Ballad Health COVID-19 Vaccine Workgroup Newsletter

Sixth Edition – Dec. 14, 2020

In this issue: Summary of Internal Analysis of Pfizer/BioNTech Vaccine for COVID-19

Vaccines and Related Biological Products Advisory Committee Briefing - FDA

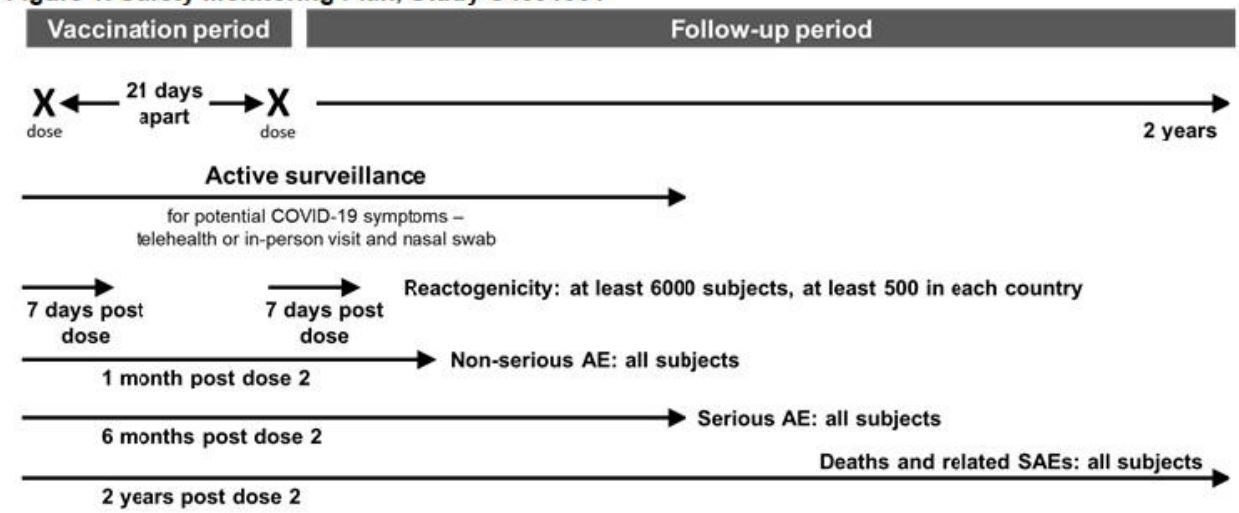
What did the FDA analysis do?

FDA scientists independently evaluated the lengthy application for emergency use authorization (EUA) from Pfizer, 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 16 years of age and older." The final efficacy analysis was planned from the beginning to occur after at least 164 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 or during the 2-dose vaccination regimen, compared to volunteers who received placebo. Safety data was analyzed for 38,000 volunteers aged ≥16 years of age who were randomized 1:1 to vaccine or placebo and with at least 50% having follow-up for a median of at least 2 months after the last dose. Adverse events were recorded daily for 7 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."

Figure 1. Safety Monitoring Plan, Study C4591001



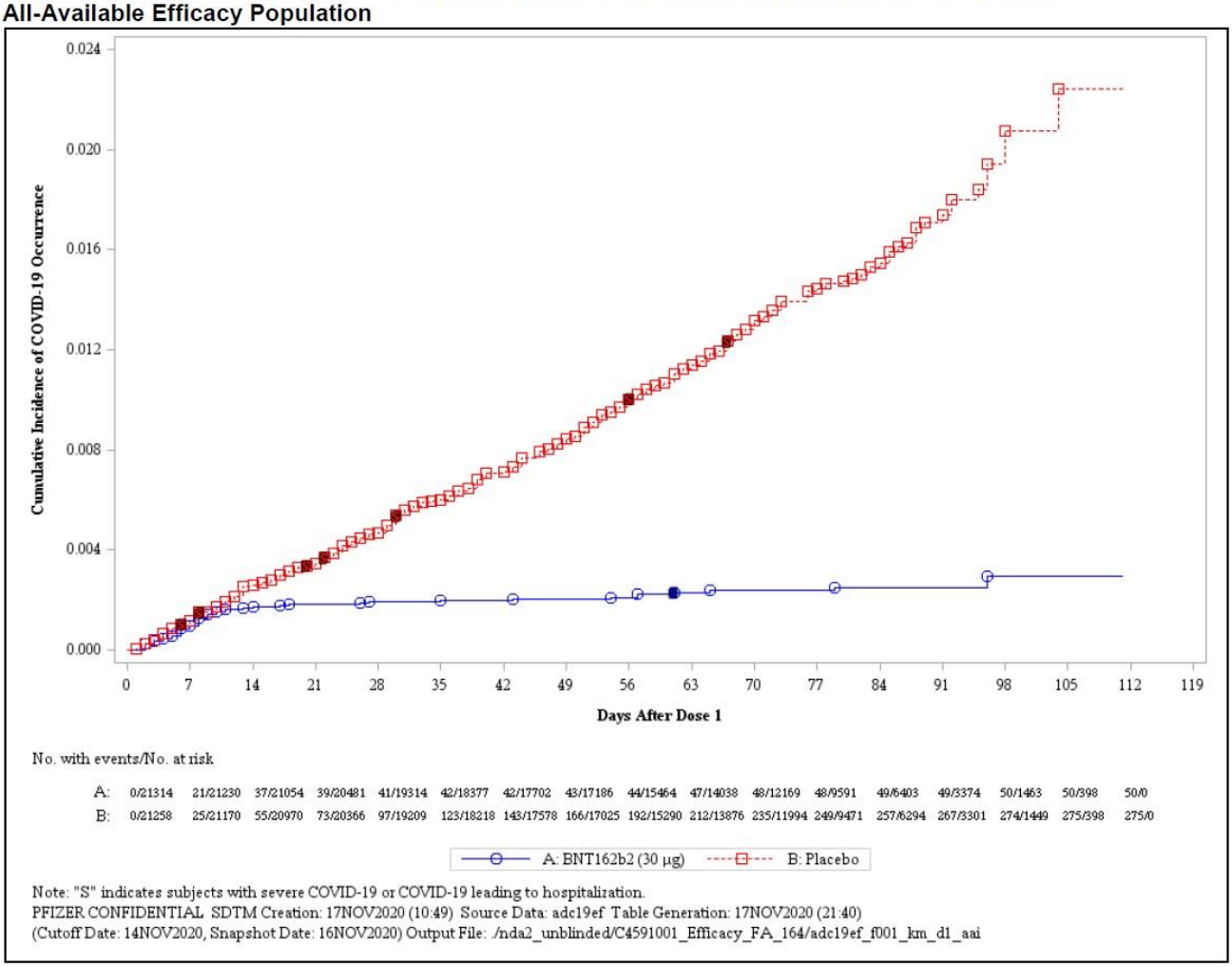
What were the demographics and characteristics of the study population?

"Overall, the phase 2/3 evaluable efficacy population included 49.4% females, 81.9% White, 9.8% African American, 4.4% Asian participants, and <3% from other racial groups; 26.2% of participants were Hispanic/Latino; 21.4% of participants were >65 years of age. The median age was 51 years. The most frequently reported comorbidities were obesity (35.1%), diabetes (with and without chronic complications, 8.4%) and pulmonary disease (7.8%). Geographically, 76.7% of participants were from the United States, 15.3% from Argentina, 6.1% from Brazil, and 2% from South Africa.

The demographic characteristics among vaccine and placebo participants in the all-available efficacy population were similar to the evaluable efficacy population."

What were the key findings for efficacy?

Figure 2. Cumulative Incidence Curves for the First COVID-19 Occurrence After Dose 1, Dose 1 All-Available Efficacy Population



- 170 people developed COVID-19 with 8 in the vaccine group and 162 in the placebo group.
- "In the planned interim and final analyses, vaccine efficacy after 7 days post Dose 2 was 95%, (95% CI 90.3; 97.6) in participants without prior evidence of SARS-CoV-2 infection and >94% in the group of participants with or without prior infection. Efficacy outcomes were consistently robust (≥93%) across demographic subgroups."

- Limited information is available to assess the efficacy of the vaccine to prevent severe infection ≥7 days after the second dose, which occurred in one patient in the vaccine group and three patients in the placebo group.
- The vaccine began to show efficacy at about 14 days after the first dose and prior to the second vaccine dose (see graph above). However, since the second dose was given at 21 days, it is not possible to make a reliable estimate of the effectiveness of a single vaccine dose.

What were the key findings for safety?

"The vaccine has been shown to elicit increased local and systemic adverse reactions as compared to those in the placebo arm, usually lasting a few days."

- Immediate, unsolicited adverse events within 30 minutes of vaccination for dose 1 were 0.4% for vaccine and 0.4% for placebo; for dose 2 they were 0.3% for vaccine and 0.2% for placebo.
- Withdrawal due to adverse events was seen in 0.6% in the vaccine group and 0.5% in placebo.
- Local site reactions were solicited daily for 7 days after each dose and were frequent (84%). Pain was far more common than redness or swelling. Pain reactions were usually mild (does not interfere with activity; (62%) or moderate (interferes with activity; 36%). Severe site reactions with pain (prevents daily activity) were reported in 1.4%.
- The next most common adverse reactions solicited daily for 7 days after each dose were fatigue (in 62.9% with 97% mild or moderate), headache (in 55.1% with 98% mild or moderate), muscle pain (in 38.3% with 97% mild or moderate), chills (in 31.9% with 97% mild or moderate), joint pain (in 23.6% with 98% mild or moderate), fever (in 14.2% with 88% less than 102°F).
- Unsolicited adverse reactions included lymphadenopathy (64 in the vaccine group versus 6 in the placebo group), and Bell's palsy (4 in the vaccine group and none in the placebo group). The analysis notes "The observed frequency of reported Bell's palsy in the vaccine group is consistent with the expected background rate in the general population, and there is no clear basis upon which to conclude a causal relationship at this time, but FDA will recommend surveillance for cases of Bell's palsy with deployment of the vaccine into larger populations."
- FDA searched participant records for adverse event terms that could represent various diseases and conditions, including but not limited to allergic, neurologic, inflammatory, and autoimmune conditions. There was one finding: more participants reported hypersensitivity-related adverse events in the vaccine group (in 137, 0.63%) than the placebo group (in 111, 0.51%). Of note, applicants with a history of serious allergic reactions to vaccines were excluded from the study.
- Serious adverse events: Death occurred in 2 vaccine recipients and 4 placebo recipients. "All deaths represent events that occur in the general population of age groups where they occurred, at a similar rate."
- "The frequency of non-fatal serious adverse events was low (<0.5%), without meaningful imbalances between study arms." The most common events in the vaccine arm were appendicitis (0.04%), acute myocardial infarction (0.02%), and cerebrovascular accident (0.02%).
- Efficacy was "uniformly high across the subgroups examined with the exception of participants identifying as multiracial and participants with evidence of prior SARS-CoV-2 infection at enrollment, for which too few COVID-19 cases occurred to interpret efficacy data for these subgroups."
- Vaccine protection did not wane during the 2-month period after the second dose.
- Limited data supported the idea that previously infected individuals could be at risk of reinfection and could benefit from vaccination.

What questions remain?

- What is the duration of protection over periods longer than 2 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 16 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 44,000 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 and people who had previous severe immunologic reactions to vaccines). Follow up will be needed to identify any serious adverse events as early as possible.

In conclusion, FDA determined the Pfizer vaccine efficacy was 95% in the large Phase III trial. Efficacy was consistently high across demographic subgroups. Safety data with a median of two months of follow-up showed a favorable safety profile, with frequent self-limited injection site pain and mild to moderate systemic side effects lasting up to a few days. No serious adverse effects were found at rates greater than their occurrence in the general population.

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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