Table of Contents

List of Figures

Abbreviation	Definition
CMV	cytomegalovirus
CoV	coronavirus
COVID-19	coronavirus disease 2019
hMPV	human metapneumovirus
IM	intramuscular
LNP	lipid nanoparticle
MERS-CoV	Middle East respiratory syndrome coronavirus
mRNA	messenger RNA
nAb	neutralizing antibody
PIV3	parainfluenza virus type 3
polyA	polyadenylated
S-2P	spike (S) protein modified with 2 proline substitutions within the heptad repeat 1 domain
SARS-CoV-1	severe acute respiratory syndrome coronavirus 1
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
Th1	T-helper 1
UTR	untranslated region

2.2. INTRODUCTION

2.2.1 Pharmacologic Class of Agent

2.2.1.1 mRNA Platform

ModernaTX, Inc. (Sponsor) has developed a rapid-response proprietary vaccine platform based on a messenger RNA (mRNA) delivery system. The platform is based on the principle and observations that cells in vivo can take up mRNA, translate it, and then express protein viral antigen(s). The precision and standardization of the mRNA vaccine platform enables rapid development and efficient manufacturing scale-up of safe and effective vaccines without reliance on systems that are specific to each pathogen. mRNA is highly precise in its translation into proteins that match viral antigens. The delivered mRNA does not enter the cell nucleus or interact with the genome, is nonreplicating, and is expressed transiently. Investigational mRNA vaccines have been used to induce immune responses against infectious pathogens such as cytomegalovirus (CMV): NCT03382405, human metapneumovirus (hMPV) and parainfluenza virus type 3 (PIV3): NCT03392389, Zika virus: NCT04917861, and influenza virus: NCT03076385 and NCT03345043.

A schematic of mRNA is provided in Figure 1. The mRNA is chemically similar to naturally occurring mammalian mRNA with the exception that the uridine nucleoside normally present is fully replaced with N1-methyl-pseudouridine, a naturally occurring pyrimidine base present in mammalian transfer RNAs (Karikó et al 2005; Rozenski et al 1999). This nucleoside is included in the mRNA in place of the normal uridine base to minimize indiscriminate recognition of the mRNA by pathogen-associated molecular pattern receptors (Desmet and Ishii 2012). The cap structure used in the mRNA is identical to the natural mammalian Cap 1 structure (Fechter and Brownlee 2005; Kozak 1991).

Each mRNA molecule contains noncoding, or untranslated, sequences that may carry instructions for the cell regarding how to handle the mRNA.

The 3' untranslated region (UTR) is at the end of the open reading frame and is followed by the polyadenoylated (polyA) tail, a length of adenine-rich nucleotides, which is usually 50 to 250 nucleotides in length. The polyA tail confers stability to the RNA molecule, plays a role in the termination of transcription, and participates in the export of the mRNA molecule from the nucleus and in initiation of translation of the target protein.

Figure 1 Structure of mRNA

Abbreviations: PolyA = polyadenylated; UTR=untranslated region.

2.2.1.2 mRNA-1273 Mechanism of Action

The Sponsor is using its mRNA-based platform to develop mRNA-1273, a novel, lipid nanoparticle (LNP)-encapsulated, mRNA-based vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The proprietary LNPs encapsulating the mRNA increase its delivery efficiency and improve vaccine tolerability.

Prior to the emergence of the novel SARS-CoV-2 coronavirus, the Sponsor had developed a foundational understanding of mRNA vaccine approaches against coronavirus (CoV) based on prior experience in the development of mRNA vaccines against Middle East respiratory syndrome CoV (MERS-CoV) and severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1). This pre-clinical effort led to the evaluation of several mRNA vaccine designs against MERS-CoV, the most effective of which were spike protein designs. Of these, a full-length spike protein modified to introduce 2 proline residues to stabilize the spike protein into a prefusion conformation (S-2P) showed improved performance versus the wild-type spike protein. These improvements included better expression of protein, stabilization of the spike protein in the prefusion conformation, and improved immunogenicity in murine studies.

This foundational work allowed the Sponsor to leverage the scientific understanding and apply it to the approach used in the development of mRNA-1273. That approach utilizes the Sponsor's proprietary LNP technology to encapsulate synthetic mRNA that encodes for the full-length SARS-CoV-2 spike protein stabilized in a prefusion conformation with 2 proline mutations. The CoV spike protein mediates attachment and entry of the virus into host cells by attachment followed by membrane fusion, making it a primary target for neutralizing antibodies (nAbs) that prevent infection (Corti et al 2015; Wang et al 2015; Yu et al 2015; Johnson et al 2016; Chen et al 2017; Wang et al 2018; Kim et al 2019; Widjaja et al 2019).

The mRNA-1273 vaccine is delivered via intramuscular (IM) injection, and mRNA is subsequently delivered into cells, primarily antigen presenting cells at the injection site and draining lymph nodes. Injected into the upper arm, mRNA does not persist past 1 to 3 days in tissues other than muscle (at the injection site), proximal popliteal and distal axillary lymph

nodes, and spleen, in which the average half-life values ranged from 14.9 to 63.0 hours in Sprague Dawley rats (Moderna 2021a). After delivery, the mRNA utilizes the cell's translational machinery to produce the SARS-CoV-2 spike protein, which after proper assembly and processing is trafficked to the cell membrane for display to the immune system.

mRNA-1273 stimulates innate immune responses, resulting in the production of proinflammatory cytokines and type 1 interferon. This process activates B-cell and T-cell responses from the adaptive immune system. mRNA-1273 directly activates B-cells, including memory B-cells, resulting in the secretion of antibodies that bind and neutralize SARS-CoV-2 viruses. mRNA-1273 also directly activates T-cells, which eliminate infected cells and support B-cell responses. mRNA-1273 also induces T-helper 1 (Th1)-biased CD4+ T-cell responses in humans (Jackson et al 2020).

2.2.2 Proposed Clinical Use

mRNA-1273 is administered as two 100 µg doses given 28 days apart for the prevention of coronavirus disease 2019 (COVID-19) in adults 18 years of age and older.

2.2.3 References

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