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2.6.3.1 PHARMACOLOGY: OVERVIEW

Study Title	Test Articles	Test System	Method of Administration	Testing Facility	Study Number (GLP Status)	Location in eCTD
Primary Pharmacodynamics						
Evaluation of Immunogenicity of a Primary Series of Monovalent and Bivalent SARS-CoV-2 XBB.1.5-containing Vaccines in Mice	PBS control mRNA-1273.045 ^a mRNA-1273.815 ^b mRNA-1273.222 ^c mRNA-1273.231 ^d	Mouse/ BALB/c	IM	ModernaTX, Inc. Cambridge, MA	MOD-6037 (non-GLP)	4.2.1.1
Evaluation of Immunogenicity of Monovalent and Bivalent SARS-CoV-2 XBB.1.5-containing Vaccine Boosters in Mice	PBS control mRNA-1273 ^e mRNA-1273.045 ^a mRNA-1273.815 ^b mRNA-1273.222 ^c mRNA-1273.231 ^d	Mouse/ BALB/c	IM	ModernaTX, Inc. Cambridge, MA	MOD-5827 (non-GLP)	4.2.1.1
Evaluation of Immunogenicity of Monovalent and Bivalent SARS-CoV-2 XBB.1.16-containing Vaccine Boosters in Mice	PBS control mRNA-1273 ^e mRNA-1273.116 ^f mRNA-1273.234 ^g	Mouse/ BALB/c	IM	ModernaTX, Inc. Cambridge, MA	MOD-5972 (non-GLP)	4.2.1.1

Abbreviations: eCTD=electronic common technical document; GLP=Good Laboratory Practice; IM=intramuscular; PBS=phosphate-buffered saline; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; S-2P=spike protein with 2 proline substitutions within the heptad repeat 1 domain.

^a mRNA-1273.045 is a monovalent vaccine that contains a single mRNA encoding the SARS-CoV-2 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.

^b mRNA-1273.815 is a monovalent vaccine that contains a single mRNA encoding the SARS-CoV-2 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.

^c mRNA-1273.222 is a coformulation of the mRNA-1273 and mRNA-1273.045 vaccines.

^d mRNA-1273.231 is a 1:1 bench side mix of separately formulated mRNA-1273.045 and mRNA-1273.815 vaccines.

^e mRNA-1273 is a monovalent vaccine that contains a single mRNA that encodes the spike protein of the Wuhan-Hu-1 isolate of SARS-CoV-2.

^f mRNA-1273.116 is a monovalent vaccine that contains a single mRNA encoding the SARS-CoV-2 S-2P antigen of the XBB.1.16 subvariant of Omicron.

^g mRNA-1273.234 is a 1:1 bench side mix of separately formulated mRNA-1273.045 and mRNA-1273.116 vaccines.

2.6.3.2 PRIMARY PHARMACODYNAMICS

Study Title	Test Articles	Test System	Method of Admin.	Doses	No. per Group	Noteworthy Findings	Study Number (GLP Status)
Evaluation of Immunogenicity of a Primary Series of Monovalent and Bivalent SARS-CoV-2 XBB.1.5-containing Vaccines in Mice	PBS control mRNA-1273.045 ^a mRNA-1273.815 ^b mRNA-1273.222 ^c mRNA-1273.231 ^d	Mouse/ BALB/c	IM	0 (PBS control) 1 µg mRNA-1273 mRNA-1273.045 mRNA-1273.815 mRNA-1273.222 mRNA-1273.231 (Day 1, Day 22)	8	<ul style="list-style-type: none"> After a 2-dose primary series, mRNA-1273.815 and mRNA-1273.231 elicited robust S-2P-binding IgG 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 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. 	MOD-6037 (non-GLP)

Study Title	Test Articles	Test System	Method of Admin.	Doses	No. per Group	Noteworthy Findings	Study Number (GLP Status)
Evaluation of Immunogenicity of Monovalent and Bivalent SARS-CoV-2 XBB.1.5-containing Vaccine Boosters in Mice	PBS control mRNA-1273.045 ^a mRNA-1273.815 ^b mRNA-1273.222 ^c mRNA-1273.231 ^d	Mouse/ BALB/c	IM	0 (PBS control), 0.5 µg mRNA-1273 (Day 1, Day 22) 0 (PBS control), 1 µg mRNA-1273.045 mRNA-1273.815 mRNA-1273.222 mRNA-1273.231 (Day 92)	8	<ul style="list-style-type: none"> 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. Two 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 consistent with the inclusion of BA.4/BA.5 in the bivalent vaccine. 	MOD-5827 (non-GLP)

Study Title	Test Articles	Test System	Method of Admin.	Doses	No. per Group	Noteworthy Findings	Study Number (GLP Status)
Evaluation of Immunogenicity of Monovalent and Bivalent SARS-CoV-2 XBB.1.16-containing Vaccine Boosters in Mice	PBS control mRNA-1273 ^e mRNA-1273.116 ^f mRNA-1273.234 ^g	Mouse/ BALB/c	IM	0.5 µg mRNA-1273 (Day 1, Day 22) 0 (PBS control), 1 µg mRNA-1273.116 mRNA-1273.234 (Day 71)	8	<ul style="list-style-type: none"> mRNA-1273.116 and mRNA-1273.234 showed a 4-fold increase in S-2P-binding IgG titers after boosting, 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 pre-boost levels. mRNA-1273.234 showed higher XBB subvariant nAb responses compared with mRNA-1273.116, likely driven by measurable pre-boost XBB nAb titers in some mice in the mRNA-1273.234 group. Postboost nAb titer levels against XBB.1.5 and XBB.1.16 were comparable, indicating that these strains are antigenically similar. mRNA-1273.234 had higher nAb titers against BA.4/BA.5 group compared with mRNA-1273.116, consistent with the inclusion of BA.4/BA.5 in the vaccine. 	MOD-5972 (non-GLP)

Abbreviations: Admin=administration; bAb=binding antibody; GLP=Good Laboratory Practice; IgG=immunoglobulin G; IM=intramuscular; nAb=neutralizing antibody; PBS=phosphate-buffered saline; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; S-2P=spike protein with 2 proline substitutions within the heptad repeat 1 domain.

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

2.6.3.3 SECONDARY PHARMACODYNAMICS

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

2.6.3.4 SAFETY PHARMACOLOGY

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

2.6.3.5 PHARMACODYNAMIC DRUG INTERACTIONS

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