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2.6.1 Introduction

List of Abbreviations

Abbreviation	Definition
COVID-19	coronavirus disease 2019
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
ERD	enhanced respiratory disease
FDA	Food and Drug Administration
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
ID ₅₀	infectious dose 50
LN	lymph node(s)
LNP	lipid nanoparticle
MERS-CoV	Middle-East respiratory syndrome coronavirus
mRNA	messenger RNA
NHP	nonhuman primate
OECD	Organisation for Economic Co-operation and Development
PEG	polyethylene glycol
PEG2000-DMG	1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000
S	spike
S-2P	spike protein modified with 2 proline substitutions within the heptad repeat 1 domain
S-2P.529	Omicron-specific S-2P
SARS-CoV	severe acute respiratory syndrome coronavirus
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SM-102	a custom-manufactured ionizable lipid
WT	wild type
VE	vaccine efficacy
VOC	variant of concern
WHO	World Health Organization

2.6.1 Introduction

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Coronaviruses are a large family of viruses that cause illness ranging from the common cold to more severe diseases, such as MERS-CoV and SARS-CoV. 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 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.

Evidence suggests that by 6 months following vaccination with the primary series, waning immunity against ancestral SARS-CoV-2 is evident and neutralization titers against VOCs are low or undetectable ([Choi et al 2021](#)). Real-world studies have shown a decline in vaccine efficacy over time, particularly against VOCs ([Bruxvoort et al 2021](#); [Puranik et al 2021](#); [Tseng et al 2022](#)). An analysis of data from the Phase 3 Study P301 (NCT04470427) during the Delta variant surge (July to August 2021) showed lower incidence rates of COVID-19 in participants more recently vaccinated than those more remotely vaccinated ([Baden et al 2021](#)). Participants with a median follow-up of 7.9 months had lower rates of breakthrough infection (49.0/1000 person-years) compared to participants with a median follow-up time of 13 months (77.1/1000 person-years). Accordingly, the Sponsor assessed the immunogenicity of a 50-µg booster of mRNA-1273 in participants previously primed with 2 doses of mRNA-1273. Results showed a robust immune response and mRNA-1273 was subsequently authorized as a 50-µg single booster dose in individuals 18 years of age and older. Health agencies are also authorizing mRNA-1273 to be given as a second booster in certain high-risk populations across multiple regions.

In November 2021, the WHO reported a new VOC, Omicron (BA.1, also known as B.1.1.529), was detected in South Africa and quickly spread in the US, becoming the dominant circulating variant ([WHO 2021](#)). Available evidence suggests that the BA.1 variant has transmission advantage over prior variants, with significant antigenic change and a potential growth advantage. In addition, it contains antibody escape site mutations (such as K417N, T478K, E484A, N501Y). The BA.1 variant contains more than 30 amino acid substitutions. Additional sub-lineages of Omicron have also emerged with one, BA.2, demonstrating increased transmissibility versus BA.1 which subsequently became the predominant circulating variant in most geographical regions. As of May 2022, Omicron sub-lineages BA.4 and BA.5 have been identified and are increasing in circulation in certain geographical regions.

A test-negative case-control analysis conducted at Kaiser Permanente Southern California using 6,657 SARS-CoV-2 positive specimens collected between 06 Dec 2021 and 23 Dec 2021 showed the 2-dose VE of mRNA-1273 against Omicron infection was 44.0% at 14 to 90 days after the second dose and declined quickly thereafter ([Tseng et al 2022](#)). The analysis also looked at the

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3-dose VE of mRNA-1273 and found that VE was high (93.7% and 86.0%) against the Delta variant but lower (71.6% and 47.4%) against Omicron infection at 14 to 60 days and >60 days respectively. Additionally, an evaluation of BA.1 neutralization (ID₅₀) in serum samples of participants who received the mRNA-1273 primary series detected Omicron neutralization in 85% of participants 1 month after the primary series, but titers observed were 35-fold lower than titers against the ancestral SARS-CoV-2 with the D614G mutations (hereafter referred to as WA1 D614G) (Pajon et al 2022). Seven months after the primary series and before a booster dose, Omicron neutralization was detected in 55% of participants and the ID₅₀ titers were 8.4-fold lower than titers against WA1 D614G. A booster dose of mRNA-1273, however, was associated with neutralization titers against Omicron that were 20-fold higher than titers against Omicron at 1 month after the second dose of the primary series.

Even with the availability of a 50-μg mRNA-1273 booster, the evolving antigenic variation of SARS-CoV-2 underscores the need for vaccination strategies that induce broader protection, specifically against VOC with increased risk of viral escape. Variant-matched booster vaccines have been suggested as a strategy to focus the antibody response against VOCs compared to the authorized, standard-of-care booster vaccines against COVID-19.

In response to the need for variant-matched boosters, the Sponsor has developed modified mRNA COVID-19 vaccines. mRNA-1273.529 is a monovalent vaccine that contains a single mRNA (CX-031302) that encodes SARS-CoV-2 S-2P for BA.1 (S-2P.529). Both mRNA-1273 (CX-024414) and mRNA-1273.529 include 2 proline mutations introduced to stabilize the S protein into the prefusion conformation. mRNA-1273.214 is a bivalent vaccine that contains 2 mRNAs: mRNA-1273 and mRNA-1273.529 in a 1:1 ratio. All vaccines were formulated into a mixture of 4 lipids: SM-102, cholesterol, DSPC, and PEG2000-DMG.

The preclinical mRNA-1273.529 vaccine encoded the following substitutions: A67V, Δ69-70, T95I, G142D, Δ143-145, Δ211, L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493K, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, and L981F.

The nonclinical testing program supporting licensure and/or conditional approval 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).

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In support of the development of mRNA-1273.214, nonclinical pharmacology evaluations were conducted in mice (BALB/c, K18-hACE2, and 129S2 strains) and NHPs (rhesus macaques) to evaluate the immunogenicity, antigen-specific B cell responses, and/or protection from Omicron challenge after administration of mRNA-1273 or Omicron-matched vaccines as primary series (mRNA-1273, mRNA-1273.529, or mRNA-1273.214) with or without boosting with mRNA-1273, mRNA-1273.529, or mRNA-1273.214. Additionally, the potential for vaccine-associated ERD after viral challenge was further evaluated in NHPs.

A ‘platform concept’ strategy has been employed by the Sponsor to support mRNA-1273.214, 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-1273.214, 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 mRNA-1273.214 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 mRNA-1273.214.

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