A Trial of the Safety and Immunogenicity of the COVID-19 Vaccine (mRNA-1273) in Participants with Hematologic Malignancies and Various Regimens of Immunosuppression, and in Participants with Solid Tumors on PD1/PDL1 Inhibitor Therapy, Including Booster Doses of Vaccine

NIH Protocol Number: 000115

IND Sponsor: Center for Cancer Research (CCR), NCI

Lead Principal Investigator: PPD

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NCT Number: NCT04847050

Drug Name:	2019-nCoV Vaccine (mRNA-1273)
IND Number:	27190
Sponsor	Center for Cancer Research, NCI
Manufacturer	ModernaTX, Inc.
Supplier	ModernaTX, Inc.

STATEMENT OF ASSURANCE

Each Institution will hold a current Federal Wide Assurance (FWA) issued by the Office of Human Research Protections (OHRP) for federally funded human participants research. Each FWA will designate at least one Institutional Review Board (IRB)/Independent Ethics Committee (IEC) registered with OHRP, for which the research will be reviewed and approved by the IRB/IEC and will be Participant to continuing review [45 CFR 46.103(b)]. The IRB/IEC designated under an FWA may include an institution's IRB/IEC, an independent IRB/IEC, or an IRB/IEC of another institution after establishing a written agreement with that other institution.

STATEMENT OF COMPLIANCE

The study trial will be carried out in accordance with Good Clinical Practice (GCP) and as required by the following:

* United States Code of Federal Regulations (CFR) 45 CFR Part 46: Protection of Human Participants
* Food and Drug Administration (FDA) Regulations, as applicable: 21 CFR Part 50 (Protection of Human Participants), 21 CFR Part 54 (Financial Disclosure by Clinical Investigators), 21 CFR Part 56 (Institutional Review Boards), 21 CFR Part 11, and 21 CFR Part 312 (Investigational New Drug Application), 21 CFR 812 (Investigational Device Exemptions)
* International Council on Harmonisation: Good Clinical Practice (ICH E6); 62 Federal Register 25691 (1997); and future revisions
* Belmont Report: Ethical Principles and Guidelines for the Protection of Human Participants of Research, Report of the National Commission for the Protection of Human Participants of Biomedical and Behavioral Research
* National Institutes of Health (NIH) Office of Intramural Research, Research Involving Human Participants, as applicable
* Applicable Federal, State, and Local Regulations and Guidance

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
ALL	Acute lymphoblastic leukemia.
AML	Acute Myeloid Leukemia
CFR	Code of Federal Regulations
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CLL	Chronic lymphocytic leukemia
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HL	Hodgkin lymphoma
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IM	Intramuscular
IND	Investigational New Drug Application

IRB	Institutional Review Board
MDS	Myelodysplastic Syndromes
MedDRA®	Medical Dictionary for Regulatory Activities
MM	Multiple myeloma
MOP	Manual of Procedures
MPN	Myeloproliferative neoplasms
N	Number (typically refers to participants)
NDA	New Drug Application
NEJM	New England Journal of Medicine
NHL	Non-Hodgkin lymphoma
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
OHSR	Office for Human Participants Research
PHI	Protected Health Information
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
RNA	Ribonucleic Acid
SAE	Serious Adverse Event/Serious Adverse Experience
SCT	Stem Cell Transplantation
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
US	United States
WHO	World Health Organization

PROTOCOL SUMMARY

Title: A Trial of the Safety and Immunogenicity of the COVID-19 Vaccine (mRNA-1273) in Participants with Hematologic Malignancies and Various Regimens of Immunosuppression, and in Participants with Solid Tumors on PD1/PDL1 Inhibitor Therapy, Including Booster Doses of Vaccine

Design of the Study: This is an open-label, multicenter clinical trial designed to evaluate the safety, reactogenicity and primary immunogenicity of the mRNA-1273 vaccine administered in 2 doses, 28 days apart, in participants who have hematological malignancy and are immunosuppressed due to their disease and/or treatment or receiving a PD-1/PDL-1 inhibitor for treatment of a solid tumor can be associated with appropriately high rates of development of neutralizing antibodies of mRNA-1273. The trial will also evaluate the safety, reactogenicity and immunogenicity after administration of additional "booster" doses of the vaccine.

Study Phase: 2

Study Population: For the vaccine-naïve cohorts, up to 80 participants will be enrolled.

- 20 participants with solid tumor malignancies who have initiated PD1/PDL1 inhibitor therapy as part of standard of care and are deemed to have a stable regimen without the need for any immunosuppressive therapy or corticosteroids.
- 60 participants with leukemia, lymphoma, multiple myeloma and participants post-allogeneic stem cell transplant will be enrolled based on their perceived risk of immunosuppression.

For the previously-vaccinated (also known as "booster") cohorts, up to 140 participants will be enrolled for booster injections. All participants on the vaccine-naïve cohorts will have the option of receiving boosters; however, they will not count towards the maximum accrual goal for each of the booster groups. Note: All participants will be eligible to receive up to three (3) booster doses of vaccine on study.

- 20 participants with solid tumor malignancies who have initiated PD1/PDL1 inhibitor therapy as part of standard of care and are deemed to have a stable regimen without the need for any immunosuppressive therapy or corticosteroids.
- 20 participants with chronic lymphocytic leukemia who are not currently on any therapies
- 20 participants with chronic lymphocytic leukemia who are on BTK inhibitor therapy alone
- 30 participants with any CAR T Cell therapy for a hematologic malignancy
- 20 participants post-allogeneic stem cell transplant
- 20 participants with other hematologic malignancies
- Up to 10 participants with any solid tumor who are not otherwise eligible for any of the other cohorts

Number of Sites: 2

Description of Study Product or Intervention:

mRNA-1273 Injection (Drug Product) is an LNP dispersion containing a single mRNA sequence (Drug Substance) that encodes the SARS-CoV-2 S glycoprotein stabilized in the prefusion conformation. The mRNA-1273 Drug Substance is combined with a mixture of 4 lipids common to the Moderna 's mRNA vaccine platform: SM-102 (a custom-manufactured, ionizable lipid) and 3 commercially available lipids, cholesterol, DSPC, and PEG2000-DMG (https://doi.org/10.1038/s41587-020-00807-1). mRNA-1273 Injection is provided as a sterile solution for injection, white to off white dispersion in appearance.

Presentation: mRNA-1273 Injection is provided as a sterile solution for injection at a concentration of 0.2 mg/mL in 20 mM trometamol (Tris) buffer containing 87 mg/mL sucrose and 4.3 mM acetate, at pH 7.5. mRNA-1273 Injection is presented in 10R USP Type I borosilicate glass vials with PLASCAP vial seal containing a 20 mm FluroTec-coated plug stopper and has a 6.3 mL nominal fill volume. This vial may be used for more than one participant.

mRNA-1273 Injection must be stored frozen at -15°C to -25°C until thawed for use and then stored refrigerated at 2°C to 8°C for up to 30 days (once thawed it must not be refrozen)

Each dose of 100 mcg (0.5 mL) will be administered via IM injection into the deltoid muscle on Days 1 and 29 (+/- 3 days) for the vaccine-naïve cohorts. Up to 3 additional ("booster") doses of the vaccine may also be administered.

Study Objectives:

Primary:

- To evaluate the safety and reactogenicity of the mRNA-1273 vaccine administered in 2 doses, 28 days apart, in participants who have a hematological malignancy and are immunosuppressed due to their disease and/or treatment, or receiving a PD-1/PDL-1 inhibitor for treatment of a solid tumor for patients who are vaccine-naïve
- To evaluate the safety and reactogenicity of booster doses of mRNA-1273 vaccine administered to participants who have previously received an mRNA or alternative vaccine regimen
- To evaluate the safety and reactogenicity of booster doses of mRNA-1273 administered to participants with CLL who are either off treatment or are engaging in a 3-week BTK inhibitor interruption to enhance vaccine immunogenicity
- To assess the immunogenicity of mRNA-1273 in participants with cancer, as assessed by the titer or level of specific binding antibody (bAb)

Secondary:

- To evaluate the immunogenicity of the mRNA-1273 vaccine administered in 2 doses 28 days apart, as assessed by the titer or level of neutralizing antibody (nAb) in the vaccine-naïve cohorts
- To evaluate the immunogenicity of booster doses of mRNA-1273 vaccine administered to participants who have previously been vaccinated against SARS-CoV2 with any prior vaccine regimen. as assessed by the titer or level of neutralizing antibody (nAb)

Exploratory:

- To assess immune responses against the SARS-CoV-2 nucleocapsid and spike proteins
- To evaluate salivary measurement of IgG antibodies against the SARS-CoV-2 nucleocapsid and spike (S) proteins

Duration of Individual Participant Participation:	The duration for each individual participation is approximately 14 months (from first contact to last visit).
Study Duration:	Study duration is anticipated to be 16 months (from start of screening to last Participant/last visit).

Figure 1: Schematic of Study Design for Vaccine-Naïve Cohorts

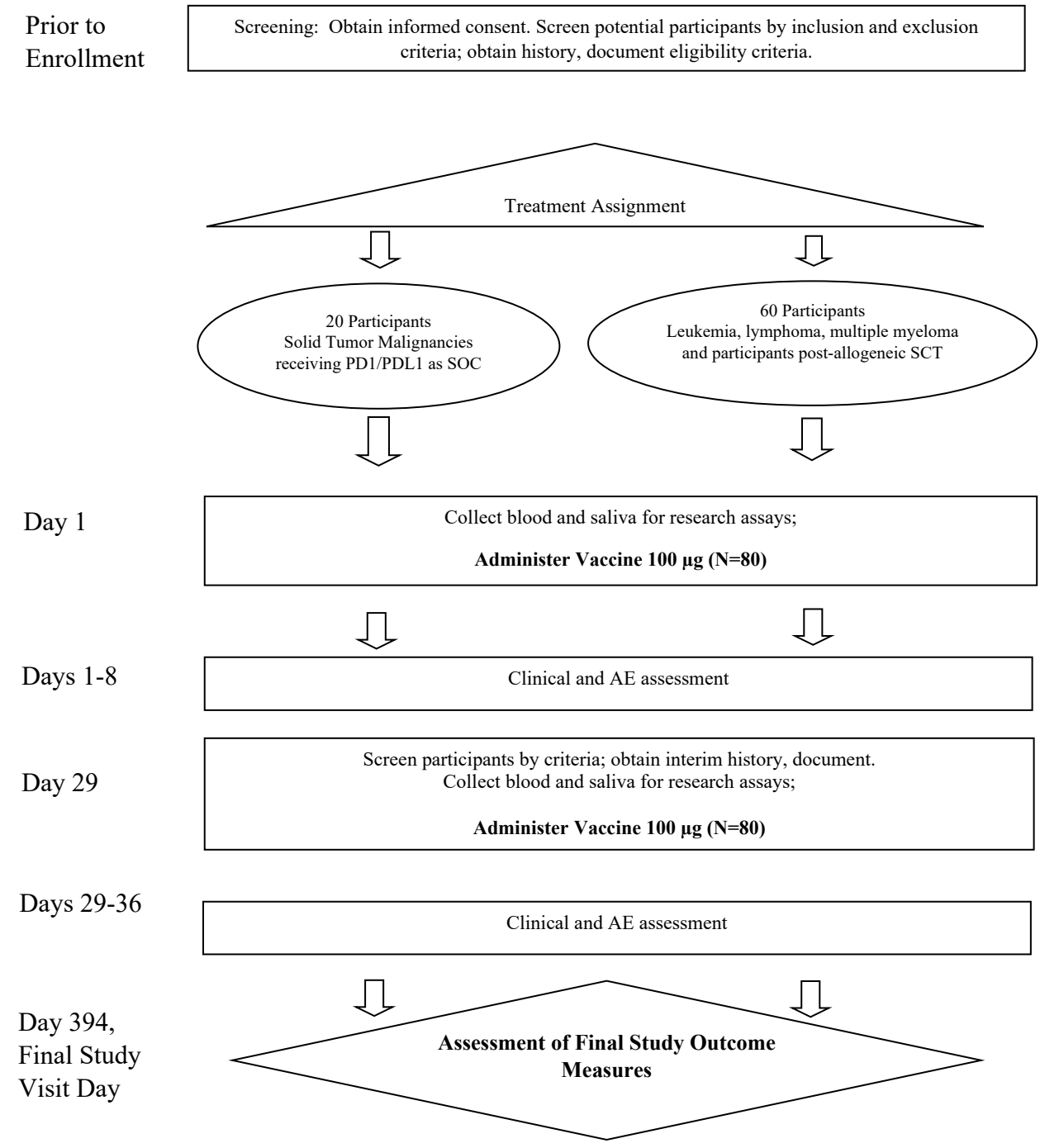
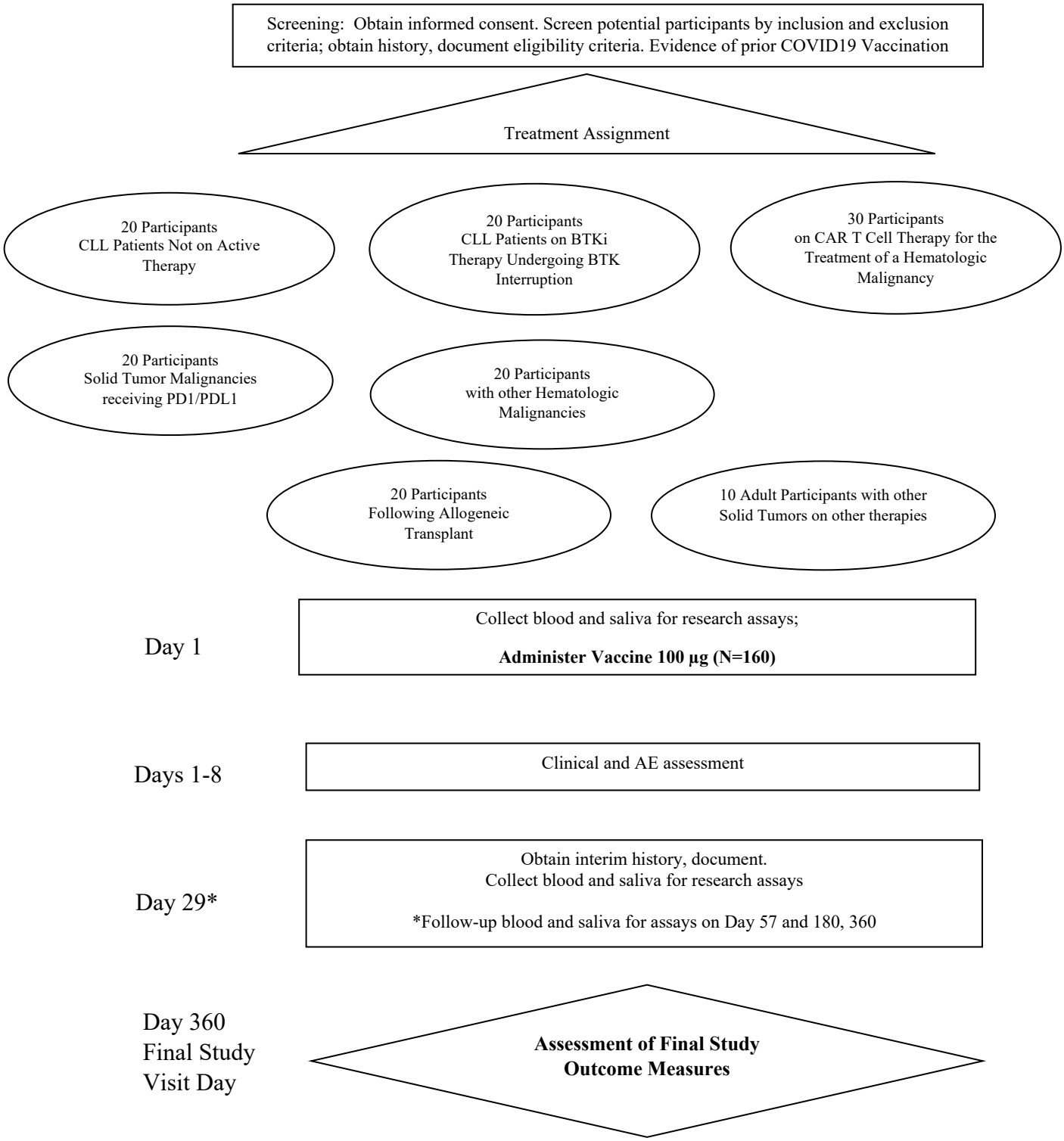


Figure 2: Schematic of Study Design for Booster Vaccine Cohorts



1 KEY ROLES

Lead Principal Investigator:	PPD Phone: PPD
Clinical Site:	National Institutes of Health Clinical Center 10 Center Drive Bethesda, MD 20814 Phone: 301-496-4000
Clinical Sites:	A limited number of participating sites within the US will be approved by the Sponsor and activated upon successful completion of regulatory requirements, including IRB approval.
Coordinating Center:	NIH National Cancer Institute Center for Cancer Research 10 Center Drive Bethesda, MD 20814
Data Management Center:	NIH National Cancer Institute Center for Cancer Research Building 82, 9030 Old Georgetown Rd Bethesda, MD 20814

2 BACKGROUND AND SCIENTIFIC RATIONALE

2.1 Background

In December 2019 the Wuhan Municipal Health Committee identified an outbreak of viral pneumonia cases of unknown cause. Coronavirus ribonucleic acid (RNA) was quickly identified in some of these participants. Per the World Health Organization (WHO), on January 5, 2020 there were 59 confirmed cases, 278 cases on January 20, rising to more than 110,000 confirmed cases and 3996 deaths as of March 9, 2020. As of December 20, 2020, the most recent figures available from the WHO suggest there were just over 75 million confirmed cases globally with over 1.68 million confirmed deaths (Source: https://www.who.int/emergencies/diseases/novel-coronavirus-2019). The WHO named the disease caused by the novel coronavirus COVID-19, and the virus causing the disease SARS-CoV2 to reflect its similarity to the genetic sequence of SARS-CoV, the virus that had previously caused Severe Acute Respiratory Syndrome (SARS) that was discovered in 2002.

On March 11, 2020, the WHO declared COVID-19 a pandemic. As of December 2020, two SARS-CoV-2 vaccines have received Emergency Use Authorization by the FDA. Despite the significant effort to deliver safe and effective vaccines, the COVID-19 pandemic has continued to overwhelm

health systems with its rapid spread across the globe. The lockdowns and other societal changes necessary to curb the spread of the disease have also triggered a severe economic crisis in the United States and globally.

In a May 12, 2020 virtual meeting of the NCI Board of Scientific Advisors, NCI Director Ned Sharpless was speaking about the pandemic, an excerpt from the discussion was provided by *The Cancer Letter* below (source: https://cancerletter.com/articles/20200515_3/):

"I'm becoming worried that, because of the pandemic, that in 2021 or 2022 or 2023, we will have the first Annual Report to the Nation since 1993 that shows an increase in cancer mortality," Sharpless said. "And I know exactly what the statistics will mean for participants. I know that that represents more cancer suffering and more bad outcomes, and more deaths."

In short, the COVID-19 pandemic threatens to undo years of progress in the reduction of cancer-specific mortality. Moreover, the negative consequences on the clinical and research enterprise of the NCI, academia, and industry appears to be incalculable but likely to negatively impact the core mission of the NCI for years to come. Therefore, there is an urgent public health need for rapid development and deployment of novel interventions.

2.2 Vaccine Development

ModernaTX, Inc. has developed a rapid response, proprietary messenger RNA (mRNA)-based vaccine platform. This is based on the principle and observations that antigens can be produced *in vivo* by delivery, uptake and expression of the corresponding mRNA by cells. ModernaTX, Inc. is using its mRNA-based technology to develop a novel lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine against SARS-CoV-2 (mRNA-1273). Prior preclinical studies have demonstrated that coronavirus spike (S) proteins are immunogenic and S protein-based vaccines, including deoxyribonucleic acid (DNA) and mRNA delivery platforms, are protective in animals. Prior clinical trials of vaccines targeting related coronaviruses and other viruses have demonstrated that DNA and mRNA-based vaccines are safe and immunogenic. It is therefore anticipated that mRNA-1273 will generate robust immune responses to the SARS- CoV-2 S protein [1].

This mRNA-based vaccine does not enter the cellular nucleus or interact with the genome, is nonreplicating, and expression is transient. Therefore, mRNA vaccines thereby offer a mechanism to stimulate endogenous production of structurally intact protein antigens in a way that mimics wild-type viral infection and are able to induce good immune responses against infectious pathogens such as cytomegalovirus (CMV) (NCT03382405), human metapneumovirus (hMPV) and parainfluenza virus type 3 (PIV3) (NCT03392389) and influenza virus (NCT03076385 and NCT03345043). The agent mRNA-1273 is a novel LNP mRNA-based vaccine that encodes for the full-length spike (S) protein of SARS-CoV-2, modified to introduce two proline residues to stabilize the S protein into a pre-fusogenic form.

The coronavirus spike S protein mediates attachment and entry of the virus into host cells, making it a primary target for neutralizing antibodies that prevent infection [2-10]. The NIH Vaccine Research Center (VRC) and collaborators have identified 2 proline mutations at the apex of the S2 central helix that stabilize the S protein in its prefusion conformation (S-2P) [11]. These mutations have been applied to 9 diverse coronaviruses from three coronavirus genera and found to stabilize

the prefusion conformation and improve protein expression. Since this mutation has consistently stabilized other beta-CoV S proteins, this mutation was applied to the SARS-CoV-2 S protein.

The VRC and collaborators found that the stabilized SARS-CoV-2 S-2P expressed well and is in the prefusion conformation based on negative-stain electron microscopy.

The S proteins of closely related betacoronavirus family members stabilized by the 2P mutation, including HKU1, Middle East Respiratory Syndrome (MERS), SARS, and WIV1, are potent immunogens in mice. In collaboration with ModernaTX, Inc, mRNA expressing the MERS S-2P protein sequence was produced and compared to mRNA expressing wild-type S protein. mRNA expressing the MERS S-2P protein was more immunogenic than mRNA expressing wild-type S protein, and mice immunized with a dose as low as 0.016 mcg of MERS S-2P mRNA had neutralizing activity above the threshold of protection in dipeptidyl peptidase 4 (hDPP4) mice and protected mice from MERS challenge. Based on the robust immunogenicity of the MERS S-2P mRNA vaccine in mice, the VRC and ModernaTX, Inc. designed mRNA expressing a membrane-anchored SARS-CoV-2 S protein stabilized with the 2P mutation. HEK293 cells transfected with mRNA expressing the SARS-CoV-2 S-2P protein successfully expressed the protein.

There is some clinical experience with vaccines targeting coronavirus S proteins. The first candidate DNA vaccine expressing SARS S protein was evaluated in 10 healthy adults age 21 to 49 years in 2004 and 2005 following a rapid vaccine development response to the SARS outbreak [12] . DNA vaccine at a dosage of 4 mg was administered IM by a Biojector needle free device at baseline, week 4 and week 8. The vaccine was safe and well tolerated. Local and systemic reactogenicity events were mild and transient. There were no SAEs and no grade 3 or 4 AEs. The SARS candidate vaccine was immunogenic as assessed by ELISA and pseudotyped lentiviral vector reporter neutralization assay following the first injection in most participants with peak response after the 3rd vaccination. Vaccine induced T cell responses as assessed by ICS and ELISPOT were detected in all participants [12].

Additionally, a candidate DNA vaccine expressing MERS S was evaluated in 75 healthy participants ages 19 to 50 years in 2016 [13] . In a dose escalation trial, DNA vaccine at a dosage of 0.67 mg, 2 mg or 6 mg was administered IM followed by electroporation at baseline, week 4 and week 12. Overall, the vaccine was safe and well tolerated. Local and systemic reactions were generally mild and transient. There were no SAEs or grade 3 or 4 laboratory abnormalities attributed to vaccination. The MERS candidate vaccine was immunogenic as assessed by seroconversion and vaccine induced T cell responses in most vaccine recipients[13].

2.3 Pre-clinical data of mRNA-1273

The expression of functional prefusion stabilized S-protein delivered by mRNA was evaluated in HEK293 cells (**Figure 3**).

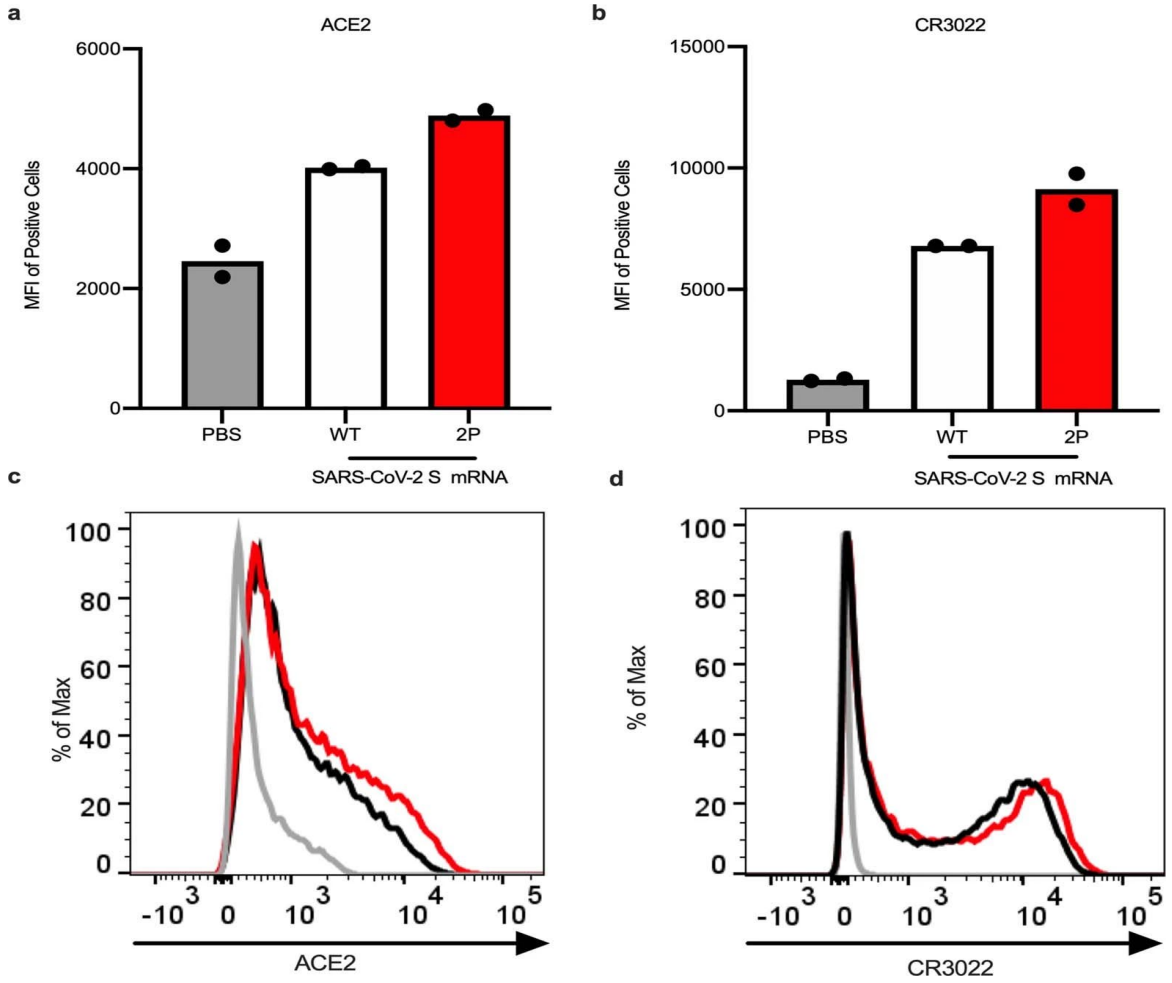


Figure 3: In vitro expression of SARS-CoV-2 spike mRNA on the cell surface.

a–d, 293T cells were transfected in duplicate with mRNA expressing SARS-CoV-2 wild-type spike (white bars, black lines) or S-2P (red), stained with ACE2 (a, c) or CR3022 (b, d), and evaluated by flow cytometry 24 post-transfection. Mock-transfected (PBS) cells served as a control (grey). (a, b) Data are presented as mean [14].

The expressed prefusion, stabilized S protein binds to the its proposed receptor, human ACE-2, and is recognized by cross reactive antibodies to SARS S protein. It is therefore anticipated that mRNA-1273 will generate robust immune responses to the SARS-CoV-2 S protein.

Preliminary clinical data from the mRNA-1273 phase I study indicates that all 45 participants tested at doses 25, 100 and 250 mcg demonstrated antibodies after one dose. After the second vaccination, serum-neutralizing activity was detected by two methods in all participants evaluated, with values generally similar to those in the upper half of the distribution of a panel of control convalescent serum specimens [15].

Recently reported data shows that mRNA-1273 induces both potent neutralizing antibody and CD8 T cell responses and protects against SARS-CoV-2 infection in the lung and nasopharyngeal tissue

of murine and non-human primates vaccinated, without any evidence of immunopathology. The results of this recent study are detailed hereafter. [16, 17]

Immunization with MERS S-2P mRNA/LNP elicited potent neutralizing activity down to a 0.1 µg dose and protected hDPP4 transgenic (288/330+/+21) mice against lethal MERS-CoV challenge in a dose-dependent manner, establishing proof-of-concept that mRNA expressing the stabilized S-2P protein is protective. Notably, the sub-protective 0.01 µg dose of MERS S-2P mRNA did not cause exaggerated disease following MERS-CoV infection, but instead resulted in partial protection against weight loss followed by full recovery without evidence of enhanced illness [16]

(Figure 4).

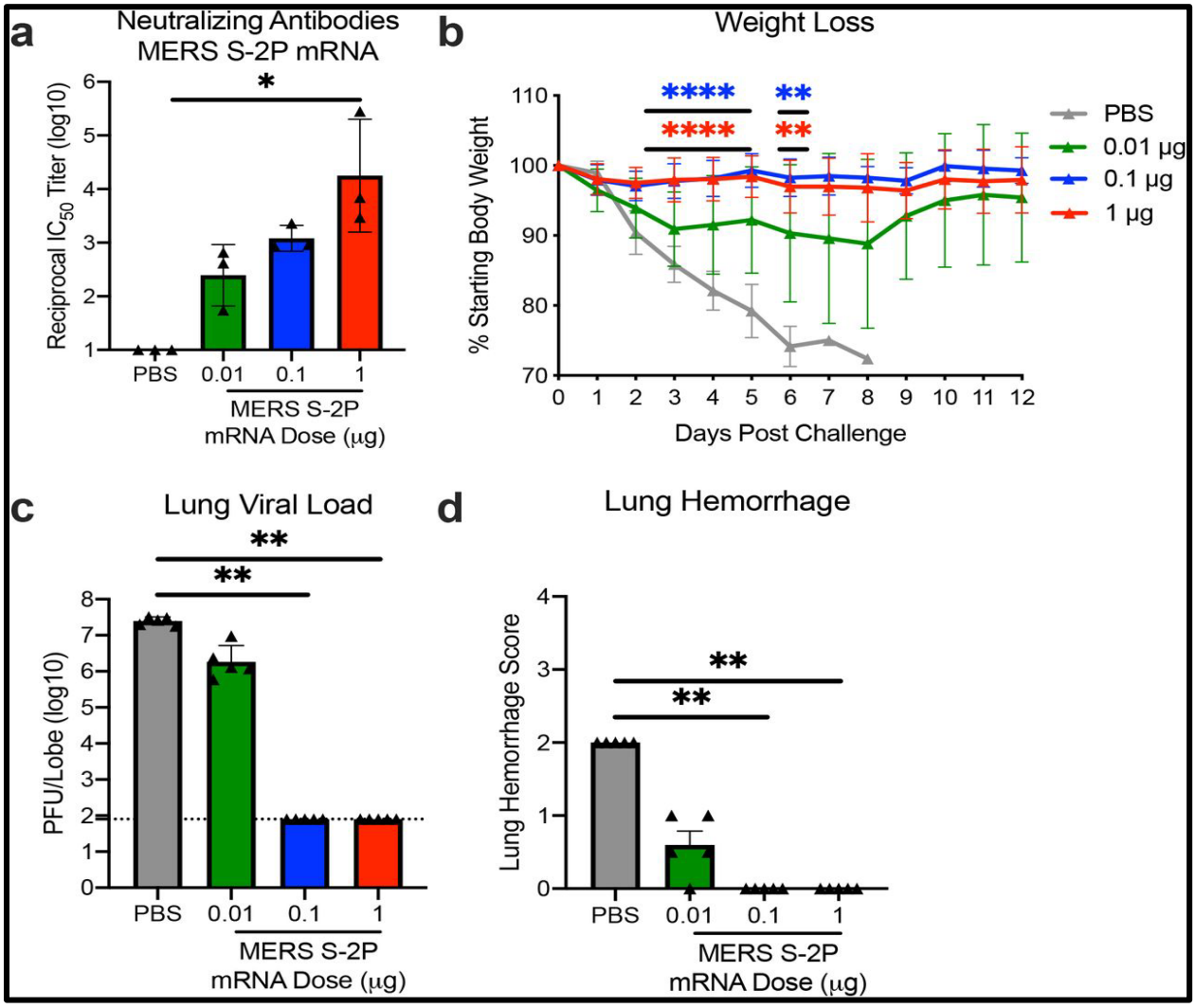


Figure 4: **MERS-CoV S-2P mRNA protects mice from lethal challenge.**

288/330+/+ mice were immunized at weeks 0 and 3 with 0.01 (green), 0.1 (blue), or 1 µg (red) of MERS-CoV S-2P mRNA. Mock-immunized mice were immunized with PBS (gray). Two weeks post-boost, sera were collected from 3 mice per group and assessed for neutralizing antibodies against MERS m35c4 pseudovirus (a). Four weeks post-boost, 12 mice per group were challenged

with a lethal dose of mouse-adapted MERS-CoV (m35c4). Following challenge, mice were monitored for weight loss (b). Two days post-challenge, at peak viral load, lung viral titers (c) and hemorrhage (0 = no hemorrhage, 4 = severe hemorrhage in all lobes) (d) were assessed from 5 animals per group. Dotted line = assay limit of detection. (a, c-d) All dose levels were compared. (b) For weight loss, all comparisons are against PBS-immunized mice.

Immunogenicity was assessed in six-week old female BALB/cJ, C57BL/6J, and B6C3F1/J mice by immunizing intramuscularly (IM) twice with 0.01, 0.1, or 1 µg of mRNA-1273 at a 3-week interval. mRNA-1273 induced dose-dependent S-specific binding antibodies after prime and boost in all mouse strains **(**Figure 5a-c**)**. Potent neutralizing activity was elicited by 1 µg of mRNA-1273, reaching 819, 89, and 1115 reciprocal IC_{50} geometric mean titer (GMT) for BALB/cJ, C57BL/6J, and B6C3F1/J mice, respectively **(**Figure 5d-f**)**.

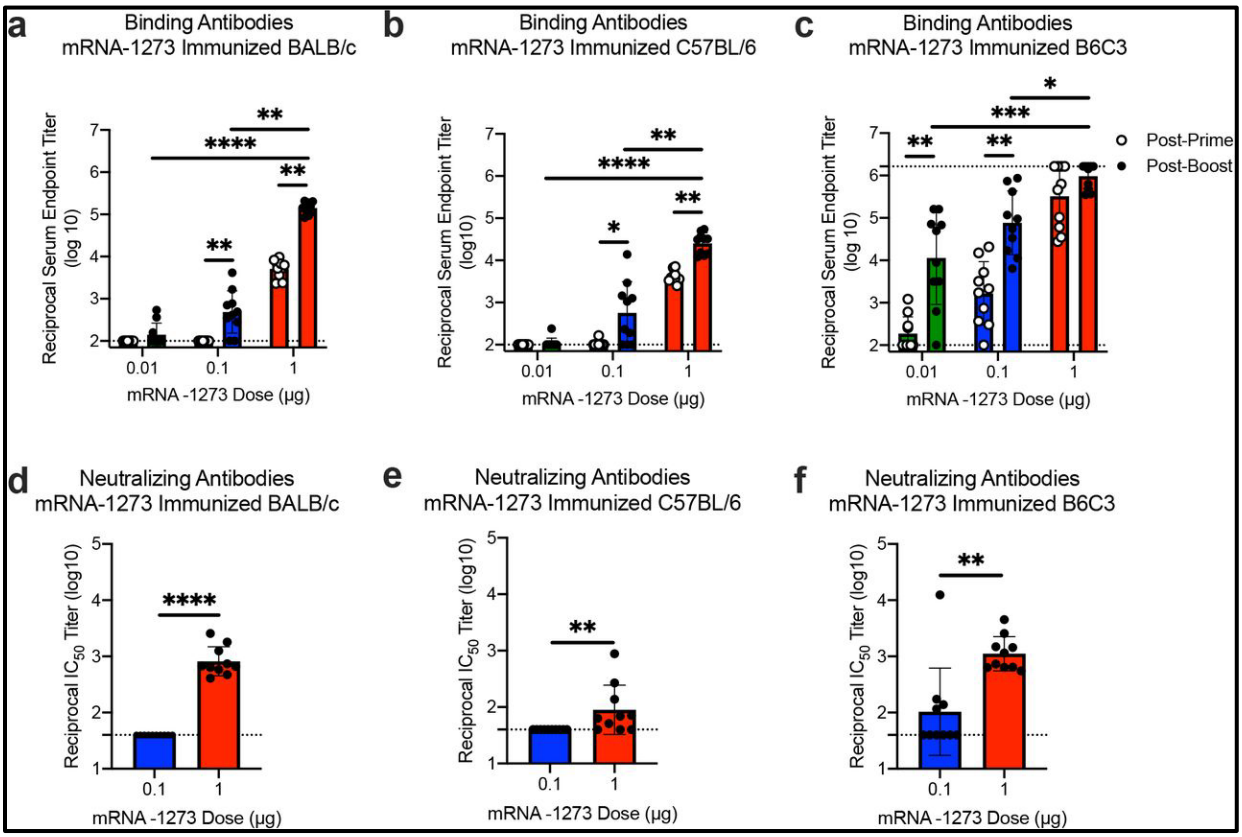


Figure 5: mRNA-1273 elicits robust binding and neutralizing antibody responses in multiple mouse strains.

BALB/cJ (a, d), C57BL/6J (b, e), or B6C3F1/J (c, f) mice were immunized at weeks 0 and 3 weeks with 0.01 (green), 0.1 (blue), or 1 µg (red) of mRNA-1273. Sera were collected 2 weeks post-prime (open circles) and 2 weeks post-boost (closed circles) and assessed for SARS-CoV-2 S-specific IgG by ELISA (a-c), and, for post-boost sera, neutralizing antibodies against homotypic SARS-CoV-2 pseudovirus (d-f). Dotted line = assay limit of detection. (a-c) Timepoints were compared within each dose level, and doses were compared post-boost.

Next, investigators evaluated the balance of Th1 and Th2, because vaccine-associated enhanced respiratory disease (VAERD) has been associated with Th2-biased immune responses in children immunized with whole-inactivated virus vaccines against RSV and measles virus [16]. A similar phenomenon has also been reported in some animal models with whole-inactivated SARS-CoV vaccines. Thus, the researchers first compared levels of S-specific IgG2a/c and IgG1, which are surrogates of Th1 and Th2 responses respectively, elicited by mRNA-1273 to those elicited by SARS-CoV-2 S-2P protein adjuvanted with the TLR4-agonist Sigma Adjuvant System (SAS). Both immunogens elicited IgG2a and IgG1 subclass S-binding antibodies, indicating a balanced Th1/Th2 response (**Figure 6**a-c). 7 weeks post-boost, the investigators also directly measured cytokine patterns in vaccine-induced memory T cells by intracellular cytokine staining (ICS); mRNA-1273-elicited CD4+ T cells re-stimulated with S1 or S2 peptide pools exhibited a Th1-dominant response, particularly at higher immunogen doses (**Figure 6**d-e). Furthermore, 1 µg of mRNA-1273 induced a robust CD8+ T cell response to the S1 peptide pool (**Figure 6**f-g). The Ig subclass and T cell cytokine data together demonstrate that immunization with mRNA-1273 elicits a balanced Th1/Th2 response in contrast to the Th2-biased response seen with S protein adjuvanted with alum, suggesting that mRNA vaccination avoids Th2-biased immune responses that have been linked to VAERD.

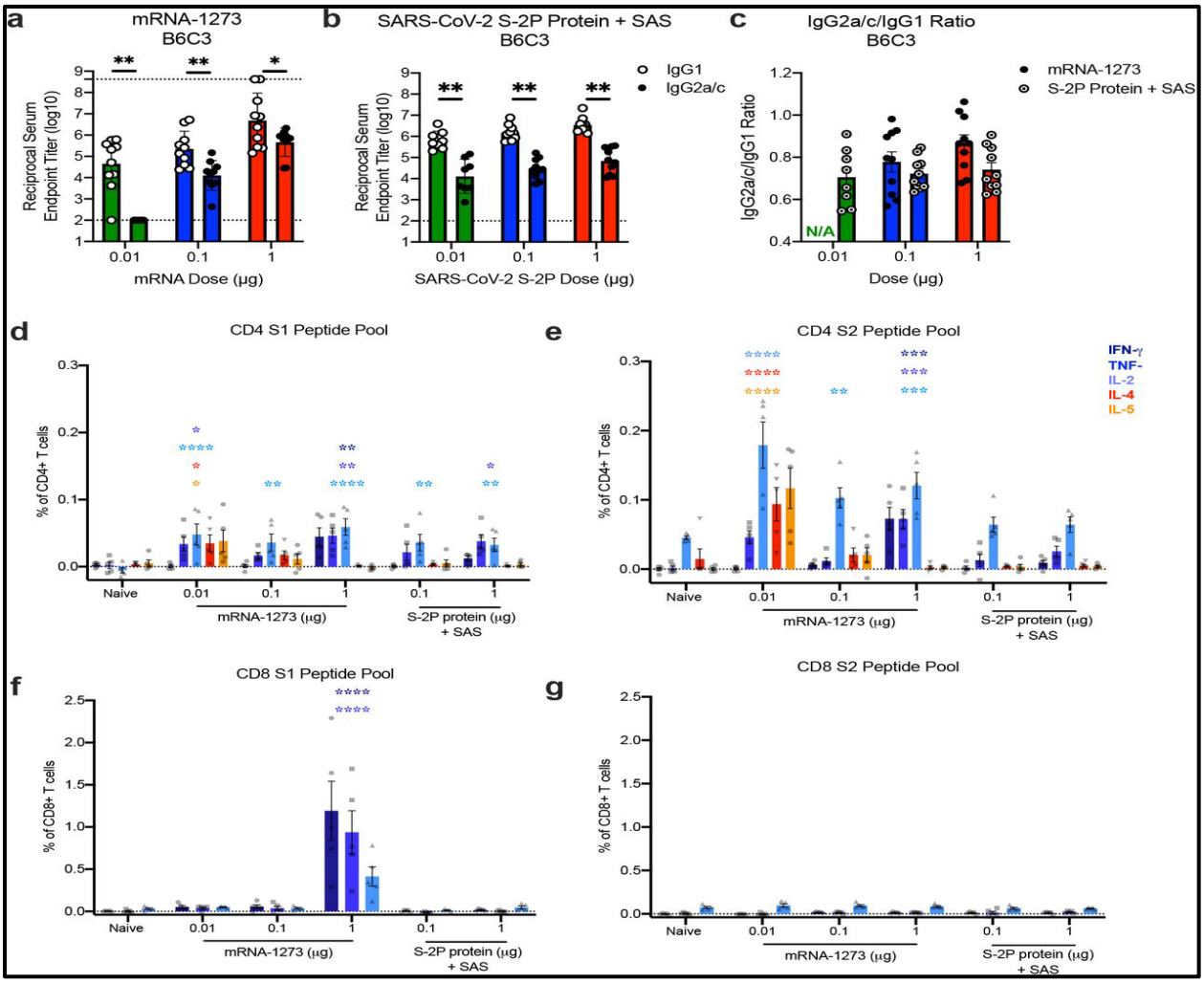


Figure 6: Immunizations with mRNA-1273 and S-2P protein, delivered with TLR4 agonist, elicit S-specific Th1-biased T cell responses.

B6C3F1/J mice were immunized at weeks 0 and 3 with 0.01, 0.1, or 1 μg of mRNA-1273 or SAS-adjuvanted SARS-CoV-2 S-2P protein. Sera were collected 2 weeks post-boost and assessed by ELISA for SARS-CoV-2 S-specific IgG1 and IgG2a/c. Endpoint titers (a-b) and endpoint titer ratios of IgG2a/c to IgG1 (c) were calculated. For mice for which endpoint titers did not reach the lower limit of detection (dotted line), ratios were not calculated (N/A). (d-g) Seven weeks post-boost, splenocytes were isolated from 5 mice per group and re-stimulated with no peptides or pools of overlapping peptides from SARS-CoV-2 S protein in the presence of a protein transport inhibitor cocktail. After 6 hours, intracellular cytokine staining (ICS) was performed to quantify CD4+ and CD8+ T cell responses. Cytokine expression in the presence of no peptides was considered background and subtracted from the responses measured from the S1 and S2 peptide pools for each individual mouse. (d-e) CD4+ T cells expressing IFN-γ, TNFα, IL-2, IL-4 and IL-5 in response to the S1 (d) and S2 (e) peptide pools. (f-g) CD8+ T cells expressing IFN-γ, TNF-α, and IL-2 in response to the S1 (f) and S2 (g) peptide pools. IgG1 and IgG2a/c (a-b) and immunogens (c) were compared at each dose level. (d-g) For each cytokine, all comparisons were compared to naïve mice.

Protective immunity was assessed in young adult BALB/cJ mice challenged with mouse-adapted (MA) SARS-CoV-2 that exhibits viral replication localized to lungs and nasal turbinates [18]. BALB/cJ mice that received two 1 μg doses of mRNA-1273 were completely protected from viral replication in lungs after challenge at a 5- **(Figure 7a)** . mRNA-1273-induced immunity also rendered viral replication in nasal turbinates undetectable in 6 out of 7 mice **(Figure 7b)**. Efficacy of mRNA-1273 was dose-dependent, with two 0.1 μg mRNA-1273 doses reducing lung viral load by ~100-fold and two 0.01 μg mRNA-1273 doses reducing lung viral load by ~3-fold **(Figure 7a)**. Of note, mice challenged 7 weeks after a single dose of 1 μg or 10 μg of mRNA-1273 were also completely protected against lung viral replication **(Figure 7c)**. Challenging animals immunized with sub-protective doses provides an orthogonal assessment of safety signals, such as increased clinical illness or pathology. Similar to what was observed with MERS-CoV S-2P mRNA, mice immunized with sub-protective 0.1 and 0.01 μg mRNA-1273 doses showed no evidence of enhanced lung pathology or excessive mucus production **(Figure 7d)**. In summary, mRNA-1273 is immunogenic, efficacious, and does not show evidence of promoting VAERD when given at sub-protective doses in mice.

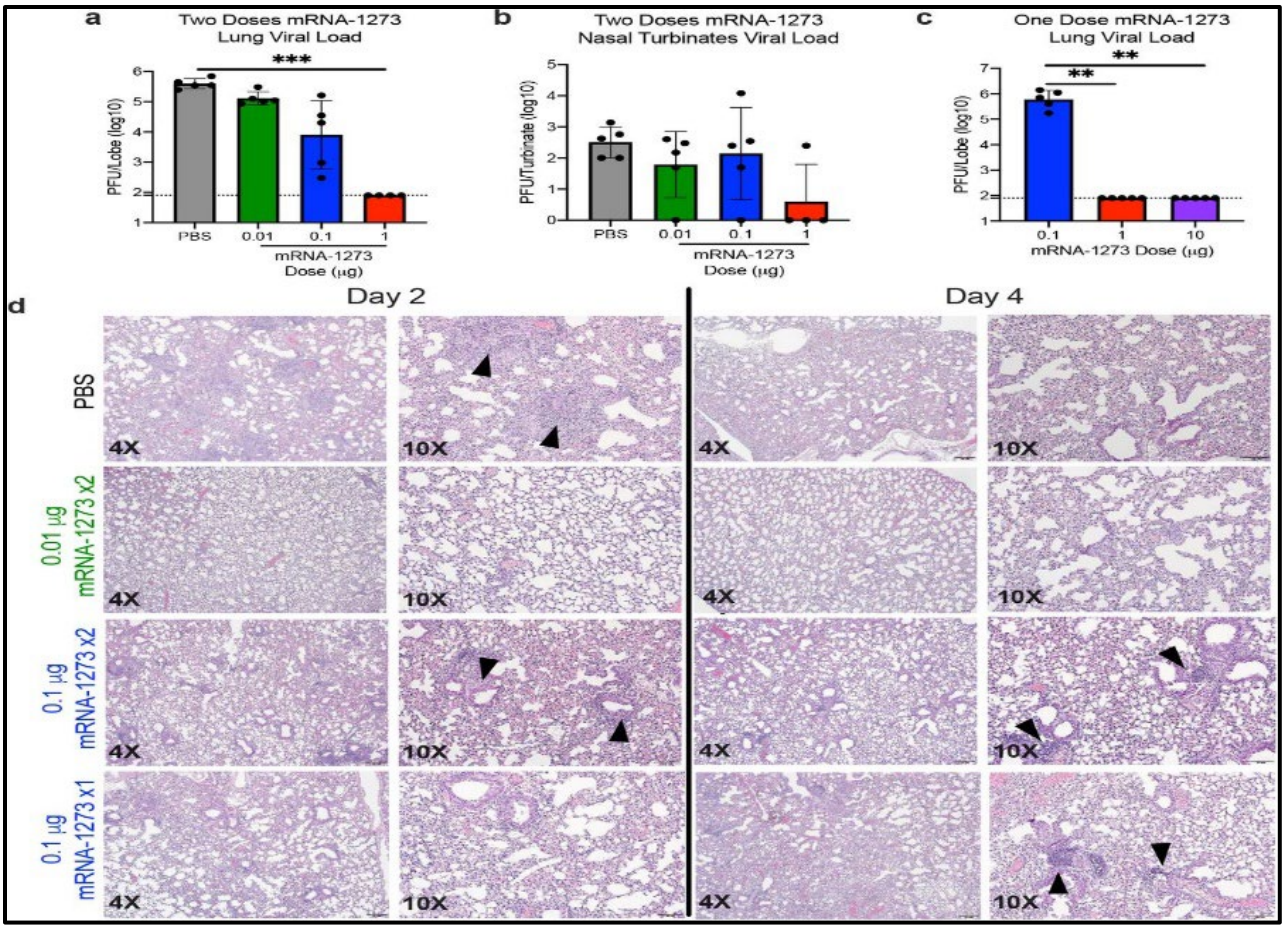


Figure 7: mRNA-1273 protects mice from upper and lower airway SARS-CoV-2 infection.

(a-b) BALB/cJ mice were immunized at weeks 0 and 3 with 0.01 (green), 0.1 (blue), or 1 µg (red) of mRNA-1273. Mock-immunized mice were immunized with PBS x2. Five weeks post-boost, mice were challenged with mouse-adapted SARS-CoV-2. (c) BALB/cJ mice were also immunized with a single dose of 0.1 (blue),1 (red), or 10 (purple) µg of mRNA-1273 and challenged 7 weeks post-immunization. Two days post-challenge, at peak viral load, mouse lungs (a,c) and nasal turbinates (b) were harvested from 5 mice group for analysis of viral titers. Dotted line = assay limit of detection. (d) At day 2 and 4 post-challenge, lungs from 5 mice per group were fixed in 10% formalin, paraffin-embedded, cut in 5 µm sections, and stained with hematoxylin and eosin. Photomicrographs (4X and 10X) are representative of lung sections from groups of mice in which virus infection was detected. At day 2, lungs from mock-immunized mice demonstrated moderate to severe, predominantly neutrophilic, inflammation that was present within, and surrounding, small bronchioles (arrowheads); the surrounding alveolar capillaries were markedly expanded by infiltrating inflammatory cells. In the 0.01 µg two-dose group, inflammation was minimal to absent. In the 0.1 µg two-dose group, occasional areas of inflammation intimately associated with small airways (bronchioles) and their adjacent vasculature (arrowheads) were seen, primarily composed of neutrophils. In the single-dose 0.1 µg group, there were mild patchy expansion of the alveolar septae by mononuclear and polymorphonuclear cells. At day 4, lungs from mock-immunized mice exhibited moderate to marked expansion of the alveolar septae (interstitial pattern) with decreased prominence of the adjacent alveolar spaces. In the 0.01 µg two-dose

group, inflammation was minimal to absent. Lungs in the 0.1 µg two-dose group showed mild, predominantly lymphocytic inflammation, intimately associated with bronchioles and adjacent vasculature (arrowheads). In the single-dose 0.1 µg group there was mild, predominantly lymphocytic, inflammation around bronchovascular bundles (arrowheads).

2.4 Scientific Rationale

2.4.1 Purpose of Study

While the need for a safe and effective vaccine is a priority for the protection of global health, there has been little attention paid to the effectiveness of a vaccine in the most vulnerable populations. Participants in these vulnerable populations are thought to be at heightened risk of severe COVID19-related complications, and the public health guidance recommend prolonged social distancing measures and enhanced isolation and quarantine procedures to the greatest extent possible. There is a need for the rapid vaccination of nearly the entire global population, but there remains a significant question as to what the proper distribution of these vaccines may be. If cancer participants undergoing treatment are deemed to be unlikely to mount an immune response to vaccines, then the most appropriate public health decision would be to continue to isolate this vulnerable population until herd immunity is achieved in their respective communities.

If, however, in spite of their treatments, cancer participants are deemed to be immune-competent and able to form neutralization of the receptor binding domain of the S protein of SARS-CoV2, then this vulnerable population should be prioritized to urgently receive effective vaccines in order to minimize suffering and death from COVID-19. As the modern era of cancer therapeutics has never co-existed with a major global pandemic, the urgency of the response of the cancer patient to vaccination is a significant question of public health importance to our community of participants, providers, academics, and our colleagues in industry.

2.4.2 Study Population

Cancer participants are presumed to be at increased risk from COVID-19 infection fatality due to underlying malignancy, treatment-related immunosuppression, or increased number of comorbidities. In a recent report by Xia Y et al, participants with cancer (n=18) had higher risk of severe events (invasive ventilation or death) compared with non-cancer participants (n=1572) with COVID-19: 39% versus 8% [19] The majority of these 18 cancer participants were in “remission” or in long-term follow-up. Among the 4 participants with chemotherapy or surgery within the past month, three had a severe event.

In a recently published study from a New York Health system a total of 218 participants with malignancies with COVID-19 were identified [20]. Case fatality rates were 2-3 times the age-specific percentages seen in non-cancer population in the same academic center and in the greater New York City area for all COVID-19 participants. A total of 61 (28%) cancer participants died from COVID-19 with a case fatality rate (CFR) of 37% (20/54) for hematologic malignancies and 25% (41/164) for solid malignancies. Myeloid malignancies such as Myelodysplastic syndromes (MDS), Acute myeloid leukemia (AML) and Myeloproliferative neoplasms (MPN) showed a trend for higher mortality compared to lymphoid neoplasms Non-Hodgkin Lymphoma (NHL), Chronic lymphocytic leukemia (CLL), Acute lymphocytic leukemia (ALL), Multiple Myeloma (MM) and Hodgkin Lymphoma (HL). Rates of ICU admission and ventilator use were slightly higher for

hematologic malignancies than solid tumors (26% vs 19% and 11% vs 10%, respectively), but this did not achieve statistical significance. The authors noted that participants with hematologic malignancies tend to be treated with more myelosuppressive therapy and are often severely immunocompromised due to underlying disease.

2.4.3 Rationale for Booster Doses of Vaccine

Decreased immune responses in patients with malignancies create a need to identify improved vaccination strategies for this vulnerable population. One approach involves repeat 'booster' vaccinations. Previous studies investigating booster vaccinations with the influenza vaccine have produced disappointing results in CLL and after allogeneic stem cell transplant[21, 22]. However, booster vaccinations appear to be effective in certain immunocompromised populations, including after solid organ transplant or in plasma cell dyscrasias [23, 24]. Importantly, it is unknown whether booster vaccinations with novel adjuvanted vaccines will be able to increase immunogenicity in patients with hematologic malignancies, particularly in patients receiving cancer directed oral targeted therapy or CAR T cell therapy. In order to determine whether booster vaccinations can improve seroconversion rates, booster vaccinations will be offered to subjects who have completed a standard vaccine series. For the purpose of this study, patients will receive booster doses of mRNA-1273 regardless of their serologic status.

All patients who receive booster vaccinations may benefit from enhanced and prolonged immunogenicity, which will be measured for all cohorts enrolled.

2.4.4 Rationale for Booster Doses for Patients on CAR T Cell Therapies for B Cell Malignancies

The development of CARTx for B cell malignancies is a major milestone in cancer treatment. However, CARTx recipients are at high risk for infectious complications due to prior anti-tumor treatments and the immune-related adverse event (irAE) of prolonged B cell depletion from on-target/off-tumor side effects.

The goals of the currently funded U01 grant within the Cancer Moonshot PI-DDN (U01 CA247548-01) are to define the humoral irAEs related to B cell depletion by studying the effects of CD19- and BCMA-targeted CARTx on pre-existing and de novo pathogen-specific immunity. We will determine the proportion of adults with seroprotection to vaccine-preventable and other infections, and how these findings change over time, in a prospective cohort study. In addition, we will perform an observational study of patients who are receiving routine vaccinations after CARTx to define the frequency and correlates of vaccine responses.

SARS-CoV-2 has rapidly emerged as a major cause of morbidity and mortality in patients treated with cellular therapies. An analysis of 318 HCT patients with SARS-CoV-2 infection reported to the CIBMTR demonstrated an ~30% probability of death within 30 days after infection in autologous and allogeneic HCT recipients. Similar rates are described after CARTx, many of whom do not generate humoral immune responses.

There are no data pertaining to the immunogenicity of SARS-CoV-2 vaccines in CARTx recipients. Given B-cell deficits after CARTx, rates of seroconversion after SARS-CoV-2 vaccination are anticipated to occur in 40-60% based on the range of routine vaccination response rates in similar contexts, preliminary data generated by our group after influenza vaccination, and

findings using mRNA vaccines in solid organ transplant recipients [25, 26].Various strategies (e.g., additional or higher doses) have been employed to increase other vaccine responses in immunocompromised patients and is standard of care for hepatitis A and B, for example.

2.4.5 Rationale for Interruption of BTK Inhibitor Therapy at time of Booster Vaccination (Applicable only to CLL patients on BTK Inhibitor Therapy)

A prior study performed by the NHLBI Lymphoid Malignancies Section investigated the recombinant Hepatitis B vaccine (HEPLISAV-B) in patients with CLL that were treatment naïve or receiving continuous Bruton tyrosine kinase inhibitor (BTKi) treatment [27]. An analysis of 58 patients revealed that only 1 of 26 (3.8%) patients on continuous BTKi achieved a serologic response (anti-HBs titers >10 mIU/ml), compared to 9 of 32 (28.1%) treatment naïve CLL patients achieving a response. Similar findings were confirmed in a more recent study investigating the Pfizer-BionTech COVID-19 vaccine in patients with CLL; only 16% (n=8 of 50) of patients receiving a BTKi developed a serologic response, compared to 55% (n=23 of 58) of treatment naïve CLL patients [28]. We therefore conclude, in keeping with the biologic role of BTK, that a de novo humoral immune response is severely impaired with continuous BTKi therapy. Given the clinical benefit of long-term continuous therapy with BTKi, [29] and the widespread use of this class of drugs, this study aims to test whether vaccination during a drug holiday could improve serologic responses. Specifically, in one of the CLL treatment arms, we plan to hold BTKi therapy up to 3 weeks at a time (see Section **4.6**).

The duration of drug holding is based on our previous data on the rate of recovery of BTK function after drug withdrawal [30] Up to ~10-15% of BTK is replaced by de novo synthesis per day in CLL patients; thus after 7 days of drug holding, we estimate that signaling pathways will reactivate. After vaccination or infection, antibody titers become detectable within approximately 10 days [31, 32] Accounting for a possible delayed immune response in patients with hematologic malignancies, we expected that holding BTKi treatment for approximately 2 weeks after vaccination is sufficient for an immune response.

We consider that drug holding has no adverse effects on patient outcome. In clinical practice, dose interruptions are commonly performed. In particular, holding BTKi treatment for 3-7 days prior to and after invasive procedures is recommended by the ibrutinib package insert in order to reduce the risk of bleeding complications. While one retrospective analysis reported that ibrutinib dose reductions or interruptions were associated with inferior progression free survival (PFS), these dose interruptions were made in patients who had only recently started ibrutinib (median treatment duration 9 months). Furthermore, some of the progression events were transient in nature, as evidenced by a significant number of patients (n=11; 42%) achieving favorable responses upon resumption of therapy [33] In our series of patients treated at the NIH, medically indicated dose interruptions of BTKi treatment did not negatively impact long-term outcomes [34] In order to minimize risk for patients and ensure their disease is well controlled, we plan to allow interruption of BTKi treatment around the time of vaccination only in patients that are clinically stable and have received BTKi therapy for at least 6 months prior to vaccination.

Achieving vaccine responses in CLL patients is clinically beneficial as this is a high-risk group for infection related morbidity and mortality. COVID-19 brings this issue to the forefront, as reported mortality is exceptionally high in CLL patients (up to 33%). [35]In summary, available evidence

suggests that the potential benefits of achieving seroprotection following vaccination outweighs the risks of undergoing a brief BTKi treatment break.

2.5 Potential Risks and Benefits

2.5.1 Potential Risks

The potential risks of participating in this trial are those associated with having blood drawn, the IM injection, possible reactions to mRNA-1273, and breach of confidentiality.

Blood Draw: Drawing blood may cause transient discomfort and fainting. Fainting is usually transient and managed by having the Participant lie down and elevate his/her legs. Bruising at the blood draw site may occur but can be prevented or lessened by applying pressure to the blood draw site for a few minutes after the blood is taken. IM injection may also cause transient discomfort and fainting. Drawing blood and IM injection may cause infection. The use of aseptic (sterile) technique will make infection at the site where blood will be drawn or where the vaccination will be given extremely unlikely.

Electrocardiogram (ECG): Other than possibly experiencing some minor skin irritation from the electrodes, there are no anticipated risks related to complete the electrocardiogram and/or the echocardiogram

Anaphylaxis: Immediate systemic allergic reactions (e.g., anaphylaxis) can occur following any vaccination. These reactions are very rare and are estimated to occur once per 450,000 vaccinations for vaccines that do not contain allergens such as gelatin or egg protein. As a precaution, all participants will remain under observation at the study site for at least 15 minutes after vaccination. Vasovagal syncope (fainting) can occur before or after any vaccination, is usually triggered by the pain or anxiety caused by the injection and is not related to the substance injected. Therefore, it is important that standard precautions and procedures be followed to avoid injury from fainting.

Intramuscular injection with other mRNA vaccines manufactured by Moderna, Inc., containing the SM-102 lipid formulation commonly results in a transient and self-limiting local inflammatory reaction. This typically includes pain, erythema (redness), or swelling (hardness) at the injection site, which are mostly mild-to-moderate in severity and usually occur within 24 hours of vaccination. More severe, but self-limited, local reactions, erythema and induration, have been observed at dose of mRNA-1273 exceeding the dose proposed in this study. As with other IM injections, the Sponsor's COVID-19 vaccines should be given with caution in individuals with bleeding disorders, such as hemophilia, or individuals currently on anticoagulant therapy, to avoid the risk of hematoma following the injection.

There have been very rare reports of myocarditis and pericarditis occurring after vaccination with COVID-19 mRNA vaccines. Myocarditis and pericarditis have been reported in greatest numbers in males under the age of 40 years following a second dose of mRNA vaccines, but cases have been reported in older males and in females as well, and also following other doses. The observed risk is highest in males 12 to 17 years of age. While some cases required intensive care support, available data from short-term follow-up suggest that symptoms resolve in most individuals with conservative management. Information is not yet available about potential long-term sequelae. The risk in children younger than 12 years old is currently being assessed, and both the size of the

database and length of follow-up in this population are relatively smaller than that of those older than 12 years old. Therefore, the characterization of the risk in pediatric populations is not as well-known as in adolescents and adults.

Most systemic adverse events observed after vaccination do not exceed mild-to-moderate severity. The most commonly reported systemic adverse reactions (ARs) are anticipated to be fever, fatigue, chills, headache, myalgias and arthralgias. More severe reactions, including erythema, induration, fever, headache and nausea, were reported after receiving doses of mRNA-1273 that were greater than the dose proposed for use in this study. In all cases, the reactions resolved spontaneously.

Laboratory abnormalities (including increases in liver functional tests and serum lipase levels) following vaccination were observed in clinical studies with similar mRNA-based vaccines. These abnormalities were without clinical symptoms or signs and returned toward baseline (Day 1) values over time. The clinical significance of these observations is unknown. Further details are provided in the current IB.

If COVID-19 mRNA vaccines are administered to immunocompromised persons, including those receiving immunosuppressive therapy, the immune response may be diminished. The administration of a third vaccine dose (0.5 mL) appears to be only moderately effective in increasing antibody titers. Patients should be counseled to maintain physical precautions to help prevent COVID-19. In addition, close contacts of immunocompromised persons should be vaccinated as appropriate for their health status.

There is a theoretical risk that active vaccination to prevent the novel viral infection caused by SARS-CoV-2 may cause a paradoxical increase in the risk of disease. This possibility is based on the rare phenomenon of vaccine-associated disease enhancement which was first seen in the 1960s with 2 vaccines made in the same way (formalin-inactivated whole virus) and designed to protect children against infection with RSV [36] or measles [37]. Disease enhancement has also been proposed as a possible explanation for cases of more serious disease associated with dengue vaccination [38]. It is not known if mRNA-1273 will increase the risk of enhanced disease.

Preclinical studies demonstrated that mRNA-1273 is immunogenic in all species assessed, showing a dose-dependent response in IgG binding antibody titers and a significant correlation between binding and neutralizing antibody activity. In addition, antigen-specific T-cell responses were observed in studies in mice and in the NHP study. Th1-directed CD4 and CD8 T-cell responses were measured post-boost in animals that were vaccinated with mRNA-1273 [14] [17]. Direct measurement of Th1-directed responses in mice and NHPs, indirect measurement of IgG2a/c/IgG1 antibody subclasses in mice, and the high levels of neutralizing antibody in all species lessens concerns regarding disease enhancement associated with administration of mRNA-1273.

The effects of 2019-nCov Vaccine on the developing human fetus are unknown so pregnant women are excluded from this study. Breastfeeding women are excluded because there is an unknown potential risk for adverse events in nursing infants secondary to treatment of the mother with 2019 nCov Vaccine. These potential risks may also apply to other agents used in this study.

2.5.2 **Potential Benefits**

There may be direct known benefit to the participants.

There is potential benefit to society resulting from insights gained from participation in this study due to the emerging threat of the SARS-CoV-2 outbreak. However, study results from the Moderna-sponsored phase 3 trial of mRNA-1273 have been released and submitted to the FDA for Emergency Use Authorization, which was granted on December 18, 2020.

Data from preclinical and clinical studies indicate that the known and potential benefits of the Moderna COVID-19 Vaccine outweigh the known and potential risks of the vaccine. In the Phase 1 and 2 clinical studies, a consistent dose response was observed across age groups by several measures of humoral immunogenicity for both binding and neutralizing antibodies. The prespecified primary efficacy results from the phase 3 trial of mRNA01273 (also known as Study 301) in more than 15,181 adult recipients of mRNA-1273 and 15,170 recipients of placebo (N=30,351) demonstrated vaccine efficacy (VE) of 94.1% (95% CI: 89.3%, 96.8%) for the prevention of symptomatic confirmed COVID-19 ($p < 0.0001$). This finding is based on 196 adjudicated cases1 that occurred at least 14 days after the second vaccination (11 cases in the mRNA-1273 arm and 185 in the placebo arm). The mRNA-1273 safety profile in Study 301 has been characterized based on a dataset including 8 weeks median exposure, demonstrating a positive benefit-risk profile that supports broad public use. The lower limit of the 95% CI for VE was 89.3%, which surpassed the prespecified lower limit of greater than 30%.

Of note, study investigators were also able to demonstrate that mRNA-1273 was also highly effective against severe COVID-19, with no cases of severe COVID-19 occurring in the mRNA-1273 group and 30 cases in the placebo group within 14 days of the second injection at the time of the primary analysis.

Evaluation of additional secondary efficacy analyses were consistent with the primary efficacy analyses. mRNA-1273 was effective against COVID-19 regardless of prior SARS-CoV-2 infection, using a less restrictive definition of COVID-19, and considering all cases of symptomatic COVID-19 disease starting 14 days after the first injection. The efficacy of mRNA-1273 was consistent across major demographic and baseline characteristic subgroups at increased risk for severe COVID-19 infections and death.

To be enrolled in Study 301, female subjects of childbearing potential had to have a negative pregnancy test at enrollment and agree to use effective contraception until at least 3 months after the final vaccination. Details of all pregnancies in female participants are being collected from first day of dosing until study completion. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) were considered SAEs.

To date, thirteen pregnancies were reported in Study 301, with 6 pregnancies occurring in the mRNA-1273 group and 7 pregnancies occurring in the placebo group. As of December 2, 2020, 10 of the 13 pregnancies were ongoing with no reported complications. One participant (placebo group) experienced spontaneous abortion at approximately 7 gestational weeks; this SAE was considered not related to the IP. One participant in the placebo group had an elective abortion at approximately 6 gestational weeks; this SAE was considered not related to the IP. One participant in the placebo group was lost to follow-up, and the pregnancy outcome is unknown. Currently, there are no reports of spontaneous abortion, fetal death, stillbirth, congenital anomalies, or ectopic pregnancy in the mRNA-1273 group. As noted, all of the reported pregnancies in the vaccine group are ongoing.

3 STUDY DESIGN, OBJECTIVES AND ENDPOINTS OR OUTCOME MEASURES

3.1 Study Design Description

This is an open-label, multicenter clinical trial designed to evaluate the safety, reactogenicity and primary immunogenicity of the novel LNP-encapsulated mRNA-based vaccine that encodes for a full-length, prefusion stabilized spike (S) protein of SARS-CoV-2 manufactured by ModernaTX, Inc. in a specific population of patients with either hematologic malignancies under active treatment or patients with solid tumors who are undergoing treatment with PD1/PDL1 inhibitors.

For the vaccine-naïve cohorts, the vaccine will be administered in 2 doses, 28 days apart. Up to 80 participants will be enrolled into one of four vaccine-naïve cohorts. Participants will receive an IM injection (0.5 mL) of mRNA-1273 on Day 1 and Day 29 in the deltoid muscle and will be followed through 12 months post second vaccination (Day 394).

For the booster-vaccine cohorts, the booster vaccine will be administered in a single dose. Up to 120 participants will be enrolled into one of 6 booster-vaccine cohorts. Participants will receive an IM injection (0.5 mL) of mRNA-1273 on Day 1 in the deltoid muscle and will be followed through 12 months post vaccination (Day 360). For participants who choose to receive an additional (second) booster dose of the vaccine, the second booster dose of mRNA-1273 must be administered at least 4 weeks after their previous dose of the vaccine. Similarly, for participants who choose to receive a third booster dose of the vaccine, the third booster dose of mRNA-1273 must be administered at least 4 weeks after their previous dose of the vaccine. Note: Participants may enroll on this study only to receive a second or a third booster dose and will be counted/analyzed in the identified booster-vaccine cohorts.

Participants initially enrolled in the vaccine naïve cohort will also have the option to receive the first booster dose no less than 4 weeks after their second dose; with the similar option for a second or third booster on the same schedule as the booster-vaccine cohorts. If they choose to receive this, they will adhere to the booster vaccine calendar and will be analyzed also as part of the booster vaccine group.

Safety data will be reviewed by the assigned Safety Monitoring Committee (SMC) as explained in section **8.10.1.**

3.2 Study Objectives and Endpoints

Objectives and Endpoints	
Primary Objective	**Primary Endpoints**
Safety Objective: To evaluate the safety and reactogenicity of the mRNA-1273 vaccine administered in 2 doses 28 days apart, in participants who have a	**Safety Endpoints:** • Solicited local and systemic Adverse Reactions (ARs) through 7 days after each injection.

Objectives and Endpoints	
Primary Objective	**Primary Endpoints**
hematological malignancy and are immunosuppressed due to their disease and/or treatment, or receiving a PD-1/PDL-1 inhibitor for treatment of a solid tumor for participants who are vaccine- naïve. To evaluate the safety and reactogenicity of booster doses of mRNA-1273 vaccine administered to participants with cancer who have previously received an mRNA or alternative vaccine regimen	• Unsolicited AEs through 28 days after each injection. • SAEs throughout the entire study period. • Vital sign measurements and physical examination findings.
Immunogenicity Objective: To assess the immunogenicity of mRNA-1273 in participants with cancer, as assessed by the titer or level of specific binding antibody (bAb)	**Immunogenicity Endpoints:** • Titer or level of specific binding antibody (bAb), in participants • Titer or level of SARS-CoV-2-specific binding antibody (bAb) measured by ELISA on Day 1, Day 29, Day 36, Day 57 Day 209 and Day 394 for participants on Vaccine-Naïve Cohorts • Titer or level of SARS-CoV-2-specific binding antibody (bAb) measured by ELISA on Day 1, Day 29, Day 180, Day 360 for participants on Booster Vaccine Cohorts

Secondary Objective	**Secondary Endpoints**
To evaluate the immunogenicity of the mRNA-1273 vaccine administered, as assessed by the titer or level of neutralizing antibody (nAb).	For Vaccine-Naïve Cohorts: • Titer or level of SARS-CoV-2-specific neutralizing antibody (nAb) on Day 1, Day 29, Day 36, Day 57, Day 209, and Day 394 • Seroconversion due to vaccination on Day 29, Day 36, Day 57, Day 209, and Day 394 measured as: • For subjects with no detectable antibody titer (<

Secondary Objective	Secondary Endpoints
	LOD) at baseline: post-vaccination titer ≥ LLOQ • For subjects with a positive baseline titer (> LOD): post-vaccination titer ≥ 4 times the LLOQ • For subjects with a baseline titer ≥ LLOQ: post-vaccination titer ≥ a 4-fold rise compared with baseline titer For Booster Cohorts: • Titer or level of SARS-CoV-2-specific neutralizing antibody (nAb) on Day 1, Day 29, Day 57, Day 180, and Day 360 • Seroconversion due to vaccination on Day 29, Day 36, Day 57, Day 180, and Day 360 measured as: • For subjects with no detectable antibody titer (< LOD) at baseline: post-vaccination titer ≥ LLOQ • For subjects with a positive baseline titer (> LOD): post-vaccination titer ≥ 4 times the LLOQ • For subjects with a baseline titer ≥ LLOQ: post-vaccination titer ≥ a 4-fold rise compared with baseline titer

Exploratory Objective	Exploratory Endpoints
To assess immune responses against the SARS-CoV-2 nucleocapsid and spike proteins.	Immune responses against the SARS-CoV-2 nucleocapsid and spike proteins on Day 1, Day 29 and Day 57.

Exploratory Objective	Exploratory Endpoints
To evaluate salivary measurement of IgG antibodies against the SARS-CoV-2 nucleocapsid and spike (S) proteins.	Salivary measurement of IgG antibodies against the SARS-CoV-2 nucleocapsid and spike proteins on Day 1, Day 29, Day 36, Day 57, Day 209, and Day 394.

4 STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

4.1 Study Product Description

Product Name	Dose	Route	Frequency of Administration
mRNA-1273	100 µg	IM to deltoid muscle	Day 1 and Day 29 for vaccine-naïve cohorts Day 1 for booster vaccine cohorts

4.1.1 Formulation, Packaging, and Labeling

mRNA-1273 Injection (Drug Product) is an LNP dispersion of an mRNA encoding the prefusion stabilized S protein of SARS-CoV-2 (Drug Substance) formulated in LNPs composed of 4 lipids (1 proprietary and 3 commercially available): the proprietary ionizable lipid SM-102; cholesterol; 1,2-distearoyl-sn-glycero3-phosphocholine (DSPC); and 1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000 (PEG2000-DMG). The mRNA-1273 is provided as a sterile liquid for injection and is a white to off white dispersion in appearance, at a concentration of 0.2 mg/mL in 20 mM Tris buffer containing 87 mg/mL sucrose and 4.3 mM acetate at pH 7.5.

Moderna will provide the investigator and study site with adequate quantities of mRNA-1273. The sterile vaccine product is packaged in a 10R glass vial with a 6.3-mL fill volume. mRNA-1273 vaccine will have all required labeling per regulations and will be supplied to the pharmacy. Each multidose (10 doses) vial of product will be individually labeled for unique vial identification on accountability and dispensing records, only if the site requires such documentation. This vial may be used for more than one participant. mRNA-1273 will be packaged and labeled in accordance with the standard operating procedures (SOPs) of the Moderna or of its designee, Code of Federal Regulations Title 21 (CFR), Good Manufacturing Practice (GMP) guidelines, International Council for Harmonisation (ICH) GCP guidelines, guidelines for Quality System Regulations, and applicable regulations.

4.1.2 **Storage and Stability**

mRNA-1273 vaccine must be stored frozen at -15°C to -25°C until thawed for use and then may be stored refrigerated at 2°C to 8°C for up to 30 days (once thawed it must not be refrozen) in a secure area with limited access and protected from moisture and light until it is prepared for administration. The refrigerator/freezer should have automated temperature recording and a 24-hour alert system in place that allows for rapid response in case of refrigerator malfunction. There must be an available backup refrigerator. The refrigerators must be connected to a backup generator. In addition, vaccine accountability study staff are required to keep a temperature log to establish a record of compliance with these storage conditions. The site is responsible for reporting any mRNA-1273 vaccine that was not temperature controlled during shipment or during storage to the site PI and study sponsor. Such mRNA-1273 will be retained for inspection and disposed of according to approved methods.

4.1.3 **Acquisition/Distribution**

The participating site PI is responsible for study product distribution and disposition and has ultimate responsibility for study product accountability. The participating site PI may delegate to the participating site's research pharmacist responsibility for study product accountability. The participating site's research pharmacist will be responsible for maintaining complete records and documentation of study product receipt, accountability, dispensation, storage conditions, and final disposition of the study product(s). Study product accountability records and dispensing logs should include, but are not limited to the following: protocol number; name, dosage form, strength of the study product; manufacturer or other source; control, lot number or other identification number; expiration or retest date; date of receipt of the study product; quantity received from supplier; Participant identification number; quantity dispensed as amount or dose per Participant; balance of study product currently available; disposition of study product if not dispensed to a study Participant (e.g., disposed/destroyed or retuned to supplier; date of vaccine preparation/administration, time of vaccine preparation, expiration of vaccine preparation; and amount of vaccine withdrawn for administration.

Time of vaccine administration to the Participant will be recorded on the appropriate data collection form (DCF). All study product(s), including the amount of mRNA-1273, whether administered or not, must be documented on the appropriate study product accountability record or dispensing log.

OSRO monitoring staff will verify the participating site's study product accountability records and dispensing logs per the CCR OSRO approved site monitoring plan.

The following must be retained for study product accountability:

- unused mRNA-1273 vials

All used supplies must be disposed after preparation. All unused supplies must be retained until study conclusion or until study product accountability has occurred by the monitor and written notification stating retention is no longer required is received. Refer to the protocol-specific MOP for details on storing used mRNA-1273 vials.

4.2 Dosage/Regimen, Preparation, Dispensing and Administration of mRNA-1273 Vaccine (IND #27190)

4.2.1 Preparation

Vials of frozen or refrigerated mRNA-1273 should be removed from freezing or refrigeration temperatures and allowed to equilibrate to room temperature (20ºC to 25ºC).

1. Gently invert the mRNA-1273 vial 20 times to mix. Do not mix vigorously, sonicate, or vortex.
2. After disinfecting vial stopper with alcohol, draw 0.5 ml dose into approved 1 mL syringe using a 20G or 22G 1 ½ inch needle or a 23G 1 inch needle.
3. Remove the preparation needle and apply approved administration needle appropriate for IM injection or a luer lock cap for storage and transportation.
4. Repeat steps 1-3, 9 more times in quick succession to prepare a total of 10 dosing syringes.
5. Apply label with patient name, preparation time and 8-hour expiration time from the time all 10 syringes are filled.
6. Maintain syringes at room temperature until administration. DO NOT REFRIGERATE OR FREEZE.

4.2.2 Administration

Investigational product will be administered as an IM injection into the deltoid muscle on a 2-dose injection schedule on Day 1 and Day 29 (+/- 3 days). Each injection will have a volume of 0.5 mL and contain mRNA-1273 100 µg. The IP will be prepared for injection as a single 0.5 mL dose for each participant. The investigator will designate medically qualified personnel to administer the IP according to the procedures stipulated in this study protocol and Pharmacy Manual. Study-specific training will be provided.

At each visit when IP is administered, participants will be monitored for a minimum of 15 minutes after administration. Assessments will include vital sign measurements and monitoring for local or systemic reactions (**Appendix E: Study Calendar**).

Eligibility for a subsequent dose of IP is determined by following the criteria outlined in Section **5.1**.

4.3 Dose Modification for an Individual Participant

No dose modifications are allowed.

4.4 Accountability Procedures for mRNA-1273 Vaccine

Once received from the pharmaceutical partner at each site, the investigational products will be stored in and dispensed by the Investigational Pharmacy.

The Food and Drug Administration (FDA) requires accounting for the disposition of all investigational products. The Investigator is responsible for ensuring that a current record of

product disposition is maintained, and product is dispensed only at an official study site by authorized personnel as required by applicable regulations and guidelines. Records of product disposition, as required by federal law, consist of the date received, date administered, quantity administered, and the Participant number to whom the drug was administered.

The Investigational Pharmacist will be responsible for maintaining accurate records of the shipment and dispensing of the investigational product. The pharmacy records must be available for inspection by the CCR monitoring contractors and is participant to inspection by a regulatory agency (e.g., FDA) at any time. An assigned Study Monitor will review the pharmacy records.

At study termination, all unused investigational product will be disposed in accordance with the pharmacy's instructions following complete drug accountability and monitoring.

It is the investigator's responsibility that the personnel maintain accurate records in an IP accountability log of receipt of all IP, inventory at the site, dispensing of mRNA-1273, IP injections, and return to the Moderna or alternative disposition of used/unused products. A site monitor will review the inventory and accountability log during site visits and at the completion of the study. Additional details are found in the mRNA-1273-P301 Pharmacy Manual.

PI or designee will reconcile the IP during the conduct and at the end of the study for compliance. Once fully reconciled at the site at the end of the study, the IP can be destroyed at the investigational site or at a Moderna -selected third party, as appropriate. Investigational product may be destroyed at the study site only if permitted by local regulations and authorized by the Sponsor . A Certificate of Destruction must be completed and sent to the Sponsor or designee.

4.5 Study Treatment Compliance

All doses of the investigational study product (IP) will be administered at the study site by medically qualified study personnel and appropriately recorded (date and time) in the participant's medical records. If a participant does not receive vaccine, does not receive a full dose of vaccine, or does not receive all of the planned doses, the reason for the missed or partial dose will be recorded.

Participants in the vaccine-naïve cohorts who miss the second dose of IP due to noncompliance with the visit schedule and not due to a safety pause will still be required to follow the per protocol visit and testing schedule. Unless consent is withdrawn, a participant who withdraws or is withheld from receiving the second dose of study vaccine, if in the vaccine-naïve cohorts, will remain in the study and complete all safety and immunogenicity assessments required through the participant's scheduled end of study. The study site is responsible for ensuring that participants comply with the study windows allowed.

If a participant misses a visit, every effort should be made to contact the participant and complete a visit within the allowed visit window (Study Calendar, Appendix insert). If a participant does not complete a visit within the time window, that visit will be classified as a missed visit and the participant will continue with subsequent scheduled study visits. All safety requirements of the missed visit will be captured and included in the subsequent visit (e.g., clinical laboratory testing, memory aids review for reactogenicity, immunologic testing, as applicable).

4.6 Treatment Assignment

Participants from all four cohorts for Table 1 will be assigned to treatment arm 1. Enrollment for all cohorts will begin concurrently.

Table 1: Vaccine-Naïve Cohorts and Treatment Arm

Cohort	Description	Arm	Sample Size	Intervention
1	Hematologic Low Immunosuppression	1	20	100 µg (0.5 mL) mRNA-1273 injection on D1 and 29
2	Hematologic Intermediate Immunosuppression	1	20	100 µg (0.5 mL) mRNA-1273 injection on D1 and 29
3	Hematologic High Immunosuppression	1	20	100 µg (0.5 mL) mRNA-1273 injection on D1 and 29
4	Solid Tumor on PD1/PDL1 Inhibitor*	1	Up to 20	100 µg (0.5 mL) mRNA-1273 injection on D1 and 29

*Solid tumor cohort is inclusive of all tumors for which PD1/PDL1 inhibitors are approved therapies, including Hodgkin Lymphoma or Primary Mediastinal B-Cell Lymphoma.

Participants from all seven cohorts in Table 2 will be assigned to treatment arm 2. Enrollment for all cohorts will begin concurrently.

Table 2: Booster Vaccine Cohorts and Treatment Arm

Cohort	Description	Arm	Sample Size	Intervention
5	CLL Not On Active Therapy	2	20	100 µg (0.5 mL) mRNA-1273 injection on D1
6	CLL Receiving BTK* Inhibitor Interruption	2	20	100 µg (0.5 mL) mRNA-1273 injection on D1
7	CAR T Cell Therapy	2	30	100 µg (0.5 mL) mRNA-1273 injection on D1
8	Solid Tumor on PD1/PDL1 Inhibitor**	2	Up to 20	100 µg (0.5 mL) mRNA-1273 injection on D1
9	Post-Allogeneic Transplant	2	Up to 20	100 µg (0.5 mL) mRNA-1273 injection on D1
10	Other Hematologic Malignancy	2	Up to 20	100 µg (0.5 mL) mRNA-1273 injection on D1
11	Other Adult Solid tumor	2	Up to 10	100 µg (0.5 mL) mRNA-1273 injection on D1

* This study will briefly interrupt BTKi therapy around the time of vaccination in a group of CLL participants in order to determine whether this approach improves vaccine response rates (discussed in detail in section **2.4.5**). CLL participants that are currently receiving treatment with a BTKi therapy and are willing to hold their treatment around the time of vaccination will be eligible. In this group, BTKi therapy will be held for 1 week before vaccination until 2 weeks after vaccination (3 weeks total).

**Solid tumor cohort is inclusive of all tumors for which PD1/PDL1 inhibitors are approved therapies, including Hodgkin Lymphoma or Primary Mediastinal B-Cell Lymphoma.

Table 3: Risk of Immunosuppression by Cohort and Risk Group for Vaccine-Naïve Cohorts

The below table serves as a guideline to assist with the assignment of immunosuppressed cohorts.

Cohort 3 High Immunosuppression	Cohort 2 Intermediate Immunosuppression	Cohort 1 Low immunosuppression
Risk groups for Leukemia		
FLAG-Ida, CLIA2, 3+7, or similar for AML	Hypomethylating agent-based combo therapy: HMA + venetoclax, HMA +FLT3i, similar	Participants in remission >6 months on observation
HyperCVAD or similar for ALL, CART or CAR NK	Targeted therapy, single or combo, completed chemotherapy or CART within 6 months	Participants in remission >6 months on maintenance
Risk groups for Lymphoma		
EPOCH-R R-HyperCVAD, R-CHOP, CART, Platinum-based regimens, Bendamustine	Anti-CD20 antibody - single agent or in combination with BTK-inhibitor, BCL-2 inhibitor, high-dose methotrexate, completed chemotherapy or CART within 6 months	Participants not receiving active therapy or in remission >6 months on maintenance therapy (e.g. BTK inhibitor, BCL-2 inhibitor).
Risk groups for Myeloma		
Hypercytoxan-based regimen (e.g., m-CBAD, DT-PACE)	Standard triplet-based therapy (Pl-IMiD-dex, mAb-IMiD-dex, mAb-PI-dex)	Maintenance Revlimid® (lenalidomide) participants or in remission >6 months on observation
Risk groups for Stem Cell Transplantation (SCT)		

Cohort 3 High Immunosuppression	Cohort 2 Intermediate Immunosuppression	Cohort 1 Low immunosuppression
Participants at least 3 months post Allogeneic Stem Cell Transplant (any donor)	Participants at least 3 months post Autologous Stem Cell Transplant	

4.7 Cohort Enrollment

Enrollment in the cohorts will begin simultaneously.

4.8 Recruitment and Screening

4.8.1 Recruitment

This protocol may be abstracted into a plain language announcement posted on NIH websites and on NIH social media platforms. The protocol abstract may also be placed in collaborating academic websites, Twitter platforms, or published in periodic clinical trial communications to help boost enrollment. Flyers will be used to assist with recruitment and will be IRB approved prior to use.

4.8.2 Screening Evaluation

Minimal risk activities that may be performed before the participant has signed an informed consent include the following:

- Email, written, in person or telephone communications with prospective participants
- Review of existing medical records to include H&P, laboratory studies, etc.
- Review of existing MRI, x-ray, or CT images
- Review of existing photographs or videos
- Review of existing pathology specimens/reports from a specimen obtained for diagnostic purposes

4.8.3 Screening activities performed after informed consent for screening has been signed

Before performing any study procedures, all potential participants will sign an informed consent form (ICF) (as detailed in Section **10.2**).

The following activities will be performed only after the participant has signed the IRB approved informed consent form for screening activities on this study. Assessments performed at outside facilities, but off protocol within the timeframes below may also be used to determine eligibility once a participant has signed the consent.

Screening procedures may be performed **within 28 days** prior to the first vaccine dose administration.

4.8.3.1 Clinical Evaluations

- History and physical exam including weight and vital signs

4.8.3.2 Laboratory Evaluations

Note: Laboratory values obtained within 28 days from labs outside the clinical site may be used to determine eligibility as these are routine laboratory assessment for which interlaboratory variability is not expected to influence outcomes.

- CBC with differential and platelet count
- Chemistry panels including: Acute care panel (Na+, K+, Cl-, total CO2, creatinine, glucose, blood urea nitrogen), Hepatic panel (AST/GOT, ALT/GPT, total bilirubin, direct bilirubin, alkaline phosphatase)
- Serum or urine pregnancy test for participants of childbearing potential (within one week prior to vaccination).

4.8.4 Baseline Evaluation

Baseline evaluations can be performed within 28 days prior to vaccine administration. The screening evaluations and baseline evaluations may be performed on the same day.

4.8.5 Clinical Evaluations

- History and physical exam including weight and vital signs

4.8.6 Laboratory Evaluations

- CBC with differential and platelet count
- Chemistry panels including: Acute care panel (Na+, K+, Cl-, total CO2, creatinine, glucose, blood urea nitrogen), Hepatic panel (AST/GOT, ALT/GPT, total bilirubin, direct bilirubin, alkaline phosphatase)
- Troponin
- Serum or urine pregnancy test for participants of childbearing potential (within one week prior to vaccination).

4.9 Participant Registration and Status Update Procedures

Registration and status updates (e.g., when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found at: https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

4.9.1 For Participating Site Registration

Registration will be a two-part process as participants are screened on this protocol. A protocol registration form will be supplied by the CCR study coordinator and updates will be provided as needed. To initially register a participant, after the participant has signed consent, complete the top portion of the form and send to CCR study coordinator. Once eligibility is confirmed, after completion of screening studies, complete the remainder of the form which is the eligibility

checklist, indicating that the patient is being registered for treatment and send to CCR study coordinator. In addition, source documents supporting the eligibility criteria must be sent to the CCR study coordinator. The CCR study coordinator will notify you either by e-mail or fax that the protocol registration form has been received which will include the unique patient/participant ID number. Questions about eligibility should be directed to the CCR study coordinator or PI. Questions related to registration should be directed to the CCR study coordinator.

When a participant has a status change (e.g., participant screened on the study, does not meet eligibility criteria and is removed from the study, participant is taken off protocol therapy or off study, etc.), the Participant Status Update Form will be supplied by the CCR study coordinator. Send the completed form to the CCR study coordinator.

4.9.2 **Screen Failure**

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of an eligibility criterion (e.g., laboratory parameter) may be rescreened, if appropriate.

4.9.3 **General considerations for study assessments and procedures:**

- Protocol waivers or exemptions are not allowed.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria.
- The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

5 STUDY POPULATION

Adults at an increased risk of COVID-19-associated mortality due to the presence of an underlying malignancy and treatment-related immunosuppression.

5.1 Inclusion Criteria

Participants must meet all the inclusion criteria in order to be eligible to participate in the study.

5.1.1 Participants must have one of the following:

- Histologically or cytologically confirmed solid tumor receiving a standard of care PD1/PDL1 inhibitor for treatment of their solid tumor (inclusive of Hodgkin Lymphoma and Primary Mediastinal B-Cell Lymphoma participants receiving PD1/PDL1 inhibitors as standard of care therapy)
- Confirmed diagnosis of acute leukemia (myeloid (AML) or lymphoid (ALL) or other acute leukemia; multiple myeloma; Waldenstrom macroglobulinemia

- Confirmed diagnosis of lymphoma, including small lymphoblastic lymphoma (i.e., chronic lymphocytic leukemia)
- Be post allogeneic stem cell transplantation (for any indication)
- Be an adult patient (aged 18 or older) with any malignancy who does not fit any of the above categories

5.1.2 Age ≥18 years.

5.1.3 History of adequate organ and marrow function on a recent laboratory assessment (within 4 weeks of administration of vaccine), as defined below:

Absolute lymphocyte count	Minimum value of 200 cells per mcL
Absolute neutrophil count	Minimum value of 500 cells per mcL
Platelets	Minimum value of 25,000 cells per mcL
Total bilirubin	Maximum value of 3.0 x upper limit of normal
AST(SGOT)/ALT(SGPT)	Maximum value of 5.0 x upper limit of normal
Creatinine	Maximum value of 3.0 x upper limit of normal (if elevated, use of creatinine calculated clearance will be necessary, as below)
Creatinine clearance (only necessary for participants with elevated creatinine)	For participants with Chronic Kidney Disease, a calculated Glomerular Filtration Rate minimum will be required as follows: >30 mL/min/1.73 m^2 for participants with creatinine levels above institutional normal.

5.1.4 Participants with history of human immunodeficiency virus (HIV) may enroll

5.1.5 Participants with history of chronic hepatitis B virus (HBV) must be on suppressive therapy (if indicated) with undetectable viral load.

5.1.6 Participants with a known history of hepatitis C virus (HCV) infection must have been treated and cured with an undetectable HCV viral load. For participants with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

5.1.7 A negative urine/serum pregnancy test for females of childbearing potential**.** The effects of mRNA-1273 Vaccine on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception prior to study entry and for 30 days after the last study treatment.

Note: A female is considered to be of "childbearing potential" if she has experienced menarche and is not permanently sterile (i.e., hysterectomy, bilateral oophorectomy, or tubal ligation) or postmenopausal (postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause and with a serum follicle-stimulating hormone test result in the postmenopausal range).

Effective methods of contraception:

- Intrauterine device.

- Stable dose of hormonal birth control, such as those listed below, for at least 3 months prior to enrollment.
  - Hormonal contraceptive tablets.
  - Injectable hormonal contraceptives.
  - Implanted hormonal contraceptives.
  - Cutaneous contraceptive patches.
  - Intravaginal hormonal contraceptive rings.

At least 1 barrier method. Effective barrier methods for use in this study are:

- Male or female condom.
- Diaphragm.
- Creams or gels that contain a chemical to kill sperm

If a female participant has a male partner who has had surgery to prevent pregnancy (vasectomy), that will be considered evidence of effective contraception.

5.1.8 Ability to understand and the willingness to sign a written informed consent document.

5.1.9 CLL participants undergoing BTKi treatment interruption: Must be receiving treatment with a BTKi for ≥6 months prior to vaccination and be willing to hold their treatment for up to 3 weeks around the time of vaccination.

5.2 Exclusion Criteria

All participants meeting any of the exclusion criteria at baseline will be excluded from study participation.

5.2.1 Within 14 days of known exposure to someone with confirmed SARS CoV2 infection or COVID-19.

5.2.2 Acutely ill or febrile 24 hours prior to or at the Screening Visit (Day 0). Fever is defined as a body temperature ≥ 38.0°C/100.4°F. Participants meeting this criterion may be rescheduled within the relevant window periods. Afebrile participants with minor illnesses can be enrolled at the discretion of the investigator.

5.2.3 Participants on the vaccine naïve arms cannot have received any doses of the COVID-19 vaccine.

Participants who have not completed a standard vaccination series due to initiation of vaccination in a foreign location (e.g., single dose of Astra-Zeneca vaccine or a similar situation) may be enrolled after discussion with the principal investigator.

Participants on the booster arms must have received all doses of their initial COVID-19 vaccine (Participants vaccinated with the Janssen vaccine must have received the single dose of that EUA vaccine for COVID19, but all others must have received 2 doses) at least 4 weeks prior to vaccination on protocol. Participants will be allowed to enroll if they have already received booster doses of vaccine prior to enrolling on the protocol at least four weeks prior to vaccination on protocol. In this case, the protocol will administer a single booster dose of vaccination. Documentation will be required.

5.2.4 Known diagnosis of chronic pulmonary disease (e.g., chronic obstructive pulmonary disease, asthma) that is not controlled.

5.2.5 Chronic cardiovascular disease that is not controlled.

5.2.6 Participants with a history of myocarditis (inflammation of the heart) or pericarditis (inflammation of the pericardium)

5.2.7 History of anaphylaxis, urticaria, or other significant adverse reaction requiring medical intervention after receipt of a vaccine.

5.2.8 Bleeding disorder considered a contraindication to intramuscular (IM) injection or phlebotomy.

5.2.9 Participated in an interventional clinical trial with an investigational agent within 28 days prior to the Screening Visit (Day 0) or plans to do so while participating in this study. The site investigator may enroll a participant on the trial earlier than 28 days if enough time has passed to ensure that at least five half-lives have occurred.

5.2.10 Prior/Concomitant Therapy

- Has received prior radiotherapy within 14 days before the first dose of study treatment. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 7-day washout is permitted for palliative radiation (≤ 2 weeks of radiotherapy) to non-central nervous system (CNS) disease.
- Has received a live vaccine within 30 days before the first dose of study treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

5.2.11 Has received an inactivated vaccine within 14 days before the first dose of study treatment.

5.2.12 Have major surgical procedures within 28 days or non-study-related minor procedures within 7 days before the first dose of study treatment. In all cases, the participant must be sufficiently recovered and stable before treatment administration.

5.2.13 History of severe allergic reactions to any components of the study treatment.

5.2.14 Has uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, severe or ongoing interstitial lung disease (ILD), serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs, or compromise the ability of the participant to give written informed consent.

5.2.15 Active tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice).

5.2.16 History of (non-infectious) pneumonitis that required steroids or has current pneumonitis.

5.2.17 Has involvement in the planning and/or conduct of the study.

5.2.18 Female who is pregnant or breastfeeding

5.2.19 Male or female participant of reproductive potential who are not willing to employ effective birth control from screening to 30 days after the last dose of study treatment.

6 STUDY PROCEDURES

6.1 Planned Study Visits After Enrollment

Participants will undergo study procedures at the time points specified in the protocol Study Calendar (**Appendix E**).

6.1.1 Prior to Vaccine Administration

6.1.1.1 Pre-Screening, Day -28 to 0

Potential Participants' information will be pre-screened for study eligibility criteria met. Potential study participants will be provided with information regarding the study and they will be asked if they wish to continue to the Screening Visit Procedures. The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other site approved remote platforms used in compliance with local policy) per discretion of the designated study investigator and with the agreement of the participant/consent designee(s).

6.1.1.2 Day -28 to -1, Visit 0, Study Screening

Potential participants may be screened for eligibility. All procedures and questions in the medical history that can be conducted by a telephonic visit will be allowed up to a week prior to the study visit. The following activities will be performed at the screening visit:

- Potential participants will be provided with a description of the study (purpose and study procedures). Participants will be asked to read and sign the informed consent form (ICF). The ICF will be signed prior to performing any other screening procedures.
- Eligibility criteria for study entry and receipt of Dose 1 will be reviewed with the participant. Vital signs will be obtained, including temperature, pulse, and blood pressure.
- Height and weight will be obtained.
- Medical history will be reviewed.
- All concomitant medications will be recorded.
- A physical examination will be performed by appropriate study personnel to assess general physical condition.

- Review of acceptable contraceptive methods (male and female participants) and recent menstrual history (female participants only).
- A urine or serum pregnancy test must be performed within one week prior to vaccination for all female participants of childbearing potential.
- Approximately 5-10 ml of venous blood will be collected for serological studies, blood chemistry

6.1.2 Vaccine Administration and Follow-Up for Vaccine-Naïve Cohorts

6.1.2.1 Day 1, Visit 1, Vaccine Dose 1

Unless otherwise indicated, the following baseline evaluations can be performed within 28 days prior the first vaccine administration. The screening evaluations and baseline evaluations may be performed on the same day. Any evaluations required at both timepoints will not need to be duplicated if this occurs.

- Eligibility baseline criteria for study entry and receipt of Dose 1 will be reviewed with the participant.
- Vital signs will be obtained, including weight, temperature, pulse, and blood pressure.
- Medical history will be reviewed to assure continued eligibility.
- All concomitant medications will be reviewed for accuracy and completeness. Any new medications will be recorded and assessed for continuing eligibility.
- A physical examination may be performed, as indicated, based on participant's recent clinical history since the screening visit.
- A urine or serum pregnancy test must be performed within one week prior to vaccination for all female participants of childbearing potential.
- Clinical safety laboratory assessments will be performed by the local laboratory. The results from this blood draw will not be available or reviewed prior to vaccination and will serve as a baseline safety assessment only. Approximately 8-10 ml of venous blood will be collected for serological studies, troponin, blood chemistry. Participants with CLL will also have LDH and Beta-2 microglobulin collected.
- Blood will be collected for baseline immunology assessments (see section **7.3**).
- Approximately 1 mL of saliva will be collected for Immunogenicity Evaluation
- An electrocardiogram (ECG) will be performed.
- Participants will receive a single dose of mRNA-1273 vaccine via intramuscular injection in the deltoid muscle of the preferred arm. Following vaccination, participants will be observed in the clinic for at least 15 minutes. The vaccination site will be examined, and any AE/SAEs will be assessed prior to discharge from the clinic.
- Participants will be provided with study related materials to record daily temperature and systemic and local AE/SAEs. Participants will be encouraged to take their temperature around the same time each day. Participants will be instructed on how to measure and record AE/SAEs prior to discharge from the clinic. Participants will be instructed to notify the study center if they develop any severe reactions following vaccination. If the site principal investigator or appropriate sub-investigator deems the reaction severe enough, s/he will give further instructions on the proper course of action, including a return to the clinic for immediate evaluation if appropriate.
- Counseling on avoidance of pregnancy will be conducted.

6.1.2.2 **Day 29, Visit 2, Vaccine Dose 2***

*NOTE: If an unavoidable delay requires the participant to receive the second vaccine on a day after day 29, this will be acceptable within a three day timeframe. All subsequent numbering will refer to this visit as the "Day 29, Visit 2" visit and the appropriate blood draws and study procedures will be noted as though the participant received the second dose on schedule, on Day 29. The participant will receive a proof of vaccination card documenting the dates of administration after receiving their second dose of the study drug.

- Vital signs will be obtained, including temperature, pulse, and blood pressure.
- All concomitant medications will be reviewed for accuracy and completeness. Any new medications will be recorded and assessed for continuing eligibility.
- A physical examination may be performed, as indicated, based on participant's recent clinical history since the screening visit. This is required for participants with CLL and optional for the other cohorts. The medical history will also be reviewed at this time.
- A urine or serum pregnancy test must be performed within one week prior to vaccination for all female participants of childbearing potential.
- Clinical safety laboratory assessments will be performed by the local laboratory. The results from this blood draw will not be available or reviewed prior to vaccination and will serve as a baseline safety assessment only. Approximately 80-100 ml of venous blood will be collected for serological studies, troponin, and blood chemistry. Participants with CLL will also have LDH and Beta-2 microglobulin collected.
- Samples will be collected for immunology/correlative studies (see section **7.3**).
- An electrocardiogram will be performed (may be performed up to 2 weeks prior to this visit).
- Participants will receive a single dose of mRNA-1273 vaccine via intramuscular injection in the deltoid muscle. Following vaccination participants will be observed in the clinic for at least 15 minutes. The vaccination site will be examined, and any AE/SAEs will be assessed prior to discharge from the clinic.
- Participants will be provided with study related materials to record daily temperature and systemic and local AE/SAEs. Participants will be encouraged to take their temperature around the same time each day. Participants will be instructed on how to measure and record AE/SAEs prior to discharge from the clinic. Participants will be instructed to notify the study center if they develop any severe reactions following vaccination. If the site principal investigator or appropriate sub-investigator deems the reaction severe enough, s/he will give further instructions on the proper course of action, including a return to the clinic for immediate evaluation if appropriate.
- Participants will be provided with proof of vaccination
- Counseling on avoidance of pregnancy will be conducted.

6.1.2.3 **Day 36, Visit 3 (+/- 1 day)**

- In-person visit
- Current health status will be reviewed and any changes since the last visit will be noted.
- Samples will be collected for immunology/correlative studies (see section **7.3**).
- Solicited AEs/reactogenicity will be reviewed.
- Unsolicited AEs, and SAEs, that have occurred since the last contact will be collected.

6.1.2.4 **Day 57, Visit 4 (+/-7 days)**

- In-person visit
- Current health status will be reviewed and any changes since the last visit will be noted.
- Standard antibody testing to assess immune response
- Samples will be collected for immunology/correlative studies (see section **7.3**).
- Samples for troponin monitoring will be collected (+/- 2 weeks).
- An electrocardiogram will be performed (+/- 2 weeks).
- Unsolicited AEs, and SAEs, that have occurred since the last contact will be collected.
- Participants with CLL will have the following procedures:
    - Medical history will be reviewed
    - Physical examination
    - LDH and Beta-2 microglobulin will be collected after resumption of BTKi therapy.

6.1.2.5 **Day 209 (6 Months), Visit 5 (+/- 28 days)**

- In-person visit
- Follow-up interim medical history and vital signs will be completed.
- Unsolicited AEs, and SAEs, that have occurred since the last contact will be collected.
- Samples will be collected for immunology/correlative studies (see section **7.3**).
- Standard antibody testing to assess immune response

6.1.2.6 **Day 394, Visit 6 (+/- 28 days)**

- In-person visit
- Follow-up interim medical history and vital signs will be completed.
- Unsolicited AEs, and SAEs, that have occurred since the last contact will be collected.
- Standard antibody testing to assess immune response
- Samples will be collected for immunology/correlative studies (see section **7.3**).
- Participants will be thanked for participating in the study

6.1.3 **Vaccine Administration and Follow-Up for Booster Vaccine Cohorts**

Participants from the Vaccine-Naïve Cohorts who receive the additional booster will follow-up per the Booster Vaccine Cohort and will follow the below timeline. They will not be required to complete any Vaccine-Naïve Assessments after receiving the booster vaccine. They will become eligible for their respective booster per the Booster Vaccine Cohort 4 weeks after their second vaccination. A physical examination may be performed, as indicated, based on participant's recent clinical history, but for participants transitioning from the Vaccine-Naïve Cohorts, this will not be required. Similarly, baseline labs will not be required for Vaccine-Naïve participants who transition into the Booster Vaccine Cohorts.

Participants who enroll on trial after a previous booster vaccination off-trial will follow the same study calendar, as below, provided at least four weeks have passed from the last booster vaccination.

Similarly, participants who receive an initial booster vaccination from this protocol will be eligible for a second and a third booster vaccination and follow the study the same study calendar as below, provided at least four weeks have passed from the last booster vaccination. The date of

their second booster dose will be considered Day 1. If they receive a third booster dose on protocol, the calendar will be reset, and the date of their third booster will be considered Day 1.

6.1.3.1 **Day 1, Visit 1, Booster Vaccine Dose 1**

- Unless otherwise indicated, the following baseline evaluations can be performed within 28 days prior to vaccine administration. The screening evaluations and baseline evaluations may be performed on the same day. Any evaluations required at both timepoints will not need to be duplicated if this occurs. As noted above, participants who are transitioning from the Vaccine-Naïve cohorts will not need any baseline labs, as they are already enrolled on the protocol.
- Participants in the BTK inhibitor interruption arm must stop their BTK inhibitor therapy no later than Day -7 and may resume no sooner than Day 15.
- Eligibility baseline criteria for study entry and receipt of Dose 1 will be reviewed with the participant.
- Vital signs will be obtained, including weight, temperature, pulse, and blood pressure.
- Medical history will be reviewed to assure continued eligibility.
- All concomitant medications will be reviewed for accuracy and completeness. Any new medications will be recorded and assessed for continuing eligibility.
- A physical examination may be performed, as indicated, based on participant's recent clinical history since the screening visit.
- A urine or serum pregnancy test must be performed within one week prior to vaccination for all female participants of childbearing potential.
- Clinical safety laboratory assessments will be performed by the local laboratory. The results from this blood draw will not be available or reviewed prior to vaccination and will serve as a baseline safety assessment only. Approximately 8-10 ml of venous blood will be collected for serological studies, troponin, blood chemistry
- Blood will be collected for baseline immunology assessments (see section **7.3**).
- An electrocardiogram will be performed
- Approximately 1 mL of saliva will be collected for Immunogenicity Evaluation
- Participants will receive a single dose of mRNA-1273 vaccine via intramuscular injection in the deltoid muscle of the preferred arm. Following vaccination, participants will be observed in the clinic for at least 15 minutes. The vaccination site will be examined, and any AE/SAEs will be assessed prior to discharge from the clinic.
- Participants will be provided with study related materials to record daily temperature and systemic and local AE/SAEs. Participants will be encouraged to take their temperature around the same time each day. Participants will be instructed on how to measure and record AE/SAEs prior to discharge from the clinic. Participants will be instructed to notify the study center if they develop any severe reactions following vaccination. If the site principal investigator or appropriate sub-investigator deems the reaction severe enough, s/he will give further instructions on the proper course of action, including a return to the clinic for immediate evaluation if appropriate.
- Counseling on avoidance of pregnancy will be conducted.

6.1.3.2 Day 8, Visit 2 (REQUIRED FOR CAR T Cell Cohort, OPTIONAL for other cohorts)

- In-person visit
- Current health status will be reviewed and any changes since the last visit will be noted.
- Standard antibody testing to assess immune response
- Samples will be collected for immunology/correlative studies (see section **7.3**).
- Solicited AEs/reactogenicity will be reviewed.
- Unsolicited AEs,and SAEs, that have occurred since the last contact will be collected.

6.1.3.3 Day 29, Visit 3

- In-person visit
- Current health status will be reviewed and any changes since the last visit will be noted.
- Standard antibody testing to assess immune response
- Samples will be collected for immunology/correlative studies (see section **7.3**).
- Samples for troponin monitoring will be collected (+/- 2 weeks)
- An electrocardiogram will be performed (+/- 2 weeks).
- Solicited AEs/reactogenicity will be reviewed.
- Unsolicited AEs,and SAEs, that have occurred since the last contact will be collected.

6.1.3.4 Day 57, Visit 4 (+/-7 days)

- In-person visit
- Current health status will be reviewed and any changes since the last visit will be noted.
- Samples will be collected for immunology/correlative studies (see section **7.3**).
- Standard antibody testing to assess immune response
- Unsolicited AEs, and SAEs, that have occurred since the last contact will be collected.
- If a participant elects to have a second or third booster vaccination on protocol, the date of administration of this dose will be considered Day 1. The minimum timeframe between booster vaccination doses will be 28 days. Day 57, Day 180, and Day 360 timepoints, if not yet reached on the original booster vaccination on protocol will be timed according to the participant's last vaccination dose.

6.1.3.5 Day 180 (6 Months), Visit 5 (+/- 28 days)

- In-person visit
- Follow-up interim medical history and vital signs will be completed.
- Unsolicited AEs, and SAEs, that have occurred since the last contact will be collected.
- Standard antibody testing to assess immune response
- Samples will be collected for immunology/correlative studies (see section **7.3**).
- If a participant elects to have a second or third booster vaccination on protocol, the date of administration of this dose will be considered Day 1. The minimum timeframe between booster vaccination doses will be 28 days. Day 180, and Day 360 timepoints, if not yet reached on the original booster vaccination on protocol will be timed according to the participant's last vaccination dose.

6.1.3.6 Day 360, Visit 6 (+/- 28 days)

- In-person visit
- Follow-up interim medical history and vital signs will be completed.
- Unsolicited AEs, and SAEs, that have occurred since the last contact will be collected.
- Samples will be collected for immunology/correlative studies (see section **7.3**).
- Standard antibody testing to assess immune response
- Participants will be thanked for participating in the study
- If a participant elects to have a second or third booster vaccination on protocol, the date of administration of this dose will be considered Day 1. The minimum timeframe between booster vaccination doses will be 28 days. Day 360 timepoint, if not yet reached on the original booster vaccination on protocol will be timed according to the participant's last vaccination dose.

6.1.4 Early Termination

- Participants may voluntarily withdraw their consent for participation in the study at any time and for any reason, without penalty. Participants may also withdraw voluntarily from receiving the study intervention for any reason. A site principal investigator may also withdraw a participant from receiving further study intervention.
- Follow-up interim medical history and vital signs will be completed, if possible, whether the participant withdraws from the study or is withdrawn from receiving further study product. Participants will be encouraged to permit continued follow-up of AE/SAEs and to donate scheduled venous blood samples for clinical safety laboratory and immunogenicity evaluations, if possible.
- For participants who withdraw within 7 days of their last dose of vaccine, a 6-month follow-up phone call should be conducted to collect any new SAEs.

6.1.5 Unscheduled Study Visits

At any time during the study a participant can also be seen for an unscheduled visit. An unscheduled visit may be prompted by reactogenicity issues, unsolicited new or ongoing adverse events.

When interim contacts or visits are completed in response to participant reports of AEs, study staff will assess the reported event clinically and provide or refer the participant to appropriate medical care. All AEs will be evaluated and reported as required. All interim contacts and visits will be documented in participants' study records and on applicable data collection forms.

The site Staff may also decide to make reminder telephone calls to inform the participant about visits, review study requirements, or follow-up on ongoing or outstanding issues.

6.2 Withdrawal from the Study or Discontinuation of the Study Product

Participants may voluntarily withdraw their consent for study participation at any time without penalty or loss of benefits to which they are otherwise entitled.

6.3 Criteria for Removal from Study Therapy and Off Study Criteria

Prior to removal from study, effort must be made to have all participants complete a safety visit approximately 28 days after the last vaccine dose of study therapy.

6.3.1 Criteria for removal from study treatment

- Participant requests to be withdrawn
- Unacceptable toxicity
- Allergic reactions, hyperimmune responses and/or SAEs considered related to the vaccine
- Participant becomes pregnant
- Investigator decision

The investigator should be explicit regarding study follow-up (e.g., safety follow-up) that might be carried out despite the fact the Participant will not receive further study product. If the Participant consents, every attempt will be made to follow all AEs through resolution. The procedures that collect safety data for the purposes of research must be inclusive in the original informed consent or the investigator may seek subsequent informed consent using an IRB-approved consent form with the revised procedures.

The investigator will inform the Participant that already collected data will be retained and analyzed even if the Participant withdraws from this study.

6.3.2 Off-Study Criteria

- Completed study follow-up period
- Participant requests to be withdrawn from study
- Participant becomes pregnant
- Death
- Screen failure
- PI decision to end the study
- Participant lost to follow-up
- Investigator decision
- Adult permanently loses capacity to consent
- Study is cancelled

6.3.3 Participant Replacement

Participants who withdraw, or are withdrawn from this study, or are lost to follow-up after signing the informed consent form (ICF) and administration of the study product will not be replaced. Participants who withdraw, or are withdrawn from this study, or are lost to follow-up after signing the ICF but before administration of the study product may be replaced.

6.3.4 Lost to Follow-up

A participant will be considered lost to follow-up if he or she fails to return for 3 consecutive scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 3 days and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, an IRB approved certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

6.3.5 Study Termination, Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and as applicable, the Food and Drug Administration (FDA).

7 DESCRIPTION OF CLINICAL AND LABORATORY EVALUATIONS

For timepoints see the Study Calendar in Appendix (**Appendix E**).

7.1 Clinical Evaluations

7.1.1 Medical History

Will be obtained by interview of the potential participant and review of their medical records. Participants will be queried regarding history of cancer and any significant medical disorders of the head, eyes, ears, nose, throat (HEENT), mouth, cardiovascular system, lungs, gastrointestinal tract, liver, pancreas, kidney, urologic, nervous system, blood, lymph glands, endocrine system, musculoskeletal system, skin, and genital/reproductive tract. A history of any allergies, immunodeficiency, psychiatric illness, and autoimmune disease will be solicited.

7.1.2 Physical Examination

At screening or Day 0 visit, a targeted physical exam will be performed based on participant's clinical history and height and weight will be collected. Vital signs (temperature, heart rate, respiration and blood pressure) will be collected at screening and prior to each vaccination. The exam will be performed by qualified study personnel to assess general physical condition and will include the following areas/systems: supraclavicular and axillary lymph nodes, cardiovascular, pulmonary, abdomen, skin.

At visits following the first vaccination a targeted physical examination may be conducted based on interim medical history.

7.1.3 Reactogenicity Assessments

Will include brief history for assessment of AE/SAEs just prior to and following vaccination, which includes an assessment of pain, tenderness, erythema, induration and warmth at the injection site; fever, chills, arthralgia/joint pain, malaise/fatigue, myalgia/body aches, headache, nausea, vomiting and abdominal pain.

The vaccination site will be examined at the end of the 15-minute observation period following each vaccination on Day 1 and Day 29 if applicable as well as all other timepoints if indicated.

7.1.4 Memory aids

Following each vaccination, all participants will complete a participant memory aid for 8 days (Days 1-8 [all participants] and Days 29-36 [participants in the vaccine naïve cohort only]).

Following each vaccination, and if applicable at Day 8 visits, memory aids will be reviewed with the participant. The study staff objective assessment of the reactogenicity will be documented. Memory aids are not source documents and will be used as a tool for the study team to interview the participants about their reactogenicity. The study team will fill up the source, based on the memory aid and the source is captured in the database. The memory aids themselves will be destroyed.

7.2 Concomitant Medications/Treatments

7.2.1 General

All ongoing medications and therapies at screening will be considered prior medications.

Concomitant medications will include all current medications and medications taken within the 30 days prior to enrollment (prescription and over-the-counter drugs, vitamins and supplements, topical products, and vaccinations) through 34 days after the second vaccination (approximately Day 57-60 for participants who receive both doses of vaccine or early termination (if prior to Day 60), whichever occurs first. Assessment of eligibility also will include a review of permitted and prohibited medications (per the exclusion criteria).

Administration of any concomitant medications, therapies or vaccines will be documented in the participant's medical record and eCRF.

Contraceptive status is assessed and documented at every scheduled clinic visit for participants who were born female and who are sexually active in a way that could lead them to becoming pregnant. Prior to enrollment and throughout the study, staff will ask participants to verbally confirm their use of effective contraceptive methods.

7.2.2 For Hematologic Malignancies Cohorts:

7.2.2.1 Supportive Care

- Supportive care measures including blood products, infection prophylaxis and growth factors will be administered according to institutional guidelines.

7.2.2.2 Concomitant Medications

Recommendations with regard to specific types of concomitant therapies, supportive care; diet and other interventions are as follows:

- Concomitant medications are recommended as prophylaxis for nausea, vomiting, and infections, and are recommended according to institutional standards. Myelosuppression is expected in participants with acute leukemia, lymphoma or myeloma, or post-stem cell transplantation due to underlying disease, as well as due to chemotherapy, or both. Many participants may have neutropenia, thrombocytopenia, or both at study entry.
- Significant or life-threatening myelosuppression may be managed with growth factor support and blood transfusion according to institutional standard of care, American Society of Clinical Oncology (ASCO) Practice Guidelines, and/or NCCN Practice Guidelines.
- Infections secondary to myelosuppression are common in participants with hematologic malignancies, and may be related to underlying disease, chemotherapy, or both. Therefore, the use of prophylactic antibiotics, antifungal agents, and antiviral agents is recommended according to institutional standards.
- If a prohibited medication is considered essential for the participant well-being, continuation on study with concomitant administration of such medication(s) will need to be discussed with and approved by the principal investigator.

7.3 Laboratory Evaluations

All clinical safety testing will be conducted at CLIA certified laboratories at each site. Blood specimens be obtained in accordance with the study calendar (Appendix C). Blood samples collected for immunology analyses and immune assessments at non-NIH sites will be processed at Moderna Inc. and the NIH using a standardized research operating protocol.

7.3.1 Clinical Laboratory Evaluations

- Urine or serum pregnancy tests will be performed within one week prior to each vaccination on all female participants of childbearing potential. Results must be known prior to each vaccination. (In order to reduce burden on female participants of childbearing potential, the vaccine doses can be prepared and verified, but not administered, while results of the pregnancy test are pending.)

- Clinical laboratory evaluations for safety will be performed by local (clinical) laboratories. Venous blood samples will be collected from each participant prior to each vaccination and according to section **7.3**
- Clinical safety labs include:
  - CBC with differential and platelet count,
  - Chemistry panels including: Acute care panel (Na+, K+, Cl-, total CO2, creatinine, glucose, blood urea nitrogen), and Hepatic panel (AST/GOT, ALT/GPT, total bilirubin, direct bilirubin, alkaline phosphatase)
  - LDH (only collected from participants with CLL)
  - Beta-2 microglobulin (only collected from participants with CLL)

7.3.2 Serological Immunogenicity Endpoint Assays

Blood samples for immunogenicity assessments will be collected before administration of study treatment. The following analytes will be measured:

- Serum bAb levels against SARS-CoV-2 as measured by ligand-binding assay specific to the SARS-CoV-2 S protein
- Serum bAb levels against SARS-CoV-2 as measured by ligand-binding assay specific to the SARS-CoV-2 nucleocapsid protein
- Serum nAb titer against SARS-CoV-2 as measured by pseudovirus and/or live virus neutralization assays

Serum will be tested using the ligand-binding assay specific to the SARS-CoV-2 nucleocapsid to determine the immunologic status of study participants at baseline and assess for seroconversion due to infection during the course of the study. Serum from a subset of participants will be tested in the other assays. The selection of the subset and timepoints to be tested are described in the statistical analysis plan. Sample aliquots will be designed to ensure that backup samples are available and that adequate vial volumes may allow for further testing.

The date of each sample collected will be recorded in the eCRF, and unique sample identification will be used to maintain the blind at the laboratory at all times and to allow for automated sample tracking and storage. Handling and preparation of the coded samples for analysis, as well as shipping and storage requirements, will be provided in a separate study manual.

The ligand-binding assay and measurement of nAb titers will be performed in Blake Warner Lab, NIH.

7.3.2.1 Endpoint Assay Biospecimen Collection for Vaccine-Naïve Cohorts

Test/Assay	Volume blood** (approx)	Type of tube**	Collection point*	Location of specimen analysis
Serological Immunogenicity Assays	5-10 mL (for plasma)	EDTA	D1, 29, 36, 57, 394, at COVID-19 infection***	NIH Blake Warner Lab
Neutralization assay using a wild-type SARS-CoV- 2	3 mL (for serum)	SST	D1, 29, 36, 57, 209, 394, at	

Test/Assay	Volume blood** (approx)	Type of tube**	Collection point*	Location of specimen analysis
			COVID-19 infection***	

* See study calendar for collection windows. Sample collection should occur prior to vaccine administration on applicable days (i.e., D1 and D29). Participants who opt to receive a booster vaccine will have their samples drawn according to the Booster Vaccine Cohort calendar.

**Tubes/media may be adjusted at the time of collection based upon materials available if approved by the PI/laboratory investigator

***If a participant tests positive for COVID-19 while on study these labs will be collected within 2 weeks of a positive PCR test. A second post-infection blood collection will occur 2-4 weeks after this initial blood draw. These post-infection blood draws are optional.

7.3.2.2 Endpoint Assay Biospecimen Collection for Booster Vaccine Cohorts

Test/Assay	Volume blood** (approx)	Type of tube**	Collection point*	Location of specimen analysis
Serological Immunogenicity Assays	5-10 mL (for plasma)	EDTA	D1, 8*, 29, 57, 180, 360, at COVID-19 infection***	NIH Blake Warner Lab
Neutralization assay using a wild-type SARS-CoV- 2	3 mL (for serum)	SST	D1, 8*, 29, 57, 180, 360, at COVID-19 infection***	

* See study calendar for collection windows. Sample collection should occur prior to vaccine administration on applicable days (i.e., D1 and D29). D8 assessments are optional except for CAR T Cell Cohort.

**Tubes/media may be adjusted at the time of collection based upon materials available if approved by the PI/laboratory investigator

***If a participant tests positive for COVID-19 while on study these labs will be collected within 2 weeks of a positive PCR test. A second post-infection blood collection will occur 2-4 weeks after this initial blood draw. These post-infection blood draws are optional.

7.3.3 Salivary Assessments

7.3.3.1 Salivary measurement of IgG antibodies against the SARS-CoV-2 nucleocapsid and spike proteins

The luciferase immunoprecipitation systems (LIPS) immunoassay was used to study IgG antibody response against SARS-CoV-2 in saliva. Due to the potential biohazard of infectious SARS-CoV-2 in saliva and a viral inactivation protocol involving heating saliva at 56ºC for 30 minutes was employed. For these SARS-CoV-2 antibody measurements, Renilla luciferase-nucleocapsid and Gaussia luciferase-spike fusion protein extracts were employed with protein A/G beads as the IgG capture reagent as previously described [39]. Due to the lower levels of immunoglobulin present in saliva, 10 ml of each saliva sample was utilized in the LIPS assay as previously described [40].

Known SARS-CoV-2 serum samples for IgG antibodies against nucleocapsid and spike proteins and saliva from uninfected controls were used for assigning seropositive cut-off values and for standardization.

- **Saliva collection procedure:**

  Participants are asked to refrain from eating or drinking 90 minutes before their appointment but are encouraged to maintain adequate hydration the day before the appointment. To collect saliva, 50mL sterile falcons are used as saliva receptacles. We ask that participants relax with their head slightly forward and to refrain from swallowing for 2-4 minutes. Participants should place their lips up to the orifice of the 50 mL falcon ("kiss the opening") and push/squeeze the saliva that pools in the floor of their mouth into the orifice of the 50 mL falcon. Participants will be asked to expectorate every 30 seconds for 2-5 minutes. Ideally, 2-4 mL of saliva should be collected.

- **Saliva specimen processing:**

  Saliva (1mL) can be transferred to individual 2.0 mL screw-top conical tubes (Sarstedt 2.0 screw cap vials preferred) using a P1000 pipet or a sterile transfer pipet (actual volume can vary significantly). This would be 2-3 tubes/participant. These tubes should be stored frozen at -80C for long term storage.

7.3.3.2 Additional assays

Saliva samples will be used for additional research, in particular whole or targeted high throughput genome sequencing and its use in the analysis of immune system modulating genomic loci such as the IGHV region and the KIR region

7.3.4 Immune Assessments by the NCI LTIB Lab

The following immune assays be performed at the Laboratory of Tumor Immunology and Biology (LTIB) at the NCI's Center for Cancer Research (CCR) and include flow cytometry-based and serum assays.

Studies may be performed in select participants where adequate samples are available:

Peripheral blood mononuclear cells (PBMCs)

- PBMCs may be analyzed for changes in standard immune cell types (CD4 and CD8 T cells, natural killer [NK] cells, regulatory T cells [Tregs], myeloid-derived suppressor cells [MDSCs], and dendritic cells) as well as over 120 immune cell subsets, as described elsewhere [41, 42]
- PBMCs from selected subjects may be analyzed for function of specific immune cell subsets, including CD4 and CD8 T cells, NK cells, Tregs, and MDSCs.
- PBMCs may be analyzed for immune responses against SARS Co-V2 using an intracellular cytokine staining assay. PBMCs will be stimulated in vitro with overlapping 15-mer peptide pools encoding proteins of SARS Co-V2 (e.g., spike glycoprotein, nucleoprotein); control peptide pools will involve the use of human leukocyte antigen peptide as a negative control and CEFT peptide mix as a positive control. CEFT is a mixture of peptides of CMV,

Epstein-Barr virus, influenza, and tetanus toxin. Post-stimulation analyses of CD4 and CD8 T cells will involve the production of IFN-γ, IL-2, TNF, and the degranulation marker CD107a. A detailed description of this assay has been previously reported [43].

Soluble Factors/Serology

- Samples for soluble factor analysis will be collected as per Study Calendar. Sera and/or plasma may be analyzed pre- and post-therapy for changes in soluble factors (e.g. sCD27, sCD40L, sPD-1, sPD-L1), and cytokines (e.g. IFN-γ, IL-10, IL-12, IL-2, IL-4, etc.), chemokines, antibodies, tumor-associated antigens, and/or other markers using ELISA or multiplexed assays (e.g. Mesoscale, Luminex, cytokine bead array).
- Coded, linked samples will be sent to Quest for antibody analysis. The code will not be shared with Quest.

7.3.4.1 Additional assays:

- Blood samples may be used for additional research studies, which may include phenotypic and functional analysis of immune-cell subsets, and analyses for other cytokines (IFN-γ, IL-10, IL-12, IL-2, IL-4, etc.), chemokines, antibodies, and/or other markers. Additionally, blood samples may be used for whole or targeted high throughput genome sequencing on which bioinformatic analysis of immune system modulating genomic loci such as the IGHV region and the KIR region could be performed.

7.3.5 Summary of Correlative Samples for Vaccine-Naïve Cohorts

7.3.5.1 Collection of salivary and other blood specimens:

Test/Assay	Volume blood**(approx)	Type of tube**	Collection point*	Location of specimen analysis
Salivary measurement of IgG antibodies	1 mL (saliva)	Sarstedt 2.0 screw cap vials	D1, D29, D36, D57, D209 and D394	NIH Blake Warner Lab
Antigen Specific T cell Immune Response by cytokine staining assay	60 mL (for PBMCs)	Sodium Heparin (Green top)	D1, D29, D36, D57, at COVID-19 infection***	NIH Laboratory of Tumor Immunology and Biology (LTIB)
Standard and Refined immune cell subsets analysis by FACS		Sodium Heparin (Green top)	D1, D29, D36, D57, at COVID-19 infection***	NIH Laboratory of Tumor Immunology and Biology (LTIB)
Cytokines/soluble factors by ELISA/multiplexed assays	8 mL (for serum)	SST	D1, D29, D36, D57, D209 and D394, at COVID-19 infection***.	NIH Laboratory of Tumor Immunology and Biology (LTIB)

* See study calendar for collection windows. Sample collection should occur prior to vaccine administration on applicable days (i.e., D1 and D29). Participants who opt to receive a booster vaccine will have their samples drawn according to the Booster Vaccine Cohort calendar.

**Tubes/media may be adjusted at the time of collection based upon materials available if approved by the PI/laboratory investigator

***If a participant tests positive for COVID-19 while on study these labs will be collected within 2 weeks of a positive PCR test. A second post-infection blood collection will occur 2-4 weeks after this initial blood draw. These post-infection blood draws are optional.

7.3.6 Summary of Correlative Samples for Booster Vaccine Cohorts

7.3.6.1 Collection of salivary and other blood specimens:

Test/Assay	Volume blood** (approx)	Type of tube**	Collection point*	Location of specimen analysis
Salivary measurement of IgG antibodies	1 mL (saliva)	Sarstedt 2.0 screw cap vials	D1, 8*, 29, 57, 180, 360	NIH Blake Warner Lab
Antigen Specific T cell Immune Response by cytokine staining assay	60 mL (for PBMCs)	Sodium Heparin (Green top)	D1, 8*, 29, 57, 180, 360, at COVID-19 infection***.	NIH Laboratory of Tumor Immunology and Biology (LTIB)
Standard and Refined immune cell subsets analysis by FACS		Sodium Heparin (Green top)	D1, 8*, 29, 57, 180, 360, at COVID-19 infection***.	NIH Laboratory of Tumor Immunology and Biology (LTIB)
Cytokines/soluble factors by ELISA/multiplexed assays	8 mL (for serum)	SST	D1, 8*, 29, 57, 180, 360, at COVID-19 infection***.	NIH Laboratory of Tumor Immunology and Biology (LTIB)

* See study calendar for collection windows. Sample collection should occur prior to vaccine administration. D8 assessments are optional except for CAR T Cell Cohort.

**Tubes/media may be adjusted at the time of collection based upon materials available if approved by the PI/laboratory investigator

***If a participant tests positive for COVID-19 while on study these labs will be collected within 2 weeks of a positive PCR test. A second post-infection blood collection will occur 2-4 weeks after this initial blood draw. These post-infection blood draws are optional.

7.3.7 Future use of stored specimens

Samples will be ordered as appropriate (e.g., at NIH, ordered in CRIS and tracked through a Clinical Trial Data Management system; should a CRIS screen not be available, the CRIS downtime procedures will be followed). Samples will not be sent outside NIH without appropriate approvals and/or agreements, if required.

All specimens obtained in the protocol are used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described below. The study will remain open so long as sample or data analysis continues. Samples from consenting

subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed.

If the participant withdraws consent the participants data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

The site PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of section **16.2.1**

7.3.8 Specimen Preparation, Handling, and Shipping

Biological specimens are to be collected in accordance with protocol specifications, as outlined in the section **7.3.5**. Study staff will follow all safety guidelines of local safety committee and/or institutional policies for handling biological specimens

7.3.8.1 Sample Management and Storage at Clinical Services Program – Leidos Biomedical Research, Inc. (CSP)

Clinical Services Program - Leidos Biomedical Research, Inc.
Attn: PPD
1050 Boyles Street Bldg. 469/Room 121
Frederick, MD 21702

On days samples are drawn, CSP (part of NCI Frederick Central Repositories) should be notified (phone: [301] 846-5893; fax [301] 846-6222). They will arrange same-day courier delivery of the specimens. All data associated with the participant samples is protected by using a secure database. All samples drawn at the NIH Clinical Center will be transported to the Clinical Support Laboratory at the Frederick National Laboratory for Cancer Research by couriers. Samples will be tracked and managed by Central Repository database, where there is no link to personal identifiable information. All samples will be stored in either a -80ºC freezer or vapor phase liquid nitrogen. These freezers are located at NCI Frederick Central Repository in Frederick, Maryland. NCI Frederick Central Repositories (managed under a subcontract) store, among other things, biological specimens in support of NIH clinical studies. All specimens are stored in secure, limited-access facilities with sufficient security, backup, and emergency support capability and monitoring to ensure long-term integrity of the specimens for research. Specimens are stored in accordance with applicable HHS and FDA Protection of Human Subjects Regulations in accordance with the subcontractor's Federal-wide Assurance. The subcontractor's role limited to clinical research databases and repositories containing participant specimens. The subcontractor does not conduct or have any vested interest in research on human subjects but does provide services and support the efforts of its customers, many of which are involved in research on human subjects. The subcontractor's IRB reviews policies and procedures for labeling, data collection and storage, access, and security. The IRB will review protection of privacy issues prior to acceptance of any new work and in the event of change impacting privacy issues in existing work. It is the intent and purpose of the subcontractor to accept only coded, linked samples and sample information. To the limit of our ability, every effort will be made to ensure that protected information is not sent electronically or by hard copy or on vial labels. Sample data is stored in the BioSpecimen Inventory System II (BSI). This inventory tracking system is used to manage the

storage and retrieval of specimens as well as to maintain specimen data. BSI is designed for controlled, concurrent access. It provides a real-time, multi-user environment for tracking millions of specimens. The system controls how and in what order database updates and searches are performed. This control prevents deadlocks and race conditions. For security, BSI has user password access, 3 types of user access levels, and 36 user permissions (levels of access) that can be set to control access to the system functions. BSI provides audit tracking for processes that are done to specimens including shipping, returning to inventory, aliquoting, thawing, additives, and other processes. BSI tracks the ancestry of specimens as they are aliquoted, as well as discrepancies and discrepancy resolution for specimens received by the repository. If a specimen goes out of the inventory, the system maintains data associated with the withdrawal request. Vials are labeled with a unique BSI ID which is printed in both eye-readable and bar-coded format. No patient-specific information is encoded in this ID. Investigators are granted view, input, and withdrawal authority only for their specimens. They may not view specimen data or access specimens for which they have not been authorized. Access to specimen storage is confined to repository staff. Visitors to the repositories are escorted by repository staff at all times.

On days where saliva samples are collected, pre-labeled/barcoded 50 mL conical tubes containing ~3.0-5.0 mL of participant saliva and 3 pre-labeled/barcoded 2.0 mL screw-top flat bottom conical vials will placed inside a sample biohazard bag placed inside another sample bag containing wet ice and couriered to OP-DEN. Once at OP-DEN receives the samples, please contact the Patient Care Coordinator (c: 240-515-8985) by phone call or text, regarding the availability of the sample for pick up and processing. Samples will be processed in the OP-DEN clinical sample laboratory and aliquoted in 1.5-2.0 mL aliquots to be stored in a secure -80ºC freezer in a locked cage.

8 ASSESSMENT OF SAFETY

8.1 Assessing and Recording Safety Parameters

Safety will be assessed by the frequency and severity of treatment related adverse events as defined by CTCAE V5, which is available here:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf

The CTCAE utilizes the System Organ Class (SOC) terminology derived from MedDRA in order to organize the adverse events into appropriate sections. SOC reflects the highest level of the MedDRA1 hierarchy. Each SOC is identified by an anatomical or physiological system, an etiology, or a purpose (e.g., SOC Investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade).

If the CTCAE V5 does not have the required term, investigators are encouraged to consult MedDRA (https://www.meddra.org/) in order to utilize the appropriate MedDRA term. Within each SOC, the final adverse event term allows for a free text "Other" term. If investigators are unable to find a specific term describing the adverse event within CTCAE, investigators should utilize the free text "Other" terminology and report the appropriate MedDRA term. This will enable appropriate comparisons of with the mRNA-1273 Phase 3 trial, which utilized MedDRA.

8.1.1 Adverse Events (AEs)

ICH E6 defines an AE as any untoward medical occurrence in a participant or clinical investigation Participant administered a pharmaceutical product regardless of its causal relationship to the study treatment. FDA defines an AE as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient presenting for medical care, or upon review by a study monitor.

All AEs, including solicited local (injection site) and systemic (subjective and quantitative) reactions, will be captured on the appropriate data collection form and eCRF. Information to be collected for AEs includes event description, date of onset, assessment of severity, relationship to study product and alternate etiology (assessed only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as an investigator), date of resolution, seriousness and outcome. AEs occurring during the trial collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

Any medical condition that is present at the time that the Participant is screened will be considered as baseline and not reported as an AE. However, if the severity of any pre-existing medical condition increases, it should be recorded as an AE.

If an event meets both the criteria of a study endpoint and an adverse event, the event will be reported either as a study endpoint or as an adverse event (not both).

8.1.1.1 Adverse Events Grading

All AEs (laboratory and clinical symptoms) will be graded for severity and assessed for relationship to study product (see definitions). AEs characterized as intermittent require documentation of onset and duration of each episode. The start and stop date of each reported AE will be recorded on the appropriate data collection form and eCRF. Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity.

8.1.1.1.1 Severity of Event:

The severity of unsolicited AEs will be assessed by the investigator using the NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.

The severity of solicited AEs will be assessed by the investigator using the clinical abnormalities section of the FDA "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" .

The following grading system utilized for the events not listed in the above scales:

* Mild (Grade 1): Events that are usually transient and may require only minimal or no treatment or therapeutic intervention and generally do not interfere with the Participant's usual activities of daily living.
    - Transient: Duration less than 48 hours

- Therapeutic Intervention: An action to alleviate the adverse event that does not require a medication or medical procedure, such as a change in diet, or application of cool pack or warm compress, or rest

* Moderate (Grade 2): Events that are usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

  - Therapeutic Intervention: Use of non-narcotic pain reliever or over-the-counter medication

* Severe (Grade 3): Events interrupt usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. Severe events are usually incapacitating.

  - Activities of Daily Living (ADLs): Negative impact on ADLs, such as missed work, unable to do housework or exercise
  - Significantly Affects Clinical Status: A medically attended event – clinical care was sought from a healthcare professional
  - Intensive Therapeutic Intervention: Required prescription medication, or intravenous fluids or medical procedure

8.1.1.2 **Relationship to Study Product:**

The assessment of the AE's relationship to study product will be done by the licensed study physician indicated on the Form FDA 1572 and the assessment will be part of the documentation process. Whether the AE is related or not, is not a factor in determining what is or is not reported in this trial. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

In a clinical trial, the study product must always be suspect. The relationship to study product will be assessed for AEs using the terms related or not related:

* Related – There is a reasonable possibility that the study product caused the AE. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the AE.
* Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

8.1.2 **Reactogenicity (Solicited AE)**

Reactogenicity events are AEs that are common and known to occur following administration of this type of study vaccine. Study clinicians will follow and collect resolution information for any reactogenicity symptoms that are not resolved within 7 days.

Solicited AEs (i.e., reactogenicity) will be collected using memory aids and recorded on the appropriate source document from the time of each vaccination through 7 days post each vaccination (Days 1-8 for the first vaccination, and Days 29-36 for the second vaccination if applicable).

For this study, solicited AEs will be:

- Injection site Pain
- Injection site Erythema
- Injection site Edema/Induration
- Headache
- Diarrhea
- Fatigue
- Myalgia
- Arthralgia
- Nausea
- Fever
- Chills

8.1.3 Serious Adverse Events (SAEs)

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse event (see section **8.1.4**)
- Inpatient hospitalization or prolongation of existing hospitalization
    - A hospitalization/admission that is pre-planned (i.e., elective or scheduled surgery/chemotherapy arranged prior to the start of the study), a planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered a serious adverse event.
    - A hospitalization/admission that is solely driven by non-medical reasons (e.g., hospitalization for patient or Participant convenience) is not considered a serious adverse event.
    - Emergency room visits or stays in observation units that do not result in admission to the hospital would not be considered a serious adverse event. The reason for seeking medical care should be evaluated for meeting one of the other serious criteria.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or Participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.4 Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or Participant at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. (21CFR312.32)

8.1.5 Adverse Events of Special Interest (AESIs)

Adverse Events of Special Interest (AESIs) represent any events for which additional data (besides the standard AE data) are desired. These may be at the request of the regulatory agency, pharmaceutical partner or the Sponsor, and driven by a regulatory requirement, or known or potential risk from the product or class.

AESIs will include:

- Hypersensitivity reactions and other allergic reactions
- Hyperimmune responses
- Thrombocytopenia
- Myocarditis (inflammation of the heart muscle) or pericarditis (inflammation of the thin tissue surrounding the heart [the pericardium]). These will be based on the CDC case definition criteria[44] of these conditions.
- SAEs considered related to the vaccine

AESI will be reported to the Sponsor on the SAE form, following the timelines for SAE reporting.

8.2 Specification of Safety Parameters

8.2.1 Solicited Events

Solicited events are AEs that are common and known to occur following administration of study product.

8.2.2 Unsolicited Events

Unsolicited events are any other AEs that occur following administration of study

8.3 Type and Duration of Follow-up of Participants after Adverse Events

All AEs will be assessed for severity and relationship to study intervention. Collection of all AEs from the participant, solicited and unsolicited, will occur during the period from study product administration on Day 1 through 28 days after the last vaccination. Adverse events that are serious need to be recorded after 28 days following the last vaccine, only if they are related to the study intervention.

8.4 Assessment of Safety Events

AE information collected will include event description, date of onset, assessment of severity and relationship to study product and alternate etiology (if not related to study product), date of resolution of the event, seriousness and outcome. The assessment of severity and relationship to

the study product will be done only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the site principal investigator or sub-investigator. AEs occurring during the collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.
- Recorded on the appropriate SAE report form, the medical record and captured in the clinical database.
- Followed through resolution by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.

An abnormal laboratory value which cannot be attributed to chemotherapy for malignancy will be recorded in the database as an AE **only** if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the study intervention and about the participant's outcome.

8.5 Reporting of Serious Adverse Events

Any AE that meets protocol-defined serious criteria or meets the definition of Adverse Event of Special Interest that require expedited reporting must be submitted immediately (within 24 hours of awareness) to OSRO Safety using the CCR SAE report form.

All SAE reporting must include the elements described in section **8.4**

SAE reports will be submitted to the Center for Cancer Research (CCR) at: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. CCR SAE report form and instructions can be found at: https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=157942842

Following the assessment of the SAE by OSRO, other supporting documentation of the event may be requested by the OSRO Safety and should be provided as soon as possible.

8.6 Safety Reporting Criteria to the Pharmaceutical Collaborators

Reporting will be per the collaborative agreement.

8.7 Reporting Pregnancy

8.7.1 Maternal exposure

Pregnant women are excluded from enrolling due to the possible deleterious effects of the investigational vaccine on the fetus.

If a participant becomes pregnant during the course of the study, the pregnancy will be reported to the Sponsor no later than 24 hours of when the Investigator becomes aware of it. If a pregnancy occurs while on study, to minimize the risks the subject will be withdrawn from the study and follow up care continued by their home obstetrics/gynecological (OB/GYN) doctor.

No inducements, monetary or otherwise, will be offered to terminate a pregnancy. No individuals engaged in the research will have any part in the decisions as to the timing, method, or procedures used to terminate a pregnancy and individuals engaged in the research will have no part in determining the viability of a neonate.

Pregnancy itself is not regarded as an SAE.

The outcome of all pregnancies should be followed up and documented per stand of care. The investigator should notify the Sponsor no later than 24 hours of when the outcome of the pregnancy becomes known.

8.7.2 Paternal exposure

Male participants should refrain from fathering a child or donating sperm during the study and use effective contraception from first vaccination until 30 days after the last vaccination.

Pregnancy of the participant's partner is not considered to be an AE. However, the outcome of all pregnancies occurring from the date of the first vaccine dose until 1 month after the last dose should, if possible, be followed up and documented. Pregnant partners may be offered the opportunity to participate in an institutional pregnancy registry protocol (e.g., the NIH IRP pregnancy registry study) to provide data about the outcome of the pregnancy for safety reporting purposes.

8.8 Regulatory Reporting for Studies Conducted Under CCR-Sponsored IND

Following notification from the investigator, CCR, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected. CCR will report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study product and the adverse event. CCR will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, in accordance to 21 CFR Part 312.32.

All serious events will be reported to the FDA at least annually in a summary format.

8.9 Halting Rules

8.9.1 Study Halting Criteria

If any of the below occurs, the Protocol Chair will halt accrual to the trial to conduct a detailed safety review. Prior to resumption of the study, an expedited safety report will be sent to and reviewed by FDA if requested. All events also must be evaluated by the SMC.

- Any participant experiences laryngospasm, bronchospasm or anaphylaxis within 24 hours after administration of vaccine that is considered related to vaccine.
- Two (2) or more participants experience an allergic reaction such as generalized urticaria defined as occurring at three or more body parts within 72 hours after administration of vaccine that is considered related to vaccine.
- Any participant experiences suspected or confirmed myocarditis and/or pericarditis related to the study vaccine within 6 weeks of administration.
- Any serious adverse event deemed related to the vaccine will result in a halt to study accrual and an ad hoc meeting of the Safety Monitoring Committee (SMC). After a discussion of the event, the decision will be made as to whether to halt further accrual or lift the hold on accrual, based on the facts of the case and emerging evidence. Participants already on trial who successfully completed the first dose without incident will be allowed to receive the second dose of the vaccine, as per the mRNA-1273 vaccine's Emergency Use Authorization (EUA) granted in December 2020.

8.10 Safety Oversight

8.10.1 Safety Monitoring Committee (SMC)

The SMC is an independent group of at least 3 experts that monitors participant safety and advises The Sponsor. SMC members will be separate and independent of study staff participating in this trial and should not have scientific, financial, or other conflicts of interest related to this trial. The SMC will consist of members with appropriate expertise to contribute to the interpretation of data from this trial. A quorum will consist of a simple majority.

Given the frequency and urgency to review data, the SMC will not need to meet unless halting rules are met.

SMC will meet to evaluate any adverse events associated with myocarditis or pericarditis within 1-2 weeks of reporting of the event.

Cumulative AE data will be provided to the SMC after all participants have completed Day 36.

The SMC will meet when trial halting criteria are met, or as requested by the sponsor or PI.

The SMC will have a final review meeting at the end of the study.

Procedures for SMC reviews/meetings will be defined in the SMC charter. The SMC will review applicable data, including, but not limited to, enrollment, demographics, dosing data, clinical laboratory data, and safety data, at scheduled timepoints during this trial as defined in the SMC charter. The SMC will review blinded aggregate data in the open session of the SMC meetings.

Additional data may be requested by the SMC, and interim statistical reports may be generated as deemed necessary and appropriate by the Sponsor. As an outcome of each review/meeting, the SMC will make a recommendation as to the advisability of proceeding with study product administration, and to continue, modify, or terminate this trial.

8.11 Sponsor Protocol Deviation Reporting

A Protocol Deviation is defined as any non-compliance with the clinical trial Protocol, Manual of Operational Procedures (MOP) and other Sponsor approved study related documents, GCP, or protocol-specific procedural requirements on the part of the participant, the Investigator, or the study site staff inclusive of site personnel performing procedures or providing services in support of the clinical trial.

Non-NIH participating sites not using the CCR Protocol Deviation Tracking System (PDTS) will report any protocol deviation on the OSRO Site Protocol Non-Adherence/Deviation Log, or a site-generated protocol deviation report approved by OSRO. The Non-Adherence/Deviation Log should be maintained in the site essential documents file and submitted to OSRO via OSROMonitoring@mail.NIH.gov on the **first business day of each month throughout the study**.

It is the responsibility of the study Staff to document any protocol deviation identified by the Staff or the site Monitor in the CCR Protocol Deviation Tracking System (PDTS) online application. The entries into the PDTS online application should be timely, complete, and maintained per CCR PDTS user requirements. In addition, any deviation to the protocol should be documented in the participant's source records and reported to the reviewing IRB per their guidelines. OSRO required protocol deviation reporting is consistent with E6(R2) GCP: Integrated Addendum to ICH E6(R1): 4.5 Compliance with Protocol; 5.18.3 (a), and 5.20 Noncompliance; and ICH E3 16.2.2 Protocol deviations.

9 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure:

- that the rights of the participants are protected;
- that the study is implemented per the approved protocol, Good Clinical Practice and standard operating procedures; and,
- the quality and integrity of study data and data collection methods are maintained.

Monitoring for this study will be performed by NCI CCR Office of Sponsor and Regulatory Oversight (OSRO) Sponsor and Regulatory Oversight Support (SROS) Services contractor. Clinical site monitoring activities will be based on OSRO standards, FDA Guidance E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) March 2018, and applicable regulatory requirements.

Details of clinical site monitoring will be documented in a Clinical Monitoring Plan (CMP) developed by OSRO. CMPs will be protocol-specific, risk-based and tailored to address human subject protections and integrity of the study data. OSRO will determine the intensity and

frequency of monitoring based on several factors, including study type, phase, risk, complexity, expected enrollment rate, and any unique attributes of the study and the site. The Sponsor will conduct a periodic review of the CMP to confirm the plan's continued appropriateness. A change to the protocol, significant or pervasive non-compliance with GCP, or the protocol may trigger CMP updates.

OSRO SROS Monitoring visits and related activities will be conducted throughout the life cycle of each protocol. The first activity is before the study starts to conduct a Site Assessment Visit (SAV) (as warranted), followed by a Site Initiation Visit (SIV), Interim Monitoring Visit(s) (IMVs), and a study Close-Out Visit (COV).

Some monitoring activities may be performed remotely, while others will occur at the study site(s). Monitoring visit reports will describe visit activities, observations, and associated action items or follow-up required for resolution of any issues, discrepancies, or deviations. Monitoring reports will be distributed to the study PI, NCI CCR QA, CCR Protocol Support Office, coordinating center (if applicable), and the Sponsor regulatory file.

The site Monitor will inform the study team of any deviations observed during monitoring visits. If unresolved, the Monitor will request that the site Staff enter the deviations in the CCR Protocol Deviation Tracking System (PDTS) for deviation reporting to the Sponsor and as applicable per institutional and IRB guidance.

10 HUMAN PARTICIPANTS PROTECTION

10.1 Institutional Review Board

Each site principal investigator will obtain IRB approval for this protocol to be conducted at his/her research site(s) and send supporting documentation to the CCR before initiating recruitment of participants. The investigator will submit applicable information to the IRB on which it relies for the review, to conduct the review in accordance with 45 CFR 46, ICH E6 GCP, and as applicable, 21 CFR 56 (Institutional Review Boards) and 21 CFR 50 (Protection of Human Participants), other federal, state, and local regulations. The IRB must be registered with OHRP as applicable to the research. CCR must receive the documentation that verifies IRB-approval for this protocol, associated informed consent documents, and upon request any recruitment material and handouts or surveys intended for the participants, prior to the recruitment and enrollment of participants.

Any amendments to the protocol or consent materials will be approved by the IRB before they are implemented. IRB review and approval will occur at least annually throughout the enrollment and follow-up of participants and may cease if annual review is no longer required by applicable regulations and the IRB. The investigator will notify the IRB of deviations from the protocol and reportable SAEs, as applicable to the IRB policy.

Each institution engaged in this research will hold a current Federalwide Assurance (FWA) issued by the Office of Human Research Protection (OHRP) for federally funded research.

Of note for this study: A single IRB of record, *NIH IRB*, will be accountable for compliance with regulatory requirements for this multi-centered study, at participating sites. A reliance agreement will be required. The reliance agreement and local policy will set forth the specific responsibilities of the IRB and each participating site. Participating sites will then rely on the IRB of record to satisfy the regulatory requirements relevant to the IRB review. The participating sites will maintain essential required documentation of IRB reviews, approvals, and correspondence, and must provide copies of any agreements and essential documentation to the CCR or regulatory authorities upon request.

10.2 Informed Consent Process

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continuing throughout the individual's trial participation. Before any study procedures are performed, informed consent will be obtained in-person or remotely (e.g., via telephone or other NIH/local approved remote secure internet-based platforms used in compliance with policy including HRPP Policy 303) and documented. Participants will receive a concise and focused presentation of key information about the clinical trial, verbally and with a physical or electronic consent form. The explanation will be organized and presented in lay terminology and language that facilitates understanding why one might or might not want to participate.

An investigator or designee will describe the protocol to potential participants in-person or remotely. The key information about the purpose of the study, the procedures and experimental aspects of the study, risks and discomforts, any expected benefits to the Participant, and alternative treatment will be presented first to the Participant.

Participants will also receive an explanation that the trial involves research, and a detailed summary of the proposed study procedures and study interventions/products. This will include aspects of the trial that are experimental, the probability for random assignment to treatment groups, any expected benefits, all possible risks (including a statement that the particular treatment or procedure may involve risks to the Participant or to the embryo or fetus, if the Participant is or may become pregnant, that are currently unforeseeable), the expected duration of the Participant's participation in the trial, alternative procedures that may be available and the important potential benefits and risks of these available alternative procedures.

Participants will be informed that they will be notified in a timely manner if information becomes available that may be relevant to their willingness to continue participation in the trial. Participants will receive an explanation as to whether any compensation and any medical treatments are available if injury occurs, and, if so, what they consist of, or where further information may be obtained. Participants will be informed of the anticipated financial expenses, if any, to the Participant for participating in the trial, as well as any anticipated prorated payments, if any, to the Participant for participating in the trial. They will be informed of whom to contact (e.g., the investigator) for answers to any questions relating to the research project.

Information will also include the foreseeable circumstances and/or reasons under which the Participant's participation in the trial may be terminated. The participants will be informed that participation is voluntary and that they are free to withdraw from the study for any reason at any time without penalty or loss of benefits to which the Participant is otherwise entitled.

The extent of the confidentiality of the participants' records will be defined, and participants will be informed that applicable data protection legislation will be followed. Participants will be informed that the monitor(s), auditors(s), IRB, NIH, and regulatory authority(ies) will be granted direct access to the Participant's original medical records for verification of clinical trial procedures and/or data without violating the confidentiality of the Participant, to the extent permitted by the applicable laws and regulations, and that, by signing a written informed consent form, the Participant is authorizing such access.

Participants will be informed that records identifying the Participant will be kept confidential, and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available and, if the results of the trial are published, the Participant's identity will remain confidential. Participants will be informed whether private information collected from this research and/or specimens will be used for additional research, even if identifiers are removed.

Participants will be allowed sufficient time to consider participation in this research trial and have the opportunity to discuss this trial with their family, friends or legally authorized representative, or think about it prior to agreeing to participate.

Informed consent forms will be IRB-approved and participants will be asked to read and review the consent form. Participants must sign the informed consent form prior to starting any study procedures being done specifically for this trial.

Once signed, a copy of the informed consent form will be given to the Participant(s) for their records. The Participant(s) may withdraw consent at any time throughout the course of the trial. The rights and welfare of the Participant(s) will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to participant) or on the electronic document.

Manual (non-electronic) signature on electronic document:

When a manual signature on an electronic document is used for the documentation of consent at the NIH Clinical Center, this study will use the following to obtain the required signatures:

- Adobe platform (which is not 21 CFR Part 11 compliant); or,
- iMedConsent platform (which is 21 CFR Part 11 compliant)

During the consent process, participants and investigators will view individual copies of the approved consent document on screens at their respective locations (if remote consent); the same screen may be used when in the same location but is not required.

Both the investigator and the participant will sign the document using a finger, stylus or mouse.

Note: Refer to the CCR SOP PM-2, Obtaining and Documenting the Informed Consent Process for additional information (e.g., verification of participant identity when obtaining consent remotely) found at: https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

Please see site specific supplement for electronic signature requirements for participating site.

Study personnel may employ recruitment efforts prior to obtaining study consent if a patient-specific screening consent is on record or if the IRB has agreed that chart review is allowed without a fully executed screening consent. In cases where there is not a patient-specific screening consent on record, site Clinical staff may pre-screen via chart review and refer potential participants to the Research staff. Research staff would obtain written consent per the standard informed consent process before conducting protocol-specific screening activities.

New information will be communicated by the site principal investigator to participants who consent to participate in this trial in accordance with IRB requirements. The informed consent document will be updated and participants will be re-consented per IRB requirements, if necessary. Participants will be given a copy of all informed consent forms that they sign.

10.3 Consent for Future Use of Stored Specimens and Data

Residual samples/specimens are those that are left over after protocol-specified testing and this study has been completed. Participants will be asked for permission to keep any remaining (residual) specimens (serum and PBMCs) derived from venous blood samples for possible use in future research studies, such as examining additional immunological assessments or testing for antibodies against other viruses or bacteria. These residual specimens will be stored coded indefinitely at NIH or designated NIH site. Specimens may be shared per protocol or as allowed per informed consent with any additional review and approval by an IRB, if required.. The recipients of specimens will be informed that these specimens have a NIH certificate of confidentiality.

10.4 Exclusion of Women, Minorities, and Children (Special Populations)

Both men and women are eligible for this trial if they meet eligibility criteria. Participants from all racial and ethnic groups are eligible for this trial. All participants meeting the criteria listed in section 2.1 are eligible for enrollment.

There are no dosing or adverse event data are currently available on the use of 2019 nCov Vaccine in participants <18 years of age; therefore, children are excluded from this study.

10.5 Participant Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality includes documentation, investigation data, Participant's clinical information, and all other information generated during participation in the study. No information concerning the study or the data generated from the study will be released to any unauthorized third party without prior written approval of the CCR and the Participant. Participant confidentiality will be maintained when study results are published or discussed in conferences. The study monitor or other authorized representatives of the sponsor or governmental regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

All records will be kept locked and all computer entry and networking programs will be carried out with coded numbers only and with password protected systems. All non-clinical specimens, evaluation forms, reports, and other records that leave the site will be identified only by a coded number.

10.6 Certificate of Confidentiality

To protect privacy, we have received a Certificate of Confidentiality. With this Certificate, the researchers cannot be forced to release information that may identify the research Participant, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify the Participant, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects, like this study, or for information that must be released in order to meet the requirements of the Federal Food and Drug Administration (FDA).

A Certificate of Confidentiality does not prevent the Participant from voluntarily releasing information about themselves or their involvement in this research. If any person or agency obtains a written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from reporting without the Participant's consent, information that would identify the Participant as a participant in the research project regarding matters that must be legally reported including: child and elder abuse, sexual abuse, or wanting to harm themselves or others.

The release of individual private information or specimens for other research will only occur if consent was obtained from the individual to whom the information, document, or biospecimen pertains, or for the purposes of other research that is in compliance with applicable Federal regulations governing the protection of human participants in research.

10.7 Costs, Participant Compensation, and Research Related Injuries

10.7.1 **NIH**

Costs:

There is no cost for the research tests, procedures, and study product that participants receive at the NIH Clinical Center while taking part in this trial. If some tests and procedures are performed outside the NIH Clinical Center, these may be billed to the Participant, Participant's insurance or third party. Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.

Participant Compensation:

Participants will not be compensated on this study.

The NCI will cover the costs of some expenses associated with protocol participation. Some of these costs may be paid directly by the NIH and some may be reimbursed to the

participant/guardian as appropriate. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy.

10.7.2 **Participating Sites**

This will be based on local guidelines (e.g., as described in the site-specific consent).

10.7.3 **All Sites**

If it is determined by the site principal investigator that an injury occurred to a Participant as a direct result of the tests or treatments that are done for this trial, then referrals to appropriate health care facilities will be provided to the Participant. Study personnel will try to reduce, control, and treat any complications from this trial. Immediate medical treatment may be provided by the participating site.

The Secretary HHS issued a Public Readiness and Emergency Preparedness (PREP) Act Declaration for certain COVID-19 countermeasures in March 2020. While study participants right to sue for significant injuries (including death) is restricted under the Declaration, U.S.-located or other certain participants with a U.S. nexus may be able to seek compensation from HRSA's Countermeasure Injury Compensation Program (CICP) for certain serious physical injuries. Participants will be notified of the same in the informed consent document.

11 STATISTICAL CONSIDERATIONS

11.1 Study Hypotheses

There is no hypothesis testing in this study; the study is intended to develop modestly precise estimates of parameters which reflect potential efficacy.

11.2 Sample Size Considerations

The number of proposed participants is considered sufficient to provide a descriptive summary of the immunogenicity and safety of mRNA-1273 with reasonable precision overall and in various cohorts of participants.

It will be assumed that there is a maximum of 220 participants available for evaluation, but that subsets of 20 and 30 participants may be considered as well, primarily based on the sub-cohorts for hematological malignancies. In addition, early results any cohort may be reported prior to final study completion after evaluation of day 57 lab results. Overall, there will be 20 evaluable participants with solid tumors and 60 participants with hematologic malignancies in the vaccine-naïve cohorts. The booster vaccine cohorts will have a maximum enrollment of 20 participants with the exception of the CAR T cell therapy cohort which will have a maximum enrollment of 30 participants and the Other Adult Solid Tumor cohort which has a maximum enrollment of 10 participants. Participants enrolled onto the vaccine naïve cohort who receive a booster dose will not be counted towards these totals.

11.3 Treatment Assignment Procedures

Participants from all four cohorts will be assigned to treatment arm 1. All cohorts will open immediately.

11.3.1 **Vaccine-Naïve Cohorts:**

Number	Description
1	Hematologic Low Immunosuppression
2	Hematologic Intermediate Immunosuppression
3	Hematologic High Immunosuppression
4	Solid Tumor

11.3.2 **Booster Vaccine Cohorts:**

Number	Description
5	CLL Not On Active Therapy
6	CLL Receiving BTK Inhibitor Interruption
7	CAR T Cell Therapy
8	Solid Tumor on PD1/PDL1 Inhibitor
9	Post Allogeneic Transplant
10	Other Hematologic Malignancy
11	Other Adult Solid Tumor

11.3.3 **Arm**

Name	Description
Arm 1	100 mcg (0.5 mL) mRNA-1273 injection (IM) on days 1 and 29; with option for subsequent booster dose, 100 mcg (0.5 mL) mRNA-1273 injection (IM) no less than 4 weeks after day 29
Arm 2	100 mcg (0.5 mL) mRNA-1273 injection (IM) on day 1

11.4 Final Analysis Plan

11.4.1 **Populations for Analyses**

11.4.1.1 **Full Analysis Set**

The Full Analysis Set (FAS) consists of all participants who a) receive at least one study injection, b) have baseline (Day 1) data available for those analyses that require baseline data, and c) have at least one post-injection assessment for the analysis endpoint.

11.4.1.2 **Per-Protocol Set**

The Per-Protocol (PP) Set consists of all FAS participants who meet all of the following criteria:

- Complied with the injection schedule.

- Complied with the timings of immunogenicity blood sampling to have post-injection results available for at least one assay component corresponding to the immunogenicity analysis objective.
- Have had no major protocol deviations that impact immune response during the period corresponding to the immunogenicity analysis objective.

The PP Set will serve as the primary set for the analysis of immunogenicity data in this study.

11.4.1.3 Solicited Safety Set

The Solicited Safety Set consists of all participants who received at least one study injection, and contribute any solicited AR data; i.e., have at least one post-baseline solicited safety assessment. The Solicited Safety Set will be used for the analyses of solicited ARs.

11.4.1.4 Safety Set

The Safety Set consists of all participants who received at least one study injection. The Safety Set will be used for analysis of safety except for the solicited ARs.

11.4.2 Statistical Analyses

11.4.2.1 Immunogenicity Analyses

The analyses of immunogenicity will be based on the PP Set. If the number of participants in the FAS and PP Set differ (defined as the difference divided by the total number of participants in the PP Set) by more than 10%, supportive analyses of immunogenicity may be conducted using the FAS.

For the primary immunogenicity endpoint, geometric mean titer (GMT) of specific bAb with corresponding 95% CI at each timepoint and geometric mean fold rise (GMFR) of specific bAb with corresponding 95% CI at each post-baseline timepoint over pre-injection baseline at Day 1 will be provided. Descriptive summary statistics including median, minimum, and maximum will also be provided.

For the secondary immunogenicity endpoint, GMT of specific nAb with corresponding 95% CI at each timepoint and GMFR of specific nAb with corresponding 95% CI at each post-baseline timepoint over pre-injection baseline at Day 1 will be provided. Descriptive summary statistics including median, minimum, and maximum will also be provided. For summarizations of GMT values, antibody values reported as below the LLOQ will be replaced by 0.5 × LLOQ. Values that are greater than the upper limit of quantification (ULOQ) will be converted to the ULOQ.

The number and percentage of participants with GMFR ≥ 2, GMFR ≥ 3, and GMFR ≥ 4 of serum SARS-CoV-2-specific nAb titers and participants with seroconversion due to vaccination from baseline will be provided with 2-sided 95% CI using the Clopper-Pearson method at each post-baseline timepoint. Seroconversion at a participant level is defined as:

- For subjects with no detectable antibody titer (< LOD) at baseline: post-vaccination titer ≥ LLOQ
- For subjects with a positive baseline titer (> LOD): post-vaccination titer ≥ 4 times the LLOQ

- For subjects with a baseline titer ≥ LLOQ: post-vaccination titer ≥ a 4-fold rise compared with baseline titer

GMT with corresponding 95% CI will be provided (for each group) at each time point. The 95% CI will be calculated based on the t-distribution of the log-transformed values and transformed back to the original scale for presentation.

11.4.2.2 **Safety Analyses**

Safety and reactogenicity will be assessed by clinical review of all relevant parameters including solicited ARs (local and systemic events), unsolicited AEs, SAEs, AEs leading to discontinuation, safety laboratory test results, vital signs, and physical examination findings.

Solicited ARs and unsolicited AEs will be coded by system organ class (SOC) and preferred term according to the MedDRA for adverse reaction terminology. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007) is used in this study with modification for rash, solicited ARs, unsolicited AEs, and vital signs.

Rash will be graded as:

- Grade 0 = no rash
- Grade 1 = localized without associated symptoms
- Grade 2 = maculopapular rash covering < 50% body surface area
- Grade 3 = urticarial rash covering > 50% body surface area
- Grade 4 = generalized exfoliative, ulcerative or bullous dermatitis

All safety analyses will be based on the Safety Set, except summaries of solicited ARs which will be based on the Solicited Safety Set. All safety analyses will be provided overall and by cohort.

The number and percentage of participants with any solicited local AR, with any solicited systemic AR and with any solicited AR during the 7-day follow-up period after each injection will be provided with a 2-sided 95% exact CI using the Clopper-Pearson method.

Number and percentage of participants with unsolicited AEs, SAEs, Grade 3 or higher ARs and AEs, treatment-related AEs and SAEs, and AEs leading to discontinuation from study vaccine or participation in the study will be summarized. Unsolicited AEs will be summarized by system organ class and/or preferred term coded by MedDRA.

For treatment-emergent safety laboratory tests results, the raw values and change from baseline values will be summarized by timepoint.

The number and percentage of participants who have chemistry, hematology, coagulation, and vital signs results below or above the laboratory normal ranges will be tabulated by timepoint.

11.4.2.3 **Baseline Descriptive Statistics**

Demographic variables and baseline characteristics will be summarized by descriptive statistics (mean, standard deviation for continuous variable, and number and percentage for categorical variables), reported overall, as well as by hematologic vs. solid tumor participants, and will be

further reported in the three categories of hematologic participants in cohorts based on degree of immunosuppression.

11.4.2.4 **Planned Interim Analysis**

None

11.4.2.5 **Sub-Group Analyses**

Analyses will be performed based on the 4 cohorts described as well as hematologic vs. solid tumor participants.

11.4.2.6 **Exploratory Analyses**

The exploratory objectives are as follows:

- To assess immune responses against the SARS-CoV-2 nucleocapsid and spike proteins
- Salivary measurement of IgG antibodies against the SARS-CoV-2 nucleocapsid and spike proteins

Each of these will be done using descriptive analyses as appropriate. If any statistical tests are performed, they will be done without formal adjustment for multiple comparisons but in the context of the number of tests performed.

12 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of participants. Each site will permit authorized representatives of the CCR, its designees, and appropriate regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress. These representatives will be permitted access to all source data and source documents, which include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participants' memory aids or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and Participant files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

13 QUALITY CONTROL AND QUALITY ASSURANCE

Following a written CCR-accepted site quality management plan, each participating site(s) and its subcontractors are responsible for conducting routine quality assurance (QA) and quality control (QC) activities to internally monitor study progress and protocol compliance. The site principal investigator will provide direct access to all study-related sites, source data/data collection forms, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities. The site principal investigator will ensure all study personnel are appropriately trained and applicable documentations are maintained on site.

The DCC will implement quality control procedures beginning with the data entry system and generate data quality control checks that will be run on the database. Any data anomalies will be communicated to the participating site(s) for clarification and resolution.

14 DATA COLLECTION AND EVALUATION

14.1 Data Collection

Each site PI will be responsible for overseeing entry of data into a 21 CFR Part 11-compliant data capture system provided by the NCI CCR and ensuring data accuracy, consistency and timeliness. The Protocol Chair/Site Principal Investigators, associate investigators/research nurses and/or data manager(s) will assist with the data management efforts. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human participant.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event.

14.2 End of study procedures

Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

14.3 Loss or destruction of data

Should we become aware that a major breach in our plan to protect Participant confidentiality and trial data has occurred, this will be reported expeditiously per requirements.

15 DATA SHARING PLANS

15.1 Human Data Sharing Plan

What data will be shared?

I will share human data generated in this research for future research as follows

* Coded, linked data in an NIH-funded or approved public repository.
* Coded, linked data in another public repository.
* Coded, linked data in BTRIS (automatic for activities in the Clinical Center)
* Identified or coded, linked data with approved outside collaborators under appropriate agreements.

How and where will the data be shared?

Data will be shared through:

* An NIH-funded or approved public repository. dbGaP, clinical trials.gov

* BTRIS (automatic for activities in the Clinical Center)
* Approved outside collaborators under appropriate individual agreements.
* Publication and/or public presentations.

When will the data be shared?

* Before publication.
* At the time of publication or shortly thereafter.

16 NIH REPORTING REQUIREMENTS

16.1 Definitions

Please refer to definitions provided in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

16.2 OHSRP Office of Compliance and Training/IRB Reporting

16.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Participants Research found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements. Note: Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported per these policies.

16.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

16.3 NCI Clinical Director Reporting

Note: This applies to NIH site only.

Problems expeditiously reviewed by the OHSRP in the NIH eIRB system will also be reported to the NCI Clinical Director/designee; therefore, a separate submission for these reports is not necessary.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention should be reported via email unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to NCICCRQA@mail.nih.gov within one business day of learning of the death.

16.4 NCI Guidance for Reporting Expedited Adverse Events for Multi-Center Trials

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802: Non-compliance in Human Participants Research, found at: https://irbo.nih.gov/confluence/display/IRBO/Policies+and+SOPs. Until such time as direct electronic reporting mechanisms are available to participating sites, the site PI must immediately report to the coordinating center PI any deaths possibly related to the research within 24 hours of PI awareness of the event. The Site PI must also report any other events required by Policy 801 to the coordinating center PI within 7 days of PI awareness.

The participating site Reportable Event Form is attached as **Appendix B**.

Once direct electronic reporting mechanisms are available, these will be utilized. Please also notify the coordinating center PI and study coordinator of your submission at the time you make it.

For IND studies, the site PI will also directly submit reports to the CCR as IND sponsor per section **16.2**

16.5 Institutional Biosafety Committee Reporting Criteria

Per the NIH Biosafety Committee: the use of the vaccine in a participant population for which it is already approved for use under an Emergency Use Authorization (EUA), will **NOT** require registration and approval with the NIH IBC.

16.6 NIH Required Data and Safety Monitoring Plan

16.6.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis weekly when participants are being actively treated on the trial to discuss each participant. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior participants.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Events meeting requirements for expedited reporting as described in section **16.2.1** will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each participant to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

16.7 COLLABORATIVE AGREEMENTS

16.7.1 Clinical Trials Agreement

A clinical trials agreement is under review with Moderna Inc.

16.7.2 **Multi-Institutional Guidelines**

Until an electronic submission system is available to participating sites, documents requiring submission to the reviewing IRB per reliance agreement, including local consent documents generated from an approved model consent, should be provided to the coordinating center for submission to the IRB. Thereafter, consents may be submitted directly to the IRB.

17 PUBLICATION POLICY

Following completion of the study, the lead Principal Investigator is expected to publish the results of this research in a scientific journal. All investigators funded by the NIH must submit or have submitted for them to the National Library of Medicine's PubMed Central (http://www.ncbi.nlm.nih.gov/pmc/) an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication. The NIH Public Access Policy ensures the public has access to the published results of NIH funded research. It requires investigators to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. Further, the policy stipulates that these papers must be accessible to the public on PubMed Central no later than 12 months after publication.

Refer to:

* NIH Public Access Policy, http://publicaccess.nih.gov/

As of January 2018, all clinical trials supported by the NIH must be registered on ClinicalTrials.gov, no later than 21 days after the enrollment of the first Participant. Results of all clinical trials supported by the NIH, generally, need to be submitted no later than 12 months following the primary completion date. A delay of up to 2 years is available for trials that meet certain criteria and have applied for certification of delayed posting.

As part of the result posting a copy of this protocol (and its amendments) and a copy of the Statistical Analysis Plan will be posted on ClincialTrials.gov.

For this trial the responsible party is NIH which will register the trial and post results.

The responsible party does not plan to request certification of delayed posting.

Refer to:

* Public Law 110-85, Section 801, Clinical Trial Databases
* 42CFR11
* NIH NOT-OD-16-149

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19 APPENDICES

19.1 Appendix A: Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

19.2 Appendix B: CCR Reportable Event Form (REF)

NCI Protocol #: Click or tap here to enter text.	
Protocol Title: Click or tap here to enter text.	
Report version: *(select one)* ☐ Initial Report ☐ Follow-up	
Site Principal Investigator: Click or tap here to enter text.	
Date site PI was notified of the problem: Click or tap to enter a date.	**Date of problem:** Click or tap to enter a date.
If delay in reporting to the coordinating center, please explain: Click or tap here to enter text.	
Location of problem: *(e.g., patient's home, doctor's office)* Click or tap here to enter text.	
Description of Participant Does this problem apply to a Participant? ☐ yes ☐ not applicable (more than one Participant is involved) **If yes, enter details below:** Participant ID: Click or tap here to enter text. (*do not use medical record number)* Sex: ☐Male ☐ Female Age: Click or tap here to enter text. Diagnosis: Click or tap here to enter text.	
Name the problem: *(select all that apply)*	

☐ Specimen collection issue

☐ Informed consent issue

☐ Ineligible for enrollment

☐ Breach of PII

☐ Other, briefly state the nature of the problem: Click or tap here to enter text.

Detailed Description of the problem: (*Include any relevant treatment, outcomes or pertinent history*): Click or tap here to enter text.

What are you reporting?

☐ unanticipated problem

☐ death

☐ non-compliance (other than a protocol deviation)

☐ protocol deviation

☐ new information that might affect the willingness of Participants to enroll or continue participation in this study

If interventional or expanded access study, please answer the following questions about your site:

How many participants are still receiving the study intervention?

Click or tap here to enter text.

How many participants completed study interventions but remain in follow up?

Click or tap here to enter text.

How many participants are enrolled but not yet receiving study interventions?

Click or tap here to enter text.

Have similar problems occurred on this protocol at your site?

☐ **Yes** ☐ **No**

Describe what steps you have already taken or will be taking as a result of this problem: Click or tap here to enter text.	
INVESTIGATOR'S SIGNATURE :	**DATE:**

19.3 Appendix C: Leukemia-specific AE Recording & Reporting Guidelines

These guidelines will be followed for the recording and reporting of adverse and serious adverse events.

a) Baseline events will be recorded in the medical history section of the case report form and will include the terminology event name, grade, and start date of the event. Baseline events are any medical condition, symptom, or clinically significant lab abnormality present before the informed consent is signed.
    i) Hematologic laboratory abnormalities will not be recorded as baseline
    ii) events for participants with acute leukemia, myelodysplastic syndrome,
    iii) chronic lymphocytic leukemia, or chronic myeloid leukemia in blast phase.
    iv) If exact start date is unknown, month and year or year may be used as the start date of the baseline event.
b) The maximum grade of the adverse event will be captured per course or protocol defined visit date.
c) These adverse events will be recorded in the case report form:
    i) Any grade adverse event that is possibly, probably, or definitely related to the study drug(s).
    ii) All serious adverse events regardless of attribution to the study drug(s).
    iii) Any grade adverse event regardless of attribution to the study drug(s) that results in any dose modification.
d) Hematologic adverse events will not be recorded or reported for studies in participants with acute leukemia, myelodysplastic syndrome, chronic lymphocytic leukemia, or chronic myeloid leukemia in blast phase except for:
    i) Prolonged myelosuppression as defined by the NCI-CTCAE criteria specific for leukemia, e.g., marrow hypocellularity on day 42 or later (6 weeks) from start of therapy without evidence of leukemia (< 5% blasts), or that results in dose modifications, interruptions or meets the protocol definition of DLT or SAE.
e) Serious adverse events will be reported according to institutional policy.
f) Protocol specific language regarding the recording and reporting of adverse and serious adverse events will be followed in the event of discordance between the protocol and Leukemia-specific adverse event recording and reporting guidelines.

19.4 Appendix D: Reactogenicity Grading Scale Tables

The term reactogenicity refers to the occurrence and intensity of selected signs and symptoms (ARs) occurring after injection of the investigational product.

Severity grading of reactogenicity will be according to the below tables modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (DHHS FDA2007).

A. Tables for Clinical Abnormalities

Local Reaction to Injectable Product	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Vital Signs *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Fever (°C) ** (°F) **	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia – beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia – beats per minte***	50 - 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) – mm Hg	141 - 150	151 - 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) – mm Hg	91 - 95	96 - 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 - 89	80 - 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 - 20	21 – 25	> 25	Intubation

* Participant should be at rest for all vital sign measurements.

** Oral temperature; no recent hot or cold beverages or smoking.

*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy participant populations, for example, conditioned athletes.

Systemic (General)	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Nausea/vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

19.5 Appendix E: Myocarditis and/or Pericarditis specific AE Evaluation and Management

Participants reporting acute chest pain, shortness of breath, palpitations, or other signs or symptoms of myocarditis or pericarditis within 4-6 weeks after vaccination must be referred to a cardiologist for evaluation and management. Cases of myocarditis and pericarditis will be followed until resolution of symptoms and abnormal test findings. Participants with events of myocarditis and/or pericarditis will be discontinued from further vaccination but will continue in follow up.

19.6 Appendix F: Study Calendar: Vaccine Naïve Arms

Procedures	Screening [e]	Baseline [e](-28 days)/ Day 1		D29 (+3 days) [e]	D36 (+/- 1 day) [e]	D57 (+/- 7 day) [e]	D 209 (+/- 28 day) [e]	Final Study Visit (+/- 28 days) [e]	Unscheduled Visit	Early Termination Visit
Day Number	0	1		29	36	57	209	394		
Visit Number	0	1		2	3	4	5	6		
Informed Consent	X									
Review Eligibility Criteria	X	X								
Medical History	X									
Concomitant Medications	X			X						
Vaccination [d]		X		X						
Telephone Contact										
Physical Examination [a]	X	X		X						
Vital Signs	X	X		X		X				
Height and Weight (for Body Mass Index [BMI])	X									
Electrocardiogram (ECG)		X		X[g]		X[g]				
Labs (see section **6.1**) [b]	X	X		X		X				
Pregnancy Test [c]	X	X		X						
Memory aids: Solicited AEs		Days 1-8		Days 29-36						
Unsolicited AEs and SAEs[f]		Days 1- 28 days after final vaccination								
Correlative Studies		Please see section **7.3**								

Study Calendar Key:

a) Full physical examination will be performed at screening and physical examination. The participants will be asked to provide all information surrounding a COVID19 infection, should this occur.
b) Hematology and Chemistry: Clinical screening laboratory evaluations will include tests as mentioned in the table.
c) For women of childbearing potential serum/urine pregnancy test at screening, and on Days 1 (within one week) and 29 with results confirmed as negative prior to administration of each vaccination. Results of the pregnancy test will not be required prior to verifying the order.
d) Participants in the vaccine naïve cohort will receive an injection of mRNA-1273 into muscle on Days 1 and 29 and will be followed through 12 months post second vaccination (Day 394). Participants will receive proof of vaccination on Day 29 after administration of their second dose of study drug.
e) In-person clinical visits will occur at screening, and on Baseline/Days 1 (may occur on same day), 29, 36, 57, 209 and at 394. These visits at clinic will take approximately 4-6 hours.
f) Collection of all AEs from the participant, solicited and unsolicited, will occur during the period from study product administration on Day 1 through 28 days after the last vaccination. Adverse events that are serious need to be recorded after 28 days following the last vaccine, only if they are related to the study intervention.
g) The ECG may be performed up to 2 weeks prior to Day 29. The ECG may be performed up to 2 weeks before or 2 weeks after Day 57.

19.7 Appendix G: Study Calendar Booster Vaccine Arms [g]

Procedures	Screening [e]	Baseline [e] (-28 days)/ Day 1	D8 (+/- 1 day). Mandatory for CAR-T Cell Cohort only	D29 (+/- 3 day) [e]	D57 (+/- 7 day) [e]	D 180 (+/- 28 day) [e]	Final Study Visit- (+/- 28 days) [e]	Unscheduled Visit	Early Termination Visit
Day Number	0	1	8	29	57	180	360		
Visit Number	0	1	2	3	4	5	6		
Informed Consent	X								
Review Eligibility Criteria	X	X							
Medical History	X								
Concomitant Medications	X								
Vaccination [d]		X							
Telephone Contact									
Physical Examination [a]	X	X							
Vital Signs	X	X							
Height and Weight (for Body Mass Index [BMI])	X								
Electrocardiogram (ECG)		X		X[i]					
Labs (see section **6.1**) [b]	X	X	X	X	X[f]103				
Pregnancy Test [c]	X	X							
Memory aids: Solicited AEs		Days 1-8							
Unsolicited AEs and SAEs[h]			Days 1-28 days after final vaccination						
Correlative Studies			Please see section **7.3**						

Study Calendar Key:

a) Full physical examination will be performed at screening and physical examination. The participants will be asked to provide all information surrounding a COVID19 infection, should this occur. Physical examination will be optional for participants transitioning from Vaccine-Naïve Cohorts.
b) Hematology and Chemistry: Clinical screening laboratory evaluations will include tests as mentioned in the table. Participants with CLL will also have LDH and Beta-2 microglobulin drawn on Days 1, 29 and 57. Results from laboratory evaluations will not be required prior to administering the vaccine on participants transitioning from Vaccine-Naïve Cohorts.
c) For women of childbearing potential serum/urine pregnancy test within one week of vaccination with results confirmed as negative prior to administration the vaccination. Results of the pregnancy test will not be required prior to verifying the order.
d) Participants on the booster vaccine cohorts will receive an injection of mRNA-1273 into muscle on Day 1 and will be followed through 12 months post vaccination (Day 360). Participants will receive proof of vaccination.
e) In-person clinical visits will occur at screening, and on Baseline/Days 1 (may occur on same day), 29, 57, 180 and at 360. These visits at clinic will take approximately 4-6 hours.
f) Participants with CLL will have LDH and Beta-2 microglobulin drawn on Day 57. Participants in other cohorts will not have safety labs drawn at this visit.
g) If a participant elects to have a second or third booster vaccination on protocol, the date of administration of the last dose will be considered Day 1. The minimum timeframe between booster vaccination doses will be 28 days. Day 57, Day 180, and Day 360 timepoints, if not yet reached on the original booster vaccination on protocol will be timed according to the participant's last vaccination dose.
h) Collection of all AEs from the participant, solicited and unsolicited, will occur during the period from study product administration on Day 1 through 28 days after the last vaccination. Adverse events that are serious need to be recorded after 28 days following the last vaccine, only if they are related to the study intervention.
i) The ECG may be performed up to 2 weeks before or 2 weeks after Day 29.