

Table of Contents

TABLE OF CONTENTS	1
LIST OF TABLES	1
LIST OF FIGURES	2
LIST OF ABBREVIATIONS	3
2.6.2.1 BRIEF SUMMARY.....	4
2.6.2.2 PRIMARY PHARMACODYNAMICS	8
2.6.2.2.1 Evaluation of Immunogenicity of a Primary Series of Monovalent and Bivalent SARS-CoV-2 XBB.1.5-containing Vaccines in Mice (MOD-6037).....	10
2.6.2.2.2 Evaluation of Immunogenicity of Monovalent and Bivalent SARS-CoV-2 XBB.1.5-containing Vaccine Boosters in Mice (MOD-5827).....	13
2.6.2.2.3 Evaluation of Immunogenicity of Monovalent and Bivalent SARS-CoV-2 XBB.1.16-containing Vaccine Boosters in Mice (MOD-5972).....	17
2.6.2.3 SECONDARY PHARMACODYNAMICS	21
2.6.2.4 SAFETY PHARMACOLOGY	21
2.6.2.5 PHARMACODYNAMIC DRUG INTERACTIONS	21
2.6.2.6 DISCUSSION AND CONCLUSIONS	21
2.6.2.7 TABLES AND FIGURES	23
2.6.2.8 REFERENCES	23

List of Tables

Table 1: Completed Nonclinical Pharmacology Studies Supporting Development of an XBB-containing Vaccine.....	7
Table 2: Test Materials and Summary of Dose Formulation Analysis Results	9

List of Figures

Figure 1:	Binding Antibody Responses in BALB/c Mice After Primary Series Vaccination	12
Figure 2:	Neutralizing Antibody Responses in BALB/c Mice After Primary Series Vaccination	13
Figure 3:	Binding Antibody Responses in BALB/c Mice After Boosting With Third Dose	15
Figure 4:	Neutralizing Antibody Responses in BALB/c Mice After Boosting With Third Dose	16
Figure 5:	Binding Antibody Responses in BALB/c Mice After Boosting (Third Dose)	19
Figure 6:	Neutralizing Antibody Responses in BALB/c Mice After Boosting (Third Dose).....	20

List of Abbreviations

Abbreviation	Definition
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
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
ELISA	enzyme-linked immunosorbent assay
GISAID	Global Initiative on Sharing All Influenza Data
GLP	Good Laboratory Practice
GMT	geometric mean titer
IDR	identity and ratio
IgG	immunoglobulin G
IL	interleukin
IM	intramuscular
LLOQ	lower limit of quantification
LNP	lipid nanoparticle
MERS-CoV	Middle Eastern Respiratory Disease Coronavirus
mRNA	messenger RNA
nAb	neutralizing antibody
PBS	phosphate-buffered saline
PEG2000-DMG	1,2 dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000
PSVNA	pseudovirus neutralization assay
RBD	receptor-binding domain
S-2P	spike protein modified with 2 proline substitutions within the heptad repeat 1 domain
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SM-102	a custom-manufactured ionizable lipid
UTR	untranslated region
VOC	variant of concern
VSV	vesicular stomatitis virus
XBB.1.5/XBB.1.9.1	subvariants of Omicron (the spike protein of XBB.1.9.1 is identical to that of XBB.1.5)
XBB.1.16	subvariant of Omicron

2.6.2.1 BRIEF SUMMARY

Coronaviruses are a large family of viruses including MERS-CoV and SARS-CoV that cause illness ranging from the common cold to more severe diseases. An outbreak of COVID-19 caused by SARS-CoV-2 began in Wuhan, Hubei Province, China in December 2019, and the disease quickly spread globally.

ModernaTX, Inc. (the Sponsor)'s scalable mRNA/LNP technology platform allowed for a rapid response to the 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 18 years of age and older.

Starting in the Summer of 2021, an increase in COVID-19 cases was observed in many populations around the world, including those who had been vaccinated, due to the emergence of the Delta variant (B.1.617.2) of SARS-CoV-2. This variant of SARS-CoV-2 was shown to have increased pathogenicity as compared to prior variants ([Barouch 2022](#); [Siddle et al 2022](#); [Twhig et al 2022](#)). Subsequently, in the Fall of 2021, multiple regulatory bodies worldwide authorized a booster vaccine for use in adults following the observed waning of effectiveness after primary series immunization. Administration of a first booster dose increased the antibody responses against variants and improved vaccine effectiveness against the Delta variant.

In November 2021, the Omicron variant (B.1.1.529; BA.1) emerged as the most antigenically divergent variant to date with > 30 mutations in the spike protein ([Hastie et al 2021](#)). Soon after its emergence, the Omicron variant rapidly became dominant worldwide, driving a wave of infections and COVID-19 disease. The 2-dose mRNA-1273 had been shown to be effective against COVID-19 and hospitalization due to COVID-19 caused by SARS-CoV-2 variants, including Alpha, Beta, Delta, and Gamma. However, the effectiveness of the original vaccine formulations appeared to be reduced with respect to infections with the Omicron variant ([Bruxvoort et al 2021](#); [Tseng et al 2022](#)).

The morbidity and mortality associated with COVID-19 caused by antigenically divergent variants such as Omicron and the decreased effectiveness of mRNA-1273 against Omicron infection created the need to develop a booster with enhanced immunogenicity to improve protection against COVID-19 and help decrease the burden on hospitals and healthcare systems ([Gilbert et al 2022](#); [Khouri et al 2021](#)). On 31 Aug 2022, the US FDA amended the mRNA-1273 EUA to authorize an Omicron-containing (BA.4/BA.5) bivalent formulation of mRNA-1273 (ie, mRNA-1273.222) for use as a single booster dose at least 2 months following primary or booster vaccination. Other agencies worldwide authorized the Omicron BA.1-containing bivalent formulation of mRNA-1273 (ie, mRNA-1273.214) and subsequently the Omicron BA.4/BA.5-containing bivalent formulation throughout the second half of 2022. Authorizations for both bivalent boosters were based on preclinical and clinical data demonstrating superior immune responses to the variant in the vaccine compared with the original mRNA-1273 booster,

a noninferior antibody response to SARS-CoV-2 (D614G), and a similar safety profile as mRNA-1273 ([Chalkias et al 2022a](#); [Chalkias et al 2022b](#)).

The SARS-CoV-2 virus is continually evolving by accumulating mutations, some which offer a significant growth advantage, leading to establishment of VOC strains that become dominant in circulation. The emergence of the Omicron variant was a significant evolutionary shift where an unprecedented number of mutations were observed that enabled significant immune escape against immunity provided by prototype vaccines and/or immunity provided by infection with SARS-CoV-2 strains prior to Omicron. Although the development and deployment of Omicron-containing vaccine boosters, specifically mRNA-1273.214 (BA.1-containing bivalent) and mRNA-1273.222 (BA.4/BA.5-containing bivalent), substantially enhanced protection against the early Omicron strains, the Omicron virus family has continued to rapidly evolve. New subvariants have emerged in early 2023 (eg, XBB.1.5, XBB.1.9.1, and XBB.1.16) with additional growth advantages, increased transmissibility, and the ability to escape authorized BA.1- or BA.4/BA.5-containing bivalent booster vaccine- or infection-derived immunity. Given the evident immune escape that these new variants exhibit to current vaccines, updating vaccine strain compositions to match such strains more closely is critical to maintaining protection against COVID-19.

The complex nature of SARS-CoV-2's continuing evolution 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. A framework to identify VOCs and 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's ongoing monitoring and variant response effort has enabled the development and preclinical evaluation of more than 19 monovalent and bivalent vaccine compositions. For example, based on real-time monitoring efforts, the Sponsor initiated the development and evaluation process for variants including XBB.1, BQ.1.1, and BN.1 in early Fall of 2022, and in early 2023, CH.1.1, XBB.1.5/1.9.1, and XBB.1.16 (among others). Additionally, from these analyses, antigenically similar variants are categorized into subvariant or "subfamily" groups, where the majority of these antigenic regions are the same except for a small number of additional mutations that are not predicted to significantly impact antibody neutralization. For example, based on these assessments, the Sponsor has categorized XBB, BA.2.75, and BA.5 as distinct subfamilies. These subfamilies are predicted to respond similarly to functional antibodies that neutralize the virus. This has been corroborated by assessments of viral neutralization by sera from BA.4/BA.5 bivalent boosted individuals from Study mRNA-1273-P205 Part H (Study P205H), in which study participants that had received 3 prior doses of mRNA-1273 were boosted with mRNA-1273.222. A subset of sera from Study P205H were tested using the Sponsor's internal, nonvalidated PSVNA, assessing neutralization against XBB.1, XBB.1.5, and XBB.1.16. All 3 XBB subvariants were neutralized similarly, likely due to antigenic similarity in their RBD. This subfamily matching approach also indicates that it is possible to reliably predict the immunogenicity of a variant antigen from neutralization studies using sera from animals

immunized with another variant antigen from the same subfamily. For instance, the neutralization titers of sera from XBB.1.5-immunized mice against XBB.1.16 would be expected to reliably predict similar titers from XBB.1.16-immunized mice.

The Sponsor has recently evaluated multiple XBB-containing vaccines concurrently, including the following: (1) the monovalent mRNA-1273.815 vaccine that contains a single mRNA encoding the SARS-CoV-2 S-2P antigen of the XBB.1.5/XBB.1.9.1 (note: the spike protein of XBB.1.9.1 is identical to that of XBB.1.5) subvariant of Omicron; (2) the monovalent mRNA-1273.116 vaccine that contains a single mRNA encoding the SARS-CoV-2 S-2P antigen of the XBB.1.16 subvariant of Omicron; (3) the bivalent mRNA-1273.231 vaccine, which is a coformulation of the mRNA-1273.045 vaccine (a monovalent vaccine containing a single mRNA encoding the SARS-CoV-2 S-2P antigen of the BA.4/BA.5 subvariants of Omicron) and the mRNA-1273.815 vaccine; and (4) bivalent mRNA-1273.234 vaccine, which is a coformulation of the mRNA-1273.045 vaccine and the mRNA-1273.116 vaccine. All mRNAs are formulated into a mixture of 4 lipids: SM-102, cholesterol, DSPC, and PEG2000-DMG.

In support of the development of XBB-containing mRNA vaccines for the 2023-2024 season, nonclinical in vivo pharmacology studies were conducted in BALB/c mice. These studies evaluated immunogenicity of XBB-containing mRNA vaccines given as a primary series or as a booster dose following primary series vaccination with mRNA-1273.

In a non-GLP immunogenicity study using BALB/c mice, after a 2-dose primary series, monovalent mRNA-1273.815 and bivalent mRNA-1273.231 elicited robust S-2P bAb titers and potently neutralized the XBB subfamily strains XBB.1.5 and XBB.1.16, with neutralization titers that were >45-fold higher than those elicited by monovalent mRNA-1273.045 or bivalent mRNA-1273.222. mRNA-1273.231 had numerically higher titers against the ancestral and BA.4/BA.5 strains compared with mRNA-1273.815, consistent with the inclusion of BA.4/BA.5 in the bivalent vaccine. All vaccines elicited nAb titers against XBB.1.5 that were similar to nAb titers against XBB.1.16 ([Section 2.6.2.2.1](#)).

In a non-GLP immunogenicity study using BALB/c mice, administering monovalent mRNA-1273.815 or bivalent mRNA-1273.231 as a booster following a primary series of mRNA-1273 elicited robust S-2P bAb titers and high nAb responses against the XBB subfamily strains XBB.1.5 and XBB.1.16, with mRNA-1273.815 driving higher nAb responses than mRNA-1273.231. mRNA-1273.231 had numerically higher titers against ancestral and BA.4/BA.5 strains compared with mRNA-1273.815, consistent with the inclusion of BA.4/BA.5 in the bivalent vaccine. All vaccines elicited nAb titers against XBB.1.5 that were similar to nAb titers against XBB.1.16 ([Section 2.6.2.2.2](#)).

In a non-GLP immunogenicity study using BALB/c mice, administering monovalent mRNA-1273.116 or bivalent mRNA-1273.234 as a booster following a primary series of mRNA-1273 elicited robust S-2P bAb titers as well as neutralizing titers against XBB subfamily strains XBB.1.16 and XBB.1.5. nAb titers against XBB.1.16 were comparable to those against XBB.1.5 ([Section 2.6.2.2.3](#)).

Overall, animals vaccinated with XBB-containing vaccines mRNA-1273.815, mRNA-1273.116, mRNA-1273.231, and mRNA-1273.234, either as a primary series or as a booster dose, elicited

robust S-2P bAb titers and potentially neutralized both XBB.1.5 and XBB.1.16. The results also support the subfamily approach proposed by the Sponsor, wherein preclinical immunogenicity studies performed with an XBB strain support registration of a vaccine with strains within the subfamily due to their antigenic similarity. This approach may enable more rapid deployment of future variant matched vaccines based on preclinical data from closely matched subfamily variants generated during routine monitoring.

The completed studies are listed in [Table 1](#), summarized in additional detail in [Section 2.6.2.2](#), and presented in a tabular format summary in [Module 2.6.3](#).

Table 1: Completed Nonclinical Pharmacology Studies Supporting Development of an XBB-containing Vaccine

Study Title	Report Number	Laboratory Name and Location	eCTD Reference
Evaluation of Immunogenicity of a Primary Series of Monovalent and Bivalent SARS-CoV-2 XBB.1.5-containing Vaccines in Mice	MOD-6037	ModernaTX, Inc. Cambridge, MA	4.2.1.1
Evaluation of Immunogenicity of Monovalent and Bivalent SARS-CoV-2 XBB.1.5-containing Vaccine Boosters in Mice	MOD-5827	ModernaTX, Inc. Cambridge, MA	4.2.1.1
Evaluation of Immunogenicity of Monovalent and Bivalent SARS-CoV-2 XBB.1.16-containing Vaccine Boosters in Mice	MOD-5972	ModernaTX, Inc. Cambridge, MA	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

Preclinical mRNA-1273, mRNA-1273.045, mRNA-1273.815, and mRNA-1273.222 vaccines used in these studies were prepared with the same method as the Good Manufacturing Practice mRNA-1273, mRNA-1273.045, mRNA-1273.815, and mRNA-1273.222 clinical Drug Products. Preclinical material for mRNA-1273.116 was prepared with the representative manufacturing process conditions for mRNA-1273.116, with the exception of the IDR sequence present in the 3' UTR. The Sponsor routinely includes IDR sequences of up to 25 nucleotides in the 3' UTR to facilitate analytical detection. Because UTR regions are noncoding and therefore will not be translated into proteins, these modifications have no impact on the quality attributes, stability profile, functional activity, or safety of the mRNA product. The Sponsor has performed extensive in vitro and in vivo equivalence studies to confirm this.

mRNA-1273 encodes the S-2P antigen of the Wuhan-Hu-1 isolate of SARS-CoV-2, mRNA-1273.045 encodes the S-2P antigen of the SARS-CoV-2 Omicron BA.4/BA.5 subvariants (note: the spike protein of BA.5 is identical to that of BA.4), mRNA-1273.815 encodes the S-2P antigen of the SARS-CoV-2 Omicron XBB.1.5/XBB.1.9.1 subvariants (note: the spike protein of XBB.1.9.1 is identical to that of XBB.1.5), and mRNA-1273.116 encodes the S-2P of the SARS-CoV-2 Omicron XBB.1.16 subvariant. All vaccines include 2 proline mutations introduced to stabilize the spike protein into the prefusion conformation. The mRNA-1273.231 and mRNA-1273.234 vaccines included mRNA-1273.045 combined with mRNA-1273.815 or mRNA-1273.116, respectively, in a 1:1 ratio of separately formulated mRNA vaccines to generate a bench side mix. mRNA-1273.222 is a coformulation of the mRNA-1273 and mRNA-1273.045 vaccines. mRNA-1273.045 and mRNA-1273.222 were used as active controls in the preclinical studies and mRNA-1273 was given as a primary series. All vaccines were formulated into a mixture of 4 lipids: SM-102, cholesterol, DSPC, and PEG2000-DMG. A summary of the dose formulation analysis results is presented in [Table 2](#).

The preclinical monovalent mRNA-1273.045 vaccine was based on sequence -GISAID: EPI_ISL_12548717 - and encoded the following substitutions from the original mRNA-1273 vaccine: T19I, L24-, P25-, P26-, A27S, H69-, V70-, G142D, V213G, G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, L452R, S477N, T478K, E484A, F486V, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K.

The preclinical monovalent mRNA-1273.815 vaccine was based on sequence -GISAID: EPI_ISL_16134259 - and encoded the following substitutions from the original mRNA vaccine: T19I, L24-, P25-, P26-, A27S, V83A, G142D, Y144-, H146Q, Q183E, V213E, G252V, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478K, E484A, F486P, F490S, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K.

The preclinical monovalent mRNA-1273.116 vaccine was based on sequence - GenBank: OQ931660, GISAID: EPI_ISL_17619088 - and encoded the following substitutions from the original mRNA-1273 vaccine: T19I, L24-, P25-, P26-, A27S, V83A, G142D, Y144-, H146Q, E180V, Q183E, V213E, G252V, G339H, R346T, L368I, S371F, S373P, S375F, T376A, D405N,

R408S, K417N, N440K, V445P, G446S, N460K, S477N, T478R, E484A, F486P, F490S, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K.

All vaccines were encapsulated in an LNP through a modified ethanol-drop nanoprecipitation process as previously described ([Hassett et al 2019](#)). Briefly, ionizable, structural, helper, and polyethylene glycol lipids were mixed with mRNA-1273 in acetate buffer, pH 5.0, at a ratio of 2.5:1 (lipids: mRNA). The mixture was neutralized with tris(hydroxymethyl)aminomethane hydrochloride, pH 7.5, sucrose was added as a cryoprotectant, and the final solution was sterile-filtered. Vials were filled with formulated LNP and stored frozen at -20°C until further use. The preclinical vaccine product underwent analytical characterization, which included the determination of particle size and polydispersity, encapsulation, mRNA purity, double-stranded RNA content, osmolality, pH, endotoxin, and bioburden, and the material was deemed acceptable for the in vivo study ([Corbett et al 2020](#)).

Table 2: Test Materials and Summary of Dose Formulation Analysis Results

Test Material	mRNA Description	mRNA Lot No(s)	Size (nm)	PDI	EE%
mRNA-1273	mRNA encoding SARS-CoV-2 spike protein ^a	6006920001	110	0.1	83
mRNA-1273.045	mRNA encoding SARS-CoV-2 BA.4/BA.5 spike protein ^b	DHM-99115	100	0.17	>97
mRNA-1273.815	mRNA encoding SARS-CoV-2 XBB.1.5 spike protein ^c	DH-78330.6	102	0.18	>97
mRNA-1273.116	mRNA encoding SARS-CoV-2 XBB.1.16 spike protein ^d	DH-78330.7	107	0.16	>97
mRNA-1273.222	mRNA encoding SARS-CoV-2 spike protein + mRNA encoding SARS-CoV-2 BA.4/BA.5 spike protein (coformulated 1:1) ^e	DHM-99116	107	0.19	>97
mRNA-1273.231	mRNA SARS-CoV-2 BA.4/BA.5 spike protein + mRNA encoding SARS-CoV-2 XBB.1.5 spike protein (bench side 1:1) ^f	NA	NA	NA	NA
mRNA-1273.234	mRNA SARS-CoV-2 BA.4/BA.5 spike protein + mRNA encoding SARS-CoV-2 XBB.1.16 spike protein (bench side 1:1) ^g	NA	NA	NA	NA

Abbreviations: EE%=encapsulation efficiency; LNP=lipid nanoparticle; NA=not applicable; No=number; PDI=polydispersity index; S-2P=spike protein modified with 2 proline substitutions within the heptad repeat 1 domain; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; SM-102=a custom-manufactured ionizable lipid.

Note: All mRNA test material stocks were formulated in SM-102-containing LNPs with a final storage buffer in 10.7 mM sodium acetate; 8.7% sucrose; 20 mM tris(hydroxymethyl)aminomethane hydrochloride at pH 7.5 and stored frozen at -20°C.

The EE% is the percentage of mRNA inside the LNP. It is calculated by determining the amount of free mRNA that is accessible to ribogreen in intact LNP and the total mRNA present in detergent-treated LNP; $EE\% = 100 - \text{the percentage of nonencapsulated/free mRNA}$.

- ^a mRNA-1273 is a monovalent vaccine that contains a single mRNA that encodes the S-2P antigen of the Wuhan-Hu-1 isolate of SARS-CoV-2.
- ^b mRNA-1273.045 is a monovalent vaccine that contains a single mRNA that encodes the S-2P antigen of the BA.4/BA.5 subvariants of Omicron. The spike protein of BA.5 is identical to that of BA.4.
- ^c mRNA-1273.815 is a monovalent vaccine that contains a single mRNA that encodes the S-2P antigen of the XBB.1.5/XBB.1.9.1 subvariants of Omicron. The spike protein of XBB.1.9.1 is identical to that of XBB.1.5.
- ^d mRNA-1273.116 is a monovalent vaccine that contains a single mRNA that encodes the S-2P antigen of the XBB.1.16 subvariant of Omicron.
- ^e mRNA-1273.222 is a coformulation of the mRNA-1273 and mRNA-1273.045 vaccines.
- ^f mRNA-1273.231 is a 1:1 bench side mix of separately formulated mRNA-1273.045 and mRNA-1273.815 vaccines.
- ^g mRNA-1273.234 is a 1:1 bench side mix of separately formulated mRNA-1273.045 and mRNA-1273.116 vaccines.

2.6.2.2.1 Evaluation of Immunogenicity of a Primary Series of Monovalent and Bivalent SARS-CoV-2 XBB.1.5-containing Vaccines in Mice (MOD-6037)

The objective of this study was to evaluate the immunogenicity of a primary series of monovalent and bivalent SARS-CoV-2 XBB.1.5-containing vaccines in mice.

Methods:

Detailed methods are provided in [Study MOD-6037](#).

To evaluate the effects of a primary series of XBB.1.5-containing vaccines on antibody responses, mice (n=8/group) received 2 IM injections of PBS control article or 1 µg of mRNA-1273.045, mRNA-1273.815, mRNA-1273.222, or mRNA-1273.231 as a primary series 3 weeks apart. Blood was collected from all animals on Day 21 (before the second dose was administered) and Day 36 (2 weeks after the second dose). Serum samples were analyzed for bAb responses via ELISA against the S-2P protein and nAb responses via VSV-based PSVNA against Wuhan-Hu-1 with D614G, BA.4/BA.5, XBB.1.5, and XBB.1.16 strain-matched mutations.

Results:

Robust bAb (IgG) titers against S-2P, were observed after a 2-dose primary series with monovalent mRNA-1273.045 and mRNA-1273.815 vaccines and bivalent mRNA-1273.222 and mRNA-1273.231 vaccines compared with control (PBS) ([Figure 1](#)).

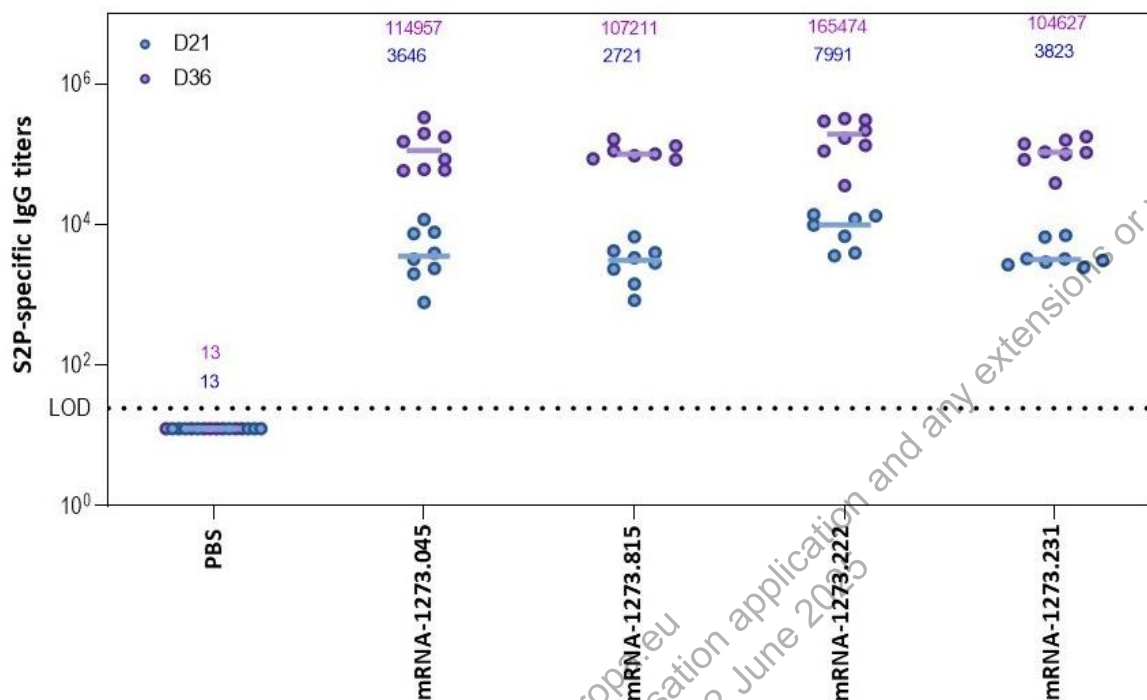
On Day 21 (3 weeks after Dose 1), S-2P IgG GMT values ranged from 2721 to 7991. On Day 36 (2 weeks after Dose 2), values ranged from 104,627 to 165,474, increasing from 21- to 39-fold from Day 21. XBB.1.5-containing vaccines (monovalent mRNA-1273.815 and bivalent mRNA-1273.231) elicited high S-2P binding antibody titers after the first dose and a substantial increase (27- to 39-fold) after the second dose. This response was comparable to the bAb response observed in mice administered monovalent mRNA-1273.045 (32-fold increase from

Day 21 to Day 36) and was higher than the response observed in mice administered bivalent mRNA-1273.222 (21-fold increase from Day 21 to Day 36).

Based on the VSV-based PSVNA (Figure 2), on Day 36 (2 weeks after the second dose), mice that received XBB.1.5/XBB.1.9.1 variant-containing vaccines (monovalent mRNA-1273.815 or bivalent mRNA-1273.231) had the highest nAb titers against XBB.1.5 (16,672 and 18,111, respectively) and XBB.1.16 (20,915 and 20,195, respectively). By comparison, mice that received mRNA-1273.045 or mRNA-1273.222 had lower serum nAb titers against XBB.1.5 (937 and 363, respectively) and XBB.1.16 (1269 and 500, respectively). nAb titers against XBB.1.5 and nAb titers against XBB.1.16 were comparable by treatment groups, suggesting that these strains are antigenically similar.

Among mice that received XBB.1.5/XBB.1.9.1 variant-containing vaccines (monovalent mRNA-1273.815 or bivalent mRNA-1273.231), nAb titers against D614G were similarly low (61 and 87, respectively). However, mRNA-1273.231 had numerically higher titers (33,030) against the BA.4/BA.5 strains compared to the mRNA-1273.815 vaccine (2,114), consistent with the inclusion of BA.4/BA.5 in the bivalent vaccine.

In the mRNA-1273.045 group, the highest nAb titers were against BA.4/BA.5, followed by XBB.1.16, XBB.1.5, and D614G. In the mRNA-1273.222 group, the highest nAb titers were against BA.4/BA.5, followed by D614G, XBB.1.16, and XBB.1.5.

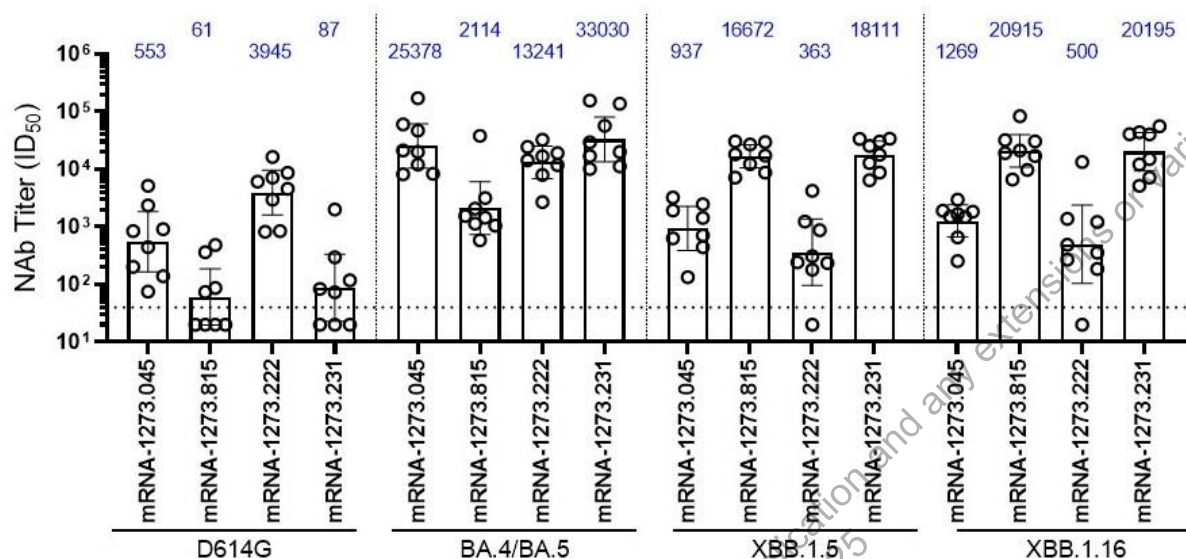
Figure 1: Binding Antibody Responses in BALB/c Mice After Primary Series Vaccination

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

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

Note: GMT values are presented at the top of each figure, with blue indicating the GMT for Day 21 (3 weeks after the first dose) and pink/purple indicating the GMT for Day 36 (2 weeks after the second dose). The dotted line indicates LOD of the assay.

Source: [Study MOD-6037](#).

Figure 2: Neutralizing Antibody Responses 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.

Note: Blue numbers and bars represent GMTs, and whiskers represent 95% confidence interval. The dotted line indicates LLOQ of the assay.

Source: [Study MOD-6037](#).

Conclusions:

Overall, after a 2-dose primary series, mRNA-1273.815 and mRNA-1273.231 elicited robust S-2P bAb titers and high nAb titers against XBB.1.5 and XBB.1.16, indicating strong immunogenicity. The nAb titers elicited by mRNA-1273.815 and mRNA-1273.231 against the XBB.1.5 and XBB.1.16 strains were >45-fold higher than those elicited by mRNA-1273.045 or mRNA-1273.222. In contrast, mRNA-1273.815 and mRNA-1273.231 elicited low titers against the SARS-CoV-2 ancestral strains (D614G). In all treatment groups, titers against XBB.1.5 were comparable to titers against XBB.1.16, indicating that these variant strains are antigenically similar. mRNA-1273.231 showed higher titers against BA.4/BA.5 compared to mRNA-1273.815, consistent with the inclusion of BA.4/BA.5 in the bivalent vaccine.

2.6.2.2.2 Evaluation of Immunogenicity of Monovalent and Bivalent SARS-CoV-2 XBB.1.5-containing Vaccine Boosters in Mice (MOD-5827)

The objective of this study was to evaluate the immunogenicity of a booster dose of monovalent and bivalent SARS-CoV-2 XBB.1.5-containing vaccines in mice that have received primary series vaccination with mRNA-1273.

Methods:

Detailed methods are provided in [Study MOD-5827](#).

To evaluate the effects of a booster dose of XBB.1.5-containing vaccines on antibody responses, mice (n=8/group) were administered 3 IM doses (2 dose primary series [Dose 1 and Dose 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 Dose 2]). Approximately 10 weeks after the second dose (Day 22), these mice were boosted (booster dose [Dose 3]) with 1.0 µg of mRNA-1273.045, mRNA-1273.815, mRNA-1273.222, or mRNA-1273.231. Blood samples were collected on Day 21 (before Dose 2 of the primary series was administered), on Day 36 (2 weeks after Dose 2), on Day 91 (before the booster dose [Dose 3] was administered), and on Day 106 (2 weeks after the booster dose [Dose 3]). Serum samples were analyzed for bAb responses against the S-2P protein via ELISA and nAb responses via VSV-based PSVNA against Wuhan-Hu-1 with D614G, BA.4/BA.5, XBB.1.5, and XBB.1.16 strain-matched mutations.

Results:

Robust bAb (IgG) titers against S-2P, were observed after a 2-dose primary series (Dose 1 and Dose 2) with mRNA-1273 and boosting (Dose 3) with monovalent mRNA-1273.815, bivalent mRNA-1273.231, monovalent mRNA-1273.045, or bivalent mRNA-1273.222 vaccines compared with control (PBS) ([Figure 3](#)).

On Day 21 (3 weeks after Dose 1), S-2P IgG GMT values ranged from 322 to 557. On Day 36 (2 weeks after Dose 2), values ranged from 13,368 to 20,745, increasing 34- to 46-fold from Day 21, with some variability between groups despite all receiving a primary series of mRNA-1273. By Day 106 (2 weeks after boosting [Dose 3]) robust IgG titers against S-2P were observed in all vaccine groups, ranging from 34,132 to 85,802, reflecting approximately 2- to 6-fold increase from Day 36. mRNA-1273.815 and mRNA-1273.231 elicited comparable S-2P-binding IgG titers after boosting that were numerically higher than the bivalent mRNA-1273.222 vaccine.

Based on the VSV-based PSVNA ([Figure 4](#)), on Day 91 (preboost), robust nAb titers against D614G were observed in all vaccine groups, as expected, considering that all mice were immunized with 0.5 µg mRNA-1273 vaccine as a primary series. nAb titers against BA.4/BA.5 at Day 91 were lower compared with those against D614G, and the lowest nAb titers were observed against XBB.1.5 and XBB.1.16, indicating substantial immune escape from mRNA-1273 vaccination for these strains.

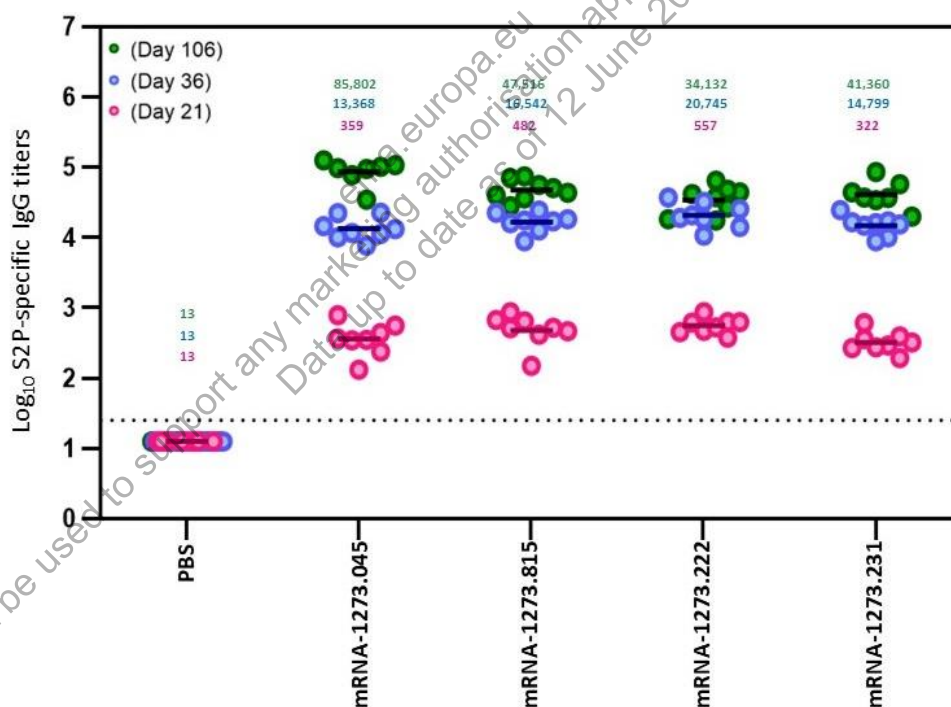
Two weeks after boosting (Day 106), mice that received XBB.1.5/XBB.1.9.1 variant-containing vaccines (monovalent mRNA-1273.815 or bivalent mRNA-1273.231) had the highest fold increase in serum nAb titers against XBB.1.5 (18- to 26-fold) and XBB.1.16 (14- to 36-fold) from Day 91 to Day 106. By comparison, mice that received mRNA-1273.045 or mRNA-1273.222 showed a more modest increase in serum nAb titers against XBB.1.5 (4.7- to 6.7-fold) and XBB.1.16 (3.8- to 7.2-fold).

Among mice that received XBB.1.5/XBB.1.9.1 variant-containing vaccines (monovalent mRNA-1273.815 or bivalent mRNA-1273.231), in the mRNA-1273.815 group, fold increases in serum nAb titers from Day 91 to Day 106 were lowest against D614G (2.1-fold) and BA.4/BA.5 (13-fold), while in the mRNA-1273.231 group, fold increase against these strains were higher (3.8-fold against D614G and 124-fold against BA.4/BA.5).

In groups that received BA.4/BA.5 variant-containing vaccines (monovalent mRNA-1273.045, bivalent mRNA-1273.222, or bivalent mRNA-1273.231), the highest fold increases in nAb titers were observed against BA.4/BA.5 (94- to 124-fold) followed by titers against D614G (3.8- to 16-fold).

Overall, at Day 106, the highest nAb titers against XBB.1.5 and XBB.1.16 were observed for mRNA-1273.815 followed by mRNA-1273.231; neutralization titers against XBB.1.5 and XBB.1.16 were comparable, suggesting that these strains are antigenically similar. mRNA-1273.231 had numerically higher titers against the ancestral and BA.4/BA.5 strains compared to the mRNA-1273.815 vaccine.

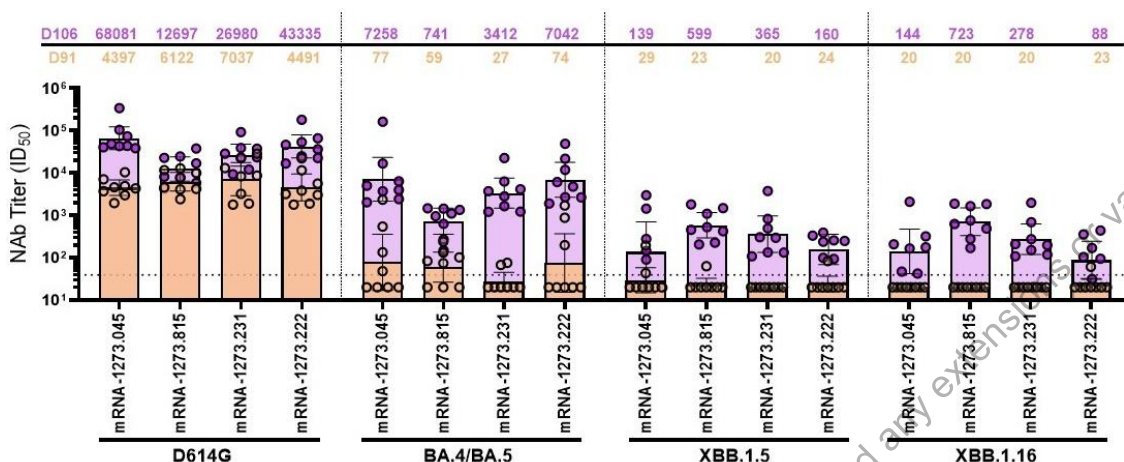
Figure 3: Binding Antibody Responses in BALB/c Mice After Boosting With Third Dose



Abbreviations: GMT=geometric mean titer; IgG=immunoglobulin G; LLOQ=lower limit of quantification; 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 pink indicating the GMT for Day 21 (3 weeks after the first dose), blue indicating the GMT for Day 36 (2 weeks after the second dose), and green indicating the GMT for Day 106 (2 weeks after the booster dose). The dotted line indicates LLOQ of the assays.

Source: [Study MOD-5827](#).

Figure 4: Neutralizing Antibody Responses in BALB/c Mice After Boosting With Third Dose

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

Note: GMT values are presented at the top of each figure, with orange indicating the GMT for Day 91 (preboost) and pink/purple indicating the GMT for Day 106 (2 weeks after the booster dose). The dotted line indicates LLOQ of the assays.

Source: [Study MOD-5827](#).

Conclusions:

After boosting, robust IgG titers against S-2P were observed in all vaccine groups. mRNA-1273.815 and mRNA-1273.231 elicited comparable S-2P-binding IgG titers that were numerically higher than the bivalent mRNA-1273.222 vaccine.

At Day 106 (2 weeks after boosting), increased serum nAb titers against all strains were observed. The highest nAb titers against XBB.1.5 and XBB.1.16 were observed for mRNA-1273.815 followed by mRNA-1273.231; neutralization titers against XBB.1.5 and XBB.1.16 were comparable, suggesting that these strains are antigenically similar. mRNA-1273.231 had numerically higher titers against the ancestral and BA.4/BA.5 strains compared to the mRNA-1273.815 vaccine.

Overall, boosting with the XBB.1.5-containing vaccines (monovalent mRNA-1273.815 or bivalent mRNA-1273.231) elicited robust S-2P-bAb titers and high nAb response against XBB.1.5 and XBB.1.16 strains, with the mRNA-1273.815 appearing to drive higher nAb responses than mRNA-1273.231. mRNA-1273.231 had numerically higher titers against the ancestral and BA.4/BA.5 strains compared to the mRNA-1273.815 vaccine, consistent with the inclusion of BA.4/BA.5 in the bivalent vaccine.

2.6.2.2.3 Evaluation of Immunogenicity of Monovalent and Bivalent SARS-CoV-2 XBB.1.16-containing Vaccine Boosters in Mice (MOD-5972)

The objective of this study was to evaluate the immunogenicity of a booster dose of monovalent (mRNA-1273.116) and bivalent (mRNA-1273.234) SARS-CoV-2 XBB.1.16-containing vaccines in mice that have received primary series vaccination with mRNA-1273.

Methods:

Detailed methods are provided in [Study MOD-5972](#).

To evaluate the effects of a booster dose of XBB.1.16-containing vaccines on antibody responses, mice (n=8/group) were administered 3 IM doses (2 dose primary series [Dose 1 and Dose 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 Dose 2]). Approximately 7 weeks after the second dose (Day 71), mice were boosted (booster dose [Dose 3]) with 1.0 µg of mRNA-1273.116 or mRNA-1273.234. Blood samples were collected on Day 21 (before Dose 2 of the primary series was administered), on Day 36 (2 weeks after Dose 2), on Day 70 (before the booster dose [Dose 3] was administered), and on Day 85 (2 weeks after the booster dose [Dose 3]). Serum samples were analyzed for bAb responses against the S-2P protein via ELISA and nAb responses via VSV-based PSVNA against Wuhan-Hu-1 with D614G, BA.4/BA.5, XBB.1.5, and XBB.1.16 strain-matched mutations.

Results:

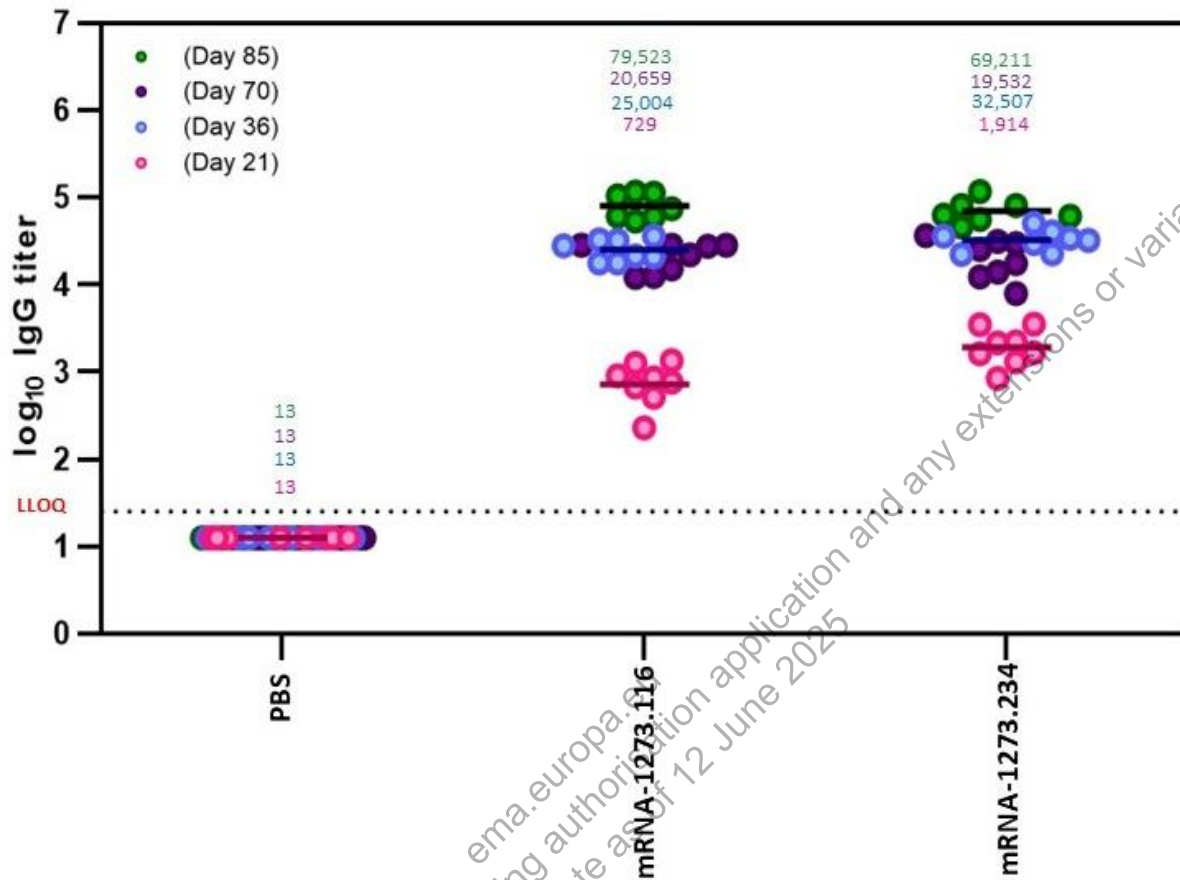
Robust bAb (IgG) titers against S-2P, were observed after a 2-dose primary series (Dose 1 and Dose 2) with mRNA-1273 and boosting (Dose 3) with monovalent mRNA-1273.116 or bivalent mRNA-1273.234, compared with control (PBS) ([Figure 5](#)).

On Day 21 (3 weeks after Dose 1), S-2P IgG GMT values for mRNA-1273.116 and mRNA-1273.234 were 729 and 1914, respectively, and by Day 36 (2 weeks after Dose 2), values increased 17- and 34-fold to 25,004 and 32,507, respectively. By Day 70 (4 weeks after Dose 2 and preboost), S-2P IgG GMT values for mRNA-1273.116 and mRNA-1273.234 dropped slightly to 20,659 and 19,532, respectively, but still reflected a 28- and 10-fold increase, respectively, from Day 21. On Day 85 (2 weeks after boosting [Dose 3]), mRNA-1273.116 elicited bAb antibody titers that were numerically higher (79,523) compared with mRNA-1273.234 (69,211); however, both vaccines elicited a 4-fold increase in bAb titers from Day 70 (preboost).

Based on the VSV-based PSVNA ([Figure 6](#)), on Day 70 (preboost), robust nAb titers against D614G were observed in both vaccine groups, as expected, considering that all mice were immunized with 0.5 µg mRNA-1273 vaccine as a primary series. nAb titers against BA.4/BA.5 at Day 70 were lower compared with those against D614G, and the lowest nAb titers were observed against XBB.1.5 and XBB.1.16, indicating substantial immune escape from mRNA-1273 vaccination for these strains.

From Day 70 to Day 85 (2 weeks after boosting [Dose 3]), mice that received mRNA-1273.234 showed a higher fold increase in serum nAb titers against XBB.1.5 (25-fold) and XBB.1.16 (33-fold) compared with mice that received mRNA-1273.116 (XBB.1.5: 17-fold; XBB.1.16: 23-fold). The higher nAb response observed postboost in the mRNA-1273.234 group was likely driven by measurable XBB subvariant titers on Day 70 (preboost) in 3 of 8 mice in the mRNA-1273.234 group, whereas preboost titers against XBB.1.5 or XBB.1.16 for all mice in the mRNA-1273.116 group were below the LLOQ.

The postboost nAb titer levels against XBB.1.5 and XBB.1.16 were comparable between both treatment groups, indicating that these strains are antigenically similar. nAb titers against BA.4/BA.5 were higher in the bivalent mRNA-1273.234 group (30-fold) compared to mRNA-1273.116 group (6-fold), consistent with the inclusion of BA.4/BA.5 in the vaccine. Bivalent mRNA-1273.234 also boosted titers against D614G to a greater extent (7.0-fold) compared to the monovalent mRNA-1273.116 (1-fold).

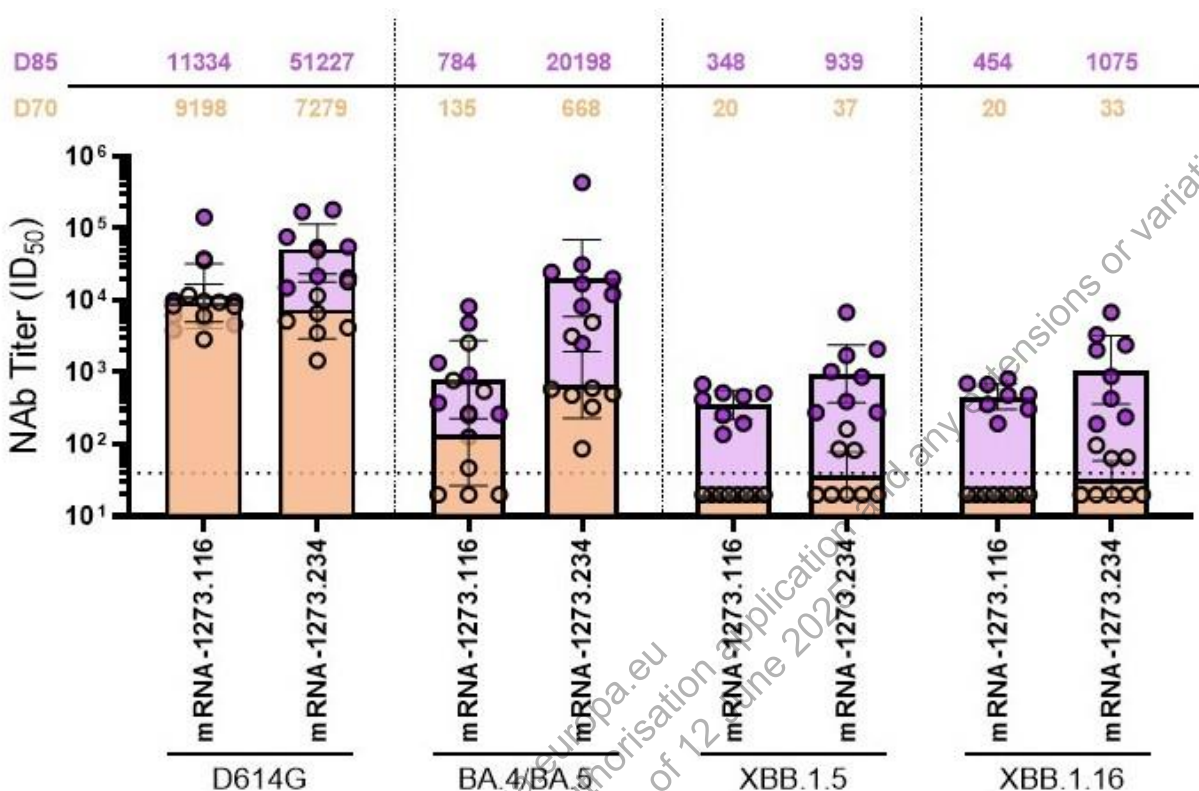
Figure 5: Binding Antibody Responses in BALB/c Mice After Boosting (Third Dose)

Abbreviations: GMT=geometric mean titer; IgG=immunoglobulin G; LLOQ=lower limit of quantification;

PBS=phosphate-buffered saline.

Note: GMT values are presented at the top of each figure, with pink indicating the GMT for Day 21 (3 weeks after the first dose), blue indicating the GMT for Day 36 (2 weeks after the second dose), purple indicating the GMT for Day 70 (4 weeks after Dose 2 and preboost), and green indicating GMT for Day 85 (2 weeks after boosting). The dotted line indicates LLOQ of the assay.

Source: [Study MOD-5972](#).

Figure 6: Neutralizing Antibody Responses in BALB/c Mice After Boosting (Third Dose)

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

Note: GMT values are presented at the top of each figure, with orange indicating the GMT for Day 70 (preboost) and pink/purple indicating the GMT for Day 85 (2 weeks after the booster dose). The dotted line indicates LLOQ of the assays.

Source: [Study MOD-5972](#).

Conclusions

Overall, after a 2-dose primary series with mRNA-1273, animals boosted with XBB.1.16-containing vaccines (mRNA-1273.116 or mRNA-1273.234), showed a 4-fold increase in bAb titers on Day 85 compared to preboost samples on Day 70, with monovalent mRNA-1273.116 eliciting numerically higher S-2P-binding IgG titers than those elicited by bivalent mRNA-1273.234.

Two weeks after boosting, the nAb titers elicited by mRNA-1273.116 and mRNA-1273.234 against the XBB.1.5 and XBB.1.16 strains were 17- to 33-fold higher compared to preboost levels. mRNA-1273.234 showed higher nAb responses against XBB.1.5 and XBB.1.16 strains compared with mRNA-1273.116. This difference was likely driven by measurable nAb titers observed preboost in 3 of 8 mice in the mRNA-1273.234 group, whereas preboost titers against XBB.1.5 or XBB.1.16 for all mice in the mRNA-1273.116 group were below the LLOQ.

The postboost nAb titer levels against XBB.1.5 and XBB.1.16 were comparable between both treatment groups, indicating that these strains are antigenically similar. nAb titers against BA.4/BA.5 were higher in the bivalent mRNA-1273.234 group compared to the monovalent mRNA-1273.116 group, consistent with the inclusion of BA.4/BA.5 in the vaccine. nAb titers against D614G were also higher in the mRNA-1273.234 group compared to mRNA-1273.116 group.

2.6.2.3 SECONDARY PHARMACODYNAMICS

No secondary pharmacodynamic studies have been performed with an XBB-containing vaccine.

2.6.2.4 SAFETY PHARMACOLOGY

No safety pharmacology studies have been performed with an XBB-containing vaccine.

2.6.2.5 PHARMACODYNAMIC DRUG INTERACTIONS

No pharmacodynamic drug interaction studies have been performed with an XBB-containing vaccine.

2.6.2.6 DISCUSSION AND CONCLUSIONS

The SARS-CoV-2 virus is continually evolving by accumulating mutations, some which offer a significant growth advantage, leading to establishment of VOC strains that become dominant in circulation. The emergence of the Omicron variant was a significant evolutionary shift where an unprecedented number of mutations were observed that enabled significant immune escape against immunity provided by prototype vaccines and/or immunity provided by infection with SARS-CoV-2 strains prior to Omicron. Although the development and deployment of Omicron-containing vaccine boosters, specifically mRNA-1273.214 (BA.1-containing bivalent) and mRNA-1273.222 (BA.4/BA.5-containing bivalent), substantially enhanced protection against the early Omicron strains, the Omicron virus family has continued to rapidly evolve. New subvariants have emerged in early 2023 (eg, XBB.1.5, XBB.1.9.1, and XBB.1.16), with additional growth advantages, increased transmissibility, and the ability to escape authorized BA.1- or BA.4/BA.5-containing bivalent booster vaccine- or infection-derived immunity. Given the evident immune escape that these new variants exhibit to current vaccines, updating vaccine strain compositions to match such strains more closely is critical to maintaining protection against COVID-19.

The complex nature of SARS-CoV-2's continuing evolution 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. A framework to identify VOCs and 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's ongoing monitoring and variant response effort has enabled the development and preclinical evaluation of more than 19 monovalent and bivalent vaccine compositions. The Sponsor has also proposed a subfamily-matching approach that has been corroborated by clinical and nonclinical studies, including the data presented in this module. This approach groups antigenically similar variants into subfamilies and hypothesizes that vaccines matched to any of these subfamily variants would provide highly comparable protection against the other members of this subfamily.

The Sponsor has recently evaluated multiple XBB-containing vaccines concurrently, including the following: (1) the monovalent mRNA-1273.815 vaccine that contains a single mRNA encoding the SARS-CoV-2 S-2P antigen of the XBB.1.5/XBB.1.9.1 (note: the spike protein of XBB.1.9.1 is identical to that of XBB.1.5) subvariant of Omicron; (2) the monovalent mRNA-1273.116 vaccine that contains a single mRNA encoding the SARS-CoV-2 S-2P antigen of the XBB.1.16 subvariant of Omicron; (3) the bivalent mRNA-1273.231 vaccine, which is a coformulation of the mRNA-1273.045 vaccine (a monovalent vaccine containing a single mRNA encoding the SARS-CoV-2 S-2P antigen of the BA.4/BA.5 subvariants of Omicron) and the mRNA-1273.815 vaccine, and (4) bivalent mRNA-1273.234 vaccine, which is a coformulation of the mRNA-1273.045 vaccine and the mRNA-1273.116 vaccine. All mRNAs are formulated into a mixture of 4 lipids: SM-102, cholesterol, DSPC, and PEG2000-DMG.

In support of the development of XBB-containing mRNA vaccines for the 2023-2024 season, nonclinical in vivo pharmacology studies were conducted in BALB/c mice. These studies evaluated immunogenicity of variant-containing mRNA vaccines given as a primary series or as a booster dose following primary series vaccination with mRNA-1273.

The results are summarized as follows:

- In a non-GLP immunogenicity study using BALB/c mice, after a 2-dose primary series, monovalent mRNA-1273.815 and bivalent mRNA-1273.231 elicited robust S-2P bAb titers and potently neutralized the XBB subfamily strains XBB.1.5 and XBB.1.16, with neutralization titers that were >45-fold higher than those elicited by monovalent mRNA-1273.045 or bivalent mRNA-1273.222. mRNA-1273.231 had numerically higher titers against the ancestral and BA.4/BA.5 strains compared with mRNA-1273.815, consistent with the inclusion of BA.4/BA.5 in the bivalent vaccine. All vaccines elicited nAb titers against XBB.1.5 that were similar to nAb titers against XBB.1.16 ([Section 2.6.2.2.1](#)).
- In a non-GLP immunogenicity study using BALB/c mice, administering monovalent mRNA-1273.815 or bivalent mRNA-1273.231 as a booster following a primary series of mRNA-1273 elicited robust S-2P bAb titers and high nAb responses against the XBB subfamily strains XBB.1.5 and XBB.1.16, with mRNA-1273.815 driving higher nAb responses than mRNA-1273.231. mRNA-1273.231 had numerically higher titers against

ancestral and BA.4/BA.5 strains compared with mRNA-1273.815, consistent with the inclusion of BA.4/BA.5 in the bivalent vaccine. nAb titers against XBB.1.5 and XBB.1.16 were also comparable in this booster study ([Section 2.6.2.2.2](#)).

- In a non-GLP immunogenicity study using BALB/c mice, administering monovalent mRNA-1273.116 or bivalent mRNA-1273.234 as a booster following a primary series of mRNA-1273 elicited robust S-2P bAb titers as well as neutralizing titers against XBB subfamily strains XBB.1.16 and XBB.1.5. nAb titers against XBB.1.16 were comparable to those against XBB.1.5 ([Section 2.6.2.2.3](#)).

Overall, animals vaccinated with XBB-containing vaccines (mRNA-1273.815, mRNA-1273.116, mRNA-1273.231, and mRNA-1273.234), either as a primary series or as a booster dose, elicited robust S-2P bAb titers and potentially neutralized both XBB.1.5 and XBB.1.16 similarly. The results suggest that such XBB-containing vaccines are likely to substantially boost protection against XBB subfamily strains including XBB.1.5, XBB.1.9.1, or XBB.1.16. The results also collectively support the subfamily approach proposed by the Sponsor, wherein preclinical immunogenicity studies performed with an XBB strain support registration of a vaccine with strains within the subfamily due to their antigenic similarity. This approach may enable more rapid deployment of future variant matched vaccines based on preclinical data from closely matched subfamily variants generated during routine monitoring.

2.6.2.7 TABLES AND FIGURES

Tables and figures are included in their respective sections.

2.6.2.8 REFERENCES

Barouch DH. Covid-19 Vaccines - Immunity, Variants, Boosters. N Engl J Med. 2022;387(11):1011-20.

Bruxvoort KJ, Sy LS, Qian L, Ackerson BK, Luo Y, Lee GS, et al. Effectiveness of mRNA-1273 against Delta, Mu, and other emerging variants of SARS-CoV-2: test-negative case-control study. BMJ. 2021;375: e068848. Chalkias S, Eder F, Essink B, Khetan S, Nestorova B, Feng J, et al. Safety, immunogenicity and antibody persistence of a bivalent Beta-containing booster vaccine against COVID-19: a phase 2/3 trial. Nat Med. 2022a;28(11):2388-97.

Chalkias S, Harper C, Vrbicky K, Walsh SR, Essink B, Brosz A, et al. A bivalent Omicron-containing booster vaccine against COVID-19. N Engl J Med. 2022b;387(14):1279-91.

Corbett KS, Flynn B, Foulds KE, Francica JR, Boyoglu-Barnum S, Werner AP, et al. Evaluation of the mRNA-1273 Vaccine against SARS-CoV-2 in Nonhuman Primates. N Engl J Med. 2020;383(16):1544-55.

Gilbert PB, Montefiori DC, McDermott AB, Fong Y, Benkeser D, Deng W, et al. Immune correlates analysis of the mRNA-1273 COVID-19 vaccine efficacy clinical trial. *Science* 2022;375(6576):43-50.

Hassett KJ, Benenato KE, Jacquinet E, Lee A, Woods A, Yuzhakov O, et al. Optimization of Lipid Nanoparticles for Intramuscular Administration of mRNA Vaccines. *Mol Ther Nucleic Acids*. 2019;15:1-11.

Hastie KM, Li H, Bedinger D, Schendel SL, Dennison SM, Li K, et al. Defining variant-resistant epitopes targeted by SARS-CoV-2 antibodies: A global consortium study. *Science*. 2021;374(6566):472-8.

Khoury DS, Cromer D, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. *Nat Med*. 2021;27(7):1205-11.

Siddle KJ, Krasilnikova LA, Moreno GK, Schaffner SF, Vostok J, Fitzgerald NA, et al. Transmission from vaccinated individuals in a large SARS-CoV-2 Delta variant outbreak. *Cell*. 2022;185(3):485-92.

Tseng HF, Ackerson BK, Luo Y, Sy LS, Talarico CA, Tian Y, et al. Effectiveness of mRNA-1273 against SARS-CoV-2 Omicron and Delta variants. *Nat Med*. 2022;28(5):1063-71.

Twohig KA, Nyberg T, Zaidi A, Thelwall S, Sinnathamby MA, Aliabadi S, et al. Hospital admission and emergency care attendance risk for SARS-CoV-2 delta (B.1.617.2) compared with alpha (B.1.1.7) variants of concern: a cohort study. *Lancet Infect Dis*. 2022;22(1):35-42.