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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)
COVID-19	coronavirus disease 2019
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
LNP	lipid nanoparticle
MERS-CoV	Middle East respiratory syndrome coronavirus
OECD	Organisation for Economic Co-operation and Development
PEG2000-DMG	1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000
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
VOC	variant of concern
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

2.6.1 INTRODUCTION

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](#); [Twohig 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 similarities 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) the 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.

The nonclinical testing program supporting licensure and/or conditional approval of mRNA-1273 or variant-containing formulations of mRNA-1273 across multiple regions was designed to adhere to international regulatory guidelines, the intended clinical development program, and traditional pharmacology and toxicology principles and was consistent with ICH guidelines for biological drug development, including ICH S6(R1) (Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals) and appropriate GLP regulations that were applicable when studies were conducted. The pivotal nonclinical safety studies were conducted according to the OECD Principles of Good Laboratory Practice (ENV/MC/CHEM[98]17) or GLP regulations in other countries that are signatories to the OECD Mutual Acceptance of Data agreement (eg, US FDA Code of Federal Regulations Title 21, Part 58: Good Laboratory Practice for Nonclinical Laboratory Studies).

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.

A 'platform concept' strategy has been employed by the Sponsor to support mRNA-1273 and variant-containing mRNA-1273 vaccines, where the safety and tolerability of mRNA vaccines that encode various antigens developed with the Sponsor's mRNA-based platform using SM-102-containing LNPs, including but not limited to mRNA-1273, have been evaluated in multiple GLP-compliant repeat-dose toxicity studies in Sprague Dawley rats. This strategy is considered relevant and sufficient to support clinical development of mRNA-1273 and variant-containing mRNA-1273 vaccines, because there is consistency in the toxicological data across GLP toxicity studies regardless of the antigen expressed, demonstrating that the toxicity associated with mRNA vaccines formulated in LNPs is driven primarily by the LNP composition and, to a lesser extent, the biologic activity of the antigen(s) encoded by the mRNA. Moreover, given that there were no new safety concerns observed with variant-containing mRNA-1273 vaccines in the nonclinical pharmacology studies, toxicological data generated with the mRNA-1273 vaccine, as well as other mRNA vaccines formulated in the same LNPs, adequately

characterize target organs of toxicity and inform the nonclinical risk assessment for variant-containing mRNA-1273 vaccines.

Nonclinical studies conducted with XBB.1.5- and XBB.1.16-containing vaccines support registration of an XBB-containing vaccine for the 2023-2024 season. The results also collectively support the subfamily approach proposed by the Sponsor, wherein preclinical immunogenicity studies performed with a SARS-CoV-2 strain support registration of 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.

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