Table of Contents

List of Abbreviations

Abbreviation	Definition
CoV	coronavirus
COVID-19	coronavirus disease 2019
CMV	cytomegalovirus
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
ERD	enhanced respiratory disease
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
Ig	immunoglobulin
IM	intramuscular(-ly)
LNP	lipid nanoparticle
mRNA	messenger RNA
NHP	nonhuman primate
OECD	Organisation for Economic Co-operation and Development
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
SARS	severe acute respiratory syndrome
SARS-CoV-2	2019 novel coronavirus
SM-102	heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate
Th	T helper
Tris	tris(hydroxymethyl)aminomethane
WHO	World Health Organization

2.6.1 INTRODUCTION

Coronaviruses (CoVs) are part of a large family of viruses that cause illnesses ranging from the common cold to more severe diseases, such as Middle East respiratory syndrome and severe acute respiratory syndrome (SARS).

An outbreak of the CoV disease 2019 (COVID-19) caused by the 2019 novel CoV (2019-nCoV, later designated SARS-CoV-2) began in Wuhan, Hubei Province, China, in Dec 2019 and the disease has since spread globally (WHO 2020). Currently, there is no FDA-approved vaccine against SARS-CoV-2. Without further advances in the use of nonpharmaceutical interventions, over 2.5 million COVID-19 deaths are projected globally by 01 Mar 2021, with daily deaths peaking at about 15,000/day during this time (IHME 2020). Global efforts to evaluate novel antivirals and therapeutic strategies to treat severe SARS-CoV-2 infections have intensified, and there is an urgent public health need for rapid development of novel prophylactic therapies, including vaccines to prevent the spread of this disease.

ModernaTX, Inc. (Sponsor) has used its messenger RNA (mRNA)-based, rapid-response proprietary vaccine platform to develop mRNA-1273, a novel lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine against SARS-CoV-2. mRNA-1273 contains a single mRNA that encodes the full-length SARS-CoV-2 spike (S) protein modified with 2 proline substitutions within the heptad repeat 1 domain (S-2P) to stabilize the S protein into the prefusion conformation. The mRNA is combined in a mixture of 4 lipids common to the Sponsor's mRNA vaccine platform: SM-102, cholesterol, DSPC, and PEG2000-DMG. The mRNA-1273 Drug Product is provided as a sterile liquid for injection at a concentration of 0.20 mg/mL in 20 mM Tris buffer containing 87 g/L sucrose and 4.3 mM acetate, at pH 7.5.

The clinical development of mRNA-1273 to support its use in the adult population consists of 3 ongoing clinical trials being conducted in the US: a Phase 1, open-label, dose-ranging study (NCT04283461) sponsored by the National Institute of Allergy and Infectious Diseases and a Phase 2a, randomized, observer-blind, placebo-controlled, dose-confirmation study (NCT04405076) and a Phase 3 randomized, stratified, observer-blind, placebo-controlled study (NCT04470427) conducted by the Sponsor to evaluate the efficacy, safety, and immunogenicity of the vaccine. The development of mRNA-1273 has been accelerated to address the current COVID-19 outbreak, benefiting from the uniquely rapid and scalable manufacturing processes that have been developed for this vaccine.

2.6.1.1 Nonclinical Development Program for mRNA-1273

The nonclinical pharmacology, pharmacokinetics and tissue distribution, and toxicology studies conducted with mRNA-1273 or other mRNA vaccines that encode various antigens developed with the Sponsor's mRNA-based platform using SM-102-containing LNPs support the intended clinical use of mRNA-1273. The program was designed in accordance with guidelines applicable at the time the studies were conducted, including relevant International Council for Harmonisation (ICH) and other global regulatory guidelines, and Good Laboratory Practice (GLP) regulations. The pivotal nonclinical safety studies were conducted according to the Organisation for Economic Co-operation and Development (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 Food and Drug Administration Code of Federal Regulations Title 21, Part 58: Good Laboratory Practice for Nonclinical Laboratory Studies).

The nonclinical studies were conducted in mice, rats, hamsters, and rhesus macaques (nonhuman primates [NHPs]), species determined to be relevant for the assessment of the immunogenicity, efficacy, and safety of mRNA-1273.

2.6.1.1.1 Nonclinical Pharmacology Program

Nonclinical primary pharmacology evaluations were conducted in vitro in HEK293T cells and in vivo in young and aged mice (BALB/c, BALB/cJ, C57/BL6/J, and B6C3F1/J strains), golden Syrian hamsters, and rhesus macaques animal models to characterize the expression and immunogenicity of mRNA-1273, as well as its effects on viral replication and disease progression after SARS-CoV-2 challenge, and to evaluate its safety profile and its potential to promote vaccine-associated enhanced respiratory disease (ERD) after viral challenge, which has previously been observed with vaccines against respiratory syncytial virus (Kim et al 1969), measles (Polack 2007), and in animal models of SARS-CoV vaccination (Czub et al 2005; Deming et al 2007; Bolles et al 2011; Corbett et al 2020). Additionally, the immunogenicity of mRNA-1273 was assessed as part of a non-GLP repeat-dose pharmacology study in Sprague Dawley rats.

The expression of the mRNA-encoded SARS-CoV-2 S-2P antigen was confirmed in vitro and in vivo. HEK293T cells transfected with a dose range (0.003125 through 0.2 µg) of mRNA expressed the encoded SARS-CoV-2 S-2P antigen, as demonstrated by surface-protein staining with monoclonal antibodies specific to the receptor binding domain (CR3022) or N-terminal domain (4A8) epitopes of the SARS-CoV-2 S protein. The expression of these epitopes was

similarly confirmed in spleen and draining lymph node immune cells (conventional dendritic cells and plasmacytoid dendritic cells) in BALB/c mice administered a single intramuscular (IM) dose (2 or 10 µg) of mRNA-1273.

Immunogenicity was characterized in young and aged mice, rats, hamsters, and NHPs through the evaluation of the humoral (immunoglobulin [Ig] G binding antibodies), cellular (T-cell cytokines and T helper [Th] 1-directed CD4+ and CD8+ responses), and/or neutralizing antibody responses elicited by prime-only or prime/boost immunization schedule with a range of mRNA-1273 dose levels.

Protection by mRNA-1273 immunization was assessed in young and aged mice, hamsters, and NHPs immunized with a prime-only or prime/boost schedule, followed by viral challenge with a high dose of SARS-CoV-2 (mice: mouse-adapted SARS-CoV-2 strain; hamsters and NHPs: WT SARS-CoV-2 strain, Washington state isolate). mRNA-1273 dose levels and immunization schedules predicted to drive optimal and suboptimal protection were included in these studies to identify immune signatures for each regimen and to assess the level of protection mediated by different dose levels. Suboptimal dose levels that confer only partial protection were also included to evaluate the theoretical risk of disease enhancement. Viral load and replication in the upper (nasal turbinates) and lower (lungs) airways, as well as lung pathology and inflammation, were evaluated after viral challenge.

The potential of mRNA-1273 to promote vaccine-associated ERD was assessed in young and aged mice, hamsters, and NHPs through the evaluation of immunogenicity endpoints (IgG1:IgG2a ratio, Th1/Th2 cytokine profiles, and the ratio of binding to neutralizing antibodies) indicative of a protective versus a disease enhancement phenotype and through monitoring of viral load, viral replication, and histopathological evaluation of lung tissues after viral challenge.

2.6.1.1.2 Nonclinical Pharmacokinetic Program

mRNA is degraded within minutes in biological fluids and is unlikely to persist in tissues; therefore, the biodistribution of mRNA-based vaccines formulated in LNPs is predicted to be driven by the LNP characteristics and mRNAs that are within LNPs of the same composition (ie, SM-102-containing LNPs) are expected to distribute similarly to the LNPs. Thus, the distribution of mRNA-1647, an mRNA-based cytomegalovirus (CMV) vaccine that contains 6 mRNA sequences combined in SM-102-containing LNPs, assessed in a non-GLP, single IM dose biodistribution study supports the development of mRNA-1273.

2.6.1.1.3 Nonclinical Toxicology Program

The toxicological profile associated with mRNA-based vaccines formulated in SM-102-containing LNPs, including mRNA-1273, is driven primarily by the LNP composition and, to a lesser extent, by the biologic activity of the antigen(s) encoded by the mRNA. The safety and tolerability of 5 mRNA-based vaccines that encode various antigens developed with the Sponsor's mRNA-based platform using SM-102-containing LNPs (2 Zika virus vaccines: mRNA-1706 and mRNA-1893; 1 human metapneumovirus and parainfluenza virus type 3 vaccine: mRNA-1653; and 2 CMV vaccines: mRNA-1647 and mRNA-1443) have been evaluated in 6 GLP-compliant repeat-dose toxicity studies in Sprague Dawley rats. Additionally, the Sponsor completed a non-GLP repeat-dose study in Sprague Dawley rats to characterize the immunogenic response and potential toxicity of mRNA-1273 at clinically relevant doses.

SM-102, the novel lipid used in mRNA-1273, and the commercially available PEG2000-DMG (b) (4) were evaluated in genotoxicity studies as individual agents using a standard ICH S2 (R1) approach (ICH 2011), including GLP-compliant bacterial reverse mutation (Ames) tests in *Salmonella typhimurium* and *Escherichia coli* and GLP-compliant in vitro micronucleus tests in human peripheral blood lymphocytes. In addition, SM-102 was evaluated for in vivo genotoxicity risk in a GLP-compliant in vivo rat micronucleus test using an mRNA-based vaccine formulated in SM-102 LNPs (mRNA-1706) and a non-GLP-compliant in vivo rat micronucleus test using a reporter mRNA (nascent peptide imaging luciferase mRNA) formulated in SM-102 LNPs.

The Sponsor completed a GLP-compliant combined developmental and perinatal/postnatal reproductive toxicity study to assess the potential effects of mRNA-1273 on fertility and pre- and postnatal development in pregnant and lactating female Sprague Dawley rats.

Overall, data from the nonclinical testing program presented in this submission demonstrate that mRNA-1273 is safe and well tolerated, is immunogenic, fully protects animals from viral challenge, and does not promote ERD at either optimal or suboptimal dose levels. These data support the clinical evaluation of the efficacy and safety of 100 µg of mRNA-1273 administered as 2 IM injections 28 days apart.

2.6.2 REFERENCES

Bolles M, Deming D, Long K, Agnihothram S, Whitmore A, Ferris M, et al. A double inactivated severe acute respiratory syndrome coronavirus vaccine provides incomplete protection in mice

and induces increased eosinophilic proinflammatory pulmonary response upon challenge. J Virol. 2011;85(23):12201-15.

Corbett KS, Edwards D, Leist SR, Abiona OM, Boyoglu-Barnum S, Gillespie RA, et al. SARS-CoV-2 mRNA vaccine design enabled by prototype pathogen preparedness. Nature. 2020;586(7830):567-71.

Czub M, Weingartl H, Czub S, He R, Cao J. Evaluation of modified vaccinia virus Ankara based recombinant SARS vaccine in ferrets. Vaccine. 2005;23(17-18):2273-9.

Deming D, Sheahan T, Heise M, Yount B, Davis N, Sims A, et al. Vaccine efficacy in senescent mice challenged with recombinant SARS-CoV bearing epidemic and zoonotic spike variants. PLoS Med. 2006;3(12):e525. Correction in: PLoS Med. 2007;4(2):e80.

Institute for Health Metrics and Evaluation (IHME). Seattle, WA: IHME, University of Washington, 2020; [cited 15 Nov 2020]. Available from: http://covid19.healthdata.org/global?view=total-deaths&tab=trend.

International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use. Guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use: S2(R1). 09 November 2011 [cited 2019 Apr 16] [29 screens]. Available from: https://database.ich.org/sites/default/files/S2%28R1%29%20Guideline.pdf.

Kim HW, Canchola JG, Brandt CD, Pyles G, Chanock RM, Jensen K, et al. Respiratory syncytial virus disease in infants despite prior administration of antigenic inactivated vaccine. Am J Epidemiol. 1969;89(4):422-34.

Polack FP. Atypical measles and enhanced respiratory syncytial virus disease (ERD) made simple. Pediatr Res. 2007;62(1):111-5.

World Health Organization (WHO). Weekly Operational Update on COVID-19 - 13 November 2020 [Internet]. Geneva, Switzerland: WHO; 2020 Nov 13 [cited 16 Nov 2020]. Available from: https://www.who.int/publications/m/item/weekly-operational-update-on-covid-19---13-november-2020.