## COVID-19 vaccine (mRNA-1893)

**Last program update: September 17, 2020**

<table>
<thead>
<tr>
<th>Modality</th>
<th>ID #</th>
<th>Program</th>
<th>Preclinical development</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3 and commercial</th>
<th>Moderna rights</th>
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<tbody>
<tr>
<td>mRNA-1273</td>
<td>COVID-19 vaccine</td>
<td></td>
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<td></td>
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<td></td>
<td>Worldwide BARDA funded</td>
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<tr>
<td>mRNA-1647</td>
<td>Cytomegalovirus (CMV) vaccine</td>
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<tr>
<td>mRNA-1653</td>
<td>hMPV/PIV3 vaccine</td>
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<tr>
<td>mRNA-1172/ Merck V172</td>
<td>Respiratory syncytial virus (RSV) vaccine</td>
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<td></td>
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<td>Merck to pay milestones and royalties</td>
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<tr>
<td>mRNA-1777</td>
<td>Respiratory syncytial virus (RSV) vaccine</td>
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<tr>
<td>mRNA-1893</td>
<td>Zika vaccine</td>
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<td>Worldwide BARDA funded</td>
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<tr>
<td>mRNA-1345</td>
<td>Pediatric respiratory syncytial virus (RSV) vaccine</td>
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<tr>
<td>mRNA-1189</td>
<td>Epstein-Barr virus (EBV) vaccine</td>
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<tr>
<td>mRNA-1851</td>
<td>Influenza H7N9 vaccine</td>
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<td>Worldwide Advancing subject to funding</td>
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</tbody>
</table>
Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) overview

- **SARS-CoV-2 virus**: novel coronavirus first identified in humans in December 2019 and cause of COVID-19

- **Disease burden (as of September 16, 2020):**
  - Global: 29,621,768 confirmed cases and 936,156 deaths from COVID-19¹
  - US: 6,609,770 confirmed cases and 196,023 deaths¹
  - Between 298,589 and 611,783 total deaths are currently projected in the US by January 1, 2021²
  - Risk of mortality increases with increasing age (estimated to be ~0.1% for 0-19, ~6% for 60+)³
  - Risk of severe disease and mortality increased for persons with pre-existing diseases or comorbid conditions (e.g. cardiovascular disease, diabetes, chronic lung disease, obesity)

- **Unmet need**: There is no approved vaccine for COVID-19

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SARS-CoV-2 vaccine (mRNA-1273)

Encodes for the full spike S protein
mRNA-1273 program timeline

**mRNA-1273 timeline: Research and development of SARS-CoV-2 vaccine**

- **January 13, 2020**
  Sequence for mRNA-1273 against the novel coronavirus finalized.

- **March 16, 2020**
  First participant in NIH-led Phase 1 study was dosed.

- **April 16, 2020**
  Award from U.S. government agency BARDA for up to $483 million to accelerate development.

- **April 16, 2020**
  First participant in NIH-led Phase 1 study was dosed.

- **April 27, 2020**
  IND submitted to US FDA for Phase 2 study.

- **May 1, 2020**
  Collaboration announced with Lonza Ltd to manufacture mRNA-1273 (goal of up to one billion doses per year).

- **May 1, 2020**
  FDA clearance to proceed with Phase 2 study.

- **May 6, 2020**
  Announcement of positive data from Phase 1.

- **May 18, 2020**
  Announcement of first dosing in Phase 2.

- **May 29, 2020**
  Announcement of completed enrollment in younger adults in Phase 2 and Phase 3 to start in July.

- **June 11, 2020**
  Phase 3 Initiated ~30,000 subjects.

- **July 27, 2020**
  Phase 3 Initiated ~30,000 subjects.
Key objective:
• To assess the safety, reactogenicity and immunogenicity of mRNA-1273

Study design:
• Phase 1, open-label dose ranging clinical trial in healthy adults
• Subjects received an intramuscular (IM) injection (0.5 milliliter [mL]) of mRNA-1273 on Days 1 and 29 in the deltoid muscle and will be followed through 12 months post second vaccination (Day 394)

Primary endpoint:
• Safety and reactogenicity of a 2-dose vaccination schedule of mRNA-1273, given 28 days apart

Secondary endpoint:
• Evaluate the immunogenicity to the SARS-CoV-2 S protein following a 2-dose vaccination schedule of mRNA-1273 at Day 57

Trial progress/details:
• Original 3 dose cohorts 25 µg, 100 µg and 250 µg (18-55 years old) Day 57 data published in The New England Journal of Medicine\(^1\)
• Interim analysis of the 100 µg dose for the 56-70 and 71+ age cohorts presented at ACIP Meeting
• 50 µg dose across three age cohorts (18-55, 56-70 and 71+) are fully enrolled

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100 µg 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 group</th>
<th>Vaccination 1</th>
<th>Vaccination 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any systemic symptom</td>
<td>18-55</td>
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<tr>
<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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<tr>
<td></td>
<td>56-70</td>
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<td></td>
<td>71+</td>
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<td></td>
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<tr>
<td>Fatigue</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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<tr>
<td>Fever</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>Chills</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>Headache</td>
<td>18-55</td>
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<td>56-70</td>
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<tr>
<td></td>
<td>71+</td>
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</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
Binding antibodies comparable across age groups

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

- 100 μg two-dose series seroconverted all participants after the first vaccination
- After the first vaccination, AUC for all age groups exceeded the median of convalescent sera
- After two vaccinations, all age groups are equivalent to high-titer convalescent sera (i.e., upper quartile)

Interim Immunogenicity Report

Distribution of antibody titers in pseudovirus neutralization assay comparable across age groups

Pseudovirus neutralization assay titers (ID$_{50}$) - 100 μg at Day 1 and Day 29

- After second vaccination, pseudovirus neutralization responses were detected in all participants
- Pseudovirus neutralization titers were comparable across age groups
- Pseudovirus neutralization titer for 56-70 and 71+ YOA above convalescent sera median titer at Day 57

Interim Immunogenicity Report
mRNA-1273 elicited Th1-biased CD4 T cell responses in all participants

Vaccination with 100 μg mRNA-1273 led to a Th1-biased CD4 T-cell response across all age groups.

Th2 phenotype was rare (data not shown)


Interim Immunogenicity Report
mRNA-1273 vaccine against COVID-19

**Data generated to date**

- **Phase 1 clinical data**
  - Neutralizing antibody titers were observed in 100% of evaluated participants
  - In the pseudovirus (ID_{50}) neutralization assay, at the 100 µg dose, mRNA-1273 induced consistently high levels of neutralizing antibody titers in all participants in the young adult and older adult cohorts
  - In the live SARS-CoV-2 (PRNT_{80}) neutralization assay in the younger adult cohort, the Day 43 geometric mean titer levels at the Phase 3 selected dose of 100 µg were above those seen in reference convalescent sera

- **Nonhuman primate data publication**
  - Two-dose vaccination schedule of mRNA-1273 led to rapid protection against SARS-CoV-2 infection in both the lungs and nose of non-human primates

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

**Phase 2 trial overview (NCT04405076)**

<table>
<thead>
<tr>
<th>Protocol Title</th>
<th>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</th>
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<tbody>
<tr>
<td>Study Groups</td>
<td><strong>Cohorts</strong></td>
</tr>
<tr>
<td></td>
<td>Cohort 1</td>
</tr>
<tr>
<td></td>
<td>Cohort 2 Sentinel</td>
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<tr>
<td></td>
<td>Cohort 2 Full</td>
</tr>
</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)

### Protocol Title
A Phase 3, Randomized, Stratified, Observer-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older

<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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥ 65 years</td>
<td>100 µg, placebo</td>
<td>25-40%</td>
<td>Started July 27</td>
</tr>
<tr>
<td></td>
<td>&lt; 65 years at increased risk for complication of COVID-19 (&quot;at risk&quot;)</td>
<td>100 µg, placebo</td>
<td></td>
<td>Started July 27</td>
</tr>
<tr>
<td></td>
<td>&lt; 65 years and not at risk</td>
<td>100 µg, placebo</td>
<td>60-75%</td>
<td>Started July 27</td>
</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
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
Phase 3 COVE study has enrolled 25,296 participants\(^1\)

### Phase 3 Enrollment Status

- **Target Subject #**
- **Randomized Subjects**
- **Subjects Receiving Dose 2**

### Phase 3 Diversity Status

- Approximately 28% of participants enrolled to date are from diverse communities

- White (72%)
- Hispanic or Latinx (16%)
- Black or African American (7%)
- Asian (3%)
- More than one race (1%)
- Other (1%)
- American Indian or Alaska Native (0.4%)
- Not reported (0.2%)
- Hawaiian or other Pacific Islander (0.2%)
- Unknown (0.1%)

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1. As of September 16, 2020
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)
An independent Data and Safety Monitoring Board (DSMB) ensures continuous data monitoring and enhances participant safety

<table>
<thead>
<tr>
<th>Independent review of data</th>
<th>Deliberation on best course of action</th>
<th>Independent regulatory review</th>
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</thead>
<tbody>
<tr>
<td>[Image] Cove Study</td>
<td>[Image] Oversight group</td>
<td>FDA</td>
</tr>
<tr>
<td>Independent DSMB</td>
<td>Moderna (sponsor)</td>
<td></td>
</tr>
</tbody>
</table>

- **A fully independent Data and Safety Monitoring Board** reviews unblinded data
- Established and supported by NIAID
- Experts in infectious disease, epidemiology, and ethics
- Monitors event rates; at pre-defined analyses unblinds and **DSMB makes a formal recommendation**

- Oversight group receives recommendation, which **includes NIAID and BARDA for transparency**
- Sponsor (Moderna) reviews the DSMB recommendation, and discusses plans with Oversight group (NIAID, BARDA)
- Sponsor determines whether to submit the data to the FDA for review

- FDA conducts independent review
- Seeks **external advisory committee (VRBPAC)** input
**Overview of primary efficacy endpoint**

<table>
<thead>
<tr>
<th>Interim Boundaries Using O’Brien-Fleming Spending Function</th>
<th>Boundary Crossing Probabilities by Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approximate # of cases (% of total cases)</td>
<td>VE: Efficacy bound</td>
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<tr>
<td>------------------------------------------</td>
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<tr>
<td><strong>Interim analysis #1</strong></td>
<td></td>
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<tr>
<td>53 (35%)</td>
<td>~0.74</td>
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<tr>
<td><strong>Interim analysis #2</strong></td>
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<tr>
<td>106 (70%)</td>
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<tr>
<td><strong>Primary analysis</strong></td>
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<tr>
<td>151 (100%)</td>
<td>~0.50</td>
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</table>

**Boundary crossing probabilities by effect size**
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