The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 31, 2020 VOL. 383 NO. 27

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

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ABSTRACT

BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the resulting coronavirus disease 2019 (Covid-19) have afflicted tens of millions of people in a worldwide pandemic. Safe and effective vaccines are needed urgently.

METHODS

In an ongoing multinational, placebo-controlled, observer-blinded, pivotal efficacy trial, we randomly assigned persons 16 years of age or older in a 1:1 ratio to receive two doses, 21 days apart, of either placebo or the BNT162b2 vaccine candidate (30 μg per dose). BNT162b2 is a lipid nanoparticle–formulated, nucleoside-modified RNA vaccine that encodes a prefusion stabilized, membrane-anchored SARS-CoV-2 full-length spike protein. The primary end points were efficacy of the vaccine against laboratory-confirmed Covid-19 and safety.

RESULTS

A total of 43,548 participants underwent randomization, of whom 43,448 received injections: 21,720 with BNT162b2 and 21,728 with placebo. There were 8 cases of Covid-19 with onset at least 7 days after the second dose among participants assigned to receive BNT162b2 and 162 cases among those assigned to placebo; BNT162b2 was 95% effective in preventing Covid-19 (95% credible interval, 90.3 to 97.6). Similar vaccine efficacy (generally 90 to 100%) was observed across subgroups defined by age, sex, race, ethnicity, baseline body-mass index, and the presence of coexisting conditions. Among 10 cases of severe Covid-19 with onset after the first dose, 9 occurred in placebo recipients and 1 in a BNT162b2 recipient. The safety profile of BNT162b2 was characterized by short-term, mild-to-moderate pain at the injection site, fatigue, and headache. The incidence of serious adverse events was low and was similar in the vaccine and placebo groups.

CONCLUSIONS

A two-dose regimen of BNT162b2 conferred 95% protection against Covid-19 in persons 16 years of age or older. Safety over a median of 2 months was similar to that of other viral vaccines. (Funded by BioNTech and Pfizer; ClinicalTrials.gov number, NCT04368728.)

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*A complete list of investigators in the C4591001 Clinical Trial Group is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Polack and Thomas contributed equally to this article.

This article was published on December 10, 2020, and updated on December 16, 2020, at NEJM.org.

N Engl J Med 2020;383:2603-15.
DOI: 10.1056/NEJMoa2034577

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Generalities

- Population
  - What is the population
  - Limitations on the conclusions
- Sample
  - Sampling strategy
  - Observational/experimental
  - Other relevant features
- Are there any issue related to sampling in this case?

Outcome measure – endpoint(s)

Outcome measure
For clinical trials, a planned measurement described in the protocol that is used to determine the effect of an intervention/treatment on participants. For observational studies, a measurement or observation that is used to describe patterns of diseases or traits, or associations with exposures, risk factors, or treatment. Types of outcome measures include primary outcome measure and secondary outcome measure.

When there are many endpoints prespecified in a clinical trial, they are usually classified into three families: primary, secondary, and exploratory.

- The set of primary endpoints consists of the outcome or outcomes (based on the drug's expected effects) that establish the effectiveness, and/or safety features, of the drug in order to support regulatory action. When there is more than one primary endpoint and success on any one alone could be considered sufficient to demonstrate the drug's effectiveness, the rate of falsely concluding the drug is effective is increased due to multiple comparisons (see section II.E).
- Secondary endpoints may be selected to demonstrate additional effects after success on the primary endpoint. For instance, a drug may demonstrate effectiveness on the primary endpoint of survival, after which the data regarding an effect on a secondary endpoint, such as functional status, would be tested. Secondary endpoints may also provide evidence that a particular mechanism underlies a demonstrated clinical effect (e.g., a drug for osteoporosis with fractures as the primary endpoint, and improved bone density as a secondary endpoint).
- All other endpoints are referred to as exploratory in this document (see section III.A).

Statistical model

- A parametric statistical model is a triplet
  - Sample space
  - Parameter space
  - Distribution family
- A Bayesian model also requires a prior distribution

(Hints: look for possible reparametrizations/ nuisance parameters/ sufficient statistics.)

Conclusion

- What is the final criterion to decide on the efficacy of the vaccine?

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