Journal Club 3: Pfizer and BioNTech Vaccine Candidate Against COVID-19

Pfizer and BioNTech are collaborating on an mRNA-based vaccine candidate, BNT162b2, against SARS-CoV-2. On November 9th 2020, the companies announced that initial results from their Phase III clinical trial demonstrated over 90 percent effectiveness. We'll be taking a look at excerpts from three documents on BNT162b2:

1. The BusinessWire Press Release for the announcement
2. Pfizer's published study protocol for their RNA based vaccines against COVID-19
3. A *Nature* news article discussing caveats to the announcement

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Document 1: BusinessWire Press Release

Pfizer and BioNTech Announce Vaccine Candidate Against COVID-19 Achieved Success in First Interim Analysis from Phase 3 Study

- *Vaccine candidate was found to be more than 90% effective in preventing COVID-19 in participants without evidence of prior SARS-CoV-2 infection in the first interim efficacy analysis*
- *Analysis evaluated 94 confirmed cases of COVID-19 in trial participants*
- *Study enrolled 43,538 participants, with 42% having diverse backgrounds, and no serious safety concerns have been observed; Safety and additional efficacy data continue to be collected*
- *Submission for Emergency Use Authorization (EUA) to the U.S. Food and Drug Administration (FDA) planned for soon after the required safety milestone is achieved, which is currently expected to occur in the third week of November*
- *Clinical trial to continue through to final analysis at 164 confirmed cases in order to collect further data and characterize the vaccine candidate's performance against other study endpoints*

November 09, 2020 06:45 AM Eastern Standard Time

NEW YORK & MAINZ, GERMANY--(BUSINESS WIRE)--Pfizer Inc. (NYSE: PFE) and BioNTech SE (Nasdaq: BNTX) today announced their mRNA-based vaccine candidate, BNT162b2, against SARS-CoV-2 has demonstrated evidence of efficacy against COVID-19 in participants without prior evidence of SARS-CoV-2 infection, based on the first interim efficacy analysis conducted on November 8, 2020 by an external, independent Data Monitoring Committee (DMC) from the Phase 3 clinical study.

After discussion with the FDA, the companies recently elected to drop the 32-case interim analysis and conduct the first interim analysis at a minimum of 62 cases. Upon the conclusion of those discussions, the evaluable case count reached 94 and the DMC performed its first analysis on all cases. The case split between vaccinated individuals and those who received the placebo indicates a vaccine efficacy rate above 90%, at 7 days after the second dose. This means that protection is achieved 28 days after the initiation of the vaccination, which consists of a 2-dose schedule. As the study continues, the final vaccine efficacy percentage may vary. The DMC has not reported any serious safety concerns and recommends that the study continue to collect additional safety and efficacy data as planned. The data will be discussed with regulatory authorities worldwide.

"Today is a great day for science and humanity. The first set of results from our Phase 3 COVID-19 vaccine trial provides the initial evidence of our vaccine's ability to prevent COVID-19," said Dr. Albert Bourla, Pfizer Chairman and CEO. "We are reaching this critical milestone in our vaccine development program at a time when the world needs it most with infection rates setting new records, hospitals nearing over-capacity and economies struggling to reopen. With today's news, we are a significant step closer to providing people around the world with a much-needed breakthrough to help bring an end to this global health crisis. We look forward to sharing additional efficacy and safety data generated from thousands of participants in the coming weeks."

"I want to thank the thousands of people who volunteered to participate in the clinical trial, our academic collaborators and investigators at the study sites, and our colleagues and collaborators around the world who are dedicating their time to this crucial endeavor," added Bourla. "We could not have come this far without the tremendous commitment of everyone involved."

"The first interim analysis of our global Phase 3 study provides evidence that a vaccine may effectively prevent COVID-19. This is a victory for innovation, science and a global collaborative effort," said Prof. Ugur Sahin, BioNTech co-founder and CEO. "When we embarked on this journey 10 months ago this is what we aspired to achieve. Especially today, while we are all in the midst of a second wave and many of us in lockdown, we appreciate even more how important this milestone is on our path towards ending this pandemic and for all of us to regain a sense of normality. We will continue to collect further data as the trial continues to enroll for a final analysis planned when a total of 164 confirmed COVID-19 cases have accrued. I would like to thank everyone who has contributed to make this important achievement possible."

The Phase 3 clinical trial of BNT162b2 began on July 27 and has enrolled 43,538 participants to date, 38,955 of whom have received a second dose of the vaccine candidate as of November 8, 2020. Approximately 42% of global participants and 30% of U.S. participants have racially and ethnically diverse backgrounds. The trial is continuing to enroll and is expected to continue through the final analysis when a total of 164 confirmed COVID-19 cases have accrued. The study also will evaluate the potential for the vaccine candidate to provide protection against COVID-19 in those who have had prior exposure to SARS-CoV-2, as well as vaccine prevention against severe COVID-19 disease. In addition to the primary efficacy endpoints evaluating confirmed COVID-19 cases accruing from 7 days after the second dose, the final analysis now will include, with the approval of the FDA, new secondary endpoints evaluating efficacy based on cases accruing 14 days after the second dose as well. The companies believe that the addition of these secondary endpoints will help align data across all COVID-19 vaccine studies and allow for cross-trial learnings and comparisons between these novel vaccine platforms. The companies have posted an updated version of the study protocol at https://www.pfizer.com/science/coronavirus.

Pfizer and BioNTech are continuing to accumulate safety data and currently estimate that a median of two months of safety data following the second (and final) dose of the vaccine candidate – the amount of safety data specified by the FDA in its guidance for potential Emergency Use Authorization – will be available by the third week of November. Additionally, participants will continue to be monitored for long-term protection and safety for an additional two years after their second dose.

Along with the efficacy data generated from the clinical trial, Pfizer and BioNTech are working to prepare the necessary safety and manufacturing data to submit to the FDA to demonstrate the safety and quality of the vaccine product produced.

Based on current projections we expect to produce globally up to 50 million vaccine doses in 2020 and up to 1.3 billion doses in 2021.

Pfizer and BioNTech plan to submit data from the full Phase 3 trial for scientific peer-review publication.

Document 2: Pfizer's Study Protocol

PF-07302048 (BNT162 RNA-Based COVID-19 Vaccines)
Protocol C4591001

A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY, IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS

Study Sponsor:	BioNTech
Study Conducted By:	Pfizer
Study Intervention Number:	PF-07302048
Study Intervention Name:	RNA-Based COVID-19 Vaccines
US IND Number:	19736
EudraCT Number:	2020-002641-42
Protocol Number:	C4591001
Phase:	1/2/3

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

3.2. For Phase 2/3

Objectives[a]	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: 100 × (1 – IRR) [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, multinational, Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals.

The study consists of 2 parts. Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema (Section 1.2).

The study will evaluate the safety, tolerability, and immunogenicity of 2 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups in Phase 1 may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The study is observer-blinded, as the physical appearance of the investigational vaccine candidates and the placebo may differ. The participant, investigator, study coordinator, and other site staff will be blinded. At the study site, only the dispenser(s)/administrator(s) are unblinded.

To facilitate rapid review of data in real time, sponsor staff will be unblinded to vaccine allocation for the participants in Phase 1.

Document 3: Nature Article

NEWS · 09 NOVEMBER 2020

What Pfizer's landmark COVID vaccine results mean for the pandemic

Scientists welcome the first compelling evidence that a vaccine can prevent COVID-19. But questions remain about how much protection it offers, to whom and for how long.

Ewen Callaway

It works! Scientists have greeted with cautious optimism a press release declaring positive interim results from a coronavirus vaccine phase III trial — the first to report on the final round of human testing.

New York City-based drug company Pfizer made the announcement on 9 November. It offers the first compelling evidence that a vaccine can prevent COVID-19 — and bodes well for other COVID-19 vaccines in development. But the information released at this early stage does not answer key questions that will determine whether the Pfizer vaccine, and others like it, can prevent the most severe cases or quell the coronavirus pandemic.

"We need to see the data in the end, but that still doesn't dampen my enthusiasm. This is fantastic," says Florian Krammer, a virologist at Icahn School of Medicine at Mount Sinai in New York City, who is one of the trial's more than 40,000 participants. "I hope I'm not in the placebo group."

The vaccine, which is being co-developed by BioNTech in Mainz, Germany, consists of molecular instructions — in the form of messenger RNA — for human cells to make the coronavirus spike protein, the immune system's key target for this type of virus. The two-dose vaccine showed promise in animal studies and early-stage clinical trials. But the only way to know whether the vaccine works is to give it to a large number of people and then follow them over weeks or months to see whether they become infected and symptomatic. These results are compared with those for a group of participants who are given a placebo.

In the press release, Pfizer and BioNTech said they had identified 94 cases of COVID-19 among 43,538 trial participants. The companies did not indicate how many of those cases were in the placebo group or among those who got the vaccine. But they said that the split of cases between the groups suggested that the vaccine was more than 90% effective at preventing disease, when measured at least one week after trial participants had received a second vaccine dose 3 weeks after the first. The trial will continue until a total of 164 COVID-19 cases are detected, so initial estimates of the vaccine's effectiveness could change.

Although the vaccine might not turn out to be quite so effective once the trial is complete and all the data have been analysed, its effectiveness is likely to stay well above 50%, says Eric Topol, a cardiologist and director of the Scripps Research Translational Institute in La Jolla, California. This is the threshold that the US Food and Drug Administration (FDA) says is required for a coronavirus vaccine to be approved for emergency use. “I think this is an extraordinary achievement, even without many details, because there was no assurance of vaccine efficacy before we got the first read-out from a trial,” Topol says.

Questions remain

What’s missing, say Topol and other scientists, are details about the nature of the infections the vaccine can protect against — whether they are mostly mild cases of COVID-19 or also include significant numbers of moderate and severe cases. “I want to know the spectrum of disease that the vaccine prevents,” says Paul Offit, a vaccine scientist at the Children’s Hospital of Philadelphia in Pennsylvania who sits on a US Food and Drug Administration advisory committee that is set to evaluate the vaccine next month. “You’d like to see at least a handful of cases of severe disease in the placebo group,” he adds, because it would suggest that the vaccine has the potential to prevent such cases.

It’s unclear whether the vaccine can prevent people who show no or only very mild symptoms of COVID-19 from spreading the coronavirus. A transmission-blocking vaccine could accelerate the end of the pandemic. But it will be difficult to determine whether the Pfizer vaccine, or others in late-stage trials, can achieve this, says Krammer, because it would involve routinely testing trial participants. “You can’t do that with 45,000 people,” he says.

Another missing detail is how well the vaccine works in different groups of trial participants. “We don’t know yet if it works in the population that needs it most, which is elderly,” says Krammer. Because of the small number of cases it will accrue before ending, the Pfizer trial is unlikely to conclusively determine the vaccine’s efficacy in particular demographic groups, such as over-65s or African Americans, says Offit. But he adds that if the trial enrolled enough participants from such groups, it could be possible to generalize the vaccine’s probable effectiveness in them from its overall efficacy. In the press release, Pfizer and BioNTech reported that 42% of participants had “racially and ethnically diverse backgrounds”.

Lasting immunity?

One key unanswered question is how long the vaccine’s effectiveness will last. On the basis of when the trial started and previously published data on immune responses in early-stage trials, many trial participants are likely to still have high levels of protective antibodies in their blood, says Rafi Ahmed, an immunologist at Emory University in Atlanta, Georgia. “To me, the main question is what about six months later, or even three months later,” he says.

There will be a chance to answer that question if the trial continues for several more months, says Ahmed. Answers could also come from analysis of the immune responses of people who took part in early-stage trials of the Pfizer vaccine, some of whom might have been given the vaccine up to six months ago. And although little is known about the vaccine’s long-term effectiveness, that is unlikely

to hold up its use, says Ahmed. “I don’t think we should say, ‘Well, I’ll only take a vaccine that protects me for five years.’ I mean, that could be crazy.”

The results are a boost for other COVID-19 vaccine candidates. That includes an mRNA vaccine being developed by Moderna, a biotechnology company in Cambridge, Massachusetts, and the US National Institute of Allergy and Infectious Diseases in Bethesda, Maryland, says Krammer. “I expect Moderna stocks will go up today.”

Shane Crotty, a vaccine immunologist at the La Jolla Institute for Immunology in California, thinks that Moderna isn’t the only developer that should celebrate Pfizer’s preliminary results. Several other candidate vaccines triggered immune responses similar to those elicited by Pfizer’s vaccine in early-stage trials, so they should work well, too.

One thing about Pfizer’s vaccine is certain: regulators will soon decide whether it’s ready for roll-out. The company said it would seek an emergency use authorization from the FDA around the third week of November, at which point half of the participants will have been followed for two months — an FDA safety requirement for COVID-19 vaccines.

And although researchers want to see the data behind Pfizer’s vaccine trial, they are prepared to accept caveats that come with them. “Right now, we need a vaccine that works,” says Krammer, even if it works for only a few months or doesn’t stop transmission. “That’s what we need in order to get half-way back to normal.”