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List of Abbreviations

Abbreviation	Definition
BA.1	subvariant of Omicron
BA.4/BA.5	subvariants of Omicron (the spike protein of BA.5 is identical to that of BA.4)
bAb	binding antibody
COVID-19	coronavirus disease 2019
ELISA	enzyme-linked immunosorbent assay
EFT	Emergency Task Force
EMA	European Medicines Agency
ETF	Emergency Task Force
FDA	Food and Drug Administration
GMT	geometric mean titer
IgG	immunoglobulin G
IM	intramuscular
JN.1	BA.2.86.1.1 subvariant of Omicron
KP.2	BA.2.86.1.1.1.1.2 subvariant of Omicron
LLOQ	lower limit of quantification
LNP	lipid nanoparticle
mRNA	messenger RNA
nAb	neutralizing antibody
PBS	phosphate-buffered saline
PSVNA	pseudovirus neutralization assay
RBD	receptor binding domain
S-2P	spike protein with 2 proline substitutions within the heptad repeat 1 domain
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
TAG-CO-VAC	Technical Advisory Group on COVID-19 Vaccine Composition
VOC	variant of concern
VSV	vesicular stomatitis virus
WHO	World Health Organization
XBB.1.5	subvariant of Omicron

2.6.2.1 Brief Summary

ModernaTX, Inc. (the Sponsor)'s scalable mRNA/LNP technology platform allowed for a rapid response to the COVID-19 pandemic and was used to develop mRNA-1273, an LNP-encapsulated mRNA-based vaccine against SARS-CoV-2. mRNA-1273 contains a single mRNA that encodes the SARS-CoV-2 spike protein with 2 proline substitutions within the heptad repeat 1 domain (S-2P). mRNA-1273 was proven highly effective against COVID-19 following SARS-CoV-2 infection and has been licensed or conditionally approved across multiple regions for the prevention of COVID-19 in individuals 6 months of age and older (SPIKEVAX™).

Starting in 2021, 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 to current vaccines that VOCs exhibit, updating vaccine strain compositions to match such strains more closely is critical to maintaining protection. In response, variant-specific booster vaccines were recommended by WHO TAG-CO-VAC, EMA, and FDA, starting in 2022 with recommendations for bivalent vaccines. In 2022, bivalent variant-specific mRNA-1273 booster vaccines were authorized, with both ancestral and Omicron BA.1 (mRNA-1273.214) and ancestral and Omicron BA.4/BA.5 (mRNA-1273.222) being developed and authorized. In 2023, monovalent Omicron subvariant XBB.1.5 vaccine was recommended, and monovalent variant-specific mRNA-1273 vaccine (mRNA-1273.815) was authorized to address rises in infection from the XBB family Omicron subvariants.

In August 2023, the WHO designated a new strain BA.2.86 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 because of the rapid increase in prevalence across WHO countries (WHO 2023). The JN.1 strain 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. The JN.1 variant continues to be the most commonly sequenced strain globally, with additional subvariants of JN.1 having more recently emerged. These subvariants of JN.1, such as KP.2 (alias for BA.2.86.1.1.11.1.2) which has 3 additional mutations in the spike protein versus JN.1 including 2 in the RBD (R346T and F456L), are predicted to be antigenically similar to JN.1. As stated by the WHO TAG-CO-VAC and EMA Emergency Task Force (ETF) in April 2024, as virus evolution is expected to continue from JN.1, future formulations of COVID-19 vaccines should aim to induce enhanced neutralizing antibody responses to JN.1 and its descendent lineages (EMA 2024; WHO 2024). As one approach, the WHO TAG-CO-VAC therefore recommends use of a monovalent JN.1 lineage antigen in vaccines.

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. As also recommended by health agencies for COVID-19 strain updates, a framework to identify VOCs and to test updated vaccine candidates

is therefore critical to preserve neutralization responses and protection against the infection/severe disease caused by SARS-CoV-2. The Sponsor has established such a process for continuous monitoring of emerging variants, classification of variants based on incorporation of immune-evading mutations, and subsequent testing of vaccine candidates matched to these variants in preparation for deployment should health agencies request it.

The Sponsor has initiated development of a monovalent JN.1-containing mRNA vaccine (mRNA-1273.167) for the 2024-2025 season, given the dominance of JN.1 and its antigenically-related subvariants, which are predicted to be similarly neutralized by JN.1 vaccine elicited antibodies. To support this, nonclinical in vivo pharmacology studies were conducted in BALB/c mice with mRNA-1273.167 (monovalent vaccine containing a single mRNA encoding the SARS-CoV-2 S-2P antigen of the JN.1 subvariant of Omicron) (Table 1). These studies evaluated immunogenicity of JN.1-containing mRNA vaccines given as a primary series or as 3rd and 5th booster doses in mice previously immunized with mRNA-1273 vaccines. The results of these studies not only demonstrate the immunogenicity of the JN.1 new variant vaccine (mRNA-1273.167), but also indicates the relative antigenic distance between the XBB and JN.1 variants, as mRNA-1273.167 neutralized matched (JN.1) or similar strain (KP.2) robustly with lower neutralization titers measured against XBB.1.5. Similarly, mRNA-1273.815 neutralized matched strain (XBB.1.5) robustly, with lower neutralization measured against JN.1 and KP.2. Overall, these data support the potential of a JN.1 monovalent formulation in driving increased immunogenicity against JN.1 as well as closely related subvariants such as KP.2.

Table 1: Completed Nonclinical Pharmacology Studies Supporting Development of a JN.1-containing Vaccine

Study Title	Report Number	Laboratory Name and Location	eCTD Reference
Evaluation of immunogenicity of a primary series of a monovalent SARS-CoV-2 JN.1-containing mRNA-1273 vaccine in mice	MOD-6764	ModernaTX, Inc. Cambridge, MA	Section 4.2.1.1
Evaluation of immunogenicity of monovalent SARS-CoV-2 JN1-containing vaccine boosters in mice	MOD-6560 and MOD-6094	ModernaTX, Inc. Cambridge, MA	Section 4.2.1.1

Abbreviations; eCTD =electronic common technical document; 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 Monovalent SARS-CoV-2 JN.1-containing mRNA-1273 Vaccine in Mice (MOD-6764)

The objective of Study MOD-6764 was to evaluate the immunogenicity of a primary series of a monovalent SARS-CoV-2 JN.1-containing mRNA-1273 vaccine (mRNA-1273.167) in mice ([Report MOD-6764](#)).

The test article used in this study was the monovalent mRNA-1273.167 vaccine. mRNA-1273.815 served as an active control and PBS a negative control.

Methods:

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

Table 2: Study Design for Study MOD-6764

Group (n=8)	Treatment (IM)	Dose Level (µg)	Dose Schedule	Readouts
1	PBS	0	Day 1, Day 22	Serum (Day 21, Day 36) bAb response (ELISA)
2	mRNA-1273.815	1		Serum (Day 36) nAb response (VSV-PSVNA)
3	mRNA-1273.167	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-6764](#).

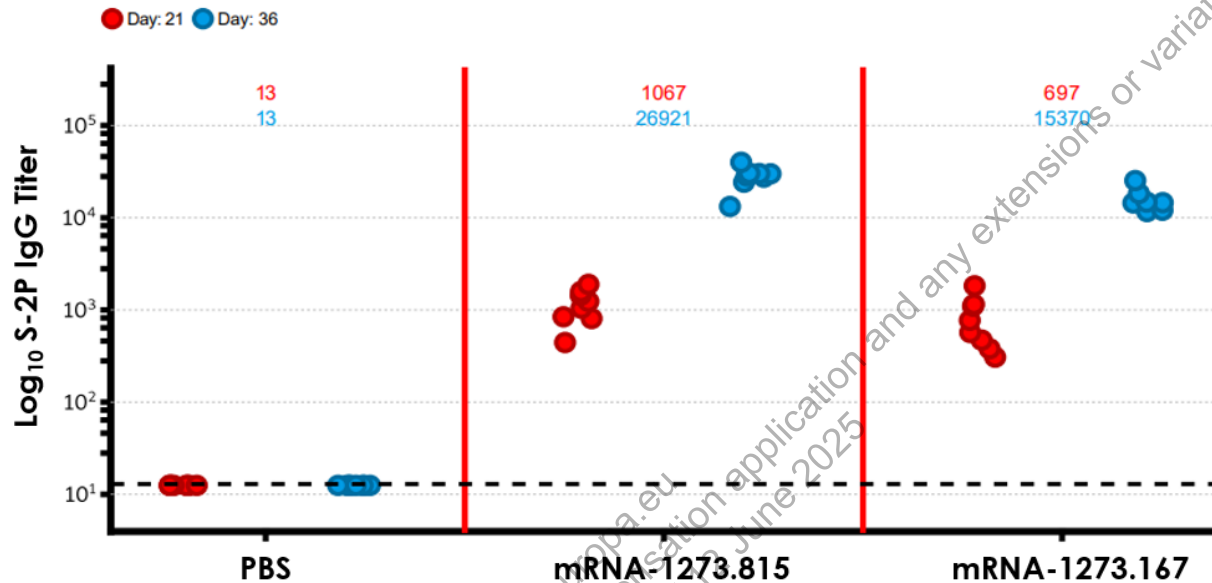
Results:

On Day 21 (3 weeks after Dose 1), mice that received mRNA-1273.167 exhibited robust bAb (IgG) titers against S-2P, which increased by 22-fold on Day 36 (2 weeks after Dose 2) ([Figure 1](#)). A similar response was observed in mice that received mRNA-1273.815, with a 25-fold increase observed on Day 36. No bAb titers were detectable in the PBS control group.

On Day 36 (2 weeks after Dose 2), mice that received mRNA-1273.167 exhibited high nAb titers against JN.1 and KP.2 (GMTs of 9758 and 3609, respectively) and low titers against XBB.1.5 (GMT of 47) ([Figure 2](#)). In contrast, mice that received mRNA-1273.815 exhibited high nAb titers against XBB.1.5 (GMT of 4461) with low titers against JN.1 and KP.2 (GMTs of 250 and

105, respectively). These results indicate that mRNA-1273.167 effectively neutralizes JN.1 and cross-neutralizes KP.2, an antigenically related strain. By contrast, mRNA-1273.815 effectively neutralized XBB.1.5 but was not able to neutralize either JN.1 or KP.2 effectively.

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



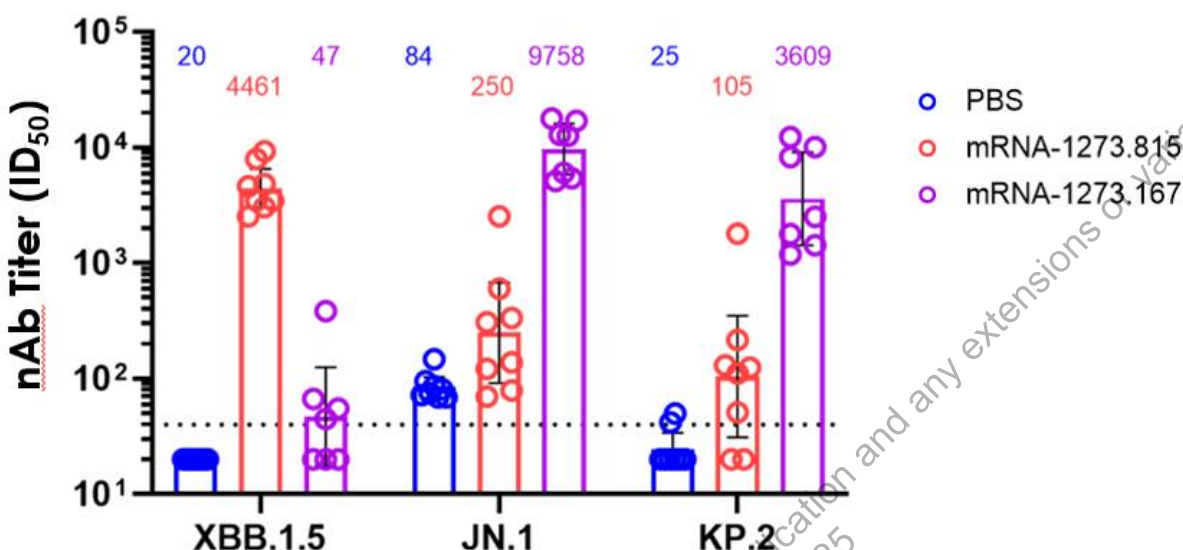
Abbreviations: GMT=geometric mean titer; IgG=immunoglobulin G; LOD=limit of detection;

PBS=phosphate-buffered saline; S-2P=spike protein with 2 proline substitutions within the heptad repeat 1 domain.

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-6764](#).

Figure 2: Neutralizing Antibody Responses Against XBB.1.5, JN.1, and KP.2 in BALB/c Mice After Primary Series Vaccination



Abbreviations: GMT=geometric mean titer; ID₅₀=inhibitory dilution 50%; LLOQ=lower limit of quantification; nAb=neutralizing antibody; PBS=phosphate-buffered saline.

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-6764](#).

Conclusions:

After a 2-dose primary series, mRNA-1273.167 elicited high bAb titers (S-2P IgG), indicating a strong immunological response. When assessed using the Sponsor's VSV-based PSVNA, mice that received mRNA-1273.167 neutralized JN.1 and KP.2 variants robustly. These neutralization results suggest that mRNA-1273.167 effectively neutralizes JN.1 and cross-neutralizes KP.2, an antigenically related strain, with lower neutralization titers measured against the antigenically distant strain XBB.1.5. By contrast, mRNA-1273.815 effectively neutralized XBB.1.5, but was not able to neutralize either JN.1 or KP.2 effectively.

2.6.2.2.2 Evaluation of Immunogenicity of SARS-CoV-2 JN.1-containing mRNA-1273 Vaccine Boosters in Mice (MOD-6560 and MOD-6094)

Studies MOD-6560 and MOD-6094 were conducted to evaluate the immunogenicity of booster doses of a monovalent SARS-CoV-2 JN.1-containing mRNA-1273 vaccine (mRNA-1273.167) administered as a 3rd dose or as 5th dose in mice previously immunized with mRNA-1273 vaccines ([Report MOD-6560](#) and [MOD-6094](#)).

The test article in both studies was the monovalent mRNA-1273.167 vaccine. The currently approved monovalent mRNA-1273.815 vaccine, which contains a single mRNA encoding the SARS-CoV-2 S-2P antigen of the XBB.1.5 subvariant of Omicron was the active control. In both studies, the monovalent mRNA-1273 vaccine, which contains a single mRNA encoding the SARS-CoV-2 S-2P antigen, was administered as a primary series (Dose 1 and 2). In Study MOD-6560, the test articles, mRNA-1273.167 and mRNA-1273.815, were administered as a single booster dose (Dose 3). In Study MOD-6094, bivalent mRNA-1273.222, which is a coformulation of mRNA-1273 (ancestral) and mRNA-1273.045 (contains a single mRNA encoding the SARS-CoV-2 S-2P antigen of the BA.4/BA.5 subvariants of Omicron) was administered as a 3rd dose (Dose 3), monovalent mRNA-1273.815 vaccine was administered as a 4th dose (Dose 4), and the test articles mRNA-1273.167 or mRNA-1273.815 were administered as a 5th dose (Dose 5). For both studies, mice administered only PBS served as negative controls.

Methods:

In Study MOD-6560, mice (n=8/group) were administered 3 IM doses (2-dose primary series [Dose 1 and 2] + 1 booster [Dose 3]) of mRNA vaccines. Animals were administered 0.5 µg mRNA-1273 on Day 1 and Day 22 (primary series [Dose 1 and 2]). Approximately 4 weeks after the second dose (Day 54), mice were boosted [Dose 3] with 1.0 µg mRNA-1273.167 or mRNA-1273.815. Blood samples were collected on Day 51 (before Dose 3 was administered) and on Day 69 (2 weeks after Dose 3). Samples were analyzed for serum bAbs using ELISA and nAbs using VSV-based PSVNA. See [Table 3](#) for a summary of the study design and treatment groups.

Table 3: Study Design for Study MOD-6560

Group (n=8)	Primary Series			Booster			Readouts
	Treatment (IM)	Dose Level (µg)	Dose Schedule	Treatment (IM)	Dose Level (µg)	Dose Schedule	
1	PBS Control	0	Day 1 Day 22	PBS Control	0	Day 54	Serum (Day 51, Day 69) bAb response (ELISA)
2	mRNA-1273	0.5		mRNA-1273.815	1		
3	mRNA-1273	0.5		mRNA-1273.167	1		Serum (Day 51, Day 69) nAb response (VSV-PSVNA)

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-6560 and MOD-6094](#).

In Study MOD-6094, mice (n=8/group) were administered 5 IM doses (2-dose primary series [Dose 1 and 2] + 3 booster doses [Dose 3, 4, and 5]) of mRNA vaccines over an approximately 7-month period. Animals were administered 0.5 µg mRNA-1273 on Day 1 and Day 22 (primary series [Dose 1 and 2]). Mice were administered a 3rd dose [Dose 3] with 0.5 µg mRNA-1273.222 on Day 106 and a 4th dose [Dose 4] with 0.5 µg mRNA-1273.815 on Day 187. On Day 210, mice were administered a 5th dose [Dose 5] with 1.0 µg of the test articles mRNA-1273.815 or mRNA-1273.167. Blood samples were collected on Day 209 (before Dose 5 was administered) and on Day 224 (2 weeks after Dose 5). Samples were analyzed for serum nAbs using VSV-based PSVNA. See [Table 4](#) for a summary of the study design and treatment groups.

Table 4: Study Design for Study MOD-6094

Study Report Group (MOD Reference Group) (n=8)	Primary Series			Booster (Dose 3 and Dose 4)			Booster (Dose 5)			Readouts
	Treatment (IM)	Dose Level (µg)	Dose Schedule	Treatment (IM)	Dose Level (µg)	Dose Schedule	Treatment (IM)	Dose Level (µg)	Dose Schedule	
1 (1)	PBS (Control)	0	Day 1 Day 22	PBS	0	Dose 3: Day 106 Dose 4: Day 187	PBS	0	Day 210	Serum (Day 209, Day 224) nAb response (VSV-PSVNA)
2 (5)	mRNA-1273	0.5		Dose 3: mRNA-1273.222 Dose 4: mRNA-1273.815	0.5		mRNA-1273.815	1		
3 (6)	mRNA-1273	0.5		Dose 3: mRNA-1273.222 Dose 4: mRNA-1273.815	0.5		mRNA-1273.167	1		

Abbreviations: IM=intramuscular; nAb=neutralizing antibody; PBS=phosphate-buffered saline; PSVNA=pseudovirus neutralization assay; VSV=vesicular stomatitis virus.

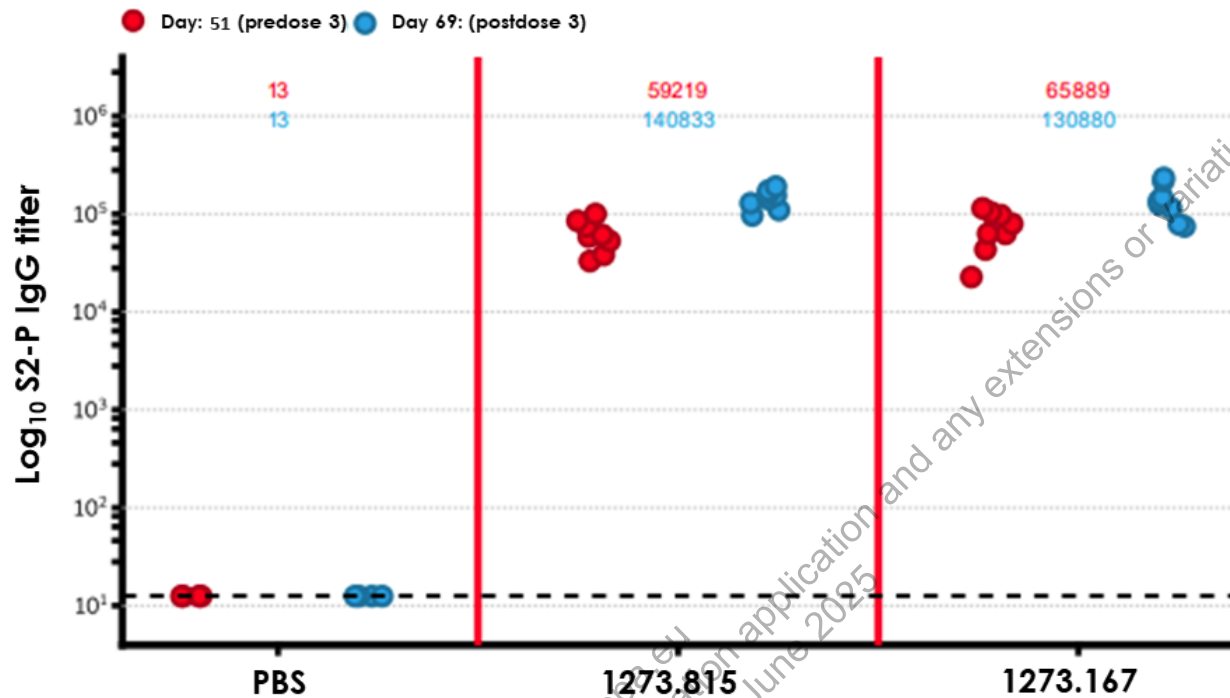
Source: [Report MOD-6560 and MOD-6094](#).

Results:***Immunogenicity of JN.1-Containing Vaccine Booster (Third Dose) in BALB/c Mice (Study MOD-6560)***

Robust bAb (IgG) titers against S-2P were observed after a booster (Dose 3) with monovalent mRNA-1273.815 or mRNA-1273.167, compared with PBS control (Figure 3). On Day 51 (4 weeks after Dose 2), the pre-boost S-2P IgG GMT values were high in all mice and comparable between the 2 groups (59,219 versus 65,889). On Day 69 (2 weeks after Dose 3), mice boosted with mRNA-1273.167 showed a 2-fold increase and mice boosted with mRNA-1273.815 showed a 2.4-fold increase in IgG titers, indicating that boosting with mRNA-1273.167 boosts bAb responses comparable to mRNA-1273.815.

On Day 51 (4 weeks after Dose 2), the pre-boost nAb titers against XBB.1.5, JN.1, and KP.2 were generally below the LLOQ, with the exception of a few mice that showed low titers just above the LLOQ against JN.1 and KP.2 (Figure 4). On Day 69 (2 weeks after Dose 3), mice boosted with mRNA-1273.167 showed high serum nAb titers (>10-fold over controls) against JN.1 (GMT 355) and KP.2 (GMT 217), while titers against XBB.1.5 remained close to the LLOQ. In contrast, mice boosted with mRNA-1273.815 showed increased serum nAb titers against XBB.1.5 (GMT 113), with lower titers measured against JN.1 and KP.2 (GMTs 101 and 51, respectively; largely driven by high titers measured in 1 of 8 mice in this group). The results indicated that mRNA-1273.167 was able to boost titers against JN.1 and KP.1 in mice previously administered mRNA-1273 primary series doses, with less than 2-fold difference in nAb titers measured between the 2 strains.

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



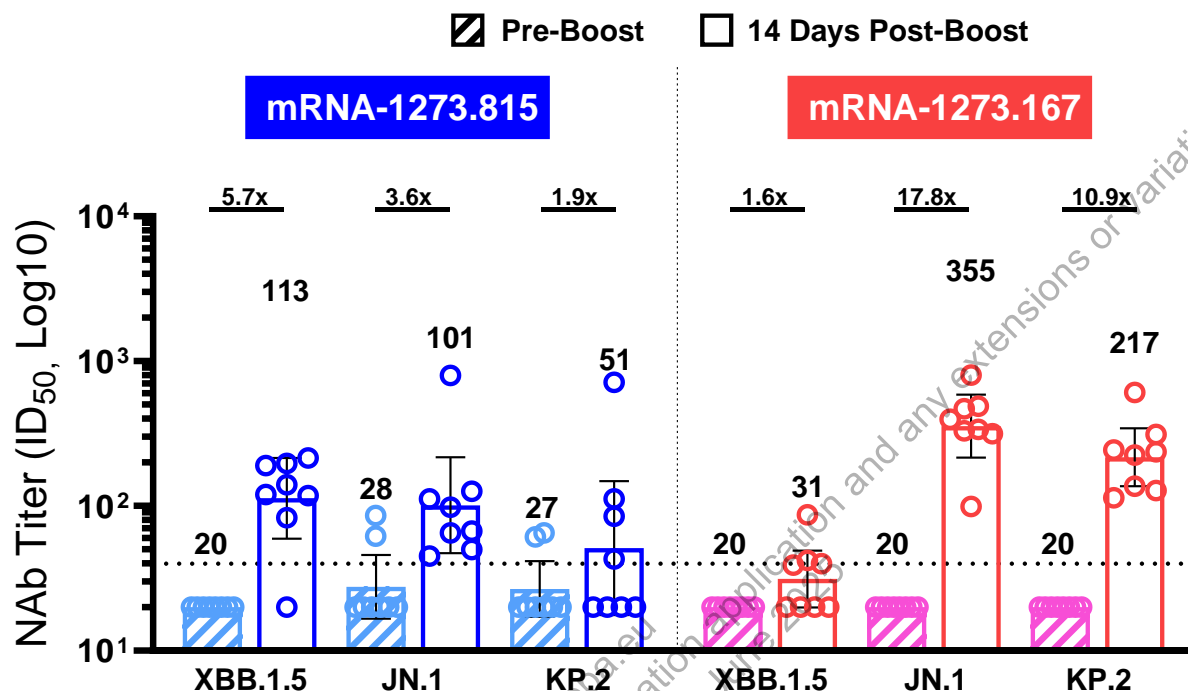
Abbreviations: GMT=geometric mean titer; IgG=immunoglobulin G; LOD=limit of detection;

PBS=phosphate-buffered saline; S-2P=spike protein with 2 proline substitutions within the heptad repeat 1 domain.

Note: GMT values are presented at the top of each figure, with red indicating the GMT for Day 51 (4 weeks after Dose 2) and blue indicating the GMT for Day 69 (2 weeks after Dose 3). The dotted line indicates the LOD of the assay.

Source: [Report MOD-6560 and MOD-6094](#).

Figure 4: Neutralizing Antibody Responses Against XBB.1.5, JN.1, and KP.2 in BALB/c Mice After Boosting (Third Dose)



Abbreviations: GMT=geometric mean titer; ID₅₀=inhibitory dilution 50%; LLOQ=lower limit of quantification; nAb=neutralizing antibody.

Note: The numbers and bars represent GMTs, and whiskers represent the 95% confidence intervals for pre-boost Day 51 (4 weeks after Dose 2) and post-boost Day 69 (2 weeks after Dose 3). The dotted line indicates the LLOQ of the assay.

Source: [Report MOD-6560](#) and [MOD-6094](#).

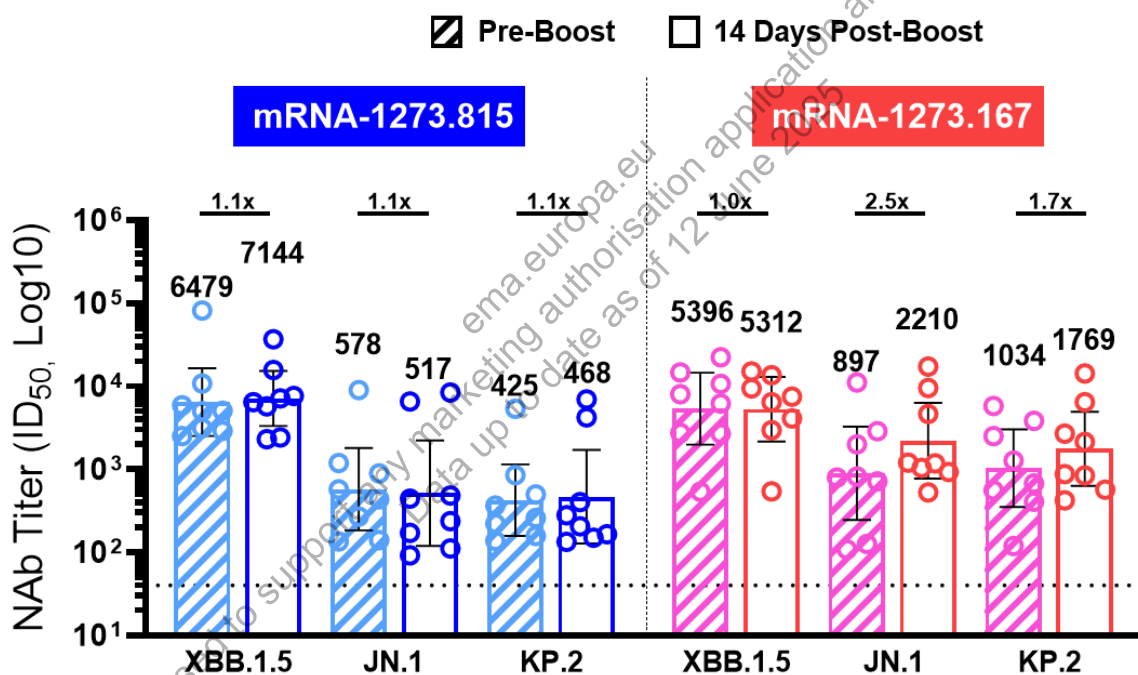
Immunogenicity of JN.1-Matched Vaccine Booster (Fifth Dose) in BALB/c Mice (Study MOD-6094)

On Day 209 (before the Dose 5 booster), mice that had previously received a primary series with mRNA-1273 (Dose 1 and 2) followed by boosters with mRNA-1273.222 (Dose 3) and mRNA-1273.815 (Dose 4) showed the high pre-Dose 5 booster nAb titers against XBB.1.5 (GMT 5396-6479) consistent with prior exposure to XBB.1.5-containing vaccine. The pre-Dose 5 nAb titers against JN.1 (GMT 578-897) and KP.2 (GMT 425-1034) were 5- to 15-fold lower than those against XBB.1.5, demonstrating increased immune escape for these new variants (Figure 5). These mice also had substantial measurable titers against JN.1 and KP.2, indicating development of increased cross-reactivity following multiple vaccinations. High pre-boost titers against XBB.1.5 and JN.1 variants also reflect the high number of vaccinations these animals received over an approximately 7-month period. Since this vaccination schedule is not reflective of the prior vaccination schedule in humans, these data are not considered to be predictive of nAb titers elicited in humans. Rather, this model allows for assessment of updated boosters where prior immunity is more diverse based on exposure to multiple strain antigens. In

this context, the principal rationale for assessments is to investigate cross-neutralization across related subvariants, such as JN.1 and KP.2, after a 5th dose booster administration.

Based on VSV-based PSVNA on Day 224 (2 weeks after Dose 5), boosting with mRNA-1273.167 elicited further increases in nAb titers against JN.1 (2.5-fold) and KP.2 (1.7-fold), with minimal differences seen between the 2 variants (1.2-fold). No increase in titer was observed against XBB.1.5. In contrast, boosting with mRNA-1273.815 did not further increase titers against JN.1, KP.2, or XBB.1.5, and the lack of an XBB.1.5 titer increase is likely due to the very high neutralization levels prior to the boost. The results indicated that administration of mRNA-1273.167 as a 5th dose booster was still able to increase nAb titers against JN.1 and KP.2, and in this model where immunity is very diverse across multiple variant antigens, minimal nAb differences were seen between the JN.1 and KP.2 strains.

Figure 5: Neutralizing Antibody Responses Against XBB.1.5, JN.1, and KP.2 in BALB/c Mice After Boosting (Fifth Dose)



Abbreviations: GMT=geometric mean titer; ID₅₀=inhibitory dilution 50%; LLOQ=lower limit of quantification; nAb=neutralizing antibody.

Note: The numbers and bars represent GMTs, and whiskers represent the 95% confidence intervals for pre-boost Day 209 (before the Dose 5 booster) and post-boost Day 224 (2 weeks after the Dose 5 booster). The dotted line indicates the LLOQ of the assay.

Source: [Report MOD-6560](#) and [MOD-6094](#).

Conclusions:

After a 2-dose primary series with mRNA-1273, boosting (Dose 3) with mRNA-1273.167 elicited S-2P IgG bAb responses comparable to mRNA-1273.815. When assessed using the

Sponsor's VSV-based PSVNA mice boosted (Dose 3) with mRNA-1273.167 effectively neutralized JN.1 and cross-neutralized KP.2, an antigenically related strain, with lower neutralization titers measured against the antigenically distant strain XBB.1.5. In contrast, mice boosted with mRNA-1273.815 effectively neutralized XBB.1.5, with lower neutralization measured against JN.1 and KP.2.

In mice that had previously received a primary series with mRNA-1273 (Dose 1 and 2) and boosters with mRNA-1273.222 (Dose 3) and mRNA-1273.815 (Dose 4), a 5th booster (Dose 5) with mRNA-1273.167 further increased nAb titers against JN.1 (2.5-fold) and KP.2 (1.7-fold) but not against XBB.1.5. In contrast, boosting with mRNA-1273.815 as a 5th dose did not further increase titers against JN.1, KP.2, or XBB.1.5.

2.6.2.3 Secondary Pharmacodynamics

No secondary pharmacodynamic studies have been performed with a JN.1-containing vaccine.

2.6.2.4 Safety Pharmacology

No safety pharmacology studies have been performed with a JN.1-containing vaccine.

2.6.2.5 Pharmacodynamic Drug Interactions

No pharmacodynamic drug interaction studies have been performed with a JN.1-containing vaccine.

2.6.2.6 Discussion and Conclusions

In support of the development of a JN.1-containing mRNA vaccine for the 2024-2025 season, nonclinical in vivo pharmacology studies were conducted in BALB/c mice with mRNA-1273.167. These studies evaluated immunogenicity of JN.1-containing mRNA vaccines given as a primary series or as 3rd and 5th booster doses in mice previously immunized with mRNA-1273 vaccines.

After a 2-dose primary series, mRNA-1273.167 elicited high bAb titers (S-2P IgG), indicating a strong immunological response. When assessed using the Sponsor's VSV-based PSVNA, mice that received mRNA-1273.167 neutralized JN.1 and KP.2 variants, with high titers measured against both variants. As expected, given the significant antigenic differences between JN.1 and XBB.1.5, lower neutralization titers measured against the XBB.1.5. By contrast, mRNA-1273.815 drives high levels of neutralization against XBB.1.5, with low neutralization against both JN.1 and KP.2. Notably, lack of cross-neutralization between XBB and JN.1 strains indicated that all immunity was solely provided by the 2-dose primary vaccination series and was specific to the strain delivered in the vaccine formulation. A small reduction in KP.2 neutralization in animals vaccinated with mRNA-1273.167 reflects the impact of the 3 mutations in KP.2 relative to JN.1. This was also noted in similar assessments of new variant vaccines in past studies where neutralization reduction from a small number of step-wise mutations found in

subvariants of the vaccine strain could be captured in this primary immunization model but was not subsequently seen in humans with diverse immune experience from prior immunization and infections across a range of SARS-CoV-2 variants.

After a 2-dose primary series with mRNA-1273, boosting (Dose 3) with mRNA-1273.167 elicited S-2P IgG bAb responses comparable to boosting with mRNA-1273.815. When assessed using the Sponsor's VSV-based PSVNA, mice boosted (Dose 3) with mRNA-1273.167 effectively neutralized JN.1 and cross-neutralized KP.2, an antigenically related strain, with lower neutralization titers measured against the antigenically distant strain XBB.1.5. In contrast, mice boosted with mRNA-1273.815 elicited the highest titers versus XBB.1.5, with lower neutralization measured against JN.1 and KP.2.

In mice that had previously received a primary series with mRNA-1273 (Dose 1 and 2) and boosters with mRNA-1273.222 (Dose 3) and mRNA-1273.815 (Dose 4), a 5th booster (Dose 5) with mRNA-1273.167 further increased nAb titers against JN.1 (2.5-fold) and KP.2 (1.7-fold) but not against XBB.1.5. In contrast, boosting with mRNA-1273.815 as a 5th dose did not further increase titers against JN.1, KP.2, or XBB.1.5, as the high pre-Dose 5 XBB.1.5 titers likely prevented additional boosting.

Across all studies, there was low cross-neutralization between JN.1 and XBB, demonstrating the antigenic differences between these strains. Notably, any small differences in titers against JN.1 and KP.2 neutralization seen following the 2-dose primary series with mRNA-1273.167 was further diminished in the booster studies, likely due to the impact of more diverse immune background elicited by prior vaccinations. The robust immunity in humans derived from multiple vaccinations and/or infection is similarly likely to drive much greater resistance to escape from such step-wise viral evolution.

Overall, these data support the potential of a JN.1-containing monovalent formulation in driving increased immunogenicity against JN.1 as well as closely related subvariants such as KP.2.

2.6.2.7 Tables and Figures

Tables and figures are included in their respective sections above.

2.6.2.8 References

European Medicines Agency. EMA recommendation to update the antigenic composition of authorized COVID-19 vaccines for 2024-2025. [Internet] Amsterdam: European Medicines Agency; 2024 Apr 30 [cited 2024 Apr 30]. Available from: https://www.ema.europa.eu/en/documents/other/ema-recommendation-update-antigenic-composition-authorized-covid-19-vaccines-2024-2025_en.pdf

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