Ballad Health COVID-19 Vaccine Workgroup Newsletter

Ninth Edition – Dec. 21, 2020

In this issue – Summary of the FAQ Internal Analysis of Moderna Vaccine for COVID-19

Vaccines and Related Biological Products Advisory Committee Briefing Moderna Vaccine - FDA

Update: ACIP releases recommendations for use of Moderna COVID-19 vaccine

On Dec. 18, 2020, the U.S. Food and Drug Administration (FDA) issued Emergency Use Authorization (EUA) for the Moderna m-RNA COVID-19 vaccine, which uses the spike protein as the basis for creating protective immunity. On Dec. 19, 2020, the Advisory Committee on Immunization Practices (ACIP) approved recommendations for Moderna vaccine use, which are remarkably similar to ACIP recommendations for the Pfizer vaccine with the following observations:

- The Moderna vaccine is indicated for persons ≥18 years old, while Pfizer is for ≥16 years old.
- The Moderna vaccine is a two-dose vaccine with 28 days between doses, while the Pfizer dosing interval is 21 days.
- The Moderna and Pfizer vaccines are not interchangeable.

Details of the ACIP recommendations can be found here. Additional considerations for use of both Moderna and Pfizer vaccines can be found here. **Additional resources** for use of vaccines in pregnant women, breastfeeding women, and women who plan to be pregnant from American College of Obstetricians and Gynecologists are found here.

What did the FDA analysts do?

FDA scientists independently evaluated the lengthy application for emergency use authorization (EUA) from Moderna, based on the Phase III randomized, placebo-controlled trial.

The proposed use is for "active immunization for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older." The final efficacy analysis was planned from the beginning to occur after at least 151 COVID-19 cases had accrued.

What are the primary end points for efficacy and safety?

The primary end point for efficacy is the incidence of COVID-19 among volunteers who were randomized to receive vaccine and were without evidence of SARS-CoV-2 infection before the first dose of vaccine in the period after 14 days after dose two, compared to volunteers who received placebo.

Safety data was analyzed for about 30,350 volunteers ≥18 years of age who were randomized 1:1 or placebo and with at least 50% having follow-up for a median of at least two months after the last dose. Adverse events were recorded daily for seven days following each dose.

Vaccine reactogenicity refers to common and expected reactions shortly following vaccination, which usually resolve in 24 to 72 hours and include injection site reactions, fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, and joint pain. Serious adverse events were recorded throughout the Phase III trial period. According to FDA, "Adverse events considered plausibly linked to vaccination generally start within six weeks of vaccine receipt."

Dosing is 100 µg on day one and day 28. The vaccine is available as a frozen suspension to be stored at -20°C in a vial containing 10 doses. Vaccine can be stored at refrigerator temperature for 30 days and when at room temperature must be used within six hours.

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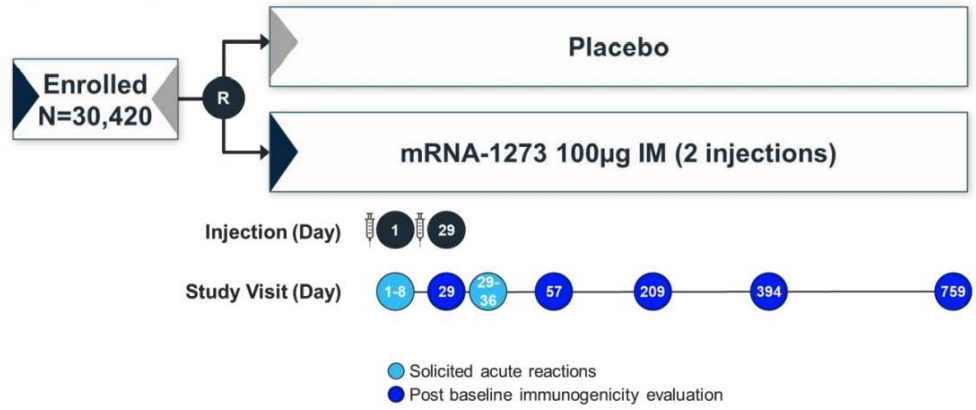
Figure 1. Safety Monitoring Plan, Study 301

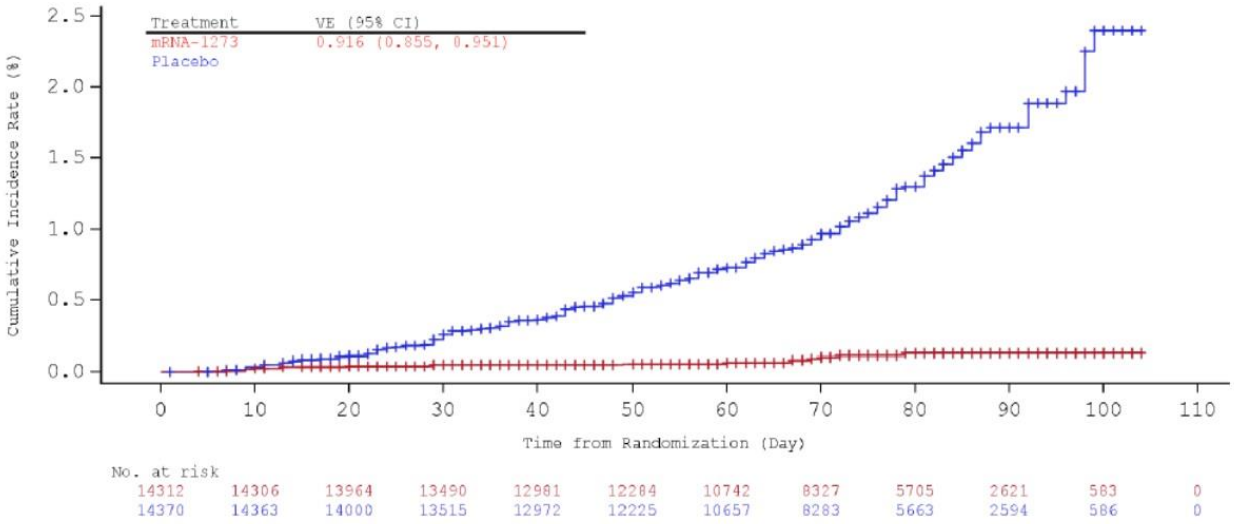


What were the demographics and characteristics of study population?

"The Per-Protocol Set included 47.4% females and 25.3% of individuals ≥65 years of age. There were 36.5% of participants considered as representing communities of color with 9.7% African American, 4.7% Asian, and <3% from other racial groups; 20% of participants were Hispanic/Latino. A majority of the participants (82%) were considered at occupational risk for SARS-CoV-2 exposure, with 25.4% of participants being healthcare workers. At least one protocol-defined high-risk condition for severe COVID-19 was present in 22.3% of participants, and 4% of participants had two or more high risk conditions."

What were the key findings for efficacy?

Figure 2. Cumulative Incidence Curves for the First COVID-19 Occurrence After Randomization, mITT Set



Note: The mITT set included all participants in the full analysis set who had no immunologic or virologic evidence of prior COVID-19 at Day 1 before the first dose of IP.

- 196 people developed COVID-19 with 11 in the vaccine group and 185 in the placebo group.
- Vaccine efficacy from the final scheduled analysis was 94.1% (95% confidence interval 89.3% to 96.8%).
- Vaccine efficacy stratified by age group was 95.6% for participants 18 to <65 years of age and 86.4% for participants ≥65 years of age.
- Vaccine efficacy for prevention of severe COVID-19 was 100%, with 30 cases in the placebo group and 0 cases in the vaccine group.
- Vaccine efficacy after one dose is encouraging but not conclusive. "Among participants in the mITT set who only received one dose of vaccine or placebo at the time of the interim analysis, efficacy against COVID-19 starting after dose one was 80.2% (95% CI: 55.2%, 92.5%). The efficacy observed after dose one and before dose two, from a post-hoc analysis, cannot support a conclusion on the efficacy of a single dose of the vaccine because the number of participants and time of observation are limited. The trial did not have a single-dose arm to make an adequate comparison."
- Vaccine protection did not wane during the two-month period after the second dose.

What were the key findings for safety?

Safety analyses "supported a favorable safety profile, with no specific safety concerns identified that would preclude issuance of an EUA."

- The most common solicited adverse reactions were injection site pain (91.6%), fatigue (68.5%), headache (63.0%), muscle pain (59.6%), joint pain (44.8%), and chills (43.4%).
- The mild to moderate short-term adverse effects (vaccine reactogenicity) were more common in people <65 years old. Otherwise, "the safety profile of mRNA-1273 was generally similar across age groups, genders, ethnic and racial groups, participants with or without medical comorbidities, and participants with or without evidence of prior SARS-CoV-2 infection at enrollment."
- Frequency of vaccine and placebo participants reporting systemic adverse reaction were as follows: Reporting any severity grade was 54.9% vs 42.2% after dose 1 and 79.3% vs 36.5% after dose 2; Grade 3 severity was 2.9% vs. 2.0% after dose on and 15.7% vs. 2.0% after dose 2, respectively. Across groups and doses <0.1% reported a grade 4 systemic reaction (mainly fever > 104 ºF). In the scoring system for pain, Grade 3 was defined as any use of Rx pain reliever/prevents daily activity; Grade 4 was defined as the patient requiring E.R. visit or hospitalization.
- Severe adverse reactions occurred in 0.2% to 9.7% of participants, were more frequent after dose two than after dose one, and were generally less frequent in participants ≥65 years of age as compared to younger participants.
- Most vaccine recipients reported onset of systemic adverse reactions while at home either on Day one (33.7%) or on Day two (37.0%), and the median duration of symptoms after any dose was two days.
- Lymphadenopathy was a solicited adverse reaction in 21.4% of vaccine recipients <65 years of age and 12.4% of vaccine recipients ≥65 years of age, as compared with 7.5% and 5.8% of placebo recipients in those age groups. The median duration following any dose was one to two days, and <1% reported Grade 3 axillary swelling/tenderness. FDA has concluded that this side effect is plausibly related to vaccination.
- There were more adverse events related to hypersensitivity in vaccine recipients (1.5%) compared with controls (1.1%). However, there were no anaphylactic or severe hypersensitivity reactions with close temporal relation to the vaccine.
- There were three reports of facial paralysis (Bell's palsy) in the vaccine group and one in the placebo group. FDA concluded that "Currently available information is insufficient

to determine a causal relationship with the vaccine."

- "The frequency of serious adverse events was low (1.0% in the mRNA-1273 arm and 1.0% in the placebo arm), without meaningful imbalances between study arms. "
- A total of 13 deaths were reported during the study (six vaccine, seven placebo). These deaths were individually reviewed and represented events and rates that occur in the general population of individuals in these age groups.

What questions remain?

- What is the duration of protection over periods longer than two months? Analysis of participant B- and T-memory cells may help us learn more about the duration of protection.
- What is vaccine effectiveness in certain populations at high-risk of severe COVID-19? The size of certain groups such as immunocompromised individuals is too small to evaluate efficacy outcomes.
- What is vaccine effectiveness in individuals previously infected with SARS-CoV-2? Very few cases of confirmed COVID-19 occurred among participants with evidence of infection prior to vaccination, so more study is needed to make conclusions about benefit in this group.
- What is vaccine effectiveness in pediatric populations (aged less than 18 years old)?
- What is vaccine safety and effectiveness during pregnancy?
- Will vaccine effectiveness be as good if the environment changes (such as characteristics of the pandemic, changes in the virus, and/or potential effects of co-infections)?
- What is vaccine effectiveness against asymptomatic infection?
- What is vaccine effectiveness against long-term effects of COVID-19 disease?
- What is vaccine effectiveness against mortality?
- What is vaccine effectiveness against transmission of SARS-CoV-2?
- Are there adverse events, which were not identified to date? This trial of about 30,350 volunteers is a large trial by usual standards for Phase III vaccine trials. This gives reasonable confidence that significant short-term adverse events have been identified. However, some people were excluded from the trial such as pregnant women. Long-term follow-up will be needed to identify any serious adverse events as early as possible.

Conclusions

In conclusion, FDA determined vaccine efficacy for COVID-19 occurring at least 14 days after the second dose of vaccine was 94.1% overall and vaccine efficacy for severe COVID-19 occurring at least 14 days after the second dose of vaccine was 100% in this Phase III trial of about 30,350 participants.

Safety data from approximately 30,350 participants ≥18 years of age with a median of two months of follow-up after the second dose suggest a favorable safety profile. The vaccine caused increased local and systemic adverse reactions as compared to placebo, usually lasting a few days. Serious adverse events were uncommon (1.0% in both treatment groups) and represented medical events that occur in the general population at similar frequency as observed in the study. No specific safety concerns were identified in subgroup analyses by age, race, ethnicity, medical comorbidities, or prior SARS-CoV-2 infection.

For additional detail, please see COVID-19 vaccine trackers:

Vizient is a healthcare performance improvement company Vizient vaccine tracker

The Regulatory Affairs Professionals Society (RAPS) https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker

The New York Times tracker has won wide endorsement, including from the Hopkins Coronavirus Resource Center COVID-19 Vaccine Tracker

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