical studies were identified; several lots were considered research lots by the applicant and intentionally excluded from Table 2. The response is acceptable.

**Table 138. Overview of Non-clinical Studies**

Study Number	Type	Submission/amendment	mRNA-1345 DP used in the study
3823-1	Immunogenicity of mRNA-1345 in Mice	IND 23342 (original submission)	(b) (4)
5368	In vivo Report: Immunogenicity assessment of mRNA-1345 Lot with (b) (4)	Summary report submitted to BLA 125796	
X-107	Immunogenicity of mRNA- 1345, (b) (4) in (b) (4) mice relative to ERD controls	IND 23342 amendment 38 (seq 39), amendment 52 (seq 52)	
XV-224	Safety, immunogenicity & efficacy of mRNA-1345 in the (b) (4) rat RSV model	IND 23342 amendments 30 (seq 31), 40 (seq 41), 47 (seq 48), 52 (seq 52)	
5002121 protocol amendment 2	A single dose intramuscular injection tissue distribution study of (b) (4) in male (b) (4) rats	(b) (4) (original submission)	N/A
NCS-BA-2022-010	Identification and profiling of metabolites of SM-102 in rat, monkey, and human hepatocytes	(b) (4) amendment 12	N/A
QV-0236-DA-RE	Metabolite profile and identification of SM-102 in rat plasma, urine, and bile following IV infusion of SM-102 containing lipid nanoparticles to male (b) (4) rats	(b) (4) amendment 12	N/A

#### 4.1 Evaluation of Immunogenicity in mice

##### Study 3823-1: In vivo report: Immunogenicity assessment of mRNA-1345 lot with (b) (4)

This study evaluated the immunogenicity of (b) (4) lots of mRNA-1345 in mice including Lots (b) (4) and (b) (4) in a dose de-escalation study as compared with RSVpreF subunit vaccine + alhydrogel (TLR4 ligand) and RSVpreF subunit vaccine + Pam3cys (TLR1/2 ligand).

**Study Design:** 6- to 8-week-old (b) (4) mice were immunized with 0.625µg, 1.25µg, or 2.5µg per animal of the test article IM on study days 1 and 22. Blood was collected from each animal on study days 21 and 36. The following immunogenicity endpoints were assessed: RSV neutralization, RSV-preF IgG, RSV-preF IgG1, RSV-preF IgG2a, ratio of RSV-preF IgG2a/IgG1, RSV-post F IgG, ratio of neutralization/(b) (4) preF IgG and ratio of neutralization/(b) (4) post-F IgG. The mRNA-1345 vaccine represents (b) (4) according to (b) (4).

. For the comparator, (b) (4) lots of RSV-preF protein (representing (b) (4)) were produced using (b) (4). (b) (4) confirmed these proteins were in the prefusion conformation. The purified (b) (4) was diluted in (b) (4).

##### Results:

**RSV neutralization titers:** On day 36 all mice given mRNA-1345 doses of 0.2µg/dose or greater developed serum neutralizing antibodies against RSV A2 in a dose dependent manner. Titers in mice given liquid and (b) (4) mRNA-1345 vaccine were similar. Both (b) (4) vaccines induced anti-RSV neutralizing antibodies in all mice with higher titers observed in the group given RSV-preF + Pam3cys than those given RSV-preF + alhydrogel. Titers observed following immunization with both mRNA-1345 formulations (liquid vs. (b) (4)) at 5µg/dose were similar to those seen following immunization with 10µg of RSVpreF protein.

**RSV-preF IgG (binding) titers: Anti-RSV-preF IgG titers followed** a pattern similar to that seen for the serum neutralizing antibody response.

**RSV preF IgG subclasses:** At all dose levels, mRNA-1345 induced similar anti-RSV-preF IgG1 and IgG2a antibody responses that indicated a balanced Th1/Th2 type response. In contrast, (b) (4) induced only IgG1 antibodies indicating a dominant Th2 type cytokine response. Interestingly, (b) (4) induced a more balanced IgG1/IgG2a response. Immunization with either 5µg or 1µg mRNA-1345 induced higher specific IgG2a/IgG1 ratios [1.3 and 1.2, respectively] than (b) (4) [0.087] and (b) (4) [0.0014] indicative of a strong Th1-type cytokine response following immunization with the mRNA vaccine.

**Neutralizing/binding (b) (4) titer ratios** were similarly high for mRNA-1345 liquid and (b) (4) formulations at doses of 5µg and 1µg while the ratios observed at lower mRNA doses were low and more like those seen for preF subunit adjuvanted vaccine with alhydrogel as shown in **Table 139** below.

**Table 139. Ratio of Group GMTs for Anti-RSV Neutralizing to pre-F or post-F IgG responses**

Vaccine	mRNA-1345 liquid µg/dose				mRNA-1345 (b) (4) µg/dose				(b) (4) µg/dose	(b) (4) µg/dose
	5	1	0.2	0.1	5	2	0.2	0.1	10	10
N:preFlgG	1.43	0.97	0.20	0.13	3.00	1.39	0.26	0.37	0.22	0.82
N:postFlgG	0.98	1.15	0.12	0.17	2.98	1.83	0.27	0.23	0.58	3.18

Abbreviations: N, neutralizing antibody titers

**Reviewer's analysis:** mRNA-1345 was immunogenic in mice and, at high doses, elicited anti-RSV-F IgG subclass responses reflecting a balanced Th1/Th2 type response. Adults aged 60 and older are the intended target population for this vaccine. Since this target group has experienced RSV multiple times during their lifetime, enhanced respiratory disease (ERD) is not a concern even though low ratios of anti-RSV-neutralizing to (b) (4) IgG antibody responses were seen in the groups given low doses (0.2 µg/dose and 0.1 µg/dose) of mRNA-1345 (both liquid formulation and lyophilized vaccine).

**Study 5368: In vivo report: Immunogenicity assessment of mRNA-1345 lot with (b) (4)**

This study compared the immunogenicity of RSV mRNA-1345 (b) (4) in (b) (4) mice. Animal immunizations occurred at (b) (4) while serology testing occurred at Integrated (b) (4). Data were transferred back to Moderna for statistical analysis.

**Study Design:** 8-week-old female (b) (4) mice (N=12 per group) were immunized IM on days 1 and 22 with 50 µL containing either 2.5 µg, 1.25 µg or 0.63 µg per mouse of test article consisting of RSV mRNA-1345 (b) (4) (Lot (b) (4)) or (b) (4) (Lot (b) (4)). Six mice were immunized with PBS as control. Blood was collected on days 21 and 36 and serum tested for RSV anti-F IgG antibodies by (b) (4). Briefly, mouse sera were (b) (4)

Antibody titers were expressed as antibody units/mL and calculated using four-parameter logistic regression derived from the standard curve.

**Results:** RSV anti-F IgG antibody responses were dose dependent following immunization with each vaccine at both time points with higher antibody titers seen following the second dose. The antibody responses observed were similar across lots (b) (4). Equivalence tests compared antibody titers obtained post-dose 1 (Day 21) and post-dose 2 (Day 36) and at each dose level (2.5 µg, 1.25 µg or 0.63 µg per mouse). All pairwise comparisons were statistically equivalent with the two-sided CIs of the GMT ratios falling within the three-fold equivalence region of 0.33 to 3.0; most CIs fell within a tighter two-fold range of 0.5 to 2.0.

**Reviewer's analysis:** Study 5368 demonstrated that mRNA-1345 (b) (4) induced similar RSV anti-F IgG antibody responses in a dose-dependent manner. Pairwise comparisons between the two groups fell within the three-fold equivalence margin, suggesting GMTs were statistically equivalent.

**Study X-107: Immunogenicity of mRNA-1345, (b) (4) in (b) (4) mice relative to ERD controls. [This study was originally dated June 6, 2022/amendment 1 dated Sept 1, 2022, in IND 23342]**

**Note:** This study evaluated (b) (4) candidate mRNA vaccines however, only mRNA-1345 and the appropriate RSV controls are reviewed below. This study evaluated the immunogenicity of the mRNA-1345 vaccine in comparison to (b) (4) in the (b) (4) mouse model. (b) (4) serve as positive controls for vaccine-enhanced respiratory disease (ERD) whereas live viruses serve as negative controls for ERD.

**Study design:** Groups of female (b) (4) mice (N=8) were given intramuscular (IM) immunization using mRNA-1345, phosphate buffered saline (PBS), (b) (4) on Days 0, 21 and 49. Wild-type RSV (10e5 pfu intranasal [IN] was given on Day 0 only. All vaccinated and control animals were bled on Days -7, 21, 35 and 56 and spleens were collected on Day 56. The following immunogenicity endpoints were determined on Day 35 or 56: RSV preF-specific -IgG, -IgG1 and -IgG2a titer by (b) (4), RSV post-F-specific IgG titer by (b) (4), RSV A2 neutralization titer, RSV preF-specific IgG:neutralization titer ratio, RSV post-F-specific IgG:neutralization titer ratio, RSV-preF-specific IgG1:IgG2a titer ratio, RSV post-F-specific IgG1:IgG2a titer ratio, RSV preF-specific IgG:postF-specific IgG titer ratio, RSV F-specific CD8+, CD4+ Th1 and Th2 cell responses measure by (b) (4). Animals were housed and experiments conducted at (b) (4). Serology testing was performed at (b) (4) (neutralization assays) while (b) (4) testing were performed in (b) (4) labs.

**Results:** RSV mRNA-1345 administered at 5µg/dose IM was strongly immunogenic in mice eliciting high titers of neutralizing, anti-RSV-preF and anti-RSV-post F IgG antibodies. Ratio of anti-RSV-preF IgG to neutralizing antibody was >1 while the ratio of anti-RSV-postF IgG to neutralizing antibody ratio <1. The ratio of anti-RSV-postF IgG1 to IgG2a was 1.1, indicating a balanced T cell response. Immunization with mRNA-1345 also induced RSV-F specific CD4+T cell responses producing Th1 cytokines (IFN $\gamma$ , IL-2 and TNF $\alpha$ ) while very few cells producing Th2 cytokines (IL-4, IL-5, and IL-13) were detected. RSV-F specific CD8+T cell responses were also induced following immunization with mRNA-1345 as measured by upregulated expression of CD107a, IFN $\gamma$  and TNF $\alpha$ .

In contrast, (b) (4) elicited lower levels of anti-RSV neutralizing antibodies, lower anti-RSV-preF IgG antibodies and lower anti-RSV-post F IgG antibodies than the mRNA vaccines; in this group the ratio of anti-RSV-post F IgG to neutralizing antibody was 5.7. Likewise, mice given (b) (4) Lot (b) (4) at 1:100 dilution had no detectable neutralizing antibodies or detectable anti-preF antibodies, as expected, but all animals developed anti-RSV-post F IgG antibodies.

Mice infected with live RSV intranasally did not develop detectable neutralizing antibody responses most likely due to the low dose used to immunize mice [10e5 pfu/dose IN], whereas other published studies typically use 10e7 pfu/dose. Likewise, anti-RSV-preF IgG titers were lower than anti- RSV-post F IgG titers in this group.

**Reviewer's analysis:** *Study X-107 demonstrated that immunization of mice with RSV mRNA-1345 elicits robust neutralizing, anti-RSV-preF and anti-RSV-post F IgG binding responses. Th1 CD4+ T cell responses were observed following immunization with mRNA-1345 as indicated by the production of cytokines IFN $\gamma$ , IL-2 and TNF $\alpha$ . The dominant Th1 type immunologic profile induced by immunization with mRNA-1345 was distinct from the profile observed for (b) (4).*

#### **4.2 Study XV-224: Safety, immunogenicity, and efficacy of mRNA-1345 in the (b) (4) rat RSV model**

**[This study was originally dated Mar 10, 2022/amendment 1 dated Sept 5, 2022, in IND 23342]**

This study evaluated immunogenicity, efficacy, and safety of mRNA-1345 in an RSV (b) (4) rat challenge model with comparison to (b) (4) and live RSV controls to assess risk of the vaccine predisposing to enhanced respiratory disease (ERD) following a live RSV challenge. Risk of ERD was assessed in animals immunized with mRNA-1345 using a dose de-escalation scheme to achieve an experimental group with detectable but suboptimal antibody responses to the vaccine that allowed virus replication in the lung after challenge (virus breakthrough). These two criteria are required for a valid test for ERD. In addition, the group given (b) (4) should also have histopathological evidence of lung inflammation including severe alveolitis following live virus challenge while animals given PBS or RSV intranasally have minimal lung inflammatory response in the lung.

Study design: Female (b) (4) rats (N=10 per group) were immunized IM using a single dose of mRNA-1345 on Day 0 (0.3  $\mu$ g, 0.03  $\mu$ g); using two doses given on Days 0 and 28 (30  $\mu$ g, 3  $\mu$ g, 0.3 $\mu$ g, 0.03  $\mu$ g, 0.003  $\mu$ g or 0.0003  $\mu$ g), using 1:100 (b) (4) (Lot (b) (4)), 1:125 (b) (4) (lot# (b) (4)), 1:125 FI-mock (lot # (b) (4)), 30  $\mu$ g mRNA/LNP control, PBS, infected with a single dose of 10e5 PFU live RSV on Day 0 or given no treatment (N=4 only). Serum was collected on Day 56 for antibody assays prior to intranasal challenge with 10e5 pfu of live RSV. Five days after challenge animals were sacrificed and noses and lungs harvested for titration of viral load, lung histopathology and lung cytokine assessment. The following endpoints were determined: RSV neutralization titer, RSV prefusion F-specific IgG titer, RSV post fusion F-specific IgG titer, RSV prefusion F IgG to neutralizing titer ratio, RSV post fusion F IgG to neutralizing titer ratio, RSV prefusion F IgG to post fusion F IgG titer ratio, RSV viral load, lung histopathology and lung cytokine responses (IL-4, IL-5, IL-13, IFN $\gamma$ , IL-2).

The criteria used to define a positive result in the RSV-preF or -post F binding (b) (4) changed during review from having a titer > 1:25 (first sample dilution tested) to having an (b) (4) (on preF antigen) or (b) (4) (on post F antigen) at the 1:25



sample dilution. These values were selected based on the (b) (4) observed for the PBS control group and allowed for a more accurate assessment of seroconversion among animals given low doses of mRNA-1345.

## Results:

**Serology: RSV neutralizing antibody responses and RSV anti preF and post F IgG by (b) (4):** Serology testing is used to document that animals in vaccine groups have received the dose as intended and allow for the assessment of vaccine safety, and risk of enhanced respiratory disease (ERD). A positive total seroresponse rate represents the total cumulative antibody response across all serology tests including: an anti-RSV neutralizing response, an anti-RSV preF IgG response or an anti-RSV-post F IgG response. In this study, RSV neutralizing and binding antibody responses were induced in a dose dependent manner. A two-dose series of 30 µg, 3 µg or 0.3 µg per dose induced comparable or higher neutralizing and binding antibody titers when compared to animals infected with RSV IN. Although neutralizing antibody responses were not detected among cotton rats immunized with a single dose of 0.3 µg or 0.03 µg, anti-RSV-preF IgG and/or -post F IgG response rates of 70% and 20% were observed, respectively. Likewise, a neutralizing antibody response was not detected following immunization with two doses of 0.03 µg, 0.003 µg or 0.0003 µg although anti-RSV-preF IgG and/or post F IgG seroresponse rates were detected at 50%, 10% and 10%, respectively, in these dose groups. Both lots of (b) (4) induced weak RSV neutralizing and preF IgG antibody responses. Animals given FI-mock, LNP control, or PBS remained seronegative post-immunization.

**Viral loads [lungs and noses] post challenge:** In the groups immunized with mRNA-1345 prior to challenge, viral loads were inversely related to serum neutralization titers. No virus replication was detected in the lungs of animals given two doses of mRNA-1345 using 30 µg or 3 µg per dose following 100% seroconversion in each group. In the group given two 0.3 µg doses of mRNA-1345, 10/10 animals seroconverted in one or more serology tests, but only 3/10 had detectable virus in the lungs post-challenge [animals 121221, 121224 and 121225].

Virus replication in the lungs was detected in the groups given two sequential doses of mRNA-1345 using 0.03 µg, 0.003 µg, or 0.0003 µg/dose with seroresponse rates of 50%, 10% and 10%, respectively. Virus replication was also detected in the groups immunized with a single dose of 0.3 µg or 0.03 µg per dose. **Among animals immunized with a single 0.3 µg dose, 9/10 had detectable virus replication in the lungs after challenge and 7/10 had a seroresponse detected by (b) (4). This group meets both validity criteria for assessing ERD risk and is further considered below in the discussion of lung histopathology after live virus challenge.** Among animals immunized with a single 0.03 µg dose, 10/10 had virus replication in the lungs but the seroresponse rate in this group was only 20% and is not considered further due to the low “vaccine take” rate.

Animals in the negative control groups had no detectable seroresponse to RSV and lungs and noses of animals given PBS, FI-mock, and LNP control were fully permissive to virus replication, as expected. All animals seroconverted following the primary

infection with RSV on Day 0 and this infection provided complete protection in lungs and noses against re-challenge. Both groups immunized with (b) (4) antigens showed seroresponse rates of 90% and 100%, respectively by (b) (4). Virus breakthrough in the lung was documented in 10/10 and 9/10 animals, respectively, in the two groups given (b) (4) antigens.

**Risk of ERD:** Data obtained from all experimental groups in this study were considered. Data obtained from the group immunized with a single dose of 0.3 µg of mRNA-1345 was used to assess ERD risk since this group met the validity criteria described above with evidence of “vaccine take” and virus breakthrough in the lung comparable to that seen in the groups given (b) (4). Risk of ERD for each group was determined by assessing lung inflammatory and cytokine responses as described below.

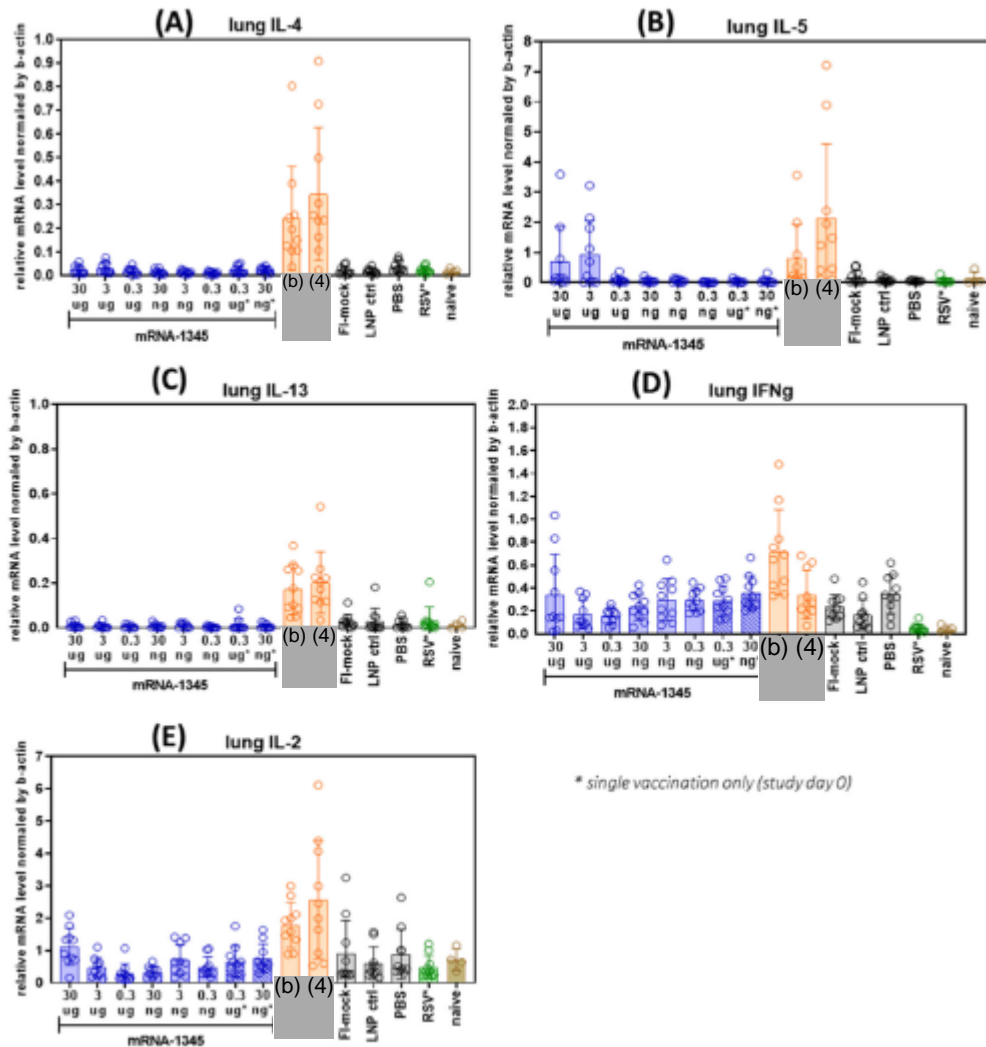
**Lung histopathology post RSV challenge:** Group mean lung inflammatory scores across each parameter were measured by two analysts blinded to group assignment to quantitate alveolitis, peri-bronchiolitis, peri-vasculitis, and interstitial pneumonia. Scores were summed across all parameters for each individual animal and a total mean score determined for each experimental group. Total mean scores were highest in the groups given (b) (4) [Lot (b) (4)] when compared to the total mean scores obtained for groups given one or two doses of mRNA-1345 or to control groups infected with RSV IN or given PBS, FI MOCK or LNP control. The total mean lung inflammatory score and the mean alveolitis score for the group given the single 0.3 µg dose were lower than those seen in the (b) (4) immunized groups and more like the scores seen following primary RSV infection. Total mean lung histopathology scores were lowest in the RSV-naïve group not challenged with live virus.

For analyst #1: Group total mean lung histopathology scores were highest in the groups given (b) (4) prior to live RSV challenge with lower total mean scores in all other groups.

For analyst #2: Group total mean lung histopathology scores were similar to those described by analyst #1 for each group.

**Lung cytokine mRNA profiles after challenge:**

Figure X below shows the mRNA cytokine profiles for lungs obtained 5 days after RSV challenge in animals immunized with one or two doses of mRNA-1345 in a dose de-escalation scheme (eight groups), (b) (4) (two groups), FI-mock, LNP control, PBS or live RSV IN on day 0. One group remained naïve and was not challenged with RSV. Total RNA was extracted from homogenized lung tissue and 1 µg was used in the RT-PCR to measure mRNA IL-4, mRNA IL-5, mRNA IL-13, mRNA IFNγ and mRNA IL-2; cDNA gene copy numbers were standardized against beta-actin gene expression. These data show that the cytokine profile seen in animals immunized with mRNA-1345 was distinctly different from the profile seen in animals immunized with (b) (4) and these data support a conclusion that immunization with (b) (4) induces a Th2-dominant cytokine response as evidenced by high mRNA levels of IL-4, IL-5 and IL-13 while immunization with mRNA-1345 does not.

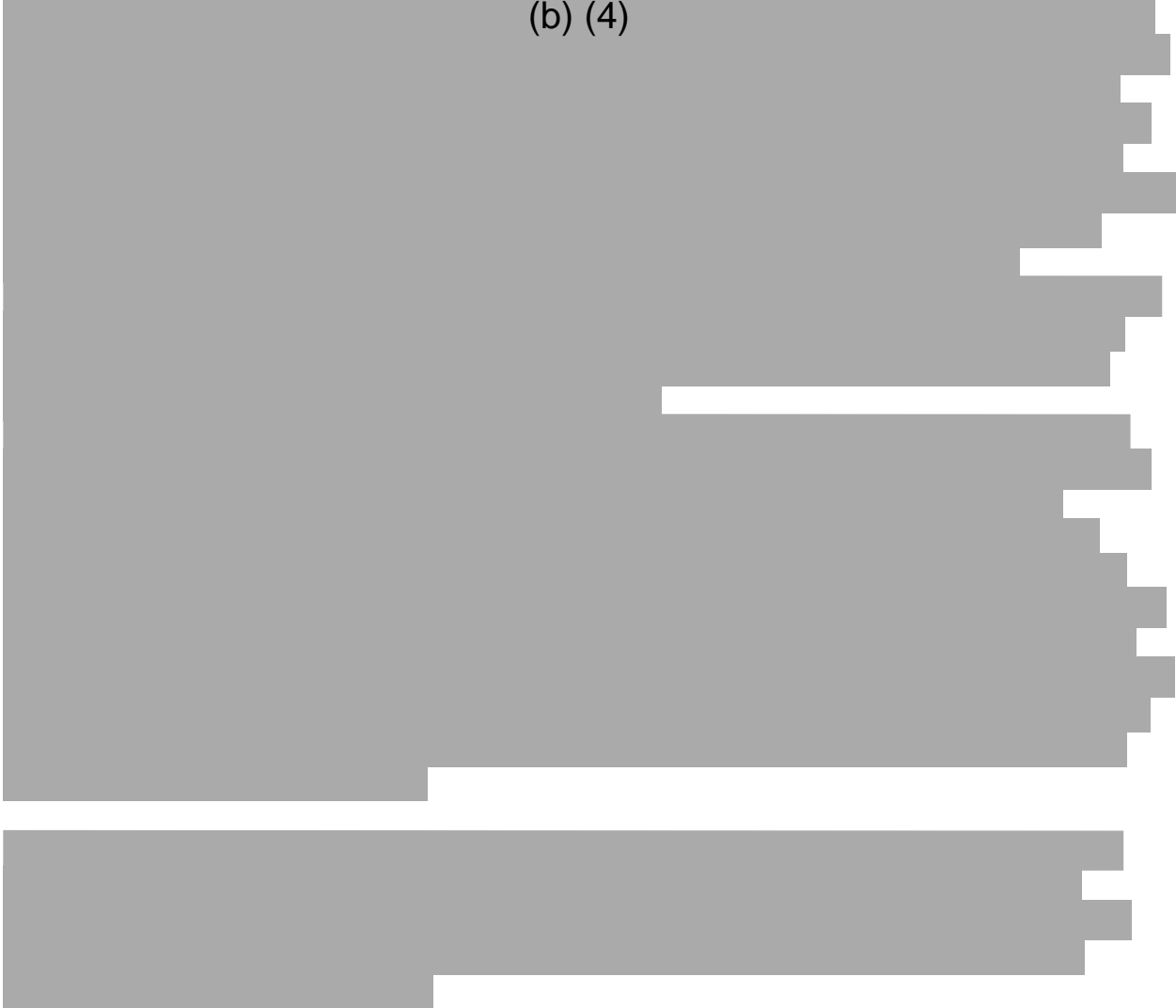
**Figure X. Lung Histopathology 5 days after RSV Challenge**

**Reviewer's analysis of XV-224:** The applicant provided mRNA cytokine data normalized to beta-actin for each individual animal in this study in Appendix 3 in the BLA. I further analyzed the data by calculating group mean mRNA cytokine levels and determined Th1/Th2 ratios for IFN $\gamma$ /IL-4, IFN $\gamma$ /IL-5, and IFN $\gamma$ /IL-13. The IFN $\gamma$ /IL-4 and IFN $\gamma$ /IL-13 ratios support a dominant Th1 cytokine response. The Th1/Th2 ratio for IFN $\gamma$ /IL-5 seen in animals immunized with a single 0.3 ug dose of mRNA-1345 also support a dominant Th1 cytokine response. In contrast, the Th1/Th2 ratio seen in animals immunized with two doses of 30  $\mu$ g mRNA-1345 did not fit this pattern and was more like animals immunized with (b) (4). The biological significance of this finding is not clear but warrants a continued cautious approach when testing mRNA-1345 vaccine in naïve infants who might be at risk for enhanced disease.

**Reviewer's overall analysis:** Study XV-224 demonstrated that immunization of cotton rats with RSV mRNA-1345 elicited a neutralizing antibody response in a dose-dependent manner, elicited both anti-RSV-preF and -post F IgG antibody responses and protected the lung from viral replication following a live RSV challenge. Protection from viral replication in the nose was only observed at the highest dose tested (30 µg). Additionally, lung histopathology revealed the highest inflammatory scores in (b) (4) immunized animals while mRNA-1345 immunized animals and controls had lower lung histopathology scores post challenge. Th1/Th2 ratios using IFN $\gamma$  versus IL-4 or IL-13 demonstrated that a Th1 cytokine profile was dominant following immunization with mRNA-1345. However, the IFN $\gamma$ /IL-5 ratio appeared to be dose dependent with a dominant Th1 profile seen in animals given a low dose of mRNA-1345 while the ratio suggested a dominant Th2 profile at high mRNA-1345 doses (30 µg). The totality of the data from this (b) (4) rat study shows that immunization with mRNA-1345 is not likely to prime for vaccine-associated enhanced respiratory disease (ERD).

**4.3 Study 5002121 amendment 02: A single dose intramuscular injection tissue distribution study of (b) (4) in male (b) (4) rats**

(b) (4)



#### 4.4 Study NCS-BA-2022-010: Identification and profiling of metabolites of SM-102 in rat, monkey, and human hepatocytes

Summary: The purpose of this study was to qualitatively characterize the *in vitro* metabolism of SM-102 in cryopreserved hepatocytes from (b) (4) rats, (b) (4) (NHP) and humans. SM-102 is an ionizable proprietary lipid and component of the Lipid Nanoparticle (LNP) that is used for mRNA encapsulation. Note that this study was also submitted to (b) (4) /amendment 12 on July 28, 2022.

**Study Design:** Primary rat, monkey, and human hepatocytes were (b) (4)

Metabolite profiling was performed by (b) (4). The following criteria were used to confirm the (b) (4) to be identified as an SM-102 metabolite: (b) (4)

**Results:** SM-102 and (b) (4) metabolites ( (b) (4) ) were detected in human and NHP hepatocytes while four metabolites ( (b) (4) ) were detected in rat hepatocytes. The SM-102 metabolites were formed by (b) (4)

No human specific metabolites were detected.

**Reviewer's analysis:** The SM-102 metabolite profiles were determined in rat, monkey, and human hepatocytes. No unexpected metabolites were identified. The study supports the safety of SM-102 and is acceptable.

#### 4.5 Study QV-0236-DA-RE: Metabolite profile and identification of SM-102 in rat plasma, urine, and bile following IV infusion of SM-102 containing lipid nanoparticles to male (b) (4) rats

This purpose of this study was to identify the metabolites of SM-102 in plasma, bile and urine samples of (b) (4) rats following intravenous infusion of SM-102 LNP. A secondary objective was to quantitate the parent SM-102 in the same sample set. Note that this study was submitted to (b) (4) amendment 12 on July 28, 2022.

**Study Design:** Urine, bile, and plasma samples were obtained either pre-dose or following IV infusion at 0-2 hours, 2-6 hours, or 6-24 hours in bile duct cannulated rats.

Pooled urine or bile samples were (b) (4), respectively, into (b) (4) prior to direct analysis by (b) (4). Metabolites from plasma samples were extracted using (b) (4) method. (b) (4) were (b) (4) prior to analysis by (b) (4). To quantitate parent SM-

102 in the sample set, SM-102 reference standards ranging from 0.2 – 500ng/mL were spiked into the matrices (plasma, bile, and urine). The (b) (4) method was used to extract the SM-102 from the bile and plasma samples while urine samples were (b) (4) used for analysis. Sample concentrations were calculated using linear regression of the reference SM-102 standard curve. The following criteria were used to confirm the (b) (4) to be identified as an SM-102 metabolite: (b) (4)

**Results:** SM-102 and (b) (4) metabolites were observed in bile, (b) (4) in plasma and (b) (4) in urine samples. Metabolism occurs primarily by (b) (4). Unchanged SM-102 was the dominant species present at all time points tested.

In plasma, (b) (4) metabolites ( (b) (4) ) appeared from 2-6 hours and by 24 hours five were detected ( (b) (4) ). In urine, (b) (4) metabolites were detected at all time points ( (b) (4) ). In bile, (b) (4) metabolites were detected ( (b) (4) ). Overall, intact SM-102 was the primary circulating species with (b) (4) cleared via both the renal and hepatic routes of elimination. In plasma, SM-102 concentrations fell to <10% and <1% by 6 and 24 hours post dose, respectively. In bile, SM-102 was detected at 14% and 9% of plasma concentrations at 2 and 6 hours post dose, respectively and dropped to 1.2% at 24 hours. Only trace amounts of SM-102 were detected in urine at any time point tested.

*Reviewer's analysis: SM-102 and all metabolites were detected at levels of <1.2% by 24 hours after dosing in plasma, bile, and urine samples, demonstrating effective clearance of the SM-102 LNP component.*

**Overall reviewer's analysis: The nonclinical studies in mice, (b) (4) rats, cryopreserved hepatocytes (rat, monkey, and human) or (b) (4) rats support the safety of the mRNA-1345 vaccine.**

## 5.0 Analytical Procedures and Validation of Analytical Procedures for Assessment of Clinical Endpoints

The following five clinical assays were used to evaluate the RSV mRNA-1345 vaccine study endpoints. RSV case confirmation was determined using the (b) (4) assay, an RT-PCR assay, while a second RT-PCR assay was used to detect SARS-CoV-2 infection. Vaccine induced humoral responses were evaluated in RSVA and RSVB neutralization assays and RSV pre- and post-F specific IgG (b) (4) assays. Vaccine induced T-cell responses were measured using (b) (4). Each clinical assay is further described below.

The clinical assays were used to test samples from a Phase 2/3 clinical efficacy study (Study P301) as well as immunogenicity data from 2 separate Phase 1 studies (Studies P101 and CRID-001) as follows. Study P101 was designed to guide selection of dose and regimen to advance to the larger, pivotal, Phase 2/3 clinical safety and efficacy Study P301. An additional Phase 1 study mRNA-CRID-001 (referred to as Study CRID-001) was conducted to assess mRNA-1345-induced specific cellular immune responses. The following three supportive clinical studies (which are ongoing for final analysis of safety) were included in the BLA:

- **Study P101** is a Phase 1 randomized, observer-blind, placebo-controlled dose-escalation study to evaluate safety, reactogenicity and immunogenicity of mRNA-1345 in 3 study populations (adults 18 to 49 years of age; adults 65 to 79 years of age; and adults of Japanese descent  $\geq 60$  years of age). RSV A and RSV B neutralizing antibody titers and RSV-preF IgG antibody endpoints were assessed. Safety and immunogenicity results supported selection of the dose (50  $\mu$ g) and regimen (single injection) for use in the pivotal Study P301.
- **Phase 1 Study CRID-001** is a Phase 1 open-label, randomized, Phase 1b study to evaluate the safety, reactogenicity, and immunogenicity of mRNA vaccines. The study uses a systems biology approach to comprehensively assess innate and adaptive immune responses to mRNA-LNP vaccines that encode different viral antigens. mRNA-1345 was evaluated in the study, which enrolled adults 18 to 75 years of age. Of the 61 participants who received a single injection of mRNA-1345 (50  $\mu$ g), a randomized subset of 30 participants (n=15 between 50 and 75 years of age; n=15 between 18 and 49 years of age) had assessments of cell-mediated immunity to evaluate RSV F-specific T-cell responses.
- **Study P301** is a pivotal, Phase 2/3 safety and efficacy study that provides the primary clinical evidence of efficacy and safety of mRNA-1345 in adults  $\geq 60$  years of age. This is a randomized, observer-blind, placebo-controlled, case-driven study in which participants were randomized 1:1 to receive a single injection of either mRNA-1345 (50  $\mu$ g) or placebo. Study P301 efficacy endpoint was defined as RSV lower respiratory track disease (RSV-LRTD) and required RT-PCR confirmation of RSV infection. The study is ongoing for safety analysis of participants who will be followed through 24 months post-injection. A secondary immunogenicity objective was to evaluate the antibody response to a single dose of mRNA-1345 (50  $\mu$ g) from baseline up to 24 months post-injection in a randomly selected subset of participants. This subset is used to assess the following endpoints: geometric mean titer (GMT) of serum neutralizing antibodies and geometric mean concentration (GMC) of serum IgG binding antibodies at prespecified timepoints, seroresponse rate (SRR) in RSV neutralizing Abs, geometric mean fold rise (GMFR) from baseline at prespecified timepoints and proportion of participants with  $\geq 2$ -fold increase in Ab titer from baseline at prespecified timepoints up to 24 months post-injection.

(b) (4)

2 pages have been determined to be not releasable: (b)(4)



**5.2 (b) (4) RTPCR**

The (b) (4) RT-qPCR assay is used for the in vitro qualitative detection of viral RNA from respiratory samples. This assay was originally reviewed by Dr. Keith Peden for BLA (b) (4), and is not re-reviewed here. A new Validation report # 21120-9142 was submitted to this BLA to compare limit of detection and accuracy when using alternate (b) (4) methods for testing in the US. An SOP and Verification report were submitted for testing at a new site in the (b) (4) and the following performance parameters were evaluated: precision, sensitivity, and linearity/dynamic range, including (b) (4) instrument comparison and inter-laboratory correlation. Additionally, an Addendum report was submitted for this site comparing assay performance using (b) (4) on the (b) (4) instrument. An SOP and Validation report were also submitted for testing at a new site in (b) (4) and the following performance parameters were evaluated: accuracy, precision, sensitivity, and linearity/dynamic range. The (b) (4) testing occurs at the (b) (4) laboratory in the United States, (b) (4) in the (b) (4) or (b) (4) in (b) (4).

All submitted documents confirm that the assay met all prespecified acceptance criteria and are suitable for their intended use. Additional details are not provided in this review since the detection of (b) (4) RNA is not a primary efficacy endpoint for this BLA.

**Reviewer's analysis:** This RT-qPCR assay to detect (b) (4) -RNA was originally validated for BLA (b) (4). The SOPs, Verification Reports, and Validation Reports provided were reviewed previously and found acceptable. The (b) (4) RT-PCR assay is suitable for its intended purpose. Additionally, the reports support the use of two new testing sites in (b) (4). Additional details were not provided since the detection of (b) (4) RNA is not a primary efficacy endpoint of the Phase 3 study supporting this BLA for ModernaTX's RSV mRNA vaccine.

**5.3 RSV A and B Neutralization Assay**

The RSV neutralization assay is a (b) (4) neutralization test performed in (b) (4)

Note that the endpoint titer does not include the (b) (4) following (b) (4). Testing is performed at (b) (4) in the (b) (4).

**SOP VC-C156 version 3 dated Feb 14, 2023**

The SOP was previously provided and reviewed under IND 23342. Briefly, (b) (4)

One page has been determined to be not releasable: (b)(4)

**Method Validation Report VC-VAL-VAL-117-RPT (dated April 1, 2021)**

The following parameters were assessed during validation and are described in **Table 140** below.

(b) (4)

2 pages have been determined to be not releasable: (b)(4)

(b) (4)

**Method Qualification Statistical Report VSDVAC 69 version 1.1 (originally dated May 17, 2021, revised January 19, 2022)**

Versions 1.0 and 1.1 of this report were previously reviewed under IND 23342. Changes consist of correcting the GMC estimates for (b) (4) samples, adding references, updating Table of Contents and page numbers along with other minor formatting updates. The qualification study evaluated the operating characteristics of the assay along with precision, ruggedness, dilutional linearity, specificity, selectivity, and relative accuracy of the (b) (4) assay. Summary results are shown in **Table 142** below.

Assay characteristics:

(b) (4)

2 pages have been determined to be not releasable: (b)(4)

(b) (4)

### **5.6 Handling of Clinical Samples Prior to Testing**

Since the original submission did not provide information for the collection, storage, and shipment of clinical samples to the testing labs, the following comment was sent to the sponsor on October 30, 2023:

***A comment was sent to the sponsor in IR#5 on October 30, 2023: Please describe how nasal swab samples and serum samples were prepared, stored, and shipped to the central testing sites.***

***On November 13, 2023, a response was submitted in amendment 9 (SN10): Nasal swabs and serum samples were handled per the instructions in Sections 3-5 of the provided (b) (4) (version 7.0 dated 24Oct2023). Briefly, NP swabs and serum samples are collected, processed, and stored (b) (4) or below until shipment to the testing site ( (b) (4) ). NP samples are usually shipped daily, while serum samples are shipped weekly. The response is acceptable.***

***Reviewer's overall assessment of the validation of Clinical Assays: All clinical assays are acceptable and suitable for their intended purpose. (b) (4)***

***RT-qPCR assay were adequately validated. The performance of the commercial (b) (4) RT-qPCR assay was verified to confirm adequate performance; the RSV specific T-cell assay (used for exploratory study endpoint) was optimized for its scientific purpose.***

## 6.0 Appendices Described in Module 3 Review

(b) (4)



One page has been determined to be not releasable: (b)(4)

**Appendix 2. Components Table**

<b>Final Product</b>	<b>Ingredient</b>	<b>UNII Code</b>
Yes	1,2-DIMYRISTOYL-RAC-GLYCERO-3-METHOXYPOLYETHYLENE GLYCOL-2000	9X2596CIE0
Yes	1,2-DISTEAROYL-SN-GLYCERO-3-PHOSPHOCHOLINE	043IP12M0K
Yes	ACETIC ACID GLACIAL	Q40Q9N063P
Yes	CHOLESTEROL	97C5T2UQ7J
Yes	RNA-100-AR02 (mRNA-1345)	2ZKG2M978D
Yes	SM-102	T7OBQ65G2I
Yes	SODIUM ACETATE TRIHYDRATE	4550K0SC9B
Yes	SUCROSE	C151H8M554
Yes	TRIS	023C2WHX2V
Yes	TRIS HYDROCHLORIDE	383V75M34E
Yes	WATER FOR INJECTION	059QF0KO0R
No	(b) (4)	
No		
No		
No		
No		
No		
No		
No		
No		
No		
No		
No		
No		
No		
No		
No		
No		
No		
No		
No		
No		
No		
No		
No		

29 pages have been determined to be not releasable: (b)(4)