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Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

CMC Review Memorandum

Date: May 14, 2025

To the files: BLA STN 125835 Amendments 37 and 49

From: (b) (6) FDA, CBER, (b) (6)

Product: mRNA-1283 mNEXSPIKE, a messenger RNA (mRNA)-based vaccine against the 2019 novel coronavirus (SARS-CoV-2)

Sponsor: ModernaTX, Inc.

Subject: JN.1 CMC/non-clinical data amendment

Received: March 28, 2025 (April 29 for Amendment 49)

Review Committee: (b) (6)

Through: (b) (6)

Cc: (b) (6)

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Recommendation: Approval

Submissions reviewed:

Date Received	Submission	Comments/ Status
March 28, 2025	STN 125835/37	Original Submission from March 28, 2025
April 29, 2025	STN 125835/49	Response to IR#42 from April 28, 2025, CMC related

The following abbreviations are used throughout the document:

(b) (4)	
(b) (4)	
CFU	Colony forming unit(s)
CoA	Certificate of Analysis
DL	Detection limit
(b) (4)	
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
DP	Drug Product
EMA	European Medicines Authority

EU	Endotoxin units
GMT	geometric mean titers
(b) (4)	
ID	Identification number
JN.1	BA.2.86.1.1 subvariant of Omicron
JP	Japanese Pharmacopeia
KP.2	JN.1.11.1.2 subvariant of JN.1
(b) (4)	
LDP	Labeled Drug Product
LNP	lipid nanoparticle
mRNA	messenger ribonucleic acid
MCB	Master Cell Bank
NF	National formulary
NTD	N-terminal domain
PEG2000-DMG	1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000
Ph.Eur	European Pharmacopoeia
PPQ	Process Performance Qualification
QL	Quantitation limit
RBD	receptor-binding domain
(b) (4)	
(b) (4)	
RT	Reverse Transcription
SM-102	an ionizable lipid
UDP	Unlabeled Drug Product
USP	United States Pharmacopoeia
VRBPAC	Vaccines and related biological products advisory committee
WCB	Working Cell Bank
XBB	subvariant family of Omicron

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Executive summary and recommendation

The sponsor has developed mRNA-1283, an LNP encapsulated mRNA-based vaccine against SARS-CoV-2, which contains a shorter mRNA sequence that enables improved refrigerated stability and has demonstrated similar or increased immunogenicity and vaccine efficacy compared with the sponsor's authorized SARS-CoV-2 vaccine (SPIKEVAX™, here referred to as mRNA-1273). mRNA-1283 encodes the N-terminal domain (NTD) and receptor-binding domain (RBD) of the SARS-CoV-2 S glycoprotein. In the polypeptide encoded by mRNA-1283, the NTD and RBD sequences are linked together with a 7-amino acid flexible linker (NTD-RBD). The linked NTD-RBD polypeptide is attached via a (b) (4) linker, to a 23-amino acid HATM (Hemagglutinin-transmembrane) anchor (NTD-RBD-HATM), which anchors the linked NTD-RBD polypeptide into the cell membrane of antigen-expressing cells. As the RBD and NTD regions of the S protein are known to contain key sites of neutralization and a high proportion of T-cell epitopes, mRNA-1283 incorporates these domains to focus the immune response to these critical domains. All mRNA-1283 vaccines contain mRNA encapsulated by LNPs comprising 4 lipids (SM-102, cholesterol, DSPC, and PEG2000-DMG), which are also the same 4 lipids in the sponsor's approved mRNA-1273 vaccine. The sponsor established a program to continuously monitor emerging SARS-CoV-2 variants that can escape humoral immune recognition and therefore lead to breakthrough cases. In August 2023, strain BA.2.86 was identified as a variant under monitoring based on a significant accumulation of mutations (> 30) compared to an early Omicron (BA.2) parental lineage. This strain quickly gave rise to sublineages, and based on updated information, BA.2.86 and its sublineages (including JN.1, which has

one additional mutation relative to BA.2.86) were classified as variants of interest due to rapid increase worldwide. JN.1 overtook the XBB lineage as the predominant strain by January 2024 and exhibited potential for immune escape in individuals who received the most recent vaccine boosters. In June 2024, FDA's VRBPAC recommended a monovalent JN.1 lineage. It should be noted that the agency further determined that the preferred JN.1-lineage for the COVID-19 vaccines (2024-2025 Formula) was the KP.2 strain, if feasible. The JN.1 strain was the variant authorized by the EMA for the 2024-2025 season and was also the strain authorized by the FDA for other protein-based SARS-CoV-2 vaccines in the US. The sponsor states that since mRNA-1283 was already in development during the 2024-2025 season, data regarding the KP.2 strain was not generated. In the initial BLA submission dated 09/30/2024, the sponsor provided CMC data for mRNA-1283 coding for the NTD and RBD of the SARS-CoV-2 Omicron variant lineage XBB.1.5, which was the recommended strain for vaccine manufacturers for the 2023-2024 season. However, as outlined above, this strain is not the strain recommended to vaccine manufacturers to be used for season 2024-2025. This fact was considered a substantive review issue by the BLA review team, and this was communicated to the sponsor via IR#32 on March 21, 2025. In response to the IR, the sponsor submitted in Amendment 37 CMC and nonclinical information for mRNA-1283.167, JN.1 [2024-2025 Formula]. Importantly, it should be noted that in an email to (b) (6) (dated March 19, 2025) the sponsor confirmed that the company (b) (4)

[REDACTED]

The mNEXSPIKE mRNA (b) (4) drug substance (DS), unlabeled drug product (UDP) and labeled drug product (LDP) products that are based on the SARS-CoV-2 Omicron variant lineage XBB.1.5 were assigned the nomenclature (b) (4), UDP- (b) (4), and LDP- (b) (4), respectively. RNA-^{(b) (4)} is the mRNA-1283 RNA platform manufacturing process code, (b) (4). UDP-^{(b) (4)} and LDP-^{(b) (4)} are the process codes for unlabeled and labeled drug product platform manufacturing processes, respectively. These platform manufacturing processes, and associated controls have been detailed under the original BLA submission for approval of the prototype vaccine (mRNA vaccine based on the SARS-CoV-2 Omicron variant lineage XBB.1.5). This memorandum covers the CMC changes in module 3 pertinent to the manufacture of the mRNA coding for the NTD and RBD of the JN.1 strain, as well as a non-clinical study under module 4.

The sponsor describes design and generation of the (b) (4) coding for the NTD and RBD of the JN.1 Spike (S) protein. The (b) (4) used for generation of RNA-^{(b) (4)} (mRNA-1283 coding for the NTD and RBD of JN.1 S protein) is designated (b) (4)

[REDACTED]

(b) (4)

All results were within specifications.

Finally, the sponsor provides information on (b) (4) of UDP ((b) (4)) and (b) (4) of LDP ((b) (4)). Batch release and stability testing results for the batch all were within specifications. Of note, the LDP- (b) (4) and UDP- (b) (4) were manufactured according to **process “B”** at ModernaTX Norwood at a nominal Batch Size of (b) (4). The DP has a target RNA content of **0.05 mg/mL** and a target lipid content of 1.0 mg/mL formulated in (b) (4) mM Tris buffer and (b) (4) g/L sucrose at pH (b) (4). It is presented in (b) (4)

(b) (4) **mL nominal fill volume.** The DP is stored at (b) (4). No lots were manufactured using the commercial process, which is at a scale of (b) (4) and a fill volume of (b) (4) mL (0.05 mg/mL) provided in prefilled syringes. No PPQ lots were manufactured for LDP- (b) (4). However, since three PPQ lots were manufactured for LDP- (b) (4) (XBB.1.5 subvariant lineage), (b) (4) (as discussed above), this is deemed acceptable.

All analytical methods for (b) (4) and UDP/LDP- (b) (4) remained the same compared to those used in the manufacture of LDP- (b) (4) except for the (b) (4) testing by (b) (4). Information on the method and verification is provided and is deemed acceptable.

In summary, the sponsor demonstrated that the change in coding sequence of mRNA-1283 from the Omicron subvariant lineage XBB.1.5 to subvariant lineage JN.1 did not have a negative impact on preset specifications and on stability of the drug product. The sponsor conducted one non-clinical study in adult female BALB/c mice. In this study, groups of mice were immunized with 3 different dose levels of mRNA-1283.167 on Day 1 and Day 22. Control animals were injected with PBS. All animals were bled on Day 21 (prior to Dose 2) and Day 36 (2 weeks after Dose 2) for measurement of SARS-CoV-2 binding Ab as well as neutralizing Ab responses. It was shown that the vaccine induced a robust immune response with both binding and neutralizing antibodies.

One IR with four comments was sent to the sponsor during evaluation of this submission and the responses were found acceptable. Approval of this strain change amendment is recommended.

CMC review:

CMC and nonclinical sections that were modified compared to the initial BLA submission are reviewed below:

Module 3:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

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

P.1. Description and Composition of the DP

The Drug Product (UDP/LDP- (b) (4)) is an RNA-lipid complex dispersion that contains the RNA- (b) (4) and four lipids that act as protectants and carriers of the RNA. The four lipids are SM-102, cholesterol, DSPC, and PEG2000-DMG (see also section S.1.1.1. (b) (4)). The buffer components and composition of the DP are listed in the Table 18 below:

Table 18: Labeled Drug Product (UDP/LDP- (b) (4)) Composition

Component	Grade	Function	Unit Formula (µg) ^{(b) (4)}
RNA- (b) (4)	Custom	Contains mRNA encoding the linked NTD and RBD of the spike glycoprotein of the SARS-CoV-2 Omicron JN.1 virus.	(b) (4)
Total Lipids: SM-102	Custom- (b) (4)	Component of the LNP	
Total Lipids: Cholesterol	(b) (4)	Component of the LNP	
Total Lipids: DSPC	(b) (4)	Component of the LNP	
Total Lipids: PEG2000-DMG	Custom, (b) (4)	Component of the LNP	
Tris ^a	(b) (4)	Buffer components in Tris buffer	
Tris-HCl ^a	(b) (4)	Buffer components in Tris buffer	
Sucrose	(b) (4)	Cryoprotection	
Water for injection	(b) (4)	Diluent	

Abbreviations: NF: National Formulary; q.s. = quantum sufficit. For USP, Ph.Eur and JP, see also Table 6.

a Tris is referred to as Tromethamine (b) (4) and as Trometamol (b) (4) .

Reviewer's comment: In the Table shown above, the sponsor indicates that the total amount of lipids is (b) (4) µg^{(b) (4)}. However, the total of the four lipids adds up to only (b) (4) µg^{(b) (4)}. Since this discrepancy is minor, no further action is deemed necessary.

The DP has a target RNA content of **0.05 mg/mL** and a target lipid content of 1.0 mg/mL formulated in (b) (4) mM Tris buffer and (b) (4) g/L sucrose at pH (b) (4). It is presented in (b) (4) and has a (b) (4) mL nominal fill volume.

P.2.1.1.2: Excipients:

The functions of SM-102, Cholesterol, DSPC and PEG2000-DMG were already described above (section S.1.1.1. (b) (4)).

Tris-Buffer: Tris is used to (b) (4) At pH (b) (4), Tris provides strong buffering capacity and optimum product stability.

Sucrose: Sucrose has been added to DP as a cryoprotectant. (b) (4)

Reviewer's comment: The sponsor does not provide information on impurities, but information is provided in the initial BLA submission for LDP- (b) (4) , and it is referred to the review memo of (b) (6) . Of note, while (b) (4) are listed as components of (b) (4) clinical trial materials, these components are no longer listed as component for commercial DP. Instead, (b) (4) has been classified as an impurity.

P.2.3. Manufacturing Process Development – Manufacturing History

The manufacturing process Development for mRNA-1283 was already reviewed in the memo for the initial BLA submission.

P.2.3.2. Lot Production Summary

The DP ID for mRNA-1283 encoding SARS-2-CoV-2 Linked NTD-RBD from Omicron strain JN.1 is provided.

LDP (labeled DP) ID: LDP- (b) (4)

UDP (unlabeled DP) ID: UDP- (b) (4)

(b) (4)

(b) (4)

RNA Input: RNA- (b) (4)

An overview of process development from clinical supply to registration is shown. The Table is identical to Table 47 of the BLA memo from (b) (6) with the exception that Clinical Study supply of (b) (4) is added in the Table in the current Amendment. The LDP- (b) (4) and UDP- (b) (4) were manufactured according to **process “B”** at ModernaTX Norwood at a DP concentration of (b) (4) mg/mL and at a nominal Batch Size of (b) (4).

Reviewer’s note: In the Column “UDP ID”, the ID is listed as “UDP- (b) (4)”. This is most likely a typo and is supposed to be UDP- (b) (4), since the corresponding LDP ID is LDP- (b) (4). No action is therefore deemed necessary.

An additional table is provided in the submission listing the clinical DP lot manufacturing history and genealogy for mRNA-1283.

Concerning LDP- (b) (4) Input Lot#, and RNA Input Lot# were already provided in section S.2.6. Manufacturing History (b) (4) above. The LDP Lot number is (b) (4) and the UDP Lot number is (b) (4). **The LDP lot is used in Clinical study (b) (4), as well as for comparability and stability analyses.**

P.2.3.3. Summary of Manufacturing Process Changes for DP.

Manufacturing process development progressed to establish unit operations and process parameter ranges for the manufacture of DP for mRNA-1283. Major changes implemented from **Version A** to commercial process, as well as an evaluation of comparability, are included in the submission and have already been reviewed in the memo for the initial BLA submission.

P.2.3. Comparability {DP}

Comparability assessments for UDP- (b) (4) have been performed. See section S.2.6. Manufacturing Process Development-Comparability (b) (4) for information on the comparability strategy. Updated, tightened acceptance criteria as detailed in BLA 125835 IR#21 SN0030, along with the release data for UDP- (b) (4), were used for the comparability assessment (Table 19).

(b) (4)

Reviewer's assessment: *All the results from release testing of UDP- (b) (4) met the predefined comparability criteria, confirming the consistent product quality despite the strain change.*

P.3.5. Process Validation

It is stated that (b) (4) has successfully completed Process Performance Qualification (PPQ) of the DP commercial scale process for mRNA-1283, as described in BLA 125835 (Section 3.2.P.3.5. Process Validation {DP}). A robust comparability assessment has demonstrated that the commercial-scale process produces DP with product quality consistent with clinical lots manufactured with DP Process Version B as described in BLA 125835 Section 3.2.P.2.3. Comparability {DP}. UDP/LDP- (b) (4) (Lot (b) (4)) was manufactured in accordance with DP Process Version B. A comparison of DP manufacturing processes from Version B to Commercial Scale was provided and reviewed in the memo for the initial BLA submission.

P.5.3. Validation of Analytical Procedure- Identity by (b) (4) {DP}

The method for Identity by (b) (4) used for release testing of mRNA-1283 DP is the same as the one used for (b) (4) testing. Please refer to section S.4.3. (b) (4) in this review for further information. The method has been verified to be suitable for its intended use by testing UDP/LDP- (b) (4) .

Reviewer's comment: The following comment was sent to the sponsor on April 29 (IR#42): "We refer to modules 3.2.R mRNA-1283 JN.1 {(b) (4)}, 3.2.R mRNA-1283 JN.1 {(b) (4)}, and 3.2.R mRNA-1283 {DP}, Sections S.4.3. (b) (4), and P.5.3.{DP} Validation of Analytical Procedures- (b) (4) by (b) (4). Please indicate which non-target controls were used to show specificity for JN.1 during verification, and which positive control for mRNA-1283 coding for JN.1 (NTD and RBD) is included in the routine assay". The response was submitted in Amendment 49 on April 29, 2025. The sponsor states that mRNA-1283.815 (XBB.1.5) and mRNA-1283.167 (JN.1) test articles were separately used to demonstrate specificity in the (b) (4) method validations. A negative control (b) (4) and a positive control (b) (4) are included in each analysis as part of system suitability. [Reviewer's note: As per SOP-1337, (b) (4) for the positive control are used in the (b) (4)]. It is stated that non-target controls were not used since Moderna methods are specific by design. Specificity of the method is established using (b) (4). It is further stated the method is validated for each Moderna product / product variant, all of which have (b) (4). The specificity of the (b) (4) method relies on (b) (4).

I deem the sponsor's response to be acceptable.

P.5.4. Batch Analysis

The batch analysis data for UDP- (b) (4) was generated according to the specifications effective at time of testing. Detailed batch information and data is provided in the Tables 20 and 21 below:

(b) (4)

(b) (4)

(b) (4)

P.8.1. Stability Summary and Conclusions

Stability studies have been started on UDP- (b) (4) (lot (b) (4)). It is stored at the intended long-term storage condition of (b) (4). It is stated that stability studies conducted in the range ((b) (4)) are representative of the full long-term

storage range, since the degradation rates are negligible at these temperatures. An overview of the study design for UDP- (b) (4) (lot (b) (4)) is presented in Table 22 below.

P.8.1.2. Stability Study Protocol

Table 22: Drug Product Stability Protocol for UDP- (b) (4)

Condition	Initial	Month 1	Month 3	Month 6	Month 9	Month 12
(b) (4)	ABC	N/A	AB	ABC	A	ABC
2°C to 8°C	ABC	AB	AB	(b) (4)	N/A	N/A

(b) (4)

A = Appearance, % RNA (b) (4), Purity and Product Related Impurities, (b) (4).
 B = pH, (b) (4), Lipid content and Lipid impurities
 C = total RNA content, Bacterial Endotoxin, Particulate matter, container closure integrity test.

P.8.1.3. Stability Data

Stability data for lot (b) (4) up to three months are provided. All results were evaluated against the specifications as shown above in Table 20. All results met the specifications at the (b) (4) condition, demonstrating no or limited change over the testing period. For the samples stored at the accelerated condition of 2 °C to 8 °C, a slight decrease in mRNA Purity was observed (from (b) (4) initially to (b) (4) at 3 months), along with increases in (b) (4) (b) (4) initially to (b) (4) at 3 months), (b) (4) (b) (4) initially to (b) (4) at three months), (b) (4) (b) (4) vs. (b) (4)), and total Lipid Impurities (b) (4) vs. (b) (4)). These observations are consistent with expected degradation patterns.

Reviewer's assessment: *The sponsor demonstrated that the strain change did not have a negative impact on specifications and on stability of the drug product.*

Module 4:

4.2.1. Primary Pharmacology

Study MOD-7153-1283.167

The sponsor conducted a non-clinical study to evaluate the Immunogenicity of JN.1-containing mRNA-1283 vaccine in BALB/c Mice following a 2-dose primary series administration. The study was performed by ModernaTX, Inc. in Cambridge, MA.

Test Articles:

mRNA-1283.167; Lot number: DH-95005.1. Date of Manufacture: (b) (4).
 Buffer/Diluent: (b) (4) mM Tris, (b) (4), (b) (4) g/L Sucrose, pH (b) (4). The mRNA was manufactured using the (b) (4) manufacturing process as the mRNA-1283.222 clinical drug product [Reviewer's note: mRNA-1283-222 is a bivalent SARS-CoV-2 vaccine].
 PBS (negative control).

A Certificate of Analysis for Lot DH-95005.1 is provided. The results are provided in the Table below. Of note, all Specifications were indicated to be "Report Results" only. Specifications shown are those that were applied to Batch release of DP.

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

(b) (4)

Test System

6-8-week-old BALB/c female mice ((b) (4)).

Methods:

The study design is presented in Table 24 below.

Table 24: Study Design for Study MOD-7153-1283.167

Study Report Group	n	Treatment (IM)	Dose Level (µg)	Dose Schedule
1	5	PBS	0	Day 1, Day 22
2	10	mRNA-1283.167	2.5	Day 1, Day 22
3	10	mRNA-1283.167	1.25	Day 1, Day 22
4	10	mRNA-1283.167	0.63	Day 1, Day 22

IM = intramuscular

Readouts for all study groups:

Serum (Day 21 and Day 36): binding antibody (bAb) response (ELISA)

Serum (Day 36): neutralizing antibody (nAb) response (VSV-PsVNA)

Bioanalytical Methods

ELISA:

(b) (4)

Vesicular Stomatitis Virus-Based Pseudovirus Neutralization Assay (VSV-PsVNA)

(b) (4)

(b) (4)

Data Presentation and Analysis:

IgG binding and neutralization titers are displayed as GMTs and described as fold changes or absolute GMT titers. No formal statistical test was performed.

Results:

Groups of female BALB/c mice were immunized with 3 different dose levels of mRNA-1283.167 on Day 1 and Day 22. Control animals were injected with PBS. All animals were bled on Day 21 (prior to Dose 2) and Day 36 (2 weeks after Dose 2) for measurement of SARS-CoV-2 bAb as well as nAb responses. The test articles were well tolerated, and animal health monitoring did not reveal any adverse findings.

SARS-CoV-2 S-2P bAb (IgG) titers on Day 21 and Day 36 were measured via ELISA. mRNA-1283.167 induced robust IgG bAb on Day 36 (GMTs ranging from 34,150 (0.63 µg to 84,108 (2.5 µg)) with the highest titers observed at a dose of 1.25 µg (GMT of 110,309), which was approximately 3.2-fold higher than titers at a dose of 0.63 µg. Increasing the dose beyond 1.25 µg did not increase the titers further suggesting a saturation at this dose.

nAb titers against the JN.1 strain were evaluated using a VSV-PsVNA on Day 36 (2 weeks after Dose 2). mRNA-1283.167 induced robust JN.1 nAb titers (GMTs ranging from 42,772 (0.63 µg) to 66,359 (2.5 µg)) in a dose dependent manner with highest titers observed at a dose of 1.25 µg (GMT of 66,359) which was approximately 1.5-fold higher than titers at a dose of 0.63 µg. Increasing the dose beyond 1.25 µg to 2.5 µg did not increase the nAb titers, suggesting saturation consistent with the observation on IgG bAb titers. Overall, mRNA-1283.167 elicited robust nAb titers that effectively neutralized the JN.1 SARS-CoV-2 strain.

Conclusions

mRNA-1283.167 was highly immunogenic, inducing robust IgG binding antibodies against SARS-CoV-2 S-2P protein and neutralizing antibodies to JN.1 strain of SARS-CoV-2. The data suggest that mRNA-1283.167 is likely to elicit protective immune responses against the JN.1 strain.

Reviewer's assessment: *Of note, ideally the sponsor should have included in the non-clinical study a group of mice inoculated with the same amounts of (b) (4) that includes mRNA-1283 coding for the NTD and RBD of SARS-CoV-2 Omicron variant lineage XBB.1.5 to demonstrate that mRNA-1283.167 elicits higher antibodies against the homologous antigen. However, following internal discussion with (b) (6) upper management, it was determined that further non-clinical studies are not necessary,*

(b) (4)