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## LIST OF ABBREVIATIONS

Abbreviation	Definition
ACE2	angiotensin-converting enzyme 2
BA.1	subvariant of Omicron
bAb	binding antibody
CDC	Centers for Disease Control and Prevention
COVID-19	coronavirus disease 2019
ELISA	enzyme-linked immunosorbent assay
GMT	geometric mean titer
IgG	immunoglobulin G
IM	intramuscular
LLOQ	lower limit of quantification
LOD	limit of detection
mRNA	messenger RNA
nAb	neutralizing antibody
PBS	phosphate-buffered saline
PSVNA	pseudovirus neutralization assay
S-2P	spike protein modified with 2 proline substitutions within the heptad repeat 1 domain
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
VOC	variant of concern
VSV	vesicular stomatitis virus
WHO	World Health Organization
XEC	a recombinant lineage of KS.1.1 (JN.1.13.1.1.1) and KP.3.3 (JN.1.11.1.3.3), which are subvariants of JN.1

## DESCRIPTION OF SARS-COV-2 VARIANTS AND MRNA-1273 DRUG PRODUCTS

Strain	Test Material	mRNA Encodes for the SARS-CoV-2:	Strain Definition
Wuhan Hu 1	mRNA-1273	S-2P	Original strain
BA.4/BA.5	mRNA-1273.045	S-2P	BA.4/BA.5 are subvariants of Omicron (the spike protein of BA.5 is identical to that of BA.4)
XBB.1.5	mRNA-1273.815	S-2P	XBB.1.5 is a subvariant of Omicron (note: spike protein of XBB.1.9.1 is identical to XBB.1.5)
JN.1	mRNA-1273.167	S-2P	BA.2.86.1.1 is a subvariant of Omicron
KP.2	mRNA-1273.712	S-2P	JN.1.11.1.2 is a subvariant of JN.1
LP.8.1	mRNA-1273.251	S-2P	JN.1.11.1.1.3.8.1 is a subvariant of JN.1

Abbreviations: mRNA = messenger RNA; S-2P = spike protein with 2 proline substitutions within the heptad repeat 1 domain; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

### 2.6.2.1 BRIEF SUMMARY

Global efforts to address the COVID-19 pandemic have resulted in the authorization of COVID-19 vaccines, such as SPIKEVAX™ (hereafter referred to as mRNA-1273). The emergence of SARS-CoV-2 variants resulted in breakthrough cases, and subsequently a public health need for immunization against these antigenically divergent strains. Given the evident immune escape that variants of concern exhibit to current vaccines, updating vaccine strain compositions to match such strains more closely is critical to maintaining protection. In response, variant-specific mRNA-1273 booster vaccines were authorized in 2022 (a bivalent vaccine containing the original and Omicron BA.4/BA.5 or Omicron BA.1), 2023 (monovalent Omicron subvariant XBB.1.5-containing vaccine), and 2024 (monovalent JN.1- or KP.2-containing vaccines). Refer to [Description of SARS-CoV-2 Variants and mRNA-1273 Drug Products](#) for variant definitions and the corresponding drug products.

By January 2024, the JN.1 strain had become the dominant SARS-CoV-2 variant, demonstrating potential for immune escape in recently vaccinated individuals. The current variant landscape (early 2025) is dominated by multiple JN.1 descendants, such as XEC and LP.8.1, with LP.8.1 rapidly increasing and overtaking XEC. LP.8.1, which has acquired 9 spike protein mutations compared to JN.1 and 8 amino acid differences compared to XEC, was classified as a variant under monitoring by the WHO on 24 Jan 2025 ([WHO 2025a](#)). Studies indicate that LP.8.1 has immune evasion capabilities versus currently approved JN.1 and KP.2 vaccines, similar to XEC, and high ACE2 binding potentially supporting a growth advantage ([Liu et al 2025](#)). As of week 5 of 2025, LP.8.1 represented 13.9% of globally available sequences, a significant rise from 1.9% just 6 weeks earlier in epidemiological week 51 of 2024 ([WHO 2025b](#)). In the United States, COVID-19 variant surveillance estimated that LP.8.1 represents 48% to 62% of cases as of 29 Mar 2025, with a 95% prediction interval ([CDC 2025](#)).

The complex nature of the continuing evolution of SARS-CoV-2 makes it impossible to accurately predict which virus strains will gain dominance in any particular region of the world and how long a strain will remain dominant. Health agencies recommend a framework to identify VOCs and test updated COVID-19 vaccines, which is critical to preserve neutralization responses and protection against the infection/severe disease caused by SARS-CoV-2. The Sponsor has established a process to monitor emerging variants, classify them by immune-evading mutations, test matching vaccine candidates, and deploy them if requested by health agencies. This approach was effective in enabling early preparation for an XBB.1.5 vaccine composition for 2023-2024, and the Sponsor recently used this process to prepare both a JN.1 new variant vaccine (mRNA-1273.167) and a KP.2 new variant vaccine (mRNA-1273.712) for the 2024-2025 season. Preliminary investigations and risk assessments suggest that, given its rapid rise and immune evasion capabilities, LP.8.1-containing vaccines should be investigated as a candidate vaccine for the 2025-2026 season.

Given that circulating XEC and LP.8.1 variants are part of the JN.1 subfamily and have some mutations that may lead to immune escape, our risk assessment predicted that the currently approved JN.1 (mRNA-1273.167) and/or KP.2 (mRNA-1273.712) vaccines will cross-neutralize these circulating variants, although with lower titers compared to those elicited against the matched JN.1 and KP.2 strains. In addition, our prediction based on our risk assessment is that a

vaccine update to the LP.8.1 will be most effective at neutralizing currently circulating strains, with cross-neutralization likely against older JN.1 strains that no longer circulate, as well as JN.1 strains yet to emerge.

Nonclinical in vivo pharmacology studies were conducted in BALB/c mice with mRNA-1273.251, which encodes the SARS-CoV-2 S-2P antigen of the LP.8.1 subvariant of JN.1 (Table 1), with studies also including assessment of the currently approved JN.1 (mRNA-1273.167) or KP.2 (mRNA-1273.712) vaccines. These studies evaluated immunogenicity of a LP.8.1-containing mRNA vaccine (mRNA-1273.251) given as a primary series or as a booster dose (Dose 3) in mice previously immunized with 2 doses of mRNA-1273 or 2 doses of variant-containing mRNA-1273 vaccines.

The results of these studies demonstrate that mRNA-1273.251, either as a primary series or as a booster vaccine, was better at eliciting a neutralizing response to LP.8.1 compared to currently approved JN.1-lineage vaccines, mRNA-1273.712 and mRNA-1273.167. Furthermore, these nAbs cross-neutralized JN.1-lineage strains JN.1, KP.2, and XEC, likely due to the antigenic similarity with the LP.8.1 strain.

**Table 1: Completed Nonclinical Pharmacology Studies Supporting Development of a LP.8.1-containing Vaccine**

Study Title	Report Number	Laboratory Name and Location	eCTD Reference
Evaluation of immunogenicity of a primary series of a SARS-CoV-2 LP.8.1-containing mRNA-1273 vaccine in mice		ModernaTX, Inc. Cambridge, MA	Section
Evaluation of immunogenicity of a monovalent SARS-CoV-2 LP.8.1-containing mRNA-1273 vaccine booster in mice		ModernaTX, Inc. Cambridge, MA	Section 4

Abbreviations: eCTD = electronic common technical document; mRNA = messenger RNA; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

## 2.6.2.2 PRIMARY PHARMACODYNAMICS

### 2.6.2.2.1 Evaluation of Immunogenicity of a Primary Series of a SARS-CoV-2 LP.8.1-containing mRNA-1273 Vaccine in Mice (MOD-7407)

The objective of Study MOD-7407 was to evaluate the immunogenicity of a primary series of a SARS-CoV-2 LP.8.1-containing mRNA-1273 vaccine (mRNA-1273.251) in mice ( ).

The test article used in this study was monovalent mRNA-1273.251, which encodes the SARS-CoV-2 S-2P antigen of the LP.8.1 subvariant of JN.1. The active controls in this study

were the mRNA-1273.712 and mRNA-1273.167 vaccine, which contain single mRNAs encoding the SARS-CoV-2 S-2P antigen of the KP.2 and JN.1 strain, respectively. PBS was used as a negative control.

### **Methods:**

Mice (n=8/group) received 2 IM injections of PBS control or 1 µg mRNA-1273.712, mRNA-1273.167, or mRNA-1273.251 vaccines as a primary series, 3 weeks apart (Day 1 and Day 22; Table 2). Blood was collected from all animals on Day 21 (before Dose 2) and Day 36 (2 weeks after the completion of the primary series). Serum samples were analyzed for bAb responses via ELISA and nAb responses via VSV-based PSVNA.

**Table 2: Study Design for Study MOD-7407**

Study Report Group (n=8)	Treatment (IM)	Dose Level (µg)	Dose Schedule	Readouts
1	PBS	0	Day 1, Day 22	<b>Serum (Day 21, Day 36)</b> bAb response (ELISA)
2	mRNA-1273.712	1		<b>Serum (Day 36)</b> nAb response (VSV-PSVNA)
3	mRNA-1273.167	1		
4	mRNA-1273.251	1		

Abbreviations: bAb = binding antibody; ELISA = enzyme-linked immunosorbent assay; IM = intramuscular; nAb = neutralizing antibody; PBS = phosphate-buffered saline; PSVNA = pseudovirus neutralization assay; VSV = vesicular stomatitis virus

Source: Report MOD-7407.

### **Results:**

The test articles were well tolerated, and animal health monitoring did not reveal any adverse findings.

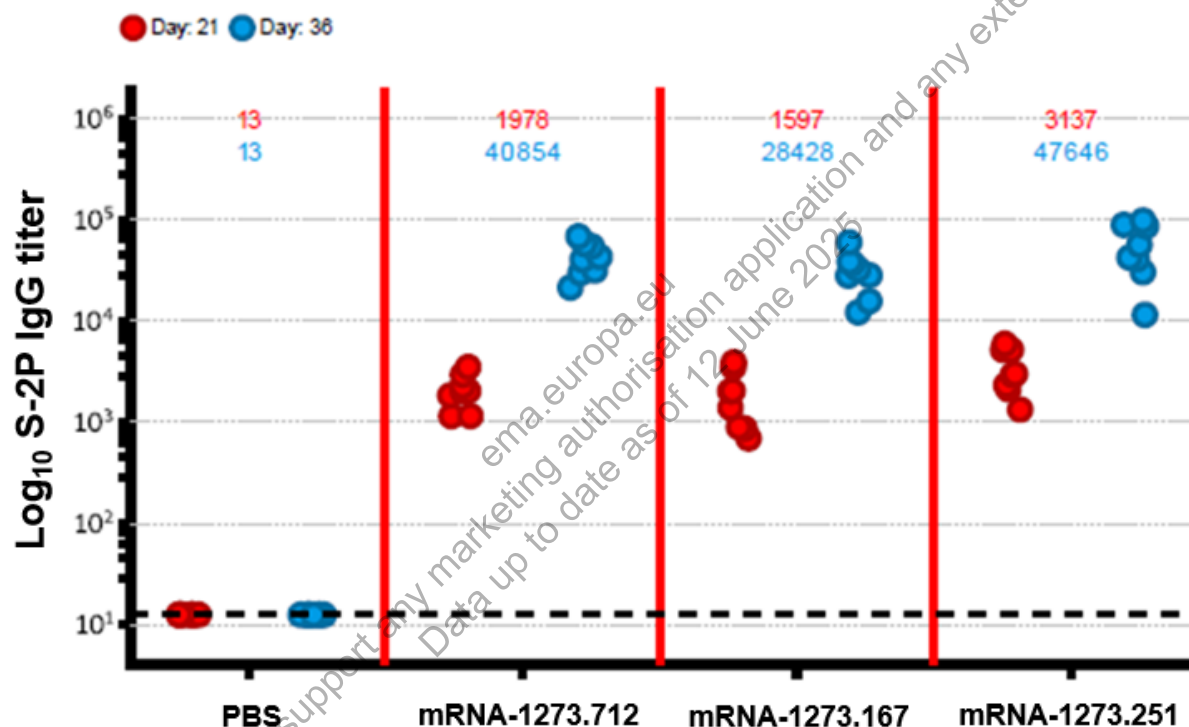
The S-2P bAb (IgG) titers were elevated at Day 21 (3 weeks after Dose 1) with GMTs ranging from 1597 to 3137 for all groups of animals receiving Dose 1 of the JN.1 lineage vaccines (mRNA-1273.712, mRNA-1273.167, and mRNA-1273.251; Figure 1). Titers increased 2 weeks after Dose 2 by approximately 15- to 21-fold for all groups administered a JN.1 lineage primary series. On Day 36, results indicate that mice administered a primary series of mRNA-1273.251 exhibited a robust boost in the S-2P IgG titers, which were comparable to mRNA-1273.712 or mRNA-1273.167 (<2-fold difference). No bAb titers were detectable in the PBS control group.

On Day 36 (2 weeks after Dose 2), the mRNA-1273.251 group elicited robust nAb titers against LP.8.1 (GMT of 21,449) which was 4-fold higher compared to LP.8.1 nAb titers elicited by mRNA-1273.712 (GMT of 5,275) and 6-fold higher than LP.8.1 nAb titers induced by mRNA-1273.167 (GMT of 3,603; Figure 2). The nAbs elicited by mRNA-1273.251 also cross-neutralized JN.1, KP.2, and XEC. The mRNA-1273.251 nAb GMTs against these variants were comparable to mRNA-1273.712: JN.1 (GMT of 14,549 vs 16,097), KP.2 (GMT of 12,925

vs 16,956), and XEC (GMT of 9,032 vs 8,293), respectively. Additionally, the GMTs exceeded those elicited by mRNA-1273.167: JN.1 (GMT of 14,549 vs 5,673), KP.2 (GMT of 12,925 vs 7,473), and XEC (GMT of 9,032 vs 5,286).

Overall, the results indicate that an mRNA-1273.251 primary series was highly immunogenic and elicited robust nAb titers to LP.8.1, while also cross-neutralizing other JN.1 subvariants (JN.1, KP.2, and XEC). While neutralization of JN.1 variants that have previously circulated (JN.1, KP.2, and XEC) was similar between the KP.2 and LP.8.1 vaccines, neutralization of LP.8.1 was higher after vaccination with the LP.8.1 new variant vaccine.

**Figure 1: Binding Antibody Responses Against S-2P in BALB/c Mice After Primary Series Vaccination**

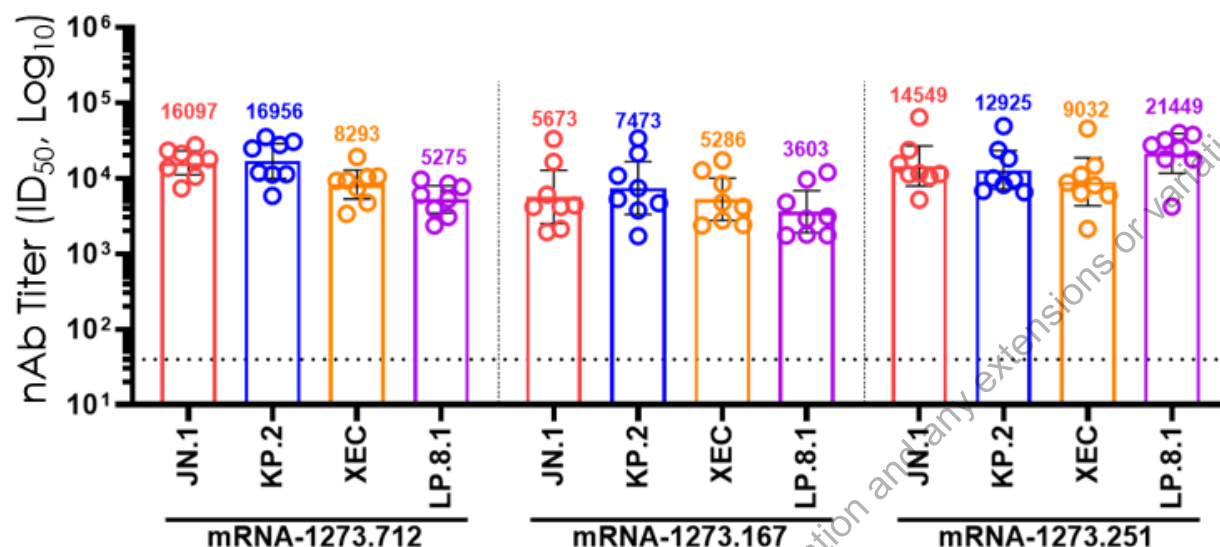


Abbreviations: GMT = geometric mean titer; IgG = immunoglobulin G; LOD = limit of detection;  
mRNA = messenger RNA; S-2P = spike protein with 2 proline substitutions within the heptad repeat 1 domain;  
PBS = phosphate-buffered saline  
Note: GMT values are presented at the top of each figure, with red indicating the GMT for Day 21 (3 weeks after Dose 1) and blue indicating the GMT for Day 36 (2 weeks after Dose 2). The dotted line indicates the LOD of the assay.

Source: Report MOD-7407



**Figure 2: Neutralizing Antibody Responses Against JN.1, KP.2, XEC, and LP.8.1 in BALB/c Mice After Primary Series Vaccination**



Abbreviations: GMT = geometric mean titer; ID<sub>50</sub> = inhibitory dilution 50%; LLOQ = lower limit of quantification; mRNA = messenger RNA; nAb = neutralizing antibody

Note: The numbers and bars represent GMTs, and whiskers represent the 95% confidence intervals for Day 36 (2 weeks after Dose 2). The dotted line indicates the LLOQ of the assay.

Source: Report MOD-7407

### **Conclusions:**

The primary series administration of the new variant vaccine, mRNA-1273.251 (LP.8.1), demonstrated high immunogenicity, supported by a robust 15-fold increase in the S-2P IgG titers after Dose 2. GMT titers were comparable after Dose 2 for mRNA-1273.251, mRNA-1273.712, and mRNA-1273.167 (<2-fold change in GMT values between groups). The mRNA-1273.251 primary series induced potent nAb titers against LP.8.1 (matched), higher than mRNA-1273.712 and mRNA-1273.167. Additionally, mRNA-1273.251 effectively cross-neutralized JN.1 lineage strains (JN.1, KP.2, and XEC), with nAb titers comparable or exceeding those elicited by mRNA-1273.712 or mRNA-1273.167.

Overall, primary series administration of mRNA-1273.251 was highly immunogenic and elicited robust nAb responses to the LP.8.1 strain and cross-neutralizing other JN.1 lineage strains. The results indicate that mRNA-1273.251 is likely to provide protective responses to LP.8.1 and antigenically-related JN.1 lineage strains.

### 2.6.2.2.2 Evaluation of Immunogenicity of a Monovalent SARS-CoV-2 LP.8.1-containing mRNA-1273 Vaccine Booster Dose in Mice (MOD-7345.1273)

The objective of this study was to evaluate the immunogenicity of a booster dose of a SARS-CoV-2 LP.8.1-containing mRNA-1273 vaccine (mRNA-1273.251) administered in mice (3).

The test article in this study was the monovalent mRNA-1273.251 vaccine, which contains a single mRNA encoding the SARS-CoV-2 S-2P antigen of the LP.8.1 subvariant of JN.1. The active controls in this study were mRNA-1273.712 and mRNA-1273.167 vaccine, which contain single mRNAs encoding the SARS-CoV-2 S-2P antigen of the KP.2 and JN.1 strain, respectively. PBS was used as a negative control.

#### **Methods:**

Mice (n=8/group) were administered 3 IM doses (2-dose primary series [Dose 1 and 2] + booster [Dose 3]) of mRNA vaccines. Mice received 2 different primary series regimens.

- Regimen 1 (Groups 2 to 4): Dose 1 (Day 1) and Dose 2 (Day 22) both contained 0.5 µg of the mRNA-1273 (original) vaccine.
- Regimen 2 (Groups 5 to 7): Dose 1 (Day 1) consisting of 0.5 µg (total) of the bivalent vaccine containing a 1:1 benchside mix of separately formulated mRNA-1273 (original) and mRNA-1273.045 (BA.4/BA.5). Dose 2 (Day 22) consisting of 0.5 µg (total) of a bivalent vaccine containing a 1:1 benchside mix of separately formulated mRNA-1273.815 (XBB.1.5) and mRNA-1273.712 (KP.2).

Regimen 1 enabled assessments using a model that has been previously used for testing updated vaccine candidates, while Regimen 2 was introduced to simulate a diverse immune experience that is more consistent with current human experience.

On Day 65, mice were boosted (Dose 3) with 1.0 µg of mRNA-1273.712 (Group 2 and 5), mRNA-1273.167 (Group 3 and 6), or mRNA-1273.251 (Group 4 and 7). Blood samples were collected on Day 65 (before Dose 3 was administered) and on Day 79 (2 weeks after Dose 3). Samples were analyzed for bAbs using ELISA and nAbs using VSV-based PSVNA. For Day 65, due to limited sample availability, equal volumes of samples for each group were pooled for bAb analysis. See Table 3 for a summary of MOD-7345.1273 study design.

**Table 3: Study Design for Study MOD-7345.1273**

Study Report Group (MOD Reference Group) (n=8)	Primary Series				Booster			Readouts
	Dose 1	Dose 2	Dose Level (µg)	Dose Schedule	Dose 3			
	Treatment (IM)	Treatment (IM)			Treatment (IM)	Dose Level (µg)	Dose Schedule	
1 (1)	PBS Control	PBS Control	0	Dose 1: Day 1  Dose 2: Day 22	PBS Control	0	Day 65	Serum (Day 65, Day 79)
2 (2)	mRNA-1273	mRNA-1273	0.5		mRNA-1273.712	1		
3 (3)	mRNA-1273	mRNA-1273	0.5		mRNA-1273.167	1		
4 (4)	mRNA-1273	mRNA-1273	0.5		mRNA-1273.251	1		bAb response (ELISA)
5 (6)	mRNA-1273 + mRNA-1273.045	mRNA-1273.815 + mRNA-1273.712	0.5		mRNA-1273.712	1		
6 (7)	mRNA-1273 + mRNA-1273.045	mRNA-1273.815 + mRNA-1273.712	0.5		mRNA-1273.167	1		nAb response (VSV-PSVNA)
7 (8)	mRNA-1273 + mRNA-1273.045	mRNA-1273.815 + mRNA-1273.712	0.5		mRNA-1273.251	1		

Abbreviations: bAb = binding antibody; ELISA = enzyme-linked immunosorbent assay; IM = intramuscular; mRNA = messenger RNA; nAb = neutralizing antibody; PBS = phosphate-buffered saline; PSVNA = pseudovirus neutralization assay; VSV = vesicular stomatitis virus.

Source: Report MOD-7345.1273

## **Results:**

The test articles were well tolerated, and animal health monitoring did not reveal any adverse findings.

On Day 65 (prior to Dose 3), the preboost bAb (IgG) titers against S-2P were comparable between all groups administered Regimen 1, with GMTs ranging from 53,032 to 62,244 (Figure 3). However, preboost S-2P IgG titers were lower and more variable (GMTs ranged from 6,373 to 37,673) in groups that received Regimen 2. The lower preboost S-2P IgG titers in mice receiving primary series Regimen 2 were likely due to the antigenic distance between the variant vaccines administered and the original strain S-2P used in the ELISA. There were no detectable bAb titers in the PBS control group.

The S-2P IgG titers were increased 2 weeks after a booster (Dose 3) with mRNA-1273.712, mRNA-1273.167, or mRNA-1273.251 in both primary series regimens (Figure 3). On Day 79 (2 weeks after Dose 3) in groups receiving Regimen 1, mice administered mRNA-1273.251 showed an approximately 3.7-fold increase in IgG titers, which was numerically higher than the fold increase in observed titers in mice that received mRNA-1273.712 or mRNA-1273.167 (2.9- and 2.3-fold, respectively). In groups receiving Regimen 2, postboost (Day 79) IgG titers following the administration of mRNA-1273.251 (GMT of 110,108) were comparable (<2-fold difference) to titers elicited by mRNA-1273.712 (GMT of 114,278) and mRNA-1273.167 (GMT of 68,531). The fold increase in IgG titers from preboost levels in these groups were variable (2.9- to 17-fold) mainly due to the variable preboost titer levels, which are likely due to the necessity of pooling samples from the group precluding the ability of identifying any significant outlier samples (Figure 3). These results indicate that in both primary series regimens, boosting (Dose 3) with mRNA-1273.251 elicited S-2P IgG bAb responses comparable to mRNA-1273.712 and mRNA-1273.167.

On Day 65 (prior to Dose 3), the preboost nAb titers against JN.1, KP.2, XEC, and LP.8.1 were generally low or below the LLOQ in groups receiving Regimen 1 (Figure 4A). This is consistent with these animals only having been exposed to the original strain-containing vaccine, which is antigenically distant from JN.1 lineage strains. In contrast, groups receiving Regimen 2 had higher but variable preboost nAb titers (GMT ranged from 119 to 793) on Day 65, which was expected given the greater antigenic diversity provided by Regimen 2, increasing immunity against JN.1 and JN.1 subvariants as measured in Day 65 samples (Figure 4B).

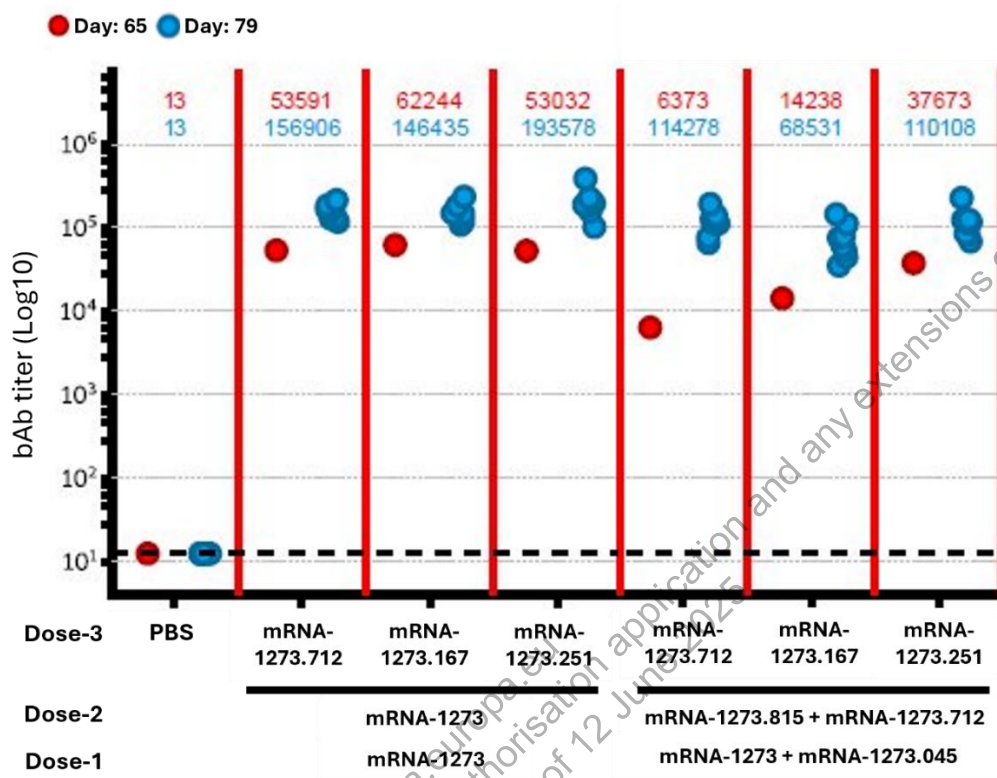
On Day 79 (2 weeks after Dose 3) in groups receiving Regimen 1, mice boosted with mRNA-1273.251 showed a 27.4-fold increase in nAb titers against LP.8.1 compared to Day 65, whereas a lower fold increase against LP.8.1 was observed when mice were boosted with mRNA-1273.712 (13.3-fold) or mRNA-1273.167 (7.9-fold). Mice boosted with mRNA-1273.251 also increased titers to JN.1 (3.6-fold), KP.2 (5.4-fold), and XEC (3.0 fold) with fold increases that did not exceed or were lower than mRNA-1273.712 (KP.2 21.0 fold; JN.1 22.9-fold; XEC 12.2-fold) or mRNA-1273.167 (KP.2 13.3-fold; JN.1 12.3-fold; XEC 9.4-fold) (Figure 4A). These results indicate that following Regimen 1, boosting with mRNA-1273.251 elicited the highest nAb titers against LP.8.1 compared to mRNA-1273.712 or

mRNA-1273.167 and cross-neutralized JN.1, KP.2, and XEC strains similar or lower than mRNA-1273.712 and mRNA-1273.167.

On Day 79 (2 weeks after Dose 3) in groups receiving Regimen 2, mice boosted with mRNA-1273.251 showed a 98.3-fold increase in nAb titers against LP.8.1 and increased titers against other JN.1 lineage strains (66.6-fold against KP.2; 33.9-fold against JN.1; and 42.3-fold against XEC) compared to Day 65. By comparison, mice boosted with mRNA-1273.712 showed an 86.1-fold increase in nAb titers against LP.8.1 and increased titers against other JN.1 lineage strains (KP.2 53.1-fold; JN.1 72.7-fold; XEC 72.4-fold). Mice boosted with mRNA-1273.167 showed 84.4-fold increase in nAb titers to LP.8.1 and increased titers against other JN.1 lineage strains (KP.2 69.4-fold; JN.1 45.0-fold; XEC 63.4-fold) (Figure 4B). These results indicate that following Regimen 2, the highest increase in titers against LP.8.1 was elicited by mRNA-1273.251, surpassing the response seen with mRNA-1273.167 and mRNA-1273.712.

In groups that received Regimen 2, increases in nAb titers against all JN.1 related strains following Dose 3 were higher across all groups when compared to groups that received Regimen 1. The higher overall nAb response in groups receiving Regimen 2 is consistent with these animals having greater immune experience and breadth, more similar to the diverse cross-variant immunity measured in the human population currently based on prior infections with a variety of variant SARS-CoV-2 viruses as well as vaccination with the original and variant-specific vaccines.

**Figure 3: Binding Antibody Responses Against S-2P in BALB/c Mice After Boosting (Third Dose)**



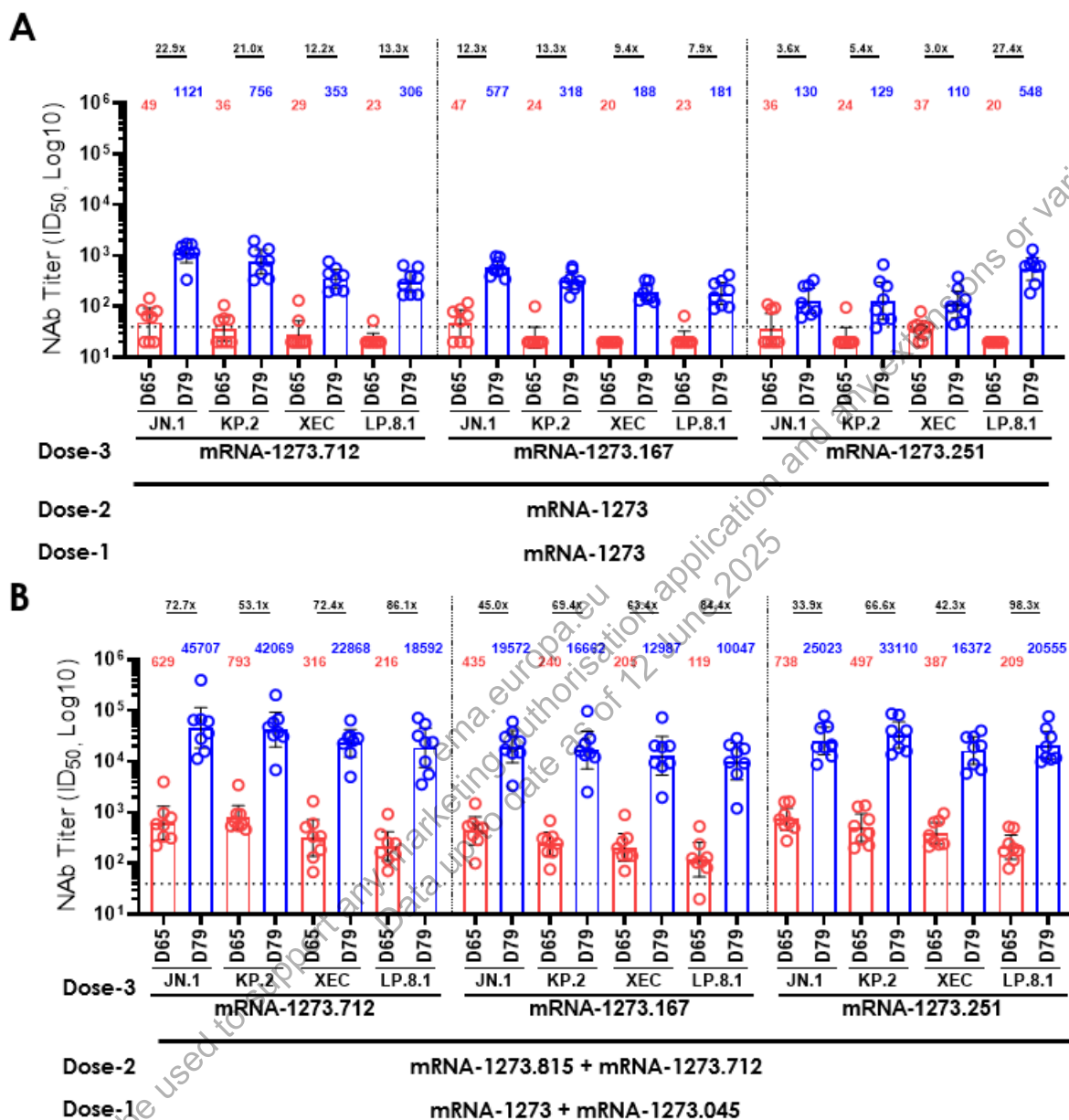
Abbreviations: bAb = binding antibody; GMT = geometric mean titer; LOD = limit of detection; mRNA = messenger RNA; nAb = neutralizing antibody; PBS = phosphate-buffered saline; S-2P = spike protein with 2 proline substitutions within the heptad repeat 1 domain.

Note: For Day 65, due to limited sample availability after samples were prioritized for nAb titer measurement, equal volumes of samples for each group were pooled and used to measure bAb to S-2P. GMT values are presented at the top of each figure, with red indicating the GMT for Day 65 (prior to Dose 3) and blue indicating the GMT for Day 79 (2 weeks after Dose 3). The dotted line indicates the LOD of the assay.

Source: Report MOD-7345.1273.



**Figure 4: Neutralizing Antibody Responses Against JN.1, KP.2, XEC, and LP.8.1 in BALB/c Mice After Boosting (Third Dose)**



Abbreviations: D = day; GMT = geometric mean titer; ID<sub>50</sub> = inhibitory dilution 50%; LLOQ = lower limit of quantification; mRNA = messenger RNA; nAb = neutralizing antibody.

Note: Panel A depicts nAb for groups that received Regimen 1 primary series. Panel B depicts nAb for groups that received Regimen 2 primary series. The numbers and bars represent GMTs, and whiskers represent the 95% confidence intervals for preboost Day 65 (prior to Dose 3) and postboost Day 79 (2 weeks after Dose 3). The dotted line indicates the LLOQ of the assay.

Source: Report MOD-7345.1273.

### **Conclusions:**

After both 2-dose primary series regimens, boosting (Dose 3) with mRNA-1273.251 elicited robust S-2P IgG bAb responses that were comparable to mRNA-1273.712 and mRNA-1273.167. Mice boosted with mRNA-1273.251 showed increased neutralizing antibodies to LP.8.1 (matched) and cross-neutralized related JN.1 lineage strains (JN.1, KP.2, and XEC), regardless of the primary series regimen, when assessed using the Sponsor's VSV-based PSVNA assay.

The overall nAb response to LP.8.1 and related JN.1 sublineage strains was higher in groups receiving Regimen 2, which is consistent with these animals having greater cross-variant immune breadth, as they had previously received mRNA-1273.712 (KP.2) as part of their primary series vaccination. Collectively, the results indicated that mRNA-1273.251 was most effective in boosting nAb titers to the LP.8.1 strain while also cross-neutralizing related JN.1 strains.

### **2.6.2.3 SECONDARY PHARMACODYNAMICS**

No secondary pharmacodynamic studies have been performed with a LP.8.1-containing vaccine.

### **2.6.2.4 SAFETY PHARMACOLOGY**

No safety pharmacology studies have been performed with a LP.8.1-containing vaccine.

### **2.6.2.5 PHARMACODYNAMIC DRUG INTERACTIONS**

No pharmacodynamic drug interaction studies have been performed with a LP.8.1-containing vaccine.

### **2.6.2.6 DISCUSSION AND CONCLUSIONS**

In support of the development of a LP.8.1-containing mRNA vaccine for the 2025-2026 season, nonclinical in vivo pharmacology studies were conducted in BALB/c mice with mRNA-1273.251. These studies evaluated immunogenicity of a LP.8.1-containing mRNA vaccine given as a primary series or as a booster dose in mice previously immunized with mRNA-1273 vaccines.

In Study MOD-7407, the primary series administration of mRNA-1273.251 (LP.8.1) demonstrated high immunogenicity with a robust 15-fold increase in S-2P IgG titers after Dose 2. The GMTs were comparable between mRNA-1273.251, mRNA-1273.712, and mRNA-1273.167 (<2-fold difference). The mRNA-1273.251 induced higher nAb titers against LP.8.1 and effectively cross-neutralized JN.1 lineage strains (JN.1, KP.2, and XEC), with nAb titers comparable or higher than mRNA-1273.712 and mRNA-1273.167. These results suggest mRNA-1273.251 provides robust protective responses to LP.8.1 and related JN.1 lineage strains.



In Study MOD-7345.1273, after both 2-dose primary series regimens, boosting with mRNA-1273.251 elicited robust S-2P IgG bAb responses comparable to those from mRNA-1273.712 and mRNA-1273.167. Mice boosted with mRNA-1273.251 showed increased neutralizing antibodies to LP.8.1 (matched) and cross-neutralized related JN.1 lineage strains (JN.1, KP.2, and XEC), regardless of the primary series regimen. The overall nAb response to LP.8.1 and related JN.1 sublineage strains was higher in groups receiving Regimen 2, which is consistent with greater immune experience with JN.1 lineage strains. Collectively, these results indicated that mRNA-1273.251 was most effective in boosting nAb titers to the LP.8.1 strain while also cross-neutralizing related JN.1 strains.

Overall, these data support the potential of an LP.8.1 formulation in driving increased immunogenicity and boosting protection against both LP.8.1 and closely related JN.1 lineage strains, as well as JN.1 strains yet to emerge.

### **2.6.2.7 TABLES and Figures**

Tables and figures are included in their respective sections above.

### **2.6.2.8 REFERENCES**

Center for Disease Control and Prevention. COVID Data Tracker. Summary of variant surveillance [database on the Internet]. Atlanta, GA: U.S. Department of Health and Human Services, CDC; 2025 Mar 28 [cited 2025 Apr 1]. Available from: <https://covid.cdc.gov/covid-data-tracker/#variant-summary>.

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