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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)
COVID-19	coronavirus disease 2019
EMA	European Medicines Agency
ETF	Emergency Task Force
FDA	Food and Drug Administration
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
JN.1	BA.2.86.1.1 subvariant of Omicron
KP.2	BA.2.86.1.1.11.1.2 subvariant of Omicron
LNP	lipid nanoparticle
mRNA	messenger RNA
OECD	Organisation for Economic Co-operation and Development
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
TAG-CO-VAC	Technical Advisory Group on COVID-19 Vaccine Composition
VOC	variant of concern
VOI	variant of interest
WHO	World Health Organization
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)

2.6.1 INTRODUCTION

Coronaviruses are a large family of viruses that cause illness ranging from the common cold to more severe diseases, such as SARS. An outbreak of a novel coronavirus, later designated SARS-CoV-2, initially emerged in Wuhan, Hubei Province, China in December 2019. The WHO declared COVID-19 a pandemic on 11 Mar 2020, and it continues to have a major global public health impact, with more than 775 million cases and 7 million deaths as of 07 Apr 2024 (WHO 2024a).

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 that VOCs exhibit to current vaccines, 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 VOIs due to 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 2024b). 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 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).

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.

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. These studies evaluated immunogenicity of mRNA-1273.167 given as a primary series, or as a booster dose following primary series vaccination with mRNA-1273. Additionally, the immunogenicity of mRNA-1273.167 as 5th booster was evaluated in BALB/c mice previously immunized with mRNA-1273 vaccines to allow assessment of updated boosters where prior

immunity is more diverse based on exposure to multiple strain antigens. Such studies are in line with regulatory expectations to generate preclinical immunogenicity data that supports the effectiveness of an updated vaccine formulation.

2.6.1.1 References

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