mRNA-1273 Clinical Development Program

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mRNA-1273 encodes for the full-length Spike Protein in the Pre-fusion Conformation (S-2P)
Pre-clinical data support human clinical trials with mRNA-1273

• Robust neutralizing antibody responses in mice\(^1\), aged mice, and non-human primates (NHPs)\(^2\) have been induced
• mRNA-1273 demonstrated robust protection against lung challenge in mice\(^1\), and pulmonary and nasal challenge in NHPs\(^2\)
• No indication of enhanced respiratory disease after viral challenge even when subprotective doses of mRNA-1273 are used\(^2\)
• A Th1-dominant phenotype of CD4+ T-cells has induced in mice\(^1\) and NHPs\(^2\)

mRNA-1273 Clinical Development Plan

- **Nonclinical**
  - **P101 First in Human and Dose Ranging (NIH Sponsored)**
  - **P201 Phase 2 Safety and Immunogenicity Trial**
  - **P301 Phase 3 Pivotal Safety, Efficacy, and Immunogenicity Trial**

- **Dose Selection for P301**
  - Safety and immunogenicity P101
  - Response relative to convalescent sera

- **Data Package Required Prior to Start P301**
  - Safety & immunogenicity from P101 (post-dose 2 data for 100ug cohorts)
  - P201 safety report from SMC
  - Animal model data demonstrating nAbs, protection from challenge, Th-1-biased CD4+ T-cells and protection from ERD

- **Other populations for further evaluation (tbd)**
  - Pediatrics
  - Pregnant women
  - Immunocompromised populations
mRNA-1273 NIH-Sponsored, Phase 1, Safety and Dose-Ranging Study (N=120)

Phase 1 trial overview (NCT04283461)

Protocol Title
Phase I, Open-Label, Dose-Ranging Study of the Safety and Immunogenicity of 2019-nCoV Vaccine (mRNA-1273) in Healthy Adults

Study Groups

<table>
<thead>
<tr>
<th>Cohorts</th>
<th>Age groups</th>
<th>Dosage (D1, D29)</th>
<th>Sample size</th>
<th>Enrollment status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-3</td>
<td>18 to 55</td>
<td>25, 100, 250 mcg</td>
<td>45</td>
<td>Fully enrolled (45/45)</td>
</tr>
<tr>
<td>4, 5</td>
<td>56 to 70</td>
<td>25, 100 mcg</td>
<td>20</td>
<td>Fully enrolled (20/20)</td>
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<tr>
<td>7, 8</td>
<td>≥71</td>
<td>25, 100 mcg</td>
<td>20</td>
<td>Fully enrolled (20/20)</td>
</tr>
<tr>
<td>10-13</td>
<td>18-55, 56-70, ≥71</td>
<td>50 mcg</td>
<td>35</td>
<td>Fully enrolled (35/35)</td>
</tr>
</tbody>
</table>

Population
Healthy males and females at or above 18 years of age
“All-comers” with regard to SARS-CoV-2 serostatus (baseline serology will be collected)

Study Endpoints
Safety (solicited AR x 7 days post each injection; unsolicited AE 28 days post-vaccination; SAE and MAAE)
Immunogenicity (e.g., ELISA, pseudoneutralization, live virus neutralization and intracellular cytokine staining assay)

Study duration
Approximately 13 months for each participant corresponding to a 12-month follow up after the last vaccine administration

1. Cohorts 6 and 9 (250 mcg cohorts) will not be enrolled on this study


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Dose selection of 100 mcg was based on comparable nAb titers to 250 mcg with improved safety profile

Pseudovirus neutralization assay titers (ID$_{50}$): age 18 – 55 Years

Key Takeaways

- Day 14 post-dose 2, nAbs were observed in all participants
- The lowest responses were in the 25 mcg dose group
- Responses in the 100 mcg and 250 mcg groups were similar to the upper half of the range of convalescent sera
100 mcg mRNA-1273 Well-Tolerated Across Age Groups

Phase 1: No Vaccine-Related SAEs Have Been Reported
Solicited Local and Systemic Symptoms Followed for 7 Days Post-vaccination
Majority of symptoms resolved within 2 days, some persisted as long as 5 days

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Age group2</th>
<th>Vaccination 1</th>
<th>Vaccination 2</th>
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<tbody>
<tr>
<td>Any systemic symptom</td>
<td>18-55</td>
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<td></td>
<td>56-70</td>
<td></td>
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<td></td>
<td>71+</td>
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<tr>
<td>Arthralgia</td>
<td>18-55</td>
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<td></td>
<td>56-70</td>
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<td></td>
<td>71+</td>
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<tr>
<td>Fatigue</td>
<td>18-55</td>
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<td></td>
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<td></td>
<td>56-70</td>
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<td></td>
<td>71+</td>
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<tr>
<td>Fever1</td>
<td>18-55</td>
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<tr>
<td></td>
<td>56-70</td>
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<tr>
<td></td>
<td>71+</td>
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<tr>
<td>Chills</td>
<td>18-55</td>
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<td></td>
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<tr>
<td></td>
<td>56-70</td>
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<tr>
<td></td>
<td>71+</td>
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<td>Headache</td>
<td>18-55</td>
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<td></td>
<td>56-70</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>71+</td>
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</tr>
</tbody>
</table>

1. Fever percentages reflect the number of subjects with at least one measurement available in the data system as the denominator. This denominator may differ from other systemic symptoms, which are solicited in-clinic at the post-dose assessment.
2. 18-55: N=15; 56-70: N=10; 71+: N=10; N = All subjects receiving Dose 1 with any solicited event data recorded in the database.


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Anti-S-2P Binding Ab (ELISA) Comparable Across Age Strata and to Convalescent Sera at one month PD2

S-2P binding antibodies (ELISA)- 100 μg at Day 1 and Day 29

Key Takeaways
• 100 mcg two-dose series seroconverted all participants PD1
• PD1 AUC for all age groups exceeded the median of convalescent sera
• PD2 all age groups is equivalent to high-titer convalescent sera (i.e., upper quartile)


Interim Immunogenicity Report
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SARS-CoV-2 nAb Comparable Across Age Strata and to Convalescent Sera out to Day 57 PD2

Pseudovirus neutralization assay titers (ID50) - 100 μg at Day 1 and Day 29

18-55 years
D57 GMT: 267
95% CI: 186, 385

56-70 years
D57 GMT: 324
95% CI: 212, 496

71+ years
D57 GMT: 242
95% CI: 147, 399

Key Takeaways
• PD2 pseudovirus neutralization responses were detected in all participants
• PsV titers were comparable across age groups
• PsV median titer for 56-70 and 71+ YOA above convalescent sera median titer at Day 57 PD2

D57: one month post-dose
GMT: geometric mean antibody titer
95% CI: 95% confidence interval
PD2 = Post-dose 2
Vaccination administered at Day 1 and Day 29

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mRNA-1273 induces CD4+ T-cells of the Th-1 Phenotype 14 days PD2

Th1 CD4+ T cell response, S1 peptide pool (100 μg at Day 1 and 29)

Key Takeaways
• Vaccination with 100 mcg mRNA-1273 led a Th1-biased CD4+ T-cell response across all age groups
• Th2 phenotype was rare (data not shown)

mRNA-1273 Phase 2 Study will Evaluate Safety and Immunogenicity of 50 mcg and 100 mcg (N=600)

**Phase 2 trial overview** (NCT04405076)

**Protocol Title**
A Phase 2a, Randomized, Observer-Blind, Placebo-Controlled, Dose-Finding Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older

<table>
<thead>
<tr>
<th>Study Groups</th>
<th>Cohorts</th>
<th>Age groups</th>
<th>Dosage IM (D1, D29) 1:1:1</th>
<th>Sample size</th>
<th>Enrollment status</th>
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<tbody>
<tr>
<td></td>
<td>Cohort 1</td>
<td>18 to &lt;55</td>
<td>50mcg, 100mcg, placebo</td>
<td>300</td>
<td>Fully enrolled (300/300)</td>
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<td>Cohort 2 Sentinel</td>
<td>≥55</td>
<td>50mcg, 100mcg, placebo</td>
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<td>Fully enrolled (50/50)</td>
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<td></td>
<td>Cohort 2 Full</td>
<td>≥55</td>
<td>50mcg, 100mcg, placebo</td>
<td>250</td>
<td>Fully enrolled (250/250)</td>
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</tbody>
</table>

**Participant Population**
Healthy males and females at or above 18 years of age

“All-comers” with regard to SARS-CoV-2 serostatus (baseline serology will be collected)

**Study Endpoints**
Safety (solicited AR x 7 days post each injection; unsolicited AE to day 57; SAE and MAAE throughout the study); assessment of any cases of Covid-19; potential assessment for asymptomatic infection

Immunogenicity (ELISA, nAb)

**Study Duration**
Approximately 13 months for each participant corresponding to a 12-month follow up after the last vaccine administration
# Pivotal Phase 3 Efficacy, Safety and Immunogenicity Study (N=30,000)

## Phase 3 trial overview (NCT04470427)

<table>
<thead>
<tr>
<th>Study Groups</th>
<th>Strata</th>
<th>Dosage IM (D1, D29) 1:1</th>
<th>Sample Size</th>
<th>Enrollment status</th>
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</thead>
<tbody>
<tr>
<td>≥ 65 years</td>
<td>100mcg, placebo</td>
<td>25-40%</td>
<td>Started July 27</td>
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<tr>
<td>&lt; 65 years at increased risk for complication of COVID-19 (&quot;at risk&quot;)</td>
<td>100mcg, placebo</td>
<td>25-40%</td>
<td>Started July 27</td>
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<tr>
<td>&lt; 65 years and not at risk</td>
<td>100mcg, placebo</td>
<td>60-75%</td>
<td>Started July 27</td>
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</tr>
</tbody>
</table>

## Participant Population

Approximately 30,000 participants (case driven) whose locations or circumstances put them at appreciable risk of acquiring COVID-19 and/or SARS-CoV-2 infection

"All-comers" with regard to SARS-CoV-2 serostatus (baseline serology will be collected)

## Study Objectives

- To demonstrate the efficacy of mRNA 1273 to prevent COVID-19
- To evaluate the safety and reactogenicity of 2 injections of the mRNA-1273 vaccine given 28 days apart

## Study Duration

Approximately 25 months for each participant corresponding to a 24-month follow up after the last vaccine administration
Primary Efficacy Endpoint: COVID-19 Disease Case Definition

To be considered a case of COVID-19 for the evaluation of the Primary Efficacy Endpoint, two criteria must be met:

1. The participant must have experienced:
   - At least TWO of the following systemic symptoms: fever (≥ 38°C), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s)
   - OR
   - At least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia

2. The participant must have at least one NP swab, nasal swab or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR

Primary analysis set is seronegative and negative NP swab at baseline without major PD (Per Protocol)
COVE D&I Advisory Committee

Remit and Role of Advisory Committee:
1. Review enrollment, race, and ethnicity demographics on a weekly basis
2. Review current outreach activities and outcomes
3. Review strategies to ensure participation of individuals from communities significantly impacted by COVID-19
4. Support the development and implementation of retention strategies

• National Institute on Allergy and Infectious Diseases
• National Institute on Minority Health and Health Disparities
• NIH, Tribal Health Research Office
• NHLBI
Limitations of Research

• Limited safety and immunogenicity data in a fairly homogeneous population

• Further evaluation needed in terms of vaccine use in:
  – Pediatric subjects
  – Pregnant women
  – Immunocompromised patients

• The ongoing COVE Study will provide significantly more data
mRNA-1273 encodes the pre-fusion-stabilized Spike protein (S-2P) in a Lipid Nanoparticle designed for delivery to the APCs of the lymph node

Pre-clinical data have demonstrated induction of neutralizing Abs and protection against viral challenge in mice and NHPs

Interim data from Phase 1 study indicate that a 100 mcg dose of vaccine:
- Is generally well-tolerated across age strata, with solicited symptoms mostly mild-to-moderate in severity and self-limited duration
- Induces neutralizing Abs in the upper half of the range of convalescent serum across age strata, with the induction of Th-1 biased, CD4+ T-cells

Phase 2 and the Phase 3 COVE study are underway

APC – Antigen presenting cells  NHP – Nonhuman primate
Thank you to our collaborators

<table>
<thead>
<tr>
<th>P101</th>
<th>P201</th>
<th>COVE Study (P301)</th>
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<tr>
<td>Division of Microbiology and Infectious Diseases, NIAID</td>
<td>BARDA</td>
<td>BARDA</td>
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<tr>
<td>Vaccine Research Center (VRC), NIAID</td>
<td>Study sites, investigators, and subjects</td>
<td>Operation Warp Speed</td>
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<td>Coalition for Epidemic Preparedness Innovation</td>
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<td>NIAID and the COVID-19 Prevention Network</td>
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<tr>
<td>Principal Investigators, Drs. Lisa Jackson (Kaiser Permanente Wash)</td>
<td></td>
<td>Members of Diversity and Inclusion Panel</td>
</tr>
<tr>
<td>Evan Anderson (Emory University School of Medicine), Nadine Rouphael</td>
<td></td>
<td>Principal Investigators, Drs. Brandon Essink</td>
</tr>
<tr>
<td>(Emory University School of Medicine), Alicia Widge (VRC)</td>
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<td>(Meridian Clinical Research), Lindsey Baden</td>
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<td>The Emmes Company</td>
<td></td>
<td>(Brigham and Women’s Hospital), Hana El Sahly</td>
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<tr>
<td>Denison Lab, Vanderbilt University</td>
<td></td>
<td>(Baylor College of Medicine)</td>
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<td>Baric Lab, University of North Carolina</td>
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<td>Study sites, investigators, and subjects</td>
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<tr>
<td>Suthar Lab, Emory University</td>
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<tr>
<td>Vaccine Immunology Program, NIAID</td>
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<tr>
<td>Study sites, investigators and subjects</td>
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