Forward-looking statements and Disclaimer

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• mRNA-1273 induced robust neutralizing antibodies and dose dependent increases in T cell responses

• mRNA-1273 led to protection against SARS-CoV-2 infection in the lungs and nose of non-human primates

• No evidence of vaccine-associated enhanced disease (VAERD) observed

Results reported provide critical data on mRNA-1273 immunogenicity and protection of the upper and lower airways that complement the immunogenicity and safety data demonstrated in an interim analysis of data from the Phase 1 clinical study.
Evaluation of the mRNA-1273 Vaccine against SARS-CoV-2 in Nonhuman Primates

Publication in The New England Journal of Medicine

1. Immunogenicity
   - After two vaccinations, the immune response observed in this non-human primate study was consistent with the recently reported Phase 1 human study of mRNA-1273
   - At the 10 µg dose, the geometric mean titer (GMT, ID$_{50}$) measured in a pseudovirus (PsV) neutralization assay was 103, similar to the GMT for a panel of convalescent sera reported previously (109)
   - At the higher dose in the non-human primates (100 µg), binding and neutralizing antibody titers increased further, with PsV GMT reaching 1,862
   - Vaccination also led to a significant increase in T cell responses, primarily Th1 CD4 T cells

2. Protection
   - Both the 10 µg and 100 µg dose levels of mRNA-1273 provided protection against lung inflammation following viral challenge with SARS-CoV-2 in non-human primates
   - Both the 10 µg and 100 µg dose groups provided protection against viral replication in the lungs, with the 100 µg dose also protecting against viral replication in the nose of the animals
   - Of note, none of the eight animals in the 100 µg group showed detectable viral replication in the nose compared to six out of eight in the placebo group on day 2
mRNA-1273 generated a robust immune response in NHPs

Animals were administered phosphate-buffered saline (PBS) as a control or 10 μg or 100 μg of mRNA-1273. Serum specimens were assessed for SARS-CoV-2 pseudovirus neutralization at all time points after the first and second vaccinations. Data are the reciprocal 50% inhibitory dilution (ID50). Faint lines represent individual animals, and bold lines represent the geometric mean titer for each group. Pseudovirus neutralization and live-virus neutralization by NanoLuc reporter assay (Promega) were assessed at 4 weeks after the second vaccination, immediately before challenge. Results were compared with the antibody responses in a panel of human convalescent-phase serum specimens (Conv.) (42 specimens in pseudovirus neutralization and 26 specimens in live-virus neutralization). In the box-and-whisker plots, the horizontal line indicates the median, the top and bottom of the box the interquartile range, and the whiskers the range. Symbols represent individual animals and overlap with one another for equal values where constrained. Dashed lines indicate the assay limit of detection.

- mRNA-1273 elicits robust neutralizing antibody responses in NHPs
- Neutralizing antibody titers were similar to convalescent sera* for the 10 μg group, and were 15-fold higher than convalescent in the 100 μg group

*panel of 42 human convalescent-phase serum specimens were obtained with mild, moderate, or severe COVID-19
mRNA-1273 generated a robust immune response in NHPs

- mRNA-1273 elicits robust binding antibody responses in NHPs
- Relative to convalescent sera*, binding antibody titers for the 100 μg group were 5-fold higher

*Panel of 42 human convalescent-phase serum specimens were obtained with mild, moderate, or severe COVID-19

Animals were administered phosphate-buffered saline (PBS) as a control or 10 μg or 100 μg of mRNA-1273. Serum specimens were assessed for severe SARS-CoV-2 S-specific IgG by enzyme-linked immunosorbent assay (ELISA) at all time points after the first and second vaccinations. Data are the reciprocal 50% inhibitory dilution (ID50). Faint lines represent individual animals, and bold lines represent the geometric mean titer for each group. S-specific IgG were assessed at 4 weeks after the second vaccination, immediately before challenge. Results were compared with the antibody responses in a panel of human convalescent-phase serum specimens (Conv.) (42 specimens in S-specific IgG). In the box-and-whisker plots, the horizontal line indicates the median, the top and bottom of the box the interquartile range, and the whiskers the range. Symbols represent individual animals and overlap with one another for equal values where constrained. Dashed lines indicate the assay limit of detection.
mRNA-1273 was protective in the lung and nose in NHPs

Bronchoalveolar lavage (BAL) fluid and nasal swab specimens were obtained on days 1, 2, 4, and 7 after challenge, where applicable, and viral replication was assessed by analysis of SARS-CoV-2 subgenomic RNA. In the box-and-whisker plots, the horizontal line indicates the median, the top and bottom of the box the interquartile range, and the whiskers the range. Symbols represent individual animals and overlap with one another for equal values where constrained. Dashed lines indicate the assay limit of detection.

- Both the 10 µg and 100 µg dose groups provided protection against viral replication in the lungs.
- None of the eight animals in the 100 µg group showed detectable viral replication in the nose compared to six out of eight in the placebo group on day 2.
mRNA-1273 protected from SARS-CoV-2 mediated inflammation in lung of NHP

• SARS-CoV-2 infection in the control animals caused **moderate-to-severe inflammation** that often involved the small airways and the adjacent alveolar interstitial. Multiple pneumocytes in the lung sections from the control group were **positive for both SARS-CoV-2 viral RNA and antigen**.

• In animals vaccinated with 10 μg of mRNA-1273, inflammation was **mild**, and **no viral RNA** was detected on Day 7 (a single pneumocyte in a single animal was positive for viral antigen on Day 8)

• **No substantial inflammation** was observed in the lungs of nonhuman primates vaccinated with 100 μg of mRNA-1273, and **neither viral RNA nor antigen** was detected at day 7 or 8 after challenge.

• By day 14 or 15 after challenge vaccinated animals had no evidence of substantial inflammation.

Seven days after challenge, lungs were harvested from two animals per group for histopathological analysis and assessment of evidence of viral infection; representative images taken at different degrees of magnification are shown for localization of virus by chromogenic in situ hybridization (CISH) and SARS-CoV-2 immunohistochemical analysis (IHC) in serial tissue sections. The images on the bottom are shown at twice the magnification of the images on top.
mRNA-1273 protected from SARS-CoV-2 mediated inflammation in lung of NHP

• Panel of innate cytokines and chemokines were assessed in BAL fluid at days 2 and 4 after challenge

• Inflammatory cytokine induction was limited in both dose groups, which suggests that there was rapid control of virus sufficient to limit innate immune activation

• Taken together with the viral replication (PCR), and immunohistochemistry, these data show rapid control of viral replication within 2 days in both the upper and lower airways

Post-challenge BAL cytokine and chemokine responses in mRNA-1273-immunized rhesus macaques. Rhesus macaques were immunized with PBS (gray) or mRNA-1273 (10 µg, blue or 100 µg, red) and challenged, as described in Figure S1. BAL collected on days 2 and 4 post-challenge were concentrated 10X and assessed for 23 chemokines and cytokines by MILLIPLEX® MAP. Graphs depict day 2 cytokines relevant to VAERD, i.e. Th1-related (A) or Th2 related (B). Additionally, selected inflammatory cytokines and chemokines are shown in (C).
Vaccination of NHPs led to a Th1-biased CD4+ T cell response

- mRNA-1273 generated a dose-dependent Th1 response, while a Th2 response, which can be associated with disease enhancement, was not evident.

- Vaccination induced responses in other T cell types that help drive a robust immune response (e.g., CD4 T follicular helper (Tfh) cells, CD40L-expressing CD4 T-cells).

Intracellular staining was performed on peripheral blood mononuclear cells at 8 weeks, immediately before challenge, to assess T-cell responses to the SARS-CoV-2 S1 peptide pool. Type 1 helper T-cell (Th1) responses (interferon-γ, interleukin-2, or tumor necrosis factor α), Th2 responses (interleukin-4 or -13), CD40L up-regulation, and interleukin-21 from peripheral follicular helper T (Tfh) cells (central memory CXCR5+PD-1+ICOS+ CD4 T cells). Response rates were determined with MIMOSA software and are shown as fractions below each group. In the box-and-whisker plots, the horizontal line indicates the median, the top and bottom of the box the interquartile range, and the whiskers the range. Unfilled symbols represent animals with a probable nonresponse, and filled symbols represent animals with a probable response.
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 live SARS-CoV-2 (PRNT_{80}) neutralization assay, the Day 43 geometric mean titer levels at the Phase 3 selected dose of 100 µg were 4.1-fold above those seen in reference convalescent sera (n=3)
- **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
- **Mouse data pre-print (currently under peer review)** – mRNA-1273 induced both potent neutralizing antibody and CD8 T cell responses and protected against SARS-CoV-2 infection in lungs and noses of mice without evidence of immunopathology

May 18, 2020
Positive interim Phase 1 data announced

June 12, 2020
Pre-clinical mouse data submitted for publication and made available on bioRxiv

July 14, 2020
New Phase 1 interim results published in *The England Journal of Medicine*

July 28, 2020
Nonhuman primate data published in *The New England Journal of Medicine*
Next steps for mRNA-1273 vaccine against COVID-19

- Phase 1 interim data for 55-70 and 71+ age groups
- Phase 2 interim data
- Phase 3 interim analysis
- BLA filing upon evidence of Phase 3 safety and efficacy

Our mission
To deliver on the promise of mRNA science to create a new generation of transformative medicines for patients.