

UT Southwestern Vaccine Science Review Committee
Scientific Review of Moderna COVID-19 Vaccine (mRNA-1273)
Dec. 19, 2020

Introduction

On Dec. 18, 2020, the U.S. Food and Drug Administration (FDA) granted an emergency use authorization (EUA) for the Moderna vaccine, mRNA-1273, for use in persons 18 years of age and older for the prevention of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Then, on Dec. 19, 2020, the Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices (CDC ACIP) voted to recommend the use of this vaccine for persons 18 years of age and older in the United States for the prevention of COVID-19 through the EUA. Furthermore, based on the initial projected limited supply of vaccine, the ACIP recommends that health care workers and residents of long-term care facilities should be offered COVID-19 vaccination in the initial phase, 1a, of vaccine deployment.

The UT Southwestern Vaccine Science Review Committee for COVID-19 is a multidisciplinary group of immunologists, infectious diseases experts, epidemiologists and other key stakeholders tasked with independently reviewing the available evidence in support of COVID-19 vaccine candidates on behalf of our campus community. Below, we summarize our current assessment of the available evidence for the Moderna mRNA-1273 vaccine based on the FDA EUA and ACIP recommendations, supporting documentation reviewed by the FDA, and the published medical literature.

Moderna COVID-19 Vaccine (mRNA-1273)

A. Vaccine Product Information

The Moderna COVID-19 vaccine, mRNA-1273, is a novel nucleoside-modified, messenger RNA vaccine that encodes a membrane-anchored, full-length SARS-CoV-2 spike (S) protein with two-point mutation proline substitutions to preferentially lock the protein in an antigenic prefusion conformation. This mRNA is encapsulated in a lipid nanoparticle formulation that allows the RNA to be taken up by host cells and translated into the viral S protein. This S protein then incorporates into the cell membrane to induce an adaptive immune response, including both B-cell mediated neutralizing antibodies as well as antigen specific T-cell mediated immunity. The vaccine is administered as a two-shot series of 100- μ g doses given as intramuscular (IM) injections at a 28-day interval. The manufacturing process, which has been in use for 10 years in the development of mRNA vaccines, is cell-free and does not use any vectors, animal products, adjuvants or preservatives. Additional product information, including the other components of the lipid nanoparticles, storage, preparation, and administration, can be found in the FDA EUA information: <https://www.fda.gov/media/144637/download>

B. Pre-clinical Animal Data

Nonclinical evaluations of mRNA-1273 included pharmacokinetic, immunogenicity and toxicity studies in rodents as well as nonhuman primates, which demonstrated robust immunogenicity with regards to SARS-CoV-2 neutralizing antibody titers, CD4+ and CD8+ T-cell responses, and protection against infection in viral challenge studies in nonhuman primates. There was also no evidence of increased viral loads in vaccinated animals with protective or subprotective dose levels, supporting that the vaccine does not lead to vaccine enhanced respiratory disease. A developmental and reproductive toxicity

(DART) studies in pregnant and lactating female Sprague Dawley rats did not show any adverse effects at the clinically relevant 100- μ g dose.

C. Phase 1/2/3 Human Clinical Trials Data

The sponsor has conducted a series of human clinical trials in collaboration with the National Institutes of Health (NIH), Biomedical Advanced Research and Development (BARDA), and Operation Warp Speed (OWS). The first-in-human trial, Study 101, was a phase 1 dose-finding study that enrolled 120 healthy subjects (stratified by ages 18-55, 56-70, and 71 years of age and older) with several mRNA-1273 doses. This trial demonstrated that the two 100- μ g dose regimen given at a 28-day interval elicited high SARS-CoV-2 neutralizing antibody titers, which exceeded those seen in human convalescent serum, as well as strong antigen-specific CD8+ and Th1-type CD4+ T-cell responses. These immunogenicity responses were consistent across all age groups and persisted at three months after the second dose. These results, along with a favorable reactogenicity profile and supporting data from the nonhuman primate challenge studies, led to its selection to move into phase 2/3 clinical development.

Study 201 is an ongoing phase 2a, randomized, placebo-controlled, dose-confirmation study in healthy adults 18 years of age and older to further evaluate the safety and efficacy of the Moderna COVID-19 vaccine. A total of 600 participants were randomized 1:1:1 to receive either placebo, a two 50- μ g dose regimen, or a two 100- μ g dose regimen, stratified by ages older, equal to or younger than 55. The results from this trial confirmed induction of binding and neutralizing Ab titers to the SARS-CoV-2 spike protein at both doses and demonstrated an acceptable reactogenicity profile to proceed with the 100- μ g dose regimen into a larger phase 3 trial.

Study 301 is the ongoing, phase 3, randomized, placebo-controlled, registration trial for mRNA-1273 co-sponsored by Moderna and the NIH/NIAID. This trial, which provides the primary basis for the EUA consideration, enrolled approximately 30,420 participants and randomized them 1:1 to receive vaccine as two IM 100- μ g doses given 28 days apart (N=15,210) or placebo (N=15,210). The trial enrolled participants 18 years of age and older, who were at high risk of SARS-CoV-2 infection based on geographic location or circumstance (such as health care workers). Randomization was stratified based on age (< or \geq 65 years old) and risk of severe COVID-19 based on medical comorbidities. Key exclusion criteria included age < 18 years of age, known history of COVID-19, pregnancy or breastfeeding, immunosuppressive medications, or an immunocompromising condition. The primary outcome of symptomatic COVID-19 with onset at least 14 days after the second dose occurred in 11 vaccine recipients and 185 placebo recipients, for an estimated vaccine efficacy of 94.1 percent (95 percent CI, 89.3-96.8 percent) in the per-protocol population. Subgroup analyses across age, sex, race, ethnicity and pre-existing comorbid conditions demonstrated generally consistent vaccine efficacy of > 90 percent, although the confidence intervals in certain subgroups were wide due to smaller case numbers.

The vaccine also appeared to protect against severe COVID-19 with 30 severe cases in the placebo arm and zero in the vaccine arm starting 14 days after the second dose, further confirming no increased risk of enhanced disease with mRNA-1273. Additionally, some immune protection was noted following the first vaccine dose as the cumulative incidence of COVID-19 cases over time began to diverge between vaccine and placebo recipients at around 14 days after the first dose. Of note, exploratory analysis also suggested partial efficacy at preventing asymptomatic infection, with an approximately 63 percent reduction. Amongst baseline negative participants, 14 in the vaccine group and 38 in the placebo group had positive SARS-CoV-2 PCR by nasopharyngeal swab prior to the second vaccine dose in the absence of COVID-19 symptoms. The safety profile of the Moderna vaccine, based on a median follow-up of nine

weeks after the second dose, was notable primarily for mild to moderate, self-limited reactogenicity in the form of injection site pain, fatigue, headaches, muscle and joint pains, and chills. Severe adverse events occurred in 0.2 to 9.7 percent of participants primarily related to solicited local or systemic reactogenicity, and were more frequent after the second vaccine dose and in participants younger than 65 years of age. Unsolicited serious adverse events were rare and occurred at a similar rate in both groups (approximately equal to 1 percent). Numerical imbalances in the incidence of axillary swelling and tenderness of the vaccination arm (173 in the vaccine group and 95 in the placebo group) and Bell's palsy (three in the vaccine group and one in the placebo group) were seen in the trial, although the latter was not deemed to be greater than the background rate in the general population. There was also a numerical imbalance in hypersensitivity adverse events with 1.5 percent of vaccine recipients and 1.1 percent of placebo recipients reporting such events. However, there were no cases of anaphylaxis or severe hypersensitivity in close temporal relation to the vaccine.

D. Regulatory Guidance from the FDA and CDC ACIP Committees

Moderna submitted an application for EUA consideration for mRNA-1273 to the FDA on Nov. 30, 2020, and its application was reviewed by the external Vaccines and Related Biological Products Advisory Committee (VRBPAC) of the FDA on Dec. 17, 2020. The FDA's prespecified criteria for COVID-19 vaccine EUA was at least 50 percent efficacy for the primary outcome (with a lower confidence bound greater than 30 percent) as well as a median follow-up of two months following vaccine completion for safety outcomes. The VRBPAC unanimously recommended (with a vote of 20 for, 0 against, and 1 abstention) that the FDA approve this vaccine for persons 18 years of age and older for the prevention of COVID-19 based on the available data. On Dec. 18, 2020, the FDA granted an EUA for this vaccine for persons 18 years of age or older for the prevention of COVID-19. The only listed contraindication is a history of severe allergic reaction (e.g. anaphylaxis) to any of the components of the Moderna COVID-19 vaccine.

The EUA does indicate that the efficacy and safety of the vaccine in certain special populations, including pregnancy and immunocompromised populations is currently unknown, and that individuals in these groups may be offered vaccination but should be counseled about the limitations of the available evidence. It also states that there is not data on the interchangeability of this vaccine with other COVID-19 vaccines. Therefore, persons who receive a first dose with the Moderna COVID-19 vaccine should receive a second dose with the same vaccine. On Dec. 19, 2020, the CDC's ACIP unanimously voted (11 in favor, 3 recusals) to recommend vaccination in the U.S. for all persons 18 years of age and older for the prevention of COVID-19 in accordance with the EUA criteria. They also recommended that, given initial projected limited vaccine supply, health care personnel and residents of long-term care facilities should be vaccinated during the initial phase 1a of vaccination.

E. Clinical Considerations when administering the Moderna COVID-19 Vaccine (mRNA-1273)

In accordance with ACIP's guidance, the Vaccine Science Review Committee recommends patients receiving the vaccine be queried for severe allergic reactions to vaccines, vaccine components or other injectables and their eligibility for vaccine or duration of observation be triaged as per Table 1 below. The vaccine should also be administered alone with a minimum interval of 14 days before or after administration with any other vaccines. Vaccination should be offered regardless of history of prior SARS-CoV-2 infection, but deferred until after recovery from acute illness. If the patient received a monoclonal antibody infusion or convalescent plasma for previous SARS CoV-2 infection, vaccination should be deferred until at least 90 days after the infusion to avoid interference of the treatment with the vaccine-induced immune response. The EUA does indicate, and the Science Review Committee agrees, that the efficacy and safety of the vaccine in certain special populations, including pregnancy

and immunocompromised populations is currently unknown, and that individuals in these groups should be offered vaccination, but should be counseled about the limitations of the available evidence.

UTSW Vaccine Science Review Committee Recommendations and Conclusions

Based on our independent review of the available scientific evidence regarding the efficacy and safety of the Moderna COVID-19 vaccine, we concur with the FDA and CDC ACIP recommendations endorsing its use in persons 18 years of age and older for the prevention of COVID-19 in accordance with the EUA. We find the peer-reviewed scientific data available meets and exceeds the prespecified EUA criteria for vaccine authorization in a rigorous phase 2/3 trial with sufficient power to assess both the efficacy and safety profile of this vaccine. Additionally, the Sponsor, in coordination with the FDA, CDC and other regulatory agencies, have implemented plans for comprehensive monitoring and reporting systems to identify any safety signals or rare vaccine-related adverse events which may become apparent with wider vaccine deployment. Consistent with ethical and legal principles, we believe that vaccine allocation to UTSW employees and patients should proceed in accordance with the previously recommended allocation phases, since there is no data to suggest modifications based on vaccine-specific efficacy or safety in particular subpopulations.

We also believe that UTSW employees should be encouraged, but not required, to receive vaccination during their appropriate allocation phase, including employees who are in populations excluded from the trial such as pregnant or lactating women or immunocompromised individuals. The Vaccine Science Review Committee will continue to monitor for additional efficacy or safety data for this vaccine, or other candidate COVID-19 vaccines, and will update its recommendations as appropriate based on new findings.

Table 1 – Triage of persons presenting for mRNA COVID-19 vaccination

	Proceed with Vaccination	Precautions to Vaccination	Contraindications to Vaccination
Conditions	<ul style="list-style-type: none"> Immunocompromising conditions Pregnancy Lactation <p>Actions</p> <ul style="list-style-type: none"> Additional information provided 15-minute observation period 	<ul style="list-style-type: none"> Moderate/severe acute illness <p>Actions</p> <ul style="list-style-type: none"> Risk assessment Potential deferral of vaccination 15-minute observation period if vaccinated 	None
Allergies	<ul style="list-style-type: none"> History of food, pet, insect, venom, environmental, latex, or other allergies not 	<ul style="list-style-type: none"> History of severe allergic reaction (e.g., anaphylaxis) to 	<ul style="list-style-type: none"> History of severe allergic reaction (e.g., anaphylaxis) to

	<p>related to vaccines or injectable therapies</p> <ul style="list-style-type: none"> • History of allergy to oral medications (including the oral equivalent of an injectable medication) • Non-serious allergy to vaccines or other injectables (e.g., no anaphylaxis) • Family history of anaphylaxis • Any other history of anaphylaxis that is not related to a vaccine or injectable therapy <p>Actions</p> <ul style="list-style-type: none"> • 30-minute observation period: Persons with a history of severe allergic reaction (e.g., anaphylaxis) due to any cause • 15-minute observation period: Persons with allergic reaction, but not anaphylaxis 	<p>another vaccine (not including mRNA COVID-19 vaccines[†])</p> <ul style="list-style-type: none"> • History of severe allergic reaction (e.g., anaphylaxis) to an injectable therapy <p>Actions</p> <ul style="list-style-type: none"> • Risk assessment • Potential deferral of vaccination • 30-minute observation period if vaccinated 	<p>any component of an mRNA COVID-19 vaccine[†]</p> <p>Actions</p> <ul style="list-style-type: none"> • Do not vaccinate
--	--	--	--

References

Sponsor Briefing Document: mRNA-1273 COVID-19 Vaccine. Vaccines and Related Biologic Products Advisory Committee, Meeting Dec. 17, 2020. [fda.gov/media/144452/download](https://www.fda.gov/media/144452/download) Accessed Dec.19, 2020.

Sponsor Briefing Document Addendum: mRNA-1273 COVID-19 Vaccine. Vaccines and Related Biologic Products Advisory Committee, Meeting Dec. 17, 2020. [fda.gov/media/144453/download](https://www.fda.gov/media/144453/download) Accessed Dec.19, 2020.

FDA Briefing Document: mRNA-1273 COVID-19 Vaccine. Vaccines and Related Biologic Products Advisory Committee, Meeting Dec. 17, 2020. [fda.gov/media/144434/download](https://www.fda.gov/media/144434/download) Accessed Dec. 19, 2020.

Jackson LA, et al. An mRNA vaccine against SARS-CoV-2—preliminary report. *N Engl J Med* 2020; 383:1920-1931. Doi:10.1056/NEJMoa2022483.

Anderson EJ, et al. Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. *N Engl J Med* 2020; 383:2427-2438. Doi:10.1056/NEJMoa2028436 Accessed Dec. 19, 2020.

Corbett KS, et al. Evaluation of the mRNA-1273 vaccine against SARS-CoV-2 in nonhuman primates. *N Engl J Med* 2020; 383: 1544-1555. Doi:10.1056/NEJMoa2024671 Accessed Dec. 19, 2020.

Widge AT, et al. Durability of responses after SARS-CoV-2 mRNA-1273 vaccination. *N Engl J Med* 2020; Dec. 3, 2020. Doi:10.1056/NEJMc2032195 Accessed Dec. 19, 2020.

Fact Sheet for Healthcare Providers: FDA Emergency Use Authorization of the Moderna COVID-19 vaccine. [fda.gov/media/144637/download](https://www.fda.gov/media/144637/download) Accessed Dec. 19, 2020.