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SYNOPSIS

CSR Title: Final Report: A Phase 1/2, Placebo-Controlled, Randomized, and Observer-Blind Study to Evaluate the Safety, Tolerability, and Immunogenicity of a SARS-CoV-2 RNA Vaccine Candidate Against COVID-19 in Healthy Japanese Adults

Study Number: C4591005

Regulatory Agency or Public Disclosure Identifier Number: Not Applicable

Study Phase: Phase 1/2 (transitioned to post marketing study in Protocol Amendment 3)

Name of Study Intervention: PF-07302048 (BNT162b2)

Name of Sponsor/Company: BioNTech SE

CSR Version and Report Date: Version 1.0, 16 November 2022

Number of Study Center(s) and Investigator(s):

A total of 160 participants were enrolled at 2 centers in Japan.

A list of study centers and investigators involved in this study is provided in Appendix 16.1.4.1.

Publications:

Not Applicable

Study Period:

Study Initiation Date: 21 Oct 2020

Study Completion Date: 25 Nov 2021

This study was neither discontinued nor interrupted.

Rationale:

The purpose of the study was to rapidly describe the safety, tolerability, and immunogenicity of BNT162b2 ribonucleic acid (RNA)-based coronavirus disease 2019 (COVID-19) vaccine candidate against COVID-19 in healthy Japanese adults. Given the global crisis of COVID-19 and fast expansion of the disease globally, including Japan, the rapid development of an effective vaccine was of utmost importance.

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Objectives, Endpoints, and Statistical Methods:

Objectives	Estimands	Endpoints
Primary Safety:		
To describe the safety and tolerability profiles of a prophylactic BNT162b2 vaccine in healthy Japanese adults after 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after Dose 2 • Serious adverse events (SAEs) from Dose 1 to 12 months after Dose 2	• Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
	In addition, in a clinical laboratory subset, the percentage of participants with: • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2	• Hematology and chemistry laboratory parameters
Primary Immunogenicity:		
To describe the immune responses elicited by a prophylactic BNT162b2 vaccine in healthy Japanese adults	In participants complying with the key protocol criteria (evaluable participants): • Geometric Mean Titers (GMTs) 1 month after Dose 2 • Geometric Mean Fold Rises (GMFR) from before vaccination to 1 month after Dose 2	• Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) serum neutralizing titers
Secondary Immunogenicity:		
To describe the immune responses elicited by a prophylactic BNT162b2 vaccine in healthy Japanese adults	In the evaluable participants, at baseline, 21 days after Dose 1; 7 and 14 days and 6 and 12 months after Dose 2: • GMTs at each time point • GMFR from before vaccination to each subsequent time point after vaccination	• SARS-CoV-2 serum neutralizing titers

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Objectives	Estimands	Endpoints
To describe the immune responses elicited by a prophylactic BNT162b2 vaccine in participants with/without confirmed COVID-19 before Dose 2	In the evaluable participants, at baseline, 21 days after Dose 1; 7 and 14 days and 1, 6, and 12 months after Dose 2: • GMTs at each time point • GMFR from before vaccination to each subsequent time point after vaccination	• SARS-CoV-2 serum neutralizing titers
Exploratory Immunogenicity:		
[redacted]		

Abbreviations: AE = adverse events; COVID-19 = coronavirus disease 2019; GMFR = geometric mean fold rise; GMT = geometric mean titer; [redacted]; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2
Source: Appendix 16.1.1, Protocol Section 3

Methodology:

This was a Phase 1/2, randomized, placebo-controlled, and observer-blind study in healthy Japanese adults.

The study evaluated the safety, tolerability, and immunogenicity of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA vaccine candidate against COVID-19 (BNT162b2), which is the same as the vaccine candidate selected for Phase 2/3 evaluation in the C4591001 study:

- As 2 doses, separated by 21 days
- At a 30-µg dose level
- In adults 20 to 85 years of age

Local reactions (redness, swelling, and pain at the injection site), systemic events (fever, vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or

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worsened joint pain), and use of antipyretic medication were prompted for and collected by all participants in an e-diary from Day 1 through Day 7 after each administration of study intervention. Adverse events (AEs) were collected from the time the participant provided informed consent through 1 month after Dose 2, and serious adverse events (SAEs) were collected from the time of informed consent through 12 months after Dose 2.

One hundred sixty participants were randomly assigned in a 3:1 ratio to study intervention (candidate vaccine: 120, placebo: 40), such that approximately 144 evaluable participants (candidate vaccine: 108, placebo: 36) were evaluated.

As this study was the first study conducted in Japan, clinical laboratory tests were performed in the first 24 participants (12 participants 20 to 64 years of age and 12 participants 65 to 85 years of age) (clinical laboratory subset). After randomization of all participants in the clinical laboratory subset was completed, the standard participants were enrolled.

Blood was collected prior to Dose 1, prior to Dose 2, and 7 and 14 days and 1, 6, and 12 months after Dose 2 to assess immunogenicity.

The study was observer-blinded, as the physical appearance of the investigational vaccine candidates and the placebo may have differed. The participant, investigator, study coordinator, and other site staff were blinded. At the study site, only the dispenser(s)/administrator(s) were unblinded.

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

Participants were expected to participate for up to a maximum of approximately 14 months.

From protocol amendment 3, this study was transitioned from a clinical trial to a postmarketing study according to the Japanese regulation, because BNT162b2 was approved by the Ministry of Health, Labour and Welfare on 14 Feb 2021.

Number of Participants (planned and analyzed):

In this study, a total of 160 participants were randomized in an approximate 3:1 ratio of BNT162b2 to placebo. A total of 130 participants were randomized in the younger age group (20 to 64 years of age) and 30 participants were randomized in the older age group (65 to 85 years of age). Of the 160 participants, 157 (98.1%) participants completed the vaccination series (2 doses). Three (3; 1.9%) participants in the BNT162b2 group discontinued study intervention.

A total of 35 participants originally randomized to placebo received BNT162b2 Dose 3 (first dose of BNT162b2) and Dose 4 (second dose of BNT162b2).

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Diagnosis and Main Criteria for Inclusion and Exclusion:

Inclusion Criteria

Participants were eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Japanese male or female participants between the ages of 20 and 85 years, inclusive, at randomization.

Type of Participant and Disease Characteristics:

2. Participants who were willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures.

3. Healthy participants who were determined by medical history, physical examination, and clinical judgment of the investigator to be eligible for inclusion in the study.

   Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, could be included.

Informed Consent:

4. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent document.

Exclusion Criteria

Participants were excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

2. Known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).

3. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).

4. Receipt of medications intended to prevent COVID-19.

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5. Previous confirmed diagnosis of COVID-19.

6. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.

7. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.

8. Women who were pregnant or breastfeeding.

Prior/Concomitant Therapy:

9. Previous vaccination with any coronavirus vaccine.

10. Individuals who received treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids had been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy had been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids were permitted.

11. Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

12. Participation in other studies involving study intervention within 28 days prior to study entry and/or during study participation.

13. Previous participation in other studies involving study intervention containing lipid nanoparticles.

Diagnostic Assessments:

14. **Clinical laboratory subset only:** Any screening hematology and/or blood chemistry laboratory value that met the definition of a ≥ Grade 1 abnormality.

    Note: With the exception of bilirubin, participants with any stable Grade 1 abnormalities (according to the toxicity grading scale) were considered eligible at the discretion of the investigator. (Note: A "stable" Grade 1 laboratory abnormality was defined as a report of Grade 1 on an initial blood sample that remained ≤ Grade 1 upon repeat testing on a second sample from the same participant.)

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Other Exclusions:

15. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

Study Interventions, Dose, Mode of Administration, and Batch Number(s):

The study evaluated a 2-dose (separated by 21 days) schedule of 30 µg of the investigational RNA vaccine candidate for active immunization against COVID-19, which was the same as that selected for Phase 2/3 evaluation in the C4591001 study. The vaccine candidate or placebo (normal saline) was administered to a study participant.

Table S 1. Investigational Product Lot Numbers

Investigational Product	Manufacturer	Vendor Lot Number (Manufacturer)	Lot Number[a] (Pfizer)
BNT162b2 (30 µg)	BioNTech	ED3938	PA2074300/P221155-0001L
Normal saline (0.9% sodium chloride solution for injection)	Pfizer	DK2074; 20-002221	PA2069407/P221155-0002L
		DK2074; 20-002221	PA2069407/P221155- 0003L

a. Lot number assigned to the investigational product by Pfizer Global Clinical Supply.
Protocol C4591005 Investigational Product Lot Numbers Table – Final, Final, Version 2.0, 22Jun2022.

Duration of Study Intervention:

Participants were expected to participate for up to a maximum of approximately 14 months.

Summary of Results:

Demographic and Other Baseline Characteristics:

- Participant demographic and baseline characteristics were balanced across the BNT162b2 and placebo groups. All participants (100%) were Japanese, with a similar number of males and females (50.6% and 49.4%, respectively), and mostly balanced between the BNT162b2 and placebo groups. The overall median age at vaccination was 47.0 years of age. The median age in the younger age group (20 to 64 years of age) was 43.0 years, while the median age in the older age group (65 to 85 years of age) was 71.0 years.

Study Intervention:

- The majority of participants in the BNT162b2 group received Dose 1 (100.0%) and Dose 2 (97.5%). The majority of participants originally in the placebo group received Dose 3 (85.4%) and Dose 4 (85.4%). The majority (96.6%) of participants in the BNT162b2 group received Dose 2 within the protocol-specified time frame after Dose 1. The majority (82.9%) of participants originally in the placebo group received Dose 4 within the protocol-specified time frame after Dose 3.

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Immunogenicity Results:

Primary Endpoint

- SARS-CoV-2 50% serum neutralizing geometric mean titers (GMTs) substantially increased in the BNT162b2 group 1 month after Dose 2 (Day 28). The GMTs were lower in the older age group (65 to 85 years of age) compared with the younger age group (20 to 64 years of age).

- The 50% serum neutralizing titer geometric mean fold rises (GMFRs) observed at 1 month after Dose 2 based on original assay methodology were 55.8 and 36.6 in the younger and older age groups, respectively.

Secondary Endpoints

- Compared to baseline, for participants in the BNT162b2 group, an increase in SARS-CoV-2 50% serum neutralizing GMTs was observed at Day 7 after Dose 2 and was maximal at 1 month after Dose 2. At 6 and 12 months after Dose 2, the GMTs decreased relative to 1 month after Dose 2, but remained higher than prevaccination levels. The GMTs were higher at each time point for the BNT162b2 group compared with the placebo group. The GMTs were lower in the older age group (65 to 85 years of age) compared with the younger age group (20 to 64 years of age) at every time point.

- After Dose 2, an increase in SARS-CoV-2 50% serum neutralizing titer was observed at Day 7 (GMFRs: 40.1 [44.3 in the younger age group and 26.2 in the older age group]) with GMFRs maximal at 1 month after Dose 2 based on original assay methodology (GMFRs: 51.5 [55.8 in the younger age group and 36.6 in the older age group]).

Safety Results:

Local Reactions

- Pain at the injection site was the most common local reaction after both Dose 1 and Dose 2 in the BNT162b2 group, regardless of age group. For each of the local reactions, the majority were mild or moderate. Severe pain at the injection site was reported by 2 (1.7%) participants after Dose 1 and by 2 (1.7%) participants after Dose 2. No Grade 4 local reactions were reported during the study.

- The frequency and severity of local reactions after Dose 2 were similar to those after Dose 1. The frequency and severity of local reactions were similar for each age group. Severe pain at the injection site was reported by participants in the younger age group (20 to 64 years) after Dose 1 (2 [2.1%] participants) and Dose 2 (2 [2.1%] participants).

- One (2.4%) participant in the placebo group reported mild pain at the injection site after Dose 1. No other local reactions were reported by the participants in the placebo group.

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Systemic Events

- Fatigue was the most common systemic event after both Dose 1 and Dose 2 in the BNT162b2 group, regardless of age group. For each of the systemic events, the majority were mild or moderate. Severe systemic events were rare after Dose 1 of BNT162b2, with 1 (0.8%) participant reporting multiple severe systemic events (fatigue, headache, chills, and new or worsening joint pain). After Dose 2, participants in the BNT162b2 group reported severe fatigue (4 [3.4%] participants), headache and chills (each 2 [1.7%] participants), and new or worsening joint pain (1 [0.9%] participant). All of the severe events after Dose 1 and Dose 2 had an onset on Day 2 and all resolved after 1 to 3 days. No Grade 4 systemic events were reported during the study. The frequency and severity of systemic events increased after Dose 2 compared with Dose 1.

- Very few participants in the placebo group reported systemic events (7 [17.1%] participants after Dose 1 and 5 [12.2%] participants after Dose 2). For each of the systemic events, the majority were mild.

- When systemic events were analyzed by age group, systemic events were more frequently reported by the younger age group overall. Fatigue was the most common systemic event after both Dose 1 and Dose 2 in the younger group. Systemic events were less common in the older age group, with headache the most common systemic event. The frequency and severity of systemic events increased after Dose 2 compared with Dose 1 for both age groups.

- In the placebo group, 1 (12.5%) participant in the older age group reported a mild headache after Dose 1. All other systemic events in the placebo group were reported by participants in the younger age group.

- In the BNT162b2 group, fever was reported more frequently after Dose 2 in both age groups (37.2% in the younger age group and 13.6% in the older age group) and was mild or moderate in severity. After Dose 2, 1 (1.1%) participant in the younger group had severe fever (>38.9°C to 40.0°C), which had an onset on Day 2 and had a duration of 2 days. There were no reports of fever in the placebo group.

- The use of antipyretic or pain medication after Dose 1 was reported by 19.3% of participants in the BNT162b2 group (22.7% in the younger age group and 4.5% in the older age group and 4.9% of participants in the placebo group).

- After Dose 2, the number of participants reporting the use of antipyretic or pain medication increased to 34.5% of participants in the BNT162b2 group (41.5% in the younger age group and 4.5% in the older age group).

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Adverse Events

- The percentage of participants who reported AEs other than local or systemic reactogenicity events from Dose 1 to 1 month after Dose 2 was low, with 10.9% of the participants in the BNT162b2 group and 7.3% of participants in the placebo group. There were no immediate AEs (reported within 30 minutes of vaccination) after either Dose 1 or Dose 2. There were no deaths, related SAEs, or life-threatening events reported from Dose 1 to 12 months after Dose 2.

- One (0.8%) participant in the BNT162b2 group (younger age group) reported severe AEs (chills, fatigue, injection site pain, arthralgia, and headache) after Dose 1. The events were considered related to BNT162b2 and study intervention was withdrawn. This participant also reported these severe AEs as severe systemic events in the e-diary.

- In the BNT162b2 group, infections and infestations was the most common system organ class and the most frequently reported AEs were nasopharyngitis (3 [2.5%] participants) and headache (2 [1.7%] participants). Nasopharyngitis and headache were each reported by 1 (2.4%) participant in the placebo group.

Severe Adverse Events

- After Dose 1, severe AEs were reported by 1 (0.8%) participant in the BNT162b2 group. The participant reported severe chills, severe fatigue, severe injection site pain, severe arthralgia, and severe headache. All of the severe AEs resolved within 2 to 7 days. This participant also reported these severe AEs as severe systemic events in the e-diary. No severe AEs were reported after Dose 2 by any participant.

Related Adverse Events

- After Dose 1, related AEs (chills, fatigue, injection site pain, arthralgia, headache) were reported by 1 (0.8%) participant in the BNT162b2 group. After Dose 2, related AEs (myalgia and erythema multiforme) were reported by 2 (1.7%) participants in the BNT162b2 group. None of the related AEs met SAE or AEs of special interest (AESI) criteria.

Immediate Adverse Events

- There were no immediate AEs reported after Dose 1 or Dose 2.

Deaths

- No participants died during the reporting period for this study.

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Serious Adverse Events

- No SAEs were reported after Dose 1. After Dose 2, SAEs were reported by 2 (1.7%) participants in the BNT162b2 group. One (0.8%) participant in the younger age group developed severe pneumonia, which was considered not related to BNT162b2. One (0.8%) participant in the older age group was diagnosed with ovarian neoplasm, which was considered not related to BNT162b2.

- There were no life-threatening AEs reported after Dose 1 or Dose 2.

Discontinuations from Study Intervention or Study Due to Adverse Events

- One (0.8%) participant in the BNT162b2 group discontinued from study intervention due to AEs. The participant, in the younger age group, reported chills, fatigue, injection site pain, arthralgia, and headache after Dose 1. All of the events were considered severe and related to BNT162b2.

Adverse Events of Special Interest

- No participants reported AESIs prior to unblinding. After unblinding, 1 (0.8%) participant in the BNT162b2 group (Study Day 141 after Dose 2) and 1 (2.4%) participant in the placebo group (Study Day 257 after Dose 2) tested positive for SARS-CoV-2. The participant in the BNT162b2 group had no signs or symptoms of potential COVID-19 and the participant in the placebo group reported new or increased cough and new or increased sore throat on Study Day 258.

Conclusions:

Immunogenicity

- SARS-CoV-2 50% serum neutralizing GMTs substantially increased in the BNT162b2 group 1 month after Dose 2 (Day 28). The GMTs were lower in the older age group (65 to 85 years of age) compared with the younger age group (20 to 64 years of age).

- The 50% serum neutralizing titer GMFRs observed at 1 month after Dose 2 based on original assay methodology were 55.8 and 36.6 in the younger and older age groups, respectively.

- After Dose 2, an increase in SARS-CoV-2 50% serum neutralizing titer was observed at Day 7 (GMFRs: 40.1 [44.3 in the younger age group and 26.2 in the older age group]) with GMFRs maximal at 1 month after Dose 2 based on original assay methodology (GMFRs: 51.5 [55.8 in the younger age group and 36.6 in the older age group]).

- At 6 and 12 months after Dose 2, the GMTs decreased relative to 1 month after Dose 2, but remained higher than prevaccination levels. The GMTs were lower in the older age

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group (65 to 85 years of age) compared with the younger age group (20 to 64 years of age) at every time point.

Safety

- BNT162b2 was well tolerated and had an acceptable safety profile in healthy Japanese adults 20 to 85 years of age.
- Local reactions in the BNT162b2 group were mostly mild or moderate in severity.
    - Pain at the injection site was the most common local reaction after both Dose 1 and Dose 2.
    - The frequency and severity of local reactions after Dose 2 were similar to those after Dose 1. The frequency and severity of local reactions were similar for each age group.
    - The median onset of local reactions was 1.0 to 3.0 days and the majority of local reactions resolved after 1.0 to 3.5 days.
- Systemic events in the BNT162b2 group were mostly mild or moderate in severity.
    - Fatigue was the most common systemic event after both Dose 1 and Dose 2.
    - The frequency and severity of systemic events increased after Dose 2 compared with Dose 1 for both age groups.
    - Fever was reported more often after Dose 2 in both age groups (37.2% in the younger age group and 13.6% in the older age group) and was mild or moderate in severity. There were no reports of fever in the placebo group.
    - The median onset of systemic events was 2.0 to 4.0 days and the majority of systemic events resolved after 1.0 to 2.0 days.
- The percentage of participants who reported AEs from Dose 1 to 1 month after Dose 2 was low, with 10.9% of the participants in the BNT162b2 group and 7.3% of participants in the placebo group reporting AEs.
- There were no immediate AEs (reported within 30 minutes of vaccination) after either Dose 1 or Dose 2.
- There were no deaths, related SAEs, or life-threatening events reported from Dose 1 to 12 months after Dose 2.

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- One (0.8%) participant in the BNT162b2 group (younger age group) reported severe AEs (chills, fatigue, injection site pain, arthralgia, and headache) after Dose 1. The events were considered related to BNT162b2 and study intervention was withdrawn.

- No participants reported AESIs prior to unblinding. After unblinding,
  1 (0.8%) participant in the BNT162b2 group (Study Day 141 after Dose 2) and
  1 (2.4%) participant in the placebo group (Study Day 257 after Dose 2) tested positive for SARS-CoV-2.

- Laboratory test abnormalities were uncommon and almost all were Grade 1 for both age groups.