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List of Abbreviations

Abbreviation	Definition
ACE-2	angiotensin converting enzyme 2
BLA	biologics license application
CDC	Centers for Disease Control and Prevention
CMV	cytomegalovirus
CoV	coronavirus
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
DTPA	diethylenetriamine pentaacetic acid
ERD	enhanced respiratory disease
gB	glycoprotein B
gH	glycoprotein H
gL	glycoprotein L
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
hMPV	human metapneumovirus
ICH	International Council for Harmonisation
Ig	immunoglobulin
IM	intramuscular(ly)
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
mRNA	messenger RNA
NHP	nonhuman primate
NPI	nascent peptide imaging
PEG2000-DMG	1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000
PIV3	parainfluenza virus type 3
S	spike
S-2P	spike protein modified with 2 proline substitutions within the heptad repeat 1 domain
SARS	severe acute respiratory syndrome
SARS-CoV-1 DIV	double-inactivated severe acute respiratory syndrome coronavirus-1
SARS-CoV-2	2019 novel coronavirus
SM-102	heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate
Th	T helper

Abbreviation	Definition
Tris	tris(hydroxymethyl)aminomethane
WHO	World Health Organization
WT	wild type

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2.4.1. OVERVIEW OF NONCLINICAL TESTING STRATEGY

2.4.1.1 Background

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 (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 2020a](#)). The WHO declared COVID-19 a pandemic on 11 Mar 2020; however, widespread community transmission was already occurring in many locations. As of Nov 2020, more than 53 million cases and over 1.3 million deaths worldwide have been attributed to the COVID-19 pandemic ([WHO 2020a](#); [WHO 2020b](#)). Widespread community transmission of SARS-CoV-2 has been reported in the Americas, Europe, Africa, and Southeast Asia, and clusters of cases continue to be reported throughout Asia and Australia ([WHO 2020a](#)). During the winter, the combination of re-opening of schools and increase in indoor activity, because of lower temperatures, is expected to further increases in COVID-19 cases and deaths in some parts of the world.

Current evidence suggests that SARS-CoV-2 is primarily transmitted via direct contact or person-to-person via respiratory droplets by coughing or sneezing from an infected individual (regardless of whether they are symptomatic) ([Chen et al 2020](#); [Licciardi et al 2020](#); [Rothan and Byrareddy 2020](#); [Shen et al 2020](#)). Airborne transmission may be possible during certain medical procedures and in indoor, crowded, and poorly ventilated environments ([WHO 2020c](#)). Common symptoms of COVID-19 include fever and cough, and other symptoms include shortness of breath or difficulty breathing, muscle aches, chills, sore throat, headache, and loss of taste or smell. Individuals at highest risk of COVID-19 and severe COVID-19 are older adults (≥ 65 years old) and people of any age who have certain underlying medical conditions such as cancer, chronic kidney disease, chronic obstructive pulmonary disease, serious heart conditions, immunocompromised state, obesity, pregnancy, sickle cell disease, and type 2 diabetes mellitus; smokers are also at increased risk for severe COVID-19 disease ([CDC 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 developed a rapid-response proprietary vaccine platform based on a messenger RNA (mRNA) delivery system. The platform is based on the principle and observation that cells can take up mRNA, translate it, and then express viral antigen(s) on the cell surface. The delivered mRNA does not enter the nucleus or interact with the genome, is nonreplicating, and is expressed transiently. mRNA vaccines developed with the Sponsor's mRNA-based platform have been used to induce immune responses against infectious pathogens such as cytomegalovirus (CMV; NCT03382405), human metapneumovirus (hMPV) and parainfluenza virus type 3 (PIV3; NCT03392389), Zika virus (NCT04064905), and influenza virus (NCT03076385 and NCT03345043).

The Sponsor has used its mRNA-based 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 CoV S protein mediates attachment and entry of the virus into host cells (by binding to the angiotensin converting enzyme 2 [ACE-2] receptor followed by membrane fusion), making it a primary target for neutralizing antibodies that prevent infection (Corti et al 2015; Wang et al 2015; Yu et al 2015; Johnson et al 2016; Chen et al 2017; Wang et al 2018; Kim et al 2019; Widjaja et al 2019). It has been confirmed that the stabilized SARS-CoV-2 S-2P mRNA expresses well in mammalian cells and is in the prefusion conformation (Wrapp et al 2020).

Nonclinical studies have demonstrated that CoV S proteins are immunogenic and that S protein-based vaccines, including those based on mRNA delivery platforms, are protective in animals (Corbett et al 2020a, Corbett et al 2020b, Graham et al 2020, Mercado et al 2020, Tian et al 2020, Tostanoski et al 2020, Vogel et al 2020). Prior clinical studies of vaccines targeting related CoVs and other viruses have assessed the immunogenicity and safety profiles of mRNA-based vaccines (Anderson et al 2020, Folegatti et al 2020, Jackson et al 2020, Keech et al 2020, Mulligan et al 2020, Sadoff et al 2020, Walsh et al 2020).

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.

2.4.1.2 Test Material

mRNA-1273 contains a single mRNA that encodes for SARS-CoV-2 S-2P combined in a mixture of 4 lipids common to the Sponsor's mRNA vaccine platform: SM-102, cholesterol, DSPC, and PEG2000-DMG, respectively. The mRNA-1273 Drug Product is provided as a sterile suspension 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 pivotal biologics license application (BLA)-enabling toxicology studies were conducted with mRNA vaccines that encode various antigens developed with the Sponsor's mRNA-based platform using SM-102-containing LNPs. A development mRNA-1273 lot (Lot AMPDP-200005), which was evaluated in the nonclinical pharmacology programs, was prepared with a manufacturing process representative of the GMP mRNA-1273 Drug Product evaluated in the Phase 3 clinical trial (as described in Module 3, [Section 3.2.P.2.3](#) [Scale A process]) and was therefore representative of the clinical presentations. Lot AMPDP-200005 was manufactured at a concentration of 0.5 mg/mL in 20 mM Tris buffer containing 87 g/L sucrose and 10.7 mM acetate, at pH 7.5.

The distribution, toxicity, and genotoxicity associated with mRNA vaccines formulated in LNPs are driven primarily by the composition of the LNPs and, to a lesser extent, by the biologic activity of the antigen(s) encoded by the mRNA. Therefore, the distribution study, Good Laboratory Practice (GLP)-compliant toxicology studies, and in vivo GLP-compliant genotoxicity study conducted with mRNA vaccines that encode various antigens developed with the Sponsor's mRNA-based platform using SM-102-containing LNPs are considered supportive and BLA-enabling for mRNA-1273. SM-102, the novel lipid used in mRNA-1273, was evaluated as an individual agent in GLP-compliant in vitro genotoxicity studies. Additionally, the immunogenicity and toxicity profiles of mRNA-1273 were assessed in a non-GLP repeat-dose study.

2.4.1.3 Nonclinical Testing Program

The nonclinical testing program was designed to adhere to international regulatory guidelines, the intended clinical development program, and traditional pharmacology and toxicology principles and was consistent with International Council for Harmonisation (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).

The route of administration of mRNA-1273 used in the nonclinical studies was intramuscular (IM), consistent with the clinical route.

Nonclinical primary pharmacology evaluations were conducted in young and aged mice (BALB/c, BALB/cJ, C57/BL6J, and B6C3F1/J strains), golden Syrian hamsters, and rhesus macaques (nonhuman primates [NHPs]) animal models to characterize the 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 2020a). Additionally, the immunogenicity of mRNA-1273 was assessed in a non-GLP repeat-dose pharmacology study in Sprague Dawley rats.

As SARS-CoV-2 is a newly emerged CoV, there were no established animal models for the evaluation of prophylactic vaccines and therapeutics. Therefore, nonclinical studies were initiated in multiple animal species in order to gain a comprehensive understanding of the effects of mRNA-1273 immunization. Wild-type (WT) mice are a convenient and easy-to-use model to assess vaccine immunogenicity; however, the ACE-2 receptor, the primary route for SARS-CoV-2 binding and entry, differs significantly between mice and humans and, as result, WT SARS-CoV-2 does not infect mice. Therefore, a mouse-adapted SARS-CoV-2 strain, which was developed by the laboratory of PPD at the University of North Carolina at Chapel Hill, was used to assess protection of immunized mice from SARS-CoV-2 challenge. Although this mouse-adapted strain infects young mice and induces mild disease symptoms, more severe

symptoms are evident in aged mice (> 12 months) (Dinnon et al 2020). Aged mice were therefore included in the nonclinical pharmacology program to further characterize the immune response and the level of protection from viral challenge. In addition, this model was used to characterize the quality of the immune response to determine if the mRNA-1273-induced immunity would be predicted to promote vaccine-associated ERD. The immunogenicity and protection study in aged mice was designed to directly address this concern through the evaluation of dose levels predicted to drive optimal or suboptimal protection from viral challenge. Golden Syrian hamsters were also selected as a relevant model for evaluation. Wild-type SARS-CoV-2 productively infects hamsters, causing weight loss and moderate to severe lung pathology. This model was selected because it is currently the only animal species in which severe respiratory disease is evident after virus challenge (Chan et al 2020). Nonhuman primates are the species most closely related to humans and have previously recapitulated several important aspects of SARS-CoV infection (Lu et al 2020). Although SARS-CoV-2 infection in NHPs result only in mild clinical symptoms, infection does cause illness with evidence of pneumonia (Johansen et al 2020).

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 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.

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 hMPV and PIV3 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.

The Sprague Dawley rat was selected as the animal model for the toxicity studies because it is an accepted rodent species for nonclinical toxicology testing by regulatory agencies and is a

relevant species to assess the toxicity and immunogenicity of mRNA vaccines, as evidenced by immunogenic responses.

Rats were administered doses up to the anticipated maximum tolerated dose of 150 µg/dose, where clinical observations included vocalization (at 100 µg/dose) and were accompanied by body weight loss and decrease in food consumption. The number of doses selected for the individual GLP studies was 1 more than the intended number of doses proposed for the individual clinical studies. The number of doses ranged from 3 to 4, and doses were administered every 2 weeks or as determined based on the frequency of the anticipated clinical dosing regimen.

SM-102, the novel lipid used in mRNA-1273, was evaluated in genotoxicity studies as an individual agent using a standard ICH S2 (R1) approach (ICH 2011), including a GLP-compliant bacterial reverse mutation (Ames) test in *Salmonella typhimurium* and *Escherichia coli* and a GLP-compliant in vitro micronucleus test 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 [NPI] luciferase mRNA) CCI [REDACTED].

2.4.2. PHARMACOLOGY

[Table 1](#) summarizes the nonclinical pharmacology program for mRNA-1273. Pharmacology results are fully summarized in [Module 2.6.2](#).

Table 1: Summary of Pharmacology Program for mRNA-1273

Study Type/Description	Test Article Dose (µg)	Species, Strain	Method of Administration; Immunization Schedule	GLP	Report Number
Primary Pharmacology					
Evaluation of immunogenicity, protective capacity, and safety in young mice	mRNA-1273: 0.01, 0.1, 1 or 10 µg SARS-CoV-2 S-2P: 0.01, 0.1, or 1 µg (+ SAS-adjuvant)	Mouse (young), BALB/cJ, C57BL/6J, B6C3F1/J	IM; prime only prime/boost (3-week interval) prime/boost (4-week interval)	No	VRC01
Immunization and protein restimulation in young BALB/c mice with enhanced respiratory disease endpoint monitoring	mRNA-1273: 1 or 10 µg SARS-CoV-2 S-2P: 10 µg (+ alum)	Mouse (young), BALB/c	IM; prime/boost (2-week interval)	No	MOD-3937
Immunogenicity and determination of titer dynamic range in young BALB/c mice	mRNA-1273: 0.0025 through 20 µg	Mouse (young), BALB/c	IM; prime/boost (3-week interval)	No	MOD-3938/ MOD-3940
Immunogenicity and characterization of cellular response in young BALB/cJ mice	mRNA-1273: 0.1, 1, or 10 µg SARS-CoV-1 DIV: 0.2 or 1 µg (+ alum) CDS: 0.2 or 1 µg (+ alum)	Mouse (young), BALB/c	IM; prime/boost (3-week interval)	No	VRC05
Efficacy and enhanced respiratory disease in aged BALB/c mice	mRNA-1273: 0.1 or 1 µg SARS-CoV-1 DIV: 0.1 µg (+ alum)	Mouse (aged), BALB/c	IM; prime/boost (3-week interval)	No	VRC02
Five-week (2 doses: prime/boost) repeat-dose immunogenicity with safety endpoints	mRNA-1273: 0, 30, 60, or 100 µg	Rat, Sprague Dawley	IM; prime/boost (3-week interval)	No	2308-123
Protection from WT SARS-CoV-2 in hamsters using optimal and suboptimal doses	mRNA-1273: 1, 5, or 25 µg	Hamster, golden Syrian	IM; prime/boost (3-week interval)	No	UTMB01

Study Type/Description	Test Article Dose (µg)	Species, Strain	Method of Administration; Immunization Schedule	GLP	Report Number
Primary Pharmacology					
Immunogenicity and protective efficacy in NHPs	mRNA-1273: 10 or 100 µg	NHP, rhesus macaque (Indian-origin)	IM; prime/boost (4-week interval)	No	VRC04
Evaluation of immunogenicity and efficacy from expanded dose range in NHPs	mRNA-1273: 2.5, 30, or 100 µg	NHP, rhesus macaque (Indian-origin)	IM; prime/boost (4-week interval)	No	VRC07

Abbreviations: alum = aluminum hydroxide; CDS = conformationally disrupted severe acute respiratory syndrome coronavirus-2 S protein; GLP = Good Laboratory Practice; IM = intramuscular; NHP = nonhuman primate; SARS-CoV-1 DIV = double-inactivated severe acute respiratory syndrome coronavirus-1; SARS-CoV-2 = 2019 novel coronavirus; S-2P = spike protein modified with 2 proline substitutions within the heptad repeat 1 domain; SAS = Sigma Adjuvant System®; WT = wild-type.

2.4.2.1 Primary Pharmacology

Nonclinical primary pharmacology studies were conducted in young and aged mice (BALB/c, BALB/cJ, C57BL/6J, and B6C3F1/J strains), golden Syrian hamsters, and rhesus macaques (NHPs) animal models to characterize the 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 potential to promote vaccine-associated ERD after viral challenge (Module 2.6.2). Additionally, the immunogenicity of mRNA-1273 was evaluated in a non-GLP repeat-dose pharmacology study in Sprague Dawley rats (Module 2.6.6; Section 2.6.6.9).

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 (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. The immune signature of mice immunized with mRNA-1273 was compared to that of vaccines that have been associated with ERD (SARS-CoV-1 DIV and conformationally disrupted spike protein [CDS] in alum adjuvant) included as controls in 2 mouse studies.

These studies demonstrated that mRNA-1273 is immunogenic in all the species assessed, showing a dose-dependent response in IgG binding antibody titers and neutralizing antibody activities. Antigen-specific T-cell responses were observed in mice and NHPs. Direct measurement of Th1-directed responses in mice and NHPs, indirect measurement of Th1-directed responses (IgG2a/c:IgG1 antibody subclasses) in mice, and the high levels of neutralizing antibody in all species lessen the concerns regarding the risk of ERD associated with mRNA-1273 immunization. Additionally, a robust and dose-dependent CD8⁺ T-cell response in mice and a low CD8⁺ T-cell response in NHPs were observed after boosting with a second dose of mRNA-1273.

In addition to measurements of the immune response, mice, hamsters, and NHPs were challenged 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); mice and hamsters were challenged intranasally and NHPs were challenged intranasally and intratracheally. Dose levels predicted to be optimal (fully protective) and suboptimal (subprotective) were included in these studies. At higher doses, mice, hamsters, and NHPs were fully protected from viral replication in both lungs and nasal passages. At suboptimal dose levels, animals were either fully protected in the lungs or had reduced viral burden after challenge compared to control animals. There were no observations of increased viral load in animals immunized with suboptimal dose levels of mRNA-1273, which further supports that mRNA-1273 immunization does not promote ERD. Lung histopathology assessments were performed to verify reduction of inflammation, immune complex deposition, and immune cell invasion in response to viral challenge in animals immunized with mRNA-1273 compared to control (PBS) animals. In animals immunized with either optimal or suboptimal mRNA-1273 dose levels, histopathological evaluation of the lungs of mice and NHPs confirmed the lack of evidence of ERD, as demonstrated by minimal

inflammation and no noteworthy neutrophilic-associated alveolar disease or eosinophil-dominant inflammatory response, which have been historically associated with vaccine-associated ERD. In contrast, moderate to severe inflammation involving the small airways and the adjacent alveolar interstitia was elicited by SARS-CoV-2 infection in PBS-control animals.

Overall, nonclinical pharmacology studies demonstrated that mRNA-1273 is well tolerated, is immunogenic, and provides protection from SARS-CoV-2 challenge. In mice, hamsters, and NHPs, a prime-only immunization schedule induced robust SARS-CoV-2-specific binding and neutralizing antibody responses that significantly increased after boosting with a second dose of mRNA-1273. A prime/boost immunization schedule elicited a substantial dose-dependent binding antibody response in rats. In addition, Th1-directed antigen-specific CD4⁺ and CD8⁺ T-cell responses were observed in mice and a Th1-directed antigen-specific CD4⁺ T-cell response was observed in NHPs. mRNA-1273 was fully protective from viral challenge in immunized mice and hamsters when administered as a prime-only or prime/boost schedule at ≥ 1 $\mu\text{g}/\text{dose}$ and in immunized NHPs when administered as a prime/boost schedule at ≥ 30 $\mu\text{g}/\text{dose}$. Furthermore, mRNA-1273 did not promote vaccine-associated ERD in mice, hamsters, and NHPs as demonstrated by balanced Th1/Th2-directed immune responses to immunization, the absence of increased lung pathology, and controlled viral replication after viral challenge when administered at doses predicted to be fully (optimal dose) or partially (suboptimal dose) protective.

2.4.3. PHARMACOKINETICS AND TISSUE DISTRIBUTION

[Table 2](#) lists the nonclinical pharmacokinetics and tissue distribution study with mRNA-1647 in support of the development of mRNA-1273. Biodistribution results are fully summarized in [Module 2.6.4](#).

Table 2: Summary of Pharmacokinetics Program for mRNA-1273

Study Type	Test Article	Species, Strain	Method of Administration, Dose	GLP	Report Number
Single-dose tissue distribution study	mRNA-1647 ^a	Rat, Sprague Dawley	IM injection dose of 100 µg on Day 1	No	5002121 Amendment 1

Abbreviations: CMV = cytomegalovirus; gB = glycoprotein B; gH = glycoprotein H; gL = glycoprotein L; GLP = Good Laboratory Practice; IM = intramuscular; mRNA = messenger RNA.

^a mRNA-1647 contains 6 mRNAs that encode the full-length CMV gB and the pentameric gH/gL/UL128/UL130/UL131A glycoprotein complex. The 6 mRNAs are combined at a target mass ratio of 1:1:1:1:1:1 in a mixture of 4 lipids (SM-102, PEG2000-DMG, cholesterol, and DSPC) and formulated in 93 mM Tris, 60 mM NaCl, and 7% PG.

2.4.3.1 Pharmacokinetics and Tissue Distribution

The results of a biodistribution, non-GLP, single dose, IM injection study of mRNA-1647 in male Sprague Dawley rats ([Table 2.6.5.5](#) [Module 2.6.5] and [Report 5002121 Amendment 1](#)) support the development of mRNA-1273. mRNA-1647 is a novel mRNA-based CMV vaccine that contains 6 distinct mRNA sequences (1 that encodes the full-length CMV glycoprotein B [gB] and 5 that encode the pentameric glycoprotein H [gH]/glycoprotein L [gL]/UL128/UL130/UL131A glycoprotein complex) combined at a target mass ratio of 1:1:1:1:1:1 in the Sponsor's standard proprietary SM-102-containing LNPs.

After a single IM dose of mRNA-1647 in male rats, concentrations of the 6 mRNA constructs of mRNA-1647 (ie, gB, gH, gL, UL128, UL130, and UL131A) were detectable in plasma and tissues in a 1:1:1:1:1:1 ratio. The time after dosing at which the maximum concentration was observed in plasma (T_{max}) was 2 hours for all constructs and was followed by a rapid elimination phase with a half-life ($T_{1/2}$) estimated to range from 2.7 to 3.8 hours. The maximum plasma concentration (C_{max}) ranged from 1.60 to 2.30 ng/mL, and the area under the concentration versus time curve (AUC) from the start of dose administration to the time after dosing at which the last quantifiable concentration was observed ($AUC_{[0-t]}$) ranged from 22.7 to 25.5 ng·h/mL.

Concentrations of the 6 mRNA constructs of mRNA-1647 were detected at levels above the lower limit of quantitation (LLOQ) in most tissues analyzed, except for the kidney, where all levels were below the LLOQ. For highly exposed tissues (injection site [muscle], lymph nodes

[proximal and distal], and spleen), the C_{\max} was observed between 2 and 24 hours post dose. The $T_{1/2}$ was calculated using the average tissue $T_{1/2}$ values for the 6 mRNA constructs; the results were 14.9 hours for injection site (muscle), 34.8 hours for proximal (popliteal) lymph nodes, 31.1 hours for distal (axillary) lymph nodes, and 63.0 hours for spleen.

As observed with other IM-delivered vaccines, the highest mRNA concentrations were observed at the injection site followed by the proximal (popliteal) and distal (axillary) lymph nodes, consistent with distribution via the lymphatic system. These tissues, as well as spleen and eye, had tissue-to-plasma AUC ratios > 1.0. Only a relatively small fraction of the administered mRNA-1647 dose distributed to distant tissues, and the mRNA constructs did not persist past 1 to 3 days in tissues other than muscle (injection site), proximal popliteal and distal axillary lymph nodes, and spleen, in which the average $T_{1/2}$ values for all constructs ranged from 14.9 to 63.0 hours.

2.4.4. TOXICOLOGY

[Table 3](#) summarizes the nonclinical toxicology program used in support of the development of mRNA-1273. Toxicology results are fully summarized in [Module 2.6.6](#).

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Table 3: Summary of Toxicology Program for mRNA-1273

Study Type	Test Article	Species, Strain	Method of Administration; Dose	GLP	Report Number
Repeat-Dose Toxicity					
1-month (3 doses) repeat-dose study with 2-week recovery	mRNA-1706 ^a	Rat, Sprague Dawley	IM; 0, 13, 65, 129 µg/dose ^b (Days 1, 15, 29)	Yes	5002045
1-month (3 doses) repeat-dose study with 2-week recovery	mRNA-1706 ^a	Rat, Sprague Dawley	IM; 0, 10, 50, 100 µg/dose (Days 1, 15, 29)	Yes	5002231
1-month (3 doses) repeat-dose study with 2-week recovery	mRNA-1653 ^c	Rat, Sprague Dawley	IM; 0, 10, 50, 150 µg/dose (Days 1, 15, 29)	Yes	5002033
1-month (3 doses) repeat-dose study with 2-week recovery	mRNA-1893 ^d	Rat, Sprague Dawley	IM; 0, 10, 30, 96 µg/dose (Days 1, 15, 29)	Yes	5002400
6-week (4 doses) repeat-dose study with 2-week recovery	mRNA-1647 ^e	Rat, Sprague Dawley	IM; 0, 8.9, 27, 89 µg/dose ^f (Days 1, 15, 29, 43)	Yes	5002034
6-week (4 doses) repeat-dose study with 2-week recovery	mRNA-1443 ^g	Rat, Sprague Dawley	IM; 0, 9.6, 29, 96 µg/dose ^h (Days 1, 15, 29, 43)	Yes	5002158
In Vitro Genotoxicity					
Bacterial reverse mutation test	SM-102	<i>Salmonella typhimurium</i> , <i>Escherichia coli</i>	Incubation for 67 hours 29 minutes with 0, 1.58, 5.0, 15.8, 50, 158, 500, 1581, 5000 µg/plate SM-102 with or without supplemented rat liver fraction	Yes	9601567
Mammalian cell micronucleus test	SM-102	Human peripheral blood lymphocytes	Incubation for 4 and 24 hours with 0, 163, 286, 500 µg/mL SM-102 with or without supplemented rat liver fraction	Yes	9601568
In Vivo Genotoxicity					
In vivo mammalian erythrocyte micronucleus test	mRNA-1706 ^a	Rat, Sprague Dawley	Single IV; 0, 0.6/6.2 (F), 1.3/13.5, 2.6/27.0, 5.2/54.1 (M) mg/kg mRNA-1706/SM-102 ^{i,j}	Yes	9800399
In vivo mammalian erythrocyte micronucleus test	NPI luciferase mRNA ^k	Rat, Sprague Dawley	Single IV; 0, 0.32/6.0, 1.07/20, 3.21/60 mg/kg NPI luciferase mRNA/SM-102	No	AF87FU.125012 NGLPICH.BTL
Other Toxicology					
5-week (2 doses) repeat-dose immunogenicity and toxicity study	mRNA-1273 ^l	Rat, Sprague Dawley	IM; 0, 30, 60, 100 µg/dose (Days 1 and 22)	No	2308-123

Abbreviations: CMV = cytomegalovirus; CoV = coronavirus; F = female; gB = glycoprotein B; gH = glycoprotein H; gL = glycoprotein L; GLP = Good Laboratory Practice; h = hour; IM = intramuscular; IV = intravenous; M = male; min = minute; mRNA = messenger RNA; NPI = nascent peptide imaging; pp65 = phosphoprotein 65; prME = pre-membrane and envelope; S-2P = spike protein modified with 2 proline substitutions within the heptad repeat 1 domain; SARS-CoV-2 = 2019 novel coronavirus; SoA = summary of analysis.

- ^a mRNA-1706 contains a single mRNA sequence that encodes the prME structural proteins of Zika virus combined in a mixture of 4 lipids (SM-102, PEG2000-DMG, cholesterol, and DSPC) and formulated in 20 mM Tris, 8% sucrose, pH 7.4.
- ^b The original dose levels selected were 0, 10, 50, and 100 µg/dose, respectively (SoA issued on 11 October 2016). The calculated dose levels were revised based on the updated concentration reported for mRNA-1706 Lot No. MTDP16064 (SoA issued on 03 May 2017). The change in the reported mRNA content for mRNA-1706 was 29%.
- ^c mRNA-1653 contains 2 distinct mRNA sequences that encode the full-length membrane-bound fusion proteins of human metapneumovirus and parainfluenza virus type 3. The 2 mRNAs are combined at a target mass ratio of 1:1 in a mixture of 4 lipids (SM-102, PEG2000-DMG, cholesterol, and DSPC) and formulated in 93 mM Tris, 7% PG, 1 mM DTPA, pH 7.4.
- ^d mRNA-1893 contains a single mRNA sequence that encodes the prME structural proteins of Zika virus in a mixture of 4 lipids (SM-102, PEG2000-DMG, cholesterol, and DSPC) and formulated in 100 mM Tris, 7% PG, 1 mM DTPA, pH 7.5.
- ^e mRNA-1647 contains 6 mRNAs that encode the full-length CMV gB and the pentameric gH/gL/UL128/UL130/UL131A glycoprotein complex. The 6 mRNAs are combined at a target mass ratio of 1:1:1:1:1:1 in a mixture of 4 lipids (SM-102, PEG2000-DMG, cholesterol, and DSPC) and formulated in 93 mM Tris, 60 mM NaCl, and 7% PG.
- ^f The original dose levels selected were 0, 10, 30, and 100 µg/dose, respectively (SoA issued on 16 Mar 2017). The calculated dose levels were revised based on the updated concentration reported for mRNA-1647 Lot No. MTDP17015 (SoA issued on 31 May 2017). The change in the reported mRNA content for mRNA-1647 was -11%.
- ^g mRNA-1443 contains a single mRNA sequence that encodes a phosphorylation mutant of the CMV phosphoprotein 65 protein (ie, deletion of amino acids 435-438) combined in a mixture of 4 lipids (SM-102, PEG2000-DMG, cholesterol, and DSPC) and formulated in 93 mM Tris, 60 mM NaCl, and 7% PG.
- ^h The original dose levels selected were 0, 10, 30, and 100 µg/dose, respectively (SoA issued on 16 Mar 2017). The calculated dose levels were revised based on the updated concentration reported for mRNA-1443 Lot No. MTDP17017 (SoA issued on 30 May 2017). The change in the reported mRNA content for mRNA-1443 was 4%.
- ⁱ A dose-range finding test was performed prior to the main phase of the study, wherein male and female rats (3 animals/sex) were given a single IV injection (doses 2.6/27.0, 3.9/40.6, and 5.2/54.1 mg/kg mRNA-1706/SM-102 for females, and 2.6/27.0, 5.2/54.1, and 10.3/107.1 mg/kg mRNA-1706/SM-102 for males).
- ^j The original dose levels selected were 0, 1.0, 2.0, 4.0, 0.5, 1.0, and 2.0 mg/kg mRNA-1706, respectively (SoA issued on 11 October 2016). The calculated dose levels were revised based on the updated concentration reported for mRNA-1706 Lot No. MTDP16064 (SoA issued on 03 May 2017). The change in the reported mRNA content for mRNA-1706 was 29%.
- ^k The NPI luciferase mRNA is combined in a mixture of 4 lipids (SM-102, PEG2000-DMG, cholesterol, and DSPC) and formulated in 25 mM Tris, 123 g/L sucrose, 1 mM DTPA, pH 7.5.
- ^l mRNA-1273 contains a single mRNA sequence that encodes the full-length SARS-CoV-2 S-2P combined in a mixture of 4 lipids (SM-102, PEG2000-DMG, cholesterol, and DSPC) and formulated in 20 mM Tris, 87 mg/mL sucrose, 10.7 mM sodium acetate, pH 7.5.

2.4.4.1 Repeat-Dose Toxicity

The safety and tolerability of mRNA vaccines that encode various antigens developed with the Sponsor's mRNA-based platform using SM-102-containing LNPs have been evaluated in multiple GLP-compliant, repeat-dose toxicity studies in Sprague Dawley rats at doses up to 150 µg administered every 2 weeks for up to 6 weeks followed by a 2-week recovery period. Additionally, the Sponsor completed a repeat-dose non-GLP study in Sprague Dawley rats to characterize the immunogenic response and potential toxicity of mRNA-1273 at clinically relevant doses ([Section 2.4.4.3](#)).

Rats were administered mRNA-based vaccines (mRNA-1706, mRNA-1653, or mRNA-1893) IM once every 2 weeks for 1 month (3 doses) at doses up to 150 µg followed by a 2-week recovery period ([Table 2.6.7.7A](#) [Module 2.6.7] and [Report 5002045](#); [Table 2.6.7.7B](#) [Module 2.6.7] and [Report 5002231](#); [Table 2.6.7.7C](#) [Module 2.6.7] and [Report 5002033](#); [Table 2.6.7.7D](#) [Module 2.6.7] and [Report 5002400](#)). In addition, rats were administered mRNA-based vaccines (mRNA-1647 or mRNA-1443) IM once every 2 weeks for 6 weeks (4 doses) at doses up to 96 µg followed by a 2-week recovery period ([Table 2.6.7.7E](#) [Module 2.6.7] and [Report 5002034](#); [Table 2.6.7.7F](#) [Module 2.6.7] and [Report 5002158](#)).

The aggregate rat repeat-dose toxicity profile from the GLP studies for mRNA-based vaccines formulated in SM-102-containing LNPs consisted of IM doses ranging from 8.9 to 150 µg/dose administered once every 2 weeks for up to 6 weeks. All doses administered were tolerated. Test article-related in-life observations at ≥ 8.9 µg/dose included reversible or reversing erythema and edema at the injection site and transient increases in body temperature at 6 hours post-dose returning to baseline 24 hours post-dose.

Test article-related, generally dose-dependent clinical pathology changes were observed at ≥ 8.9 µg/dose. Hematology changes included increases in white blood cells, neutrophils, and eosinophils and decreased lymphocytes; coagulation changes included increases in fibrinogen and activated partial thromboplastin time; and clinical chemistry changes included decreases in albumin, increases in globulin, and a corresponding decrease in albumin/globulin ratio. Clinical pathology changes generally reversed or were reversing by the end of the 2-week recovery period. Test article-related, transient cytokine increases were observed at ≥ 8.9 µg/dose at 6 hours post-dose, including in IP-10, MCP-1, and MIP-1- α . Cytokine changes were generally reversing by the end of the 2-week recovery period.

Post-mortem test article-related and generally dose-dependent changes in organ weights and macroscopic and microscopic findings were observed at ≥ 8.9 µg/dose. Organ weight increases

were observed in the spleen, liver, and adrenal gland. Organ weight changes were generally reversing by the end of the 2-week recovery period. Macroscopic changes included skin thickening at the injection site and enlarged lymph nodes. Injection site changes completely recovered, and lymph node changes were recovering by the end of the 2-week recovery period. Microscopic changes included mixed cell inflammation at the injection site; increased cellularity and mixed cell inflammation in the inguinal, iliac, and popliteal lymph nodes; decreased cellularity in the splenic periarteriolar lymphoid sheath; increased myeloid cellularity in the bone marrow; and hepatocyte vacuolation and Kupffer cell hypertrophy in the liver. Microscopic changes were generally reversing by the end of the 2-week recovery period.

2.4.4.2 Genotoxicity

SM-102, the novel lipid used in mRNA-1273, was evaluated in genotoxicity studies as an individual agent using a standard ICH S2 (R1) approach (ICH 2011), including a GLP-compliant in vitro bacterial reverse mutation (Ames) test in *S. typhimurium* and *E. coli* (Table 2.6.7.8A [Module 2.6.7] and Report 9601567) and a GLP-compliant in vitro micronucleus test in human peripheral blood lymphocytes (Table 2.6.7.8B [Module 2.6.7] and Report 9601568).

In addition, SM-102 was evaluated for in vivo genotoxicity risk in a GLP-compliant in vivo rat micronucleus test using a similar mRNA-based vaccine formulated in SM-102 LNPs (Table 2.6.7.9A [Module 2.6.7] and Report 9800399) and in a non-GLP-compliant in vivo rat micronucleus test using a reporter mRNA (NPI luciferase mRNA) CCI (Table 2.6.7.9B [Module 2.6.7] and Report AF87FU.125012NGLPICH.BTL).

Genotoxicity assessments of the SM-102 lipid concluded that the lipid is not genotoxic in the bacterial mutagenicity and human peripheral blood lymphocytes chromosome aberration assays. Two intravenous in vivo micronucleus assays were conducted with mRNA-based vaccines formulated in the SM-102-containing LNPs. Results from Report AF87FU.125012NGLPICH.BTL were negative up to 3.21/60 mg/kg NPI luciferase mRNA/SM-102, while results from Report 9800399 were positive at 2.6/27.0 mg/kg mRNA-1706/SM-102 in females and at 5.2/54.1 mg/kg mRNA-1706/SM-102 in males, indicating that there was minimal bone marrow toxicity. The equivocal results are likely driven by micronuclei formation secondary to elevated body temperature induced by LNP-driven systemic inflammation at high systemic (intravenous) doses. Overall, the genotoxic risk to humans is considered to be low due to minimal systemic exposure following IM administration, limited duration of exposure, and negative in vitro results.

2.4.4.3 Other Toxicity

A non-GLP study in Sprague Dawley rats was conducted to characterize the immunogenic response and potential toxicity of mRNA-1273 at IM doses levels of 30, 60, and 100 µg/dose administered on Days 1 and 22 ([Section 2.6.2.2.6](#) [Module 2.6.2], [Table 2.6.7.17](#) [Module 2.6.7], and [Report 2308-123](#)).

A strong immunogenic response against SARS-CoV-2 S-2P was observed on Day 35, with measured IgG antibody titers above 10^6 at all dose levels. mRNA-1273 had no effect on body weights and limited, transient clinical signs starting at 30 µg/dose consisting of transient dose-dependent injection site edema with or without hindlimb impairment. Clinical pathology findings consisted, in part, of changes associated with inflammation starting at 30 µg/dose. In general, the changes observed are consistent with the results from the previous GLP rat toxicity studies conducted with other mRNA-based vaccines formulated with SM-102-containing LNPs.

2.4.4.4 Summary of Nonclinical Safety Margins

Pending the outcome of the Phase 3 clinical trial with mRNA-1273, a human dose of 100 µg/dose is anticipated to be safe and to provide protective immunization against SARS-CoV-2 infection.

In the rat repeat-dose toxicity studies in which up to 100 µg/dose of mRNA-1273 administered on Day 1 and Day 22, up to 150 µg/dose of mRNA-1706, mRNA-1653, or mRNA-1893 administered once every 2 weeks for 1 month (3 doses), or up to 96 µg/dose of mRNA-1647 and mRNA-1443 administered once every 2 weeks for 6 weeks (4 doses) were evaluated, the administered mRNA/LNP vaccines were well tolerated. Typical vaccine-associated findings included increases in body temperature and spleen weight, changes in cytokine profile reflecting an inflammatory pattern, and injection site reaction characteristics for vaccines, with all findings showing reversibility. In addition, no exaggerated immune reactions were observed in the rat toxicity studies or in the completed immunogenicity studies in mice (young and old), rats, hamsters, and NHPs.

If a 100 µg/dose of mRNA-1273 is well tolerated in a rat with a conservative body weight estimate of 0.30 kg as compared to a human subject with a conservative body weight of 60.0 kg, there is a 200-fold safety margin for the human dose as compared to the rat dose based on body weight. The efficacy and safety profile of the mRNA-1273 vaccine in the Phase 3 clinical trial will be the ultimate determinant in identifying the approved dose for human subjects.

2.4.5. INTEGRATED OVERVIEW AND CONCLUSIONS

In support of the development of mRNA-1273 against SARS-CoV-2, nonclinical pharmacology, biodistribution, and toxicology studies have been completed using mRNA-1273 or other mRNA vaccines that encode various antigens developed with the Sponsor's mRNA-based platform using SM-102-containing LNPs.

Data from the nonclinical testing program presented in this submission support the clinical efficacy and safety of mRNA-1273 at doses up to 100 µg administered twice IM 28 days apart.

- mRNA-1273 induced high levels of binding and neutralizing antibodies in young and aged mice, rats, hamsters, and NHPs; protected against viral replication in the upper (nasal turbinates) and lower (lung) airways; and did not promote vaccine-associated ERD in these nonclinical models.
- The biodistribution of mRNA-based vaccines formulated in LNPs is predicted to be driven by the characteristics of the LNPs. mRNAs that are within similar LNPs (eg, mRNA-1273 and mRNA-1647) are therefore expected to distribute similarly, and the biodistribution study of mRNA-1647 supports the clinical development of mRNA-1273. This study demonstrated that mRNA constructs do not persist past 1 to 3 days in tissues other than muscle (injection site), proximal popliteal and distal axillary lymph nodes, and spleen, in which the average $T_{1/2}$ values for the 6 mRNA constructs of mRNA-1647 ranged from 14.9 to 63.0 hours.
- The aggregate repeat-dose toxicity profile of mRNA vaccines that were developed with the Sponsor's mRNA-based platform in rats at IM doses ranging from 8.9 to 150 µg/dose administered once every 2 weeks for up to 6 weeks was similar and consistent despite the fact that the different mRNA constructs encode different antigens. Therefore, the Sponsor proposes that the toxicity associated with mRNA vaccines formulated in similar LNPs is driven primarily by the LNP composition and, to a lesser extent, by the biologic activity of the antigens encoded by the mRNA; therefore, the aggregate GLP repeat-dose rat data are considered to be representative of mRNA vaccines formulated in the same SM-102 LNPs and support the clinical development of mRNA-1273.

Overall, the nonclinical studies demonstrates 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.

2.4.6. REFERENCES

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