FOSUN PHARMA
Innovation for Good Health

Clinical Protocol

Safety and Immunogenicity of SARS-CoV-2 mRNA Vaccine (BNT162b2) in Chinese Healthy Population: A Phase II, Randomized, Placebo-controlled, Observer-blind Study

Protocol Number: BNT162-06

Clinical Phase: Phase II

Executive Agency

Shanghai Fosun Pharmaceutical Development, Inc.

1289 Yishan Road, Shanghai, China 200233

Sponsor

BioNTech SE

An der Goldgrube 12, Mainz, Germany 55131

Version 1.5 **Date:** 23 July 2021

Compliance: This study will be conducted in compliance with this protocol, Good Clinical Practice, and applicable regulatory requirements.

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site. Contact information is also provided in **Table 1** .

Fosun Pharma will provide investigators with a site-specific emergency medical contact information card for each subject.

General advice on protocol procedures should be obtained through the monitor assigned to the investigational site.

Table 1 Contact Information

Issue	Contact
Serious adverse event and pregnancy reporting	Fosun Pharma Email: [redacted] Telephone numbers for serious adverse event and pregnancy reporting will be provided to the site
MEDICAL MONITORS (medical advice on conduct of protocol or vaccine)	Emergency medical contact information will be provided to the site

1.2 Document History

Document history	Date	Protocol number and version number	Valid for
Draft version/ China IND submission	7 November 2020	1.0	China
First submission to EC	14 November 2020	1.1	China
Amendment 1	26 November 2020	1.2	China
Amendment 2	8 December 2020	1.3	China
Amendment 3	21 June 2021	1.4	China
Amendment 4	23 July 2021	1.5	China

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2.0 TRIAL SUMMARY

BioNTech SE An der Goldgrube 12, 55131 Mainz, Germany	**Name of the Product:** SARS-CoV-2 mRNA Vaccine (BNT162b2)
Trial Title: Safety and Immunogenicity of SARS-CoV-2 mRNA Vaccine (BNT162b2) in Chinese Healthy Population: A Phase II, Randomized, Placebo-controlled, Observer-blind Study	
IND No.:	**Phase:** II
Study Identifier: BNT162-06	**Blinding:** Observer-blind

Background and Rationale:

SARS-CoV-2 is a single-stranded positive-sense ribonucleic acid (RNA) virus which belongs to the coronavirus family that presents about 78% of structural similarities with other members of the coronavirus, including SARS virus. Coronaviruses are a large family of viruses that are common in many different species of animals, including camels, cattle, cats, and bats. It is rarely for animal coronaviruses to infect people and then spread among infected people just like SARS-CoV-2[1].

SARS-CoV-2 was discovered in January 2020 in Wuhan. The first human disease cases were reported in December 2019 in China. The virus circulated in areas of over 200 countries worldwide, and was considered Acute Respiratory disease syndrome (COVID-19) with mild to severe symptoms. The primary mode of transmission of SARS-CoV-2 is person-to-person contact through respiratory droplets. Patients with mild or asymptomatic infections may account for 60% of all infected patients. Some clinical manifestations include, but are not limited to, fever, cough and diarrhea[2, 3].

Despite mild clinical symptoms in the most adults, SARS-CoV-2 infection over 65 years old has been associated with serious outcomes. The severity of the disease is related to the attack of autoimmunity on the alveoli. Since the beginning of these outbreaks to September 3, 2020, more than 26.1 million COVID-19 infections and more than 860,000 deaths have been confirmed to be associated with SARS-CoV-2 in more than 200 countries and regions worldwide[4].

SARS-CoV-2 is a respiratory virus that can cause the respiratory system disease. The overall incidence of SARS-CoV-2-associated COVID-19 is unknown currently. In the epidemic curve up to January 4, 2020, the epidemic growth rate was 0.10 per day (95% CI, 0.050 to 0.16) and the doubling time was 7.4 days (95% CI, 4.2 to 14). Using the serial interval distribution above, we estimated that R0 was 2.2 (95% CI, 1.4 to 3.9)[3].

No specific antiviral treatment is available for SARS-CoV-2 infections and no vaccine against SARS-CoV-2 is currently available. As the disease is self-limiting, treatment for uncomplicated COVID-19 infection is mainly supportive and focuses on symptoms. The main recommendations to prevent outbreaks are through social distance (avoiding person-to-person contact transmission), and personal protective equipment (PPE) measures.

The risk of infection with SARS-CoV-2 is increasing given that the spread of SARS-CoV-2 is rapid and intense in over 200 countries, areas or territories. SARS-CoV-2 has posed a challenging situation for health, public and economic sectors of affected countries.

The World Health Organization (WHO) declared on 30 January 2020 the SARS-CoV-2 outbreak as a Public Health Emergency of International Concern (PHEIC) and recommended to focus the research on the causal association of SARS-CoV-2 infection. Considering the spread to more new countries, this novel coronavirus disease COVID-19 outbreak was assessed as very high of global risk level on February 28 2020, and was declared as a pandemic by the WHO on March 11 2020. Considering the conclusive associations between SARS-CoV-2 infections and severe acute respiratory syndrome, the development of a vaccine that can provide protection is crucial for countries where the epidemic is expected to arrive and/or persist, as well as in countries in which there has been no outbreak of viral infection. In order to address the urgent medical need and in anticipation of possible outbreaks with rapid onsets, the sponsor has initiated the development of a SARS-CoV-2 mRNA vaccine (BNT162b2), for use in endemic areas and non-endemic areas for prevention of SARS-CoV-2 associated illness of any severity and/or infection.

The urgent engagement in the efforts to investigate, make available safe and effective SARS-CoV-2 interventions are needed to assist in the control of the outbreak. Given the severity of the situation, time to vaccine development was an important aspect of the highly unmet needs. In response to this need, an accelerated vaccine development effort was initiated.

At present, Phase I clinical studies of BNT162b2 have been carried out in Germany (BNT162-01) and the United States (BNT162-02 / C4591001). Phase II/III parts of clinical study BNT162-02 / C4591001 are currently ongoing in the United States and South American countries. At the same time, immunogenicity, repeated dose toxicology study and viral challenge study are conducted in BALB/c mice in accordance with Good Laboratory Practice (GLP) to continuously analyze the effectiveness and safety of BNT162b2 at animal level and human body level. Results of data analyses for pre-clinical studies and clinical studies will be provided by continuously updating in the Investigator's Brochure (IB).

Phase I clinical study of candidate vaccine BNT162b1 from the same modRNA platform has been carried out in China, and the interim report of the United States and German Phase I clinical studies of BNT162b1 have been published[5,13]. BNT162b1 clinical studies conducted in Germany and the United States are first-in-human trials, so dose escalation is adopted. The maximum dose tested in these two studies for Prime and Boost dosing is 50 µg, whilst single doses of up to 100 µg have also been explored. Safety results shows that the local reaction of injection site and vaccine related systemic reactions are dose-dependent which is mostly mild to moderate with short duration, reactions after two vaccinations are similar, and reaction is slightly less in elderly group; immunogenicity result shows that serum RBD specific IgG antibody concentration and SARS-CoV-2 neutralizing antibody titer escalate with dose level and increase after boost vaccination. The geometric mean neutralizing titer is 1.8 to 2.8 times that of a group of COVID-19 human serum during recovery period. In both younger and older adults, the BNT162b1 and BNT162b2 vaccine candidates elicited similar dose-dependent SARS-CoV-2–neutralizing geometric mean titers (GMTs), comparable to or higher than the GMT of a panel of SARS-CoV-2 convalescent sera. BNT162b2 was associated with less systemic reactogenicity, particularly in older adults[14].

The results of the BNT162b1 and BNT162b2 vaccine candidates would support further evaluation of either candidate, however the BNT162b2 vaccine candidate was selected as the lead candidate for ongoing development. Currently, the optimal dose range is predicted as 30 µg according to immunogenicity and safety data of foreign subjects. Since preliminary safety and immunological data have been obtained, and clinical studies conducted in Germany and the United States will continue to support the study in China, China plans to

conduct local trials bridging through safety and immunogenicity, to confirm consistency between the results in foreign subjects in Chinese subjects.

This study is a confirmatory phase II study conducted in China. Medically stable subjects 18 to 85 years of age (stratified as ≤55 or >55 years of age) are randomized 3:1 in 30 µg BNT162b2 group and placebo group. The study is intended to confirm that the immunogenicity and safety seen in foreign subjects is consistent with that observed in Chinese subjects.

The study will also set up an Independent Data Monitoring Committee (IDMC) to conduct overall supervision. The IDMC is required to review the unblinded data when significant event(s) or risk(s) occurs in the study that might cause the study to be suspended. Placebo serves as the control for the study vaccine and in the absence of effective treatment or prevention for COVID-19, the use of placebo in this study is justified. Based on the different physical appearance of the trial vaccine compared to the selected saline placebo, an independent, unblinded team is adopted in this study to keep the subjects and observers blinded. Based on the different physical appearance of the investigational vaccine compared to the saline solution placebo that will be selected, an independent non-blind team is adopted in this study for blinding subjects and observers. All enrolled subjects will be randomized to receive either SARS-CoV-2 vaccine (BNT162b2) or placebo intramuscularly (IM), two doses separated by 21 days.

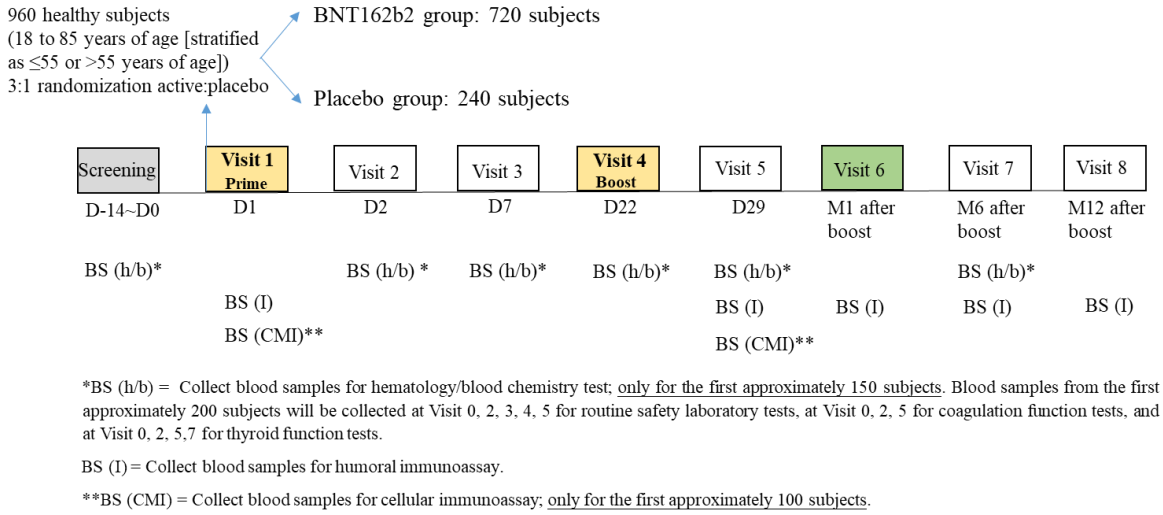
The main basis for selecting the vaccine dose level is the current obtained safety and immunogenicity data of phase I/II/III global clinical trials in Germany and the United States, and the predicted optimal dose is 30 µg, which is the same as that used in the ongoing international multi-center phase II/III clinical trial (which has already treated over 30 000 subjects, half with active vaccine), to further validate that BNT162b2 has similar immunogenicity and safety in the Chinese population.

The trial will be conducted in accordance with the protocol, the International Council for Harmonization of Technical Requirements for Pharmaceuticals (ICH) GCP Guidelines and applicable regulatory requirements.

Trial Design:

This is a phase II, randomized, placebo-controlled, observer-blind study of the safety and immunogenicity of SARS-CoV-2 mRNA vaccine (BNT162b2) in Chinese healthy population. After randomization, the trial for each subject will last for approximately 13 months. Screening period is 2 weeks prior to randomization (Day -14 to Day 1), and two doses of either SARS-CoV-2 vaccine (BNT162b2) or placebo will be given intramuscularly (IM) separated by 21 days. Safety and immunogenicity analysis data through 1-month post Dose 2 will be also conducted and submitted. Safety and immunogenicity analysis data through 6 and12 months post Dose 2 will also be conducted and submitted. For schematic diagram of parallel design, see study design in **Figure 1**.

The two age stratifications of 18~55 and 56~85 years will be enrolled at the same time; however, the Elderly group (56~85 years) will follow the sentinel design: 40 subjects served as sentinels will be randomized, and followed for 48 hours for safety observation. The Safety Review Committee (SRC) composed of principle investigators and Fosun Pharma's medical delegates will review the safety data (including lab tests) of the sentinels and decide if the random enrollment of elderly subjects could be continued.



*BS (h/b) = Collect blood samples for hematology/blood chemistry test; only for the first approximately 150 subjects. Blood samples from the first approximately 200 subjects will be collected at Visit 0, 2, 3, 4, 5 for routine safety laboratory tests, at Visit 0, 2, 5 for coagulation function tests, and at Visit 0, 2, 5,7 for thyroid function tests.

BS (I) = Collect blood samples for humoral immunoassay.

**BS (CMI) = Collect blood samples for cellular immunoassay; only for the first approximately 100 subjects.

Figure 1 Schematic diagram of Study Design

When the first approximately 150 subjects have completed the visit 2, SRC will review the safety data (including lab tests) of these subjects and make decision if the random enrollment of remaining subjects could be continued.

For the planned assessments and visits, see the Schedule of activities in Table 2.

If BNT162b2 is approved by Chinese regulatory authority and the vaccine is available in the region, subjects may request to be unblinded after the 6 months visit after Dose 2 (Visit 7) on an individual basis. Subjects ,who based on unblinding have got placebo within BNT 162-06 study, will be withdrawn from the study and will have the opportunity to be vaccinated with BNT162b2 or with other available on market vaccine via the government program. Subjects who receive BNT162b2 vaccination will enter the post-marketing safety observation.

Subjects enrollment:

Healthy (medically stable) subjects 18 to 85 years of age, inclusive, (stratified as ≤55 or >55 years of age) are enrolled. Approximately 960 subjects will be randomized (3:1) into two groups: 720 subjects in BNT162b2 group and 240 subjects in placebo group. Subjects aged between 56~85 years account for about 40% of the total subjects, which should be adjusted appropriately when necessary, to keep the proportion of the elderly population consistent with the global Phase 2 study.

Vaccination and Visit Schedule

Each randomized subject will receive two intramuscular (IM) injections of BNT162b2 or placebo intramuscularly (IM), into one third of the deltoid muscle, preferably in the non-dominant arm.

From the screening, each subject will be required to attend 9 clinical visits:

Subjects will attend Screening visit (0~14 days before Visit 1), Visit 1 (Dose 1 vaccination) on Day 1, Visit 2 (1 to 3 days after prime vaccination), Visit 3 (1 week after Dose 1 vaccination), Visit 4 (Dose 2 vaccination), Visit 5 (1 week after Dose 2 vaccination), Visit 6 (1 month after boost vaccination), Visit 7 (6 months after Dose 2 vaccination), Visit 8 (12 months after Dose 2 vaccination). Visit 2 will be only conducted in the first approximately 150 subjects.

Blood samples from the first approximately 150 subjects will be collected for different tests at the following visits: for eligibility screening (including clinical laboratory tests) at Screening Visit, and for routine safety laboratory tests at Visit 2, 3, 4, 5 (Visit 2, 5 for coagulation function tests and Visit 2, 5, 7 for thyroid function tests). Blood samples from all subjects will be collected for detecting the humoral immune response (antibody) at Visit 1 (before Dose 1) and Visit 5, 6, 7 and 8. Blood samples from the first approximately 100 subjects will be collected for detecting the cellular immune response (specific T cells) at Visit 1 (before Dose 1) and Visit 5. Blood samples from about 80 subjects will be collected at visit 1 (before the first dose inoculation) and visit 5 (7 days post Dose 2) for the comparative study of neutralization ability of epidemic strains. For these subjects, immunogenic blood samples collected at Visit 6 will also be used for the cross neutralization protection study against SARS-COV-2 epidemic strains to evaluate the neutralization ability of BNT162b2 against circulating epidemic strains at the additional time point of 1 month post Dose 2. Urine samples from the first approximately 150 subjects will be collected at Screening Visit (Visit 0) for eligibility screening and will be collected at Visit 2, 3, 4 and 5 for routine safety laboratory examination. Blood samples of women of childbearing potential (WOCBP) will be collected at Screening Visit (Visit 0), and urine samples. Blood samples will be collected from all subjects at Screening Visit for SARS-COV-2 antibody screening. Each subject will receive a diary card to collect the local reactions, systemic events and antipyretic medication usage for 14 days post each vaccination (including the day of vaccine/placebo vaccination). These data are collected independently in CRF. The ongoing local reactions, systemic events and antipyretic medication usage after 14 days post each vaccination are also collected, and the stop time needs to be reported. Oral temperature is recorded if axillary temperature is ≥37.3ºC.

Objective, Estimands, and Endpoints

Objectives	**Estimands**	**Endpoints**
	Primary Efficacy	
To describe the humoral immune responses to BNT162b2 prophylactic vaccine in Chinese healthy participants at 1-month after Dose 2.	• Seroconversion rates (SCR) of SARS-CoV-2 serum neutralizing titers at 1-month after Dose 2. Seroconversion is defined as ⩾4-fold rise from before vaccination to 1-month post Dose 2. Seronegative is defined as titers	SARS-CoV-2 serum neutralizing titers.

	below the starting dilution (1:10). • The geometric mean titer (GMT) of SARS-CoV-2 serum neutralizing titers at 1 month after dose 2.	
	Secondary Efficacy	
To observe the humoral immune response in Chinese healthy participants vaccinated with BNT162b2 until the end of study.	• Compared with baseline before Vaccination 1, SCR of SARS-CoV-2 serum neutralizing titers at 1 week, 6 and 12 months after dose 2. • The geometric mean titer (GMT) of SARS-CoV-2 serum neutralizing titers at 1 week, 6 and 12 months after dose 2. • Compared with baseline before Vaccination 1, SCR of SARS-CoV-2 anti-S1 IgG antibody level at 1 week, 1, 6 and 12 months after dose 2. • GMT of SARS-CoV-2 anti-S1 IgG antibody level at 1 week, 1, 6 and 12 months after dose 2. • Compared with baseline before Vaccination 1, the geometric mean fold rise (GMFR) of SARS-CoV-2 serum neutralizing antibody titers at 1 week, 1, 6 and 12 months after dose 2. • Compared with baseline before Vaccination 1, GMFR of SARS-CoV-2 anti-S1 IgG antibody level at 1 week, 1, 6 and 12 months after dose 2.	• SARS-CoV-2 serum neutralizing titers. • SARS-CoV-2 anti-S1 IgG antibody level.
	Secondary Safety	
Within 7 days and 14 days post each vaccination, to observe the safety and tolerability profile of	• Local reactions occur in subjects within 7 days and 14 days after each vaccination.	• Local reactions (pain at the injection site, redness, and swelling). • Systemic events (fever,

BNT162b2 or placebo given 21 days apart.	• Systemic events occur in subjects within 7 days and 14 days after each vaccination. • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1, before Dose 2, 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.	fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain). • Hematology and chemistry laboratory assessments.
To observe the safety of BNT162b2 vaccination in Chinese healthy participants until the end of study.	• Adverse events (AEs) from Dose 1 to 1 month after the last dose. • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose.	• Adverse events (AEs). • Serious AEs (SAEs).
	Exploratory Efficacy	
To evaluate the efficacy of prophylactic BNT162b2 vaccine against confirmed COVID-19 in Chinese healthy participants.	Compare the number of confirmed COVID-19 cases (including COVID-19 severity categorization).	Confirmed COVID-19 cases.
To evaluate the efficacy of prophylactic BNT162b2 vaccine against confirmed severe COVID-19 in Chinese healthy participants.	Comparison of severe and critical cases of COVID-19 suggesting enhanced respiratory disease.	Confirmed severe and critical COVID-19 cases.
To describe the cellular immune response of healthy Chinese participants after 2 doses of BNT162b2 prophylactic vaccine.	Cellular immune response determined by ELISpot test etc. at 1 week after Dose 2.	IFNγ etc.
To explore the humoral immune response in Chinese healthy participants vaccinated with BNT162b2.	GMT of anti-S1 subtype IgG antibodies.	Anti-S1 subtype IgG antibodies.
The comparative study of neutralization ability of epidemic strains.	To compare the neutralization ability of serum of subjects before and after vaccination against different SARS-Cov-2	Cross protection neutralization test.

	epidemic strains.	

Subject Population:

Enrolled subject: Healthy (medically stable) volunteers

Planned Age Range: 18 to 85 years of age (stratified as ≤55 or >55 years of age)

Planned Number of Subjects: approximately 960

Inclusion criteria:

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

Age and Gender

1. Male or female participants between the ages of 18 and 85 years, inclusive, at randomization.

• Please refer to 9.1.8 for reproductive criteria for male and female participants.

Type of Participant and Disease Characteristics

2. Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures.
3. Healthy participants who are determined by medical history, physical examination (if required), 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, can be included.

Informed consent

4. Capable of giving personal signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form and this protocol.

SARS-CoV-2 Screening

5. SARS-CoV-2 antibody test is negative.
6. Negative SARS-CoV-2 test in throat swabs by RT-PCR (only for the first approximately 150 subjects).
7. Normal in chest CT scans (no imaging features of COVID-19, only for the first approximately 150 subjects).

Exclusion criteria:

Participants are 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.
5. Immunocompromised individuals with known or suspected immunodeficiency, determined by history and/or laboratory/physical examination.
6. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.
7. Women who are pregnant or breastfeeding.

Prior and Concomitant Treatment

8. Previous vaccination with any coronavirus vaccine.
9. Individuals who receive 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 have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.
10. Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.

Prior/contemporaneous clinical study experience

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

Epidemiological history screening

13. Have had contact with confirmed COVID-19 patients or persons tested positive for SARS-CoV-2 within the 30 days prior to Screening Visit.
14. Travel or live in any country or region with a high SARS-CoV-2 infection risk (as defined at Screening Visit) within the 14 days prior to Screening Visit.
15. Symptoms of COVID-19, e.g., respiratory symptoms, fever, cough, shortness of breath and breathing difficulties.
16. Fever, defined as axillary temperature ≥37.3℃ or oral temperature ≥38.0°C.
17. History of SARS, SARS-CoV-2 or MERS infection. Suspected SARS patients should be screened for SARS antibodies.

Other Exclusions

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

Investigational Vaccines:

Investigational Vaccine:

This drug product is a preservative-free, sterile dispersion of RNA formulated in lipid nanoparticles (LNP) in aqueous cryoprotectant buffer for intramuscular administration. The RNA drug substance is the only active ingredient in the drug product. The composition meets the supplier's specifications. Please refer to the pharmacy manual for specific preparation and use protocol.

Vaccination frequency:	Twice (interval of 21 days).
Vaccination route:	Intramuscular (IM); upper arm, musculus deltoideus; the P/B regimens.

Placebo:

0.9% NaCl solution is used as placebo. The placebo is a sterile, clear, colorless liquid sodium chloride solution without preservative designed for parenteral use only. The placebo is commercially packaged and stored according to the instructions. The placebo is vaccinated by IM with an interval of 21 days.

Trial duration/evaluation period:

Approximately 13 months (after screening period).

Statistical Considerations:

Analysis Population:

- *Safety analysis population:* The safety analysis population will include all randomized subjects who receive at least one dose of the investigational vaccine/placebo.
- *Intention-To-Treat population (ITT):* The ITT will include all randomized subjects who received at least one dose of the investigational vaccine/placebo. and could provide a valid baseline according to the Intention-To-Treat principle.
- *Per protocol set (PPS):* The PPS will include subjects in the ITT except those who have major protocol violations and do not complete the two vaccinations. Protocol violations review is a part of the blinded data review. The categories of major protocol violations include:
  - Did not meet inclusion criteria, or did meet exclusion criteria,
  - receiving a wrong investigational vaccine/placebo,
  - receiving prohibited therapies, and
  - major protocol violations influencing the evaluation of immunogenicity identified during blinded data reviews.
- *Dose 2 evaluable immunogenicity:* All eligible randomized participants who receive 2 doses of the vaccine to which they are randomly assigned, within the predefined window, have at least 1 valid and determinate immunogenicity result after Dose 2, have blood

collection within an appropriate window after Dose 2, and have no other important protocol deviations as determined by the clinician.

- *Dose 2 all-available immunogenicity:* All randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 2.

All summaries and analyses of safety data will be based on subjects in the Safety population.

The analysis of primary immunogenicity endpoint will be based on ITT, with sensitivity analysis based on PPS, and the analysis of other immunogenicity endpoints will be based on ITT.

Analysis of demographic and other baseline characteristics: A summary of age, sex, race and ethnicity, and other baseline characteristics will be presented by BNT162b2 and placebo group.

Immunogenicity analysis: Descriptive statistics including estimates and bilateral 95% confidence intervals (95% CIs) for GMT/GMC, GMFR and SCR will be calculated for the primary and secondary immunogenicity endpoints by time point, BNT162b2 group and the placebo group. Parallel comparisons are made between BNT162b2 group and placebo group, and point estimates and 95% CIs are calculated for the differences in SCR between the two groups.

Safety analysis: Descriptive statistics of reactogenicity endpoints will be provided by time period, BNT162b2 group and placebo group. Within 7 and 14 days after each vaccination (including the day of vaccine/placebo vaccination), the collected local and systemic events will be presented cumulatively according to severity to assess reactogenicity. Descriptive summary statistics will include the number and percentage of subjects at the specified endpoints, as well as the associated Clopper-Pearson 95% CI. Missing reactogenicity diary card data will not be imputed.

All AEs and SAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA v. 23.0) and summarized by system organ class (SOC) and preferred term (PT) for each group (BNT162b2 and placebo), including exacerbations after primary vaccination and new onset medical conditions.

Descriptive summary statistics (counts, percentages and the associated Clopper-Pearson 95% CI) of any AE events in BNT162b2 group and placebo group will be provided. SAEs will be categorized according to MedDRA terms. SAEs counts, percentages, and associated Clopper-Pearson 95% CI will be provided for BNT162b2 group and placebo group from Dose 1 to 6 months after Dose 2.

The grading shifts in hematology and chemistry laboratory assessments of the BNT162b2 group and the placebo group at 1 and 7 days after Dose 1 and, before Dose 2 and 7 days after dose 2 will be tabulated and summarized.

Sample Size Determination:

Several factors are considered in the evaluation of sample size determination.

From efficacy perspective, this is a phase II, randomized, placebo-controlled study. Superiority comparison will be performed between the BNT162b2 vaccinated group and the placebo group in a 3:1 randomization ratio. [redacted]

[redacted] will be needed to test the significant difference between groups for both age stratifications.

From safety perspective, as per the requirement of vaccine clinical development guidance (2004) in China, a minimal sample size of 300 subjects in the vaccine groups is required for phase 2 trials. Considering a 20% of dropout, 360 subjects will be enrolled in the BNT162b2 group and 120 subjects in the placebo group. From regulatory perspectives, to meet China local registration requirement, per CDE's recommendations on 28Aug2020, representable sample size for each age stratification need to considered for this trial. The sample size of approximately 960 subjects is sufficient for bridging evaluation.
In summary, a total of approximately 960 subjects will be enrolled in the study. Subjects will be randomly allocated to one of the two groups, including 720 subjects in the BNT162b2 group and 240 subjects in the placebo group in a 3:1 randomization ratio.

Statistical Analyses Time Points:

The safety and immunogenicity data of 1 month after Dose 2 will be preliminarily analyzed and submitted for approval in China. The safety and immunogenicity analysis data at 6 and 12 months after Dose 2 will also be analyzed. Unblinding will be carried out for the initial analysis, but the subjects will remain blinded throughout the study. For more details regarding the analysis and the bridging analysis of China and foreign studies, please refer to the Statistical Analysis Plans (SAPs).

Safety Review Committee (SRC):

SRC will be established comprising investigators and Fosun medical representatives.

- When the elderly sentinels of 40 subjects are dosed and followed up for 48 hours after the first dose for safety observation, SRC will review the safety data (including lab tests) for safety and make decision if the random enrollment of remaining elderly subjects could be continued.
- When the first approximately 150 subjects (including the elderly sentinels of 40 subjects) completed the visit 2, SRC will review the safety data (including lab tests) of these subjects for safety and make decision if the random enrollment of remaining subjects could be continued.
- AE of special interest (AESI) will be evaluated. This includes enhanced respiratory disease (ERD) cases.

Detail information will be provided in the SRC charter.

Independent Data Monitoring Committee (IDMC):

This study is supervised by the independent data monitoring committee. IDMC will consist of 3 independent members (including a chair/statistician, an epidemiologist and a clinical expert) and 1 non-voting independent statistician. IDMC will be requested by the Fosun Pharma in the event of suspicious significant events and risks that may lead to study suspension.

The IDMC will review both blinded and unblinded safety data in the event of risks that may lead to suspension. Unblinded data will be provided by unblinded statistician who is no Fosun employee or consultant. The IDMC could request suspension of the study based on review results of safety data. If no recommendation for suspension or modification is received from the IDMC, the study may proceed per the protocol.

The IDMC meetings will consist of open and closed sessions, either a face-to-face meetings or teleconference calls will be scheduled by the Fosun Pharma. The type and frequency of scheduled meetings will depend on the subject enrollment and safety event rates. Unscheduled ad hoc meetings will occur if a stopping rule occurs, or at any time IDMC is requested by the Pharmacovigilance Study Team.

Further information will be provided in the IDMC charter.

Suspension Criteria:

During the enrollment period, the investigators will collect AE up to 14 days after vaccination and reported newly emerging grade ≥3 AE and SAE to the IDMC on a weekly basis. The IDMC evaluates the safety of subjects after vaccination based on the reported data. If one of the following situations occurs, the trial enrollment will be evaluated for possible suspension, and the Fosun Pharma will convene an expert panel meeting involving investigators and IDMC, to determine the correct path forwards for the clinical trial:

1. Any subject experience an SAE that is considered possibly related to the vaccination by the investigators;

2. Any subject experience a Grade ≥4 adverse event (potentially life threatening or resulting in death) that is considered related to vaccination by the investigators;

3. Occurrence of grade ≥3 adverse events that lasts for at least 48 hours and unresolved AE (Grade 1 or 2) in more than 15% of subjects.

BNT162-06 Version 1.5 (July 19, 2021)

Table 2 Schedule of Activities

STUDY SCHEDULES

Number of visits	**VISIT 0**	**VISIT 1** Before Dose 1	**VISIT 1** Dose 1 & post vaccination	**VISIT 2 ***	**VISIT 3** 1 week after Dose 1	**VISIT 4** Before Dose 2	**VISIT 4** Dose 2 & post vaccination	**VISIT 5** 1 week after Dose 2	**VISIT 6** 1 month after Dose 2	**VISIT 7** 6 months after Dose 2	**VISIT 8** 12 months after Dose 2	**Unplanned**	**Unplanned**
Time points	Screening Day -14~Day 1	Day 1		1~3 days after Dose 1	6~8 days after Dose 1	19~23 days after Dose 1		6~8 days after Dose 2	28~35 days after Dose 2	175~189 days after Dose 2	350~378 days after Dose 2	Preferably within 3 days of the potential occurrence of COVID-19 disease	28 to 35 days after visit for the potential occurrence of COVID-19 disease
Informed consent	x												
Inclusion/exclusion criteria	x	x (review)											
Demographic data [a]	x												
Medical history (incl. Alcohol intake) [b]	x	x (update)											
Travel history and contact history	x	x		x	x	x		x	x	x	x	x	x
Physical Examination [c]	x	x		x	x	x		x	x	x	x	x	x
Vital Signs [d]	x	x	x	x	x	x	x	x	x	x	x	x	x
12-Lead ECG [e]	x												
WOCBP pregnancy test [f]	x					x							
Clinical laboratory tests (urinalysis)[g]	x			x	x	x		x					
Clinical laboratory tests (blood routine, blood chemistry) [h]	x			x	x	x		x		x			

Number of visits	**VISIT 0**	**VISIT 1** Before Dose 1	**VISIT 1** Dose 1 & post vaccination	**VISIT 2 ***	**VISIT 3** 1 week after Dose 1	**VISIT 4** Before Dose 2	**VISIT 4** Dose 2 & post vaccination	**VISIT 5** 1 week after Dose 2	**VISIT 6** 1 month after Dose 2	**VISIT 7** 6 months after Dose 2	**VISIT 8** 12 months after Dose 2	**Unplanned**	**Unplanned**
Time points	Screening Day -14~Day 1	Day 1		1~3 days after Dose 1	6~8 days after Dose 1	19~23 days after Dose 1		6~8 days after Dose 2	28~35 days after Dose 2	175~189 days after Dose 2	350~378 days after Dose 2	Preferably within 3 days of the potential occurrence of COVID-19 disease	28 to 35 days after visit for the potential occurrence of COVID-19 disease
Clinical laboratory tests (thyroid function)[i]	x			x				x		x			
Clinical laboratory tests (coagulation function)[j]	x			x				x		x			
SARS-CoV-2 testing/ COVID-19 screening [k]	x											x	
Treatment randomization		x											
Immunization [l]			x				x						
Blood sampling for IgG antibodies testing		x				x		x	x	x	x		
Blood sampling for neutralizing titers testing		x				x		x	x	x	x		
Blood sampling for CMI testing [m]		x						x					
Blood sampling for comparative study of neutralization capacity of epidemic strains [n]		x						x					
Issue subject diaries [o]			x	x	x		x	x					
Collect Subject Diary				x	x	x		x	x				

Number of visits	**VISIT 0**	**VISIT 1** Before Dose 1	**VISIT 1** Dose 1 & post vaccination	**VISIT 2 ***	**VISIT 3** 1 week after Dose 1	**VISIT 4** Before Dose 2	**VISIT 4** Dose 2 & post vaccination	**VISIT 5** 1 week after Dose 2	**VISIT 6** 1 month after Dose 2	**VISIT 7** 6 months after Dose 2	**VISIT 8** 12 months after Dose 2	**Unplanned**	**Unplanned**
Time points	Screening Day -14~Day 1	Day 1		1~3 days after Dose 1	6~8 days after Dose 1	19~23 days after Dose 1		6~8 days after Dose 2	28~35 days after Dose 2	175~189 days after Dose 2	350~378 days after Dose 2	Preferably within 3 days of the potential occurrence of COVID-19 disease	28 to 35 days after visit for the potential occurrence of COVID-19 disease
AE/SAE [p]			←								→		
Local reaction assessment [q]			x	x	x	x	x	x	x				
Collect prohibited concomitant medications/ products/ vaccinations		x	x	x	x	x	x	x	x	x	x	x	x
Ask subjects about their health	x	x	x	x	x	x	x	x	x	x	x	x	x

* Visit 2 will be conducted in only first approximately 150 subjects.

a Demographic information, to be obtained at Screening Visit, will include age (date of birth), sex, race, and ethnicity as provided by the subject.

b Medical history (incl. alcohol intake) will be collected at Screening Visit and at Visit 1 (Day 1) and will include any medical history that may be relevant to subject eligibility for trial participation such as prior vaccinations, concomitant medications, and previous and ongoing illnesses or injuries. Relevant medical history can also include any medical history that contributes to the understanding of an AE that occurs during trial participation, if it represents an exacerbation of an underlying disease/preexisting problem. The clinically significant findings evaluated by the investigator before Dose 1 of investigational vaccine/placebo are considered medical history.

c Complete physical examination (incl. height and weight) will be performed at Screening Visit. All subsequent are brief (symptom-directed) physical examinations, performed if deemed necessary or indicated by review of the subject's medical history, should assess clinically significant changes from the baseline examination. The findings should be

documented in the subject's source document and transcribed into the electronic Case Report Form (eCRF). For any procedures at the study site, the investigator should follow his/her standard practice.

d All subjects will complete vital signs (systolic pressure/diastolic blood pressure, pulse rate, respiratory rate, and body temperature) at the screening visits. At each immunization visit, for the first approximately 150 subjects, vital signs will be performed at 1, 3, and 6 h post each immunization, including systolic pressure/diastolic blood pressure, pulse rate, respiratory rate, and body temperature. Abnormal body temperature at other times on the day of vaccination will also be recorded. For the first approximately 150 subjects, vital signs will be performed at each on site visit, and including systolic pressure/diastolic blood pressure, pulse rate, respiratory rate, and body temperature. The remaining subjects will stay on site for 30 min, vital will performed at each on site visit, and including only body temperature.

e 12-Lead ECG only for the first approximately 150 subjects.

f WOCBP women only: blood sampling for β-hCG test at screening visit, and urine sampling at Visit 4.

g Urine analysis only for the first approximately 150 subjects: glucose, bilirubin, ketone, specific gravity, occult blood, pH, protein, urobilinogen, nitrite, and white blood cells. Microscopic urine analysis (depends on Dipstick results): urine sediment will be microscopically examined for the presence of red blood cells, white blood cells, casts, crystals, epithelial cells, and bacteria.

h Clinical laboratory (chemistry) only for the first approximately 150 approximately subjects: alkaline phosphatase, creatinine, ferritin, C-reactive protein, albumin, alanine aminotransferase, amylase, aspartate aminotransferase, γ glutamyl transpeptidase, total bilirubin, blood urea nitrogen, fasting blood glucose, lipase, sodium, potassium, calcium; (hematology) hemoglobin, hematocrit, red blood cell count, white blood cell count and classification (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count.

i Clinical laboratory tests (thyroid function) only for the first approximately 150 subjects: triiodothyronine (T3), thyroxine (T4), thyrotropin.

j Clinical laboratory tests (coagulation function) only for the first approximately 150 approximately subjects: prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen (FIB).

k Blood samples will be collected from all subjects for SARS-COV-2 antibody screening. RT-PCR test of nasopharyngeal swabs and chest CT scan will also be performed at the screening visit for the first approximately 150 subjects. SARS-CoV-2 testing at the unplanned visit include throat swab testing and SARS-CoV-2 antibody screening. The sample will be collected in accordance with national CDC standards of practice.

l Each randomized subject will receive two intramuscular (IM) injections of BNT162b2 or placebo – one at Visit 1 and one at Visit 4, in one third of the deltoid.

m Blood samples are collected from the first approximately 100 subjects for CMI test (ELISpot).

n Blood samples are collected from about 80 subjects for comparative study of the neutralization capacity of epidemic strains. For these subjects, immunogenic blood samples collected at Visit 6 will also be used for the cross neutralization protection study against SARS-COV-2 epidemic strains to evaluate the neutralization ability of BNT162b2 against circulating epidemic strains at the additional time point of 1 month post Dose 2.

o Each subject will receive diary cards to collect the solicited responses for 14 days after each vaccination (including the days of vaccine/placebo vaccination), and unsolicited AEs from Vaccination1 to within 1 month after Dose 2.

p All SAEs will be collected throughout the study, and only the AEs related to the study vaccine will be reported after Visit 6 (1 month post Dose 2).

q Assessment of local reactions will be performed after each vaccination and at each on-site visit after vaccination (from Dose 1 to within 1 month after Dose 2).

Blood Sampling Schedule

Number of visits	**VISIT 0**	**VISIT 1** Prior to prime vaccination	**VISIT 2**	**VISIT 3** 1st week post prime vaccination	**VISIT 4** Prior to the vaccination	**VISIT 5** 1 week post the Dose 2	**VISIT 6** 1 months post the Dose 2	**VISIT 7** 6 months post the Dose 2	**VISIT 8** 12 months post the Dose 2
Time points	Screening Day -14~Day 1	Day 1	1~3 days after Dose 1	6~8 days after Dose 1	19~23 days after Dose 1	6~8 days after Dose 2	28~35 days after Dose 2	175~189 days after Dose 2	350~378 days after Dose 2
Blood routine (anticoagulation) [a]	2 ml	---	2 ml	2 ml	2 ml	2 ml	---	---	---
Blood chemistry [a] (procoagulant)	4 ml	---	4 ml	4 ml	4 ml	4 ml	---	---	---
Ferritin [a] (procoagulant)	4 ml	---	4 ml	4 ml	4 ml	4 ml	---	---	---
Thyroid function [a] (procoagulant)	3 ml	---	3 ml	---	---	3 ml	---	3 ml	---
Coagulation function [a] (anticoagulation)	2 ml	---	2 ml	---	---	2 ml	---	---	---
SARS-CoV-2 antibody test	2 ml	---	---	---	---	---	---	---	---
Pregnancy test (procoagulant)	3 ml	---	---	---	---	---	---	---	---
IgG antibody test (procoagulant)[l]	---	10 ml	---	---	---	10 ml	10 ml	10 ml	10 ml
Neutralizing antibody test (procoagulant)[l]	---	7.5 ml	---	---	---	7.5 ml	7.5 ml	7.5 ml	7.5 ml
CMI test (anticoagulant) **	---	33 ml	---	---	---	33 ml	---	---	---
Comparative study of neutralization capacity of epidemic strains	---	10 ml	---	---	---	10 ml	---	---	---
Total volume of blood sampling (max.)	20 ml	50.5 ml	15 ml	10 ml	10 ml	65.5 ml	17.5 ml	20.5 ml	17.5 ml

Total blood collection: Maximum of 226.5 mL for the first approximately 100 subjects, maximum of 160.5 mL for the first approximately 101~150 subjects, maximum of 112.5 mL for approximately 80 subjects, and maximum of 92.5 mL for the remaining subjects. Among them, an additional 20 mL of venous blood is collected from 80 subjects for comparative study of the neutralization capacity of epidemic strains.

a Only for the first approximately 150 subjects. b Only for the WOCBP.
c Blood samples are collected from the first approximately 100 subjects for CMI test.
d Blood samples are collected from about 80 subjects for comparative study of the neutralization capacity of epidemic strains. For these subjects, immunogenic blood samples collected at Visit 6 will also be used for the cross neutralization protection study against SARS-COV-2 epidemic strains to evaluate the neutralization ability of BNT162b2 against circulating epidemic strains at the additional time point of 1 month post Dose 2.

3.0 LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse event of special interest
BMI	Body mass index
BNT162b2	RNA-LNP vaccine utilizing nucleoside modified Messenger RNA (the variants BNT162b2 will be tested in this trial)
CI	Confidence Interval
CMI	Cell-Mediated Immunity
CRO	Contract Research Organizations
CoV	Coronavirus
COVID-19	Coronavirus Disease 2019
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture system
ELISA	Enzyme-linked Immunosorbent Assay
ELISpot	Enzyme-Linked Immuno-Spot Test
EMA	European Medicines Agency
GBS	Guillain-Barré Syndrome
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMT	Geometric Mean Titer
β-hCG	Beta Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEC	Independent ethics committee
Ig	Immunoglobulin
IM	Intramuscular
IMP	Investigational Medicinal Product; in this trial, BNT162b2 vaccines
IRB	Institutional Review Board
ISF	Investigator’s Site File
ITT	Total Vaccinated Population

LOD	Limit of Detection
mRNA	Messenger RNA
MedDRA	Medical Dictionary for Regulatory Activities
modRNA	Nucleoside modified messenger RNA
NHP	Non-Human Primate
NMPA	National Medical Products Administration
PBS	Phosphate buffered saline solution, i.e. a water-based salt solution containing potassium dihydrogen phosphate (KH_2PO_4), disodium hydrogen phosphate (Na_2HPO_4) and sodium chloride
PEI	German Federal Institute for Vaccines and Biomedicine
PPS	per protocol analysis set
PT	Preferred Term
RBD	Receptor Binding Domain
RNA-LNP	RNA lipid nanoparticle
RT-PCR	Reverse Transcription-Polymerase Chain Reaction
SAEs	Serious Adverse Event
saRNA	Self-amplifying messenger RNA
SAP	Statistical Analysis Plan
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	The virus leading to COVID-19
SCR	Seroconversion rate
SOC	System Organ Class
SPR	Seropositivity Rate
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment-emergent Adverse Events
TMF	Trial Master File
uRNA	Unmodified uridine-containing messenger RNA
VED	Vaccine-Enhanced Disease
WHO	World Health Organization
WOCBP	Women of Child-Bearing Potential

4.0 INTRODUCTION

4.1 Background

4.1.1 SARS-CoV-2

SARS-CoV-2 is a single-stranded positive-sense ribonucleic acid (RNA) virus which belongs to the coronavirus family that presents about 78% of structural similarities with other members of the coronavirus, including SARS virus. Coronaviruses are a large family of viruses that are common in many different species of animals, including camels, cattle, cats, and bats. Like SARS-CoV-2, it is rare for animal coronaviruses to infect humans and then spread in infected populations[1].

The genetic sequence of the SARS-CoV-2 became available to the WHO and public (MN908947.3) on January 12th, 2020, and the virus is categorized into the Beta-coronavirus subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to severe acute respiratory syndrome (SARS) virus isolates than to another Coronavirus infecting humans, namely the Middle East respiratory syndrome (MERS) virus.

Coronaviruses are a (+) ssRNA enveloped virus family that encode for a total of four structural proteins. Within these four structural proteins, the spike protein (S protein) is the most dominant one when it comes to vaccine development. Similar to the influenza virus hemagglutinin, the S protein itself is responsible for receptor-recognition, attachment to the cell, infection via the endosomal pathway, and the genomic release driven by fusion of viral and endosomal membranes. Caused by the multiple functions of the S protein, the immune system targets this antigen with antibodies, which were shown to have the capacity of virus neutralization[6].

4.1.2 Epidemiology

SARS-CoV-2 was discovered in January 2020 in Wuhan. The first human disease cases were reported in December 2019 in China. The virus circulated in areas of over 200 countries worldwide, and was considered acute respiratory disease syndrome (COVID-19) with mild to severe symptoms. The primary mode of transmission of SARS-CoV-2 is person-to-person contact through respiratory droplets. Mild or asymptomatic infections may account for 60% of all infections. Some clinical manifestations include, but are not limited to, fever, cough and diarrhea[2, 3].

Despite mild clinical symptoms in the most adults, SARS-CoV-2 infection over 65 years old has been associated with serious outcomes. The severity of the disease is related to the attack of autoimmunity on the alveoli. Since the beginning of these outbreaks until September 3, 2020, there have been more than 26,100,000 confirmed COVID-19 associated with SARS-CoV-2 infection with 860,000 deaths in over 200 countries, areas or territories worldwide[4].

SARS-CoV-2 is a respiratory virus that can cause the respiratory system disease. The overall incidence of SARS-CoV-2-associated COVID-19 is unknown currently. In the epidemic curve up to January 4, 2020, the epidemic growth rate was 0.10 per day (95% CI, 0.050 to 0.16) and the doubling time was 7.4 days (95% CI, 4.2 to 14). Using the serial interval distribution above, we estimated that R0 was 2.2 (95% CI, 1.4 to 3.9)[3].

No specific antiviral treatment is available for SARS-CoV-2 infections and no vaccine against SARS-CoV-2 is currently available. As the disease is self-limiting, treatment for uncomplicated SARS-Cov-2 infection is supportive and focuses on symptoms. The main recommendations to prevent outbreaks are through the control of social distances (avoiding person-to-person contact transmission), and personal protective equipment (PPE) measures."

The risk of infection with SARS-CoV-2 is increasing given that the spread of SARS-CoV-2 is rapid and intense in over 200 countries, areas or territories. SARS-CoV-2 has posed a challenging situation for health, public and economic sectors of affected countries.

The World Health Organization (WHO) declared on 30 January, 2020 the SARS-CoV-2 outbreak as a Public Health Emergency of International Concern (PHEIC) and recommended to focus the research on the causal association of SARS-CoV-2 infection. Considering the spread to more new countries, this novel coronavirus disease COVID-19 outbreak was assessed as very high of global risk level on February 28, 2020, and was characterized as a pandemic by the WHO on March 11, 2020[4].

4.2 Test Plan Rationale

4.2.1 Medical Need

Considering the conclusive associations between SARS-CoV-2 infections and severe acute respiratory syndrome, the development of a vaccine that can provide protection is crucial for countries where the epidemic is expected to arrive and/or persist, as well as in countries in which the virus has not yet been introduced. In order to address urgent medical needs and anticipate possible rapid outbreaks, the sponsor has initiated the development of a SARS-CoV-2 vaccine (BNT162b2) for use in endemic and non-endemic areas to prevent SARS-CoV-2 associated disease of varying severity and/or infection.

To control outbreaks, efforts must be made to study and deliver safe and effective SARS-CoV-2 interventions. Given the importance of the outbreak, vaccine development time is an important aspect of this high unmet need. In response to this need, an accelerated vaccine development effort was initiated.

4.2.2 RNA Vaccines under Development

A LNP-formulated RNA based vaccine would provide one of the most flexible, scalable and fastest approaches to provide protection against the emerging viruses like SARS-CoV-2[7, 8].

The development of a RNA-based vaccine encoding a viral antigen that is translated by the vaccinated organism to protein to induce a protective immune response provides significant advantages over more conventional vaccine approaches. Unlike live attenuated vaccines, RNA vaccines do not carry the risks associated with infection and may be given to people who cannot be administered live virus (such as pregnant women and the immunocompromised persons). RNA-based vaccines are manufactured via a cell-free in vitro transcription process, which allows an easy and rapid production and the prospect of producing high numbers of vaccination doses within a shorter time period than achieved with conventional vaccine approaches. This capability is pivotal to enable the most effective response in outbreak scenarios.

The development of in vitro transcribed RNA as an active platform for the use in infectious disease vaccines is based on the extensive knowledge of the BioNTech in RNA technology, which has been gained over the last decade. The core innovation is based on in vivo delivery of a pharmacologically optimized, antigen-encoding RNA to induce robust neutralizing antibodies and a concomitant T cell response to achieve protective immunization with minimal vaccine doses[9-11].

A recently published clinical trial using an influenza vaccine based on modRNA encapsulated in LNPs highly related to those used in this trial and also administered IM reported good safety and well tolerability[12].

4.2.3 Summary of Available Non-clinical Data

4.2.3.1 Nonclinical Pharmacology Study

A series of nonclinical pharmacology studies were performed in vivo and in vitro to assess the primary pharmacodynamics of the BNT162b2 vaccine. [redacted]

4.2.3.2 Nonclinical PK study

[redacted]

4.2.3.3 Toxicology Studies

[redacted]

[redacted]

A favorable clinical safety profile was predicted based on the combination of previous nonclinical and clinical experience and preliminary results from toxicity studies with the BNT162b2 vaccine.

4.2.4 Summary of Available Clinical Data

Phase I clinical study of BNT162b2 was performed in the United States, and phase Ⅱ/Ⅲ clinical studies are currently ongoing in the United States, immunogenicity and repeated administration toxicology studies in compliance with Good Laboratory Practice (GLP) and challenge tests are also performed in BALB/c mice to continuously analyze the efficacy and safety of BNT162b2 at the animal level and human level. The results of the data analysis of clinical studies and pre-clinical studies will be provided in the Investigator's Brochure (IB) in an ongoing update.

Phase I clinical study of candidate vaccine BNT162b1 from the same modRNA platform has been carried out in China, and the interim report of the United States and German Phase I clinical studies of BNT162b1 have been published[5,13]. BNT162b1 clinical studies conducted in Germany and the United States are first-in-human trials, so dose escalation mode is adopted. The maximum dose examined in these two studies for Prime and Boost dosing is 50 μg, whilst single doses of up to 100 μg have also been explored. Safety results shows that the local reaction of vaccination site and vaccine-type systemic reactions are dose-dependent which is mostly mild to moderate with short duration, reactions after two vaccinations are similar, and reaction is slightly less in elderly group; immunogenicity result shows that serum RBD specific IgG antibody concentration and SARS-CoV-2 neutralizing antibody titer escalate with dose level and increase after boost vaccination. The geometric mean neutralizing titer is 1.8 to 2.8 times that of a group of COVID-19 human serum during recovery period. In both younger and older adults, the BNT162b1 and BNT162b2 vaccine candidates elicited similar dose-dependent SARS-CoV-2–neutralizing geometric mean titers (GMTs), comparable to or higher than the GMT of a panel of SARS-CoV-2 convalescent sera. BNT162b2 was associated with less systemic reactogenicity, particularly in older adults[14].

4.2.5 BioNTech RNA-based Vaccine Candidate

At BioNTech, there are three different RNA platforms under development, namely non-modified uridine containing mRNA (uRNA, BNT162a), nucleoside modified mRNA (modRNA, BNT162b), and self-amplifying mRNA (saRNA, BNT162c).

All three RNA platforms have been tested in more than a dozen non-clinical GLP safety studies and, for uRNA and modRNA, there is pre-existing clinical safety data (see the BNT162 investigator's brochure [IB]). These data have been obtained primarily with RNAs formulated with liposomes which are related, but not identical, to those to be used in this trial.

The non-clinical toxicity data generated by BioNTech suggest a favorable safety profile for uRNA and modRNA, as well as saRNA formulated with different nanoparticles for various administration routes including intravenous (IV) injection. The favorable safety profile after IV dosing is notable because it results in a higher systemic exposure than the planned intramuscular injection (IM) dosing in this trial. Overall, adverse events were predominantly mild and related to the mode of action of innate immune receptors and intrinsic stimulation of RNA. No unsuspected target organs of toxicity were identified. The non-clinical safety profile of uRNA and modRNA in rodents was predictive for clinical safety. For further details, see the BNT162 IB. At present, two phase I/II clinical studies of BNT162b2 are being conducted in Germany and the United States, and immunogenicity and repeated-dose toxicology studies in compliance with Good Laboratory Practice (GLP) and challenge tests are also conducted in BALB/c mice to continuously analyze the efficacy and safety of BNT162b2 at the animal level and human level. The results of the data analysis will be provided in the Investigator's Brochure (IB) in an ongoing update. Based on the safety and efficacy data, the best dose of the foreign subjects is 30 μg.

4.2.6 BNT162-06 Testing Rationale

The results of BNT162b1 and BNT162b2 vaccines candidates supports further assessment of BNT162b2 vaccine candidate. Based on the foreign subject's safety and efficacy data, the expected best dose is 30 μg. As the preliminary safety and immunological data is available, and the clinical studies conducted by Germany and the United States continuously support the studies of China, China plans to conduct bridging study to confirm the foreign study results in Chinese objects.

The study is a confirmatory phase II study conducted in China, and the medically stable subjects 18 to 85 years of age, inclusive, (stratified as ≤55 or >55 years of age) are randomly assigned in a ratio of 3:1 to 30 μg BNT162b2 group and placebo group. The study is aimed to further confirm the safety and immunogenicity data in Chinese subjects is similar to the foreign study results.

The IDMC will be established for the entire study to provide overall study supervision. The IDMC will review unblinded data in the event of significant events or risks that may lead

to protocol suspension. Placebo serves as the control for the study vaccine and in the absence of effective treatment or prevention for COVID-19, the use of placebo in this study is justified." Based on the different physical appearance of the investigational vaccine compared to the saline solution placebo, independent non-blind team was participated in the study, with regard to subjects and observers. All enrolled subjects will receive SARS-CoV-2 vaccine (BNT162b2) or placebo intramuscularly (IM) twice 21 days apart.

The vaccine dose levels were mainly based on the safety and immunogenicity data of clinical trials of Germany and the United States phase I/II/III global clinical studies, the expected best dose is 30 μg, equal to adopted dose of international multi-center phase II/III clinical trials, further confirm the immunogenicity and safety of BNT162b2 in Chinese population are found to be similar.

The trial will be conducted in accordance with the protocol, the International Council for Harmonization of Technical Requirements for Pharmaceuticals (ICH) GCP Guidelines and applicable regulatory requirements.

4.3 Benefit/risk assessment

4.3.1 Risk assessment

Risks and relevant mitigations associated with specific test procedures are as follows:

- The volume of blood collected from each subject will be maintained at a minimum throughout the trial (i.e. approximately 13 months) and less than that collected at the time of donation.
- All specific test procedures will be performed by qualified study site personnel.
- Vaccination will be done by a physician or designee under medical supervision.
- Two phase I/II clinical studies of BNT162b2 are being conducted in Germany and the United States. No official clinical data of BNT162b2 has been released yet. However, clinical data is available for RNAs formulated with related but not identical liposomal compositions or non-formulated RNAs and can support risk assessment of BNT162 products.

Based on such data, the risks linked to the immunization with the BNT162b2 vaccines are as follows:

- Due to the IM administration, there is a risk of local reactions at the vaccination site such as blush, itching, pain, tenderness, swelling, sweating.
- Systemic flu-like reactions, such as temporary headache, fatigue, anorexia, myalgia, arthralgia, fever, may also occur due to the immunomodulatory effects of the vaccine.
- Due to the IM route, the risk of systemic reactions is considered low.
- A modRNA vaccine based on IM administration encapsulated in a related but not identical vaccine has reported mostly mild to moderate, mostly local solicited AEs (mostly vaccination site pain) of 1-3 days duration that resolved without intervention. Fever was the only systemic solicited AE[12].
- As with other vaccines and with single stranded RNA being an innate immune sensor-agonist, BNT162b2 administration may cause temporary headache, fatigue or loss of appetite. Rarely, certain prophylactic vaccines (such as the use of attenuated viral vaccines) have developed severe allergic reactions or neurological side effects, such as seizures. Although these rare side effects are a concern, the risk of a vaccine causing serious harm or death is considered to be extremely small, in particular for BNT162b2 vaccines, which are molecularly defined, highly purified, subunit vaccines.
- Available nonclinical data of the BNT162b2 vaccine indicate good safety, mainly mild adverse events, related to the action mode of innate immune sensors and intrinsic stimulation of RNA.

  Based on the available clinical and non-clinical data on the RNA components (uRNA) that make up the BNT162b2 product and the individual components (modRNA,

saRNA) in the associated RNA platform, the BNT162 product is expected to have a good safety profile with mild local reactions (see IB for details on these tests).

o [redacted]

- To date, there has been very limited clinical experience with the BNT162b2 vaccine in human trials. It is expected and believed that reactogenicity contributes to the mode of action to induce an immune response to the vaccine. The initial dose-ranging studies showed that the AE profile was consistent with a similar structure previously used in cancer patients, and AEs were generally classified into two groups: local injection site reactions and systemic influenza-like illness. To date, most of the reported AEs with the BNT162b2 vaccine were mild to moderate and no serious AEs were reported. Severe fever has been reported. Most AEs can be managed with simple methods and resolve spontaneously. Transient effects on immune parameters may be seen due to PD effects, such as decreased lymphocytes due to temporary entry into the lymphatic system or increased CRP These changes are considered AEs only if they have clinical consequences

The listed risks can be managed using standard treatment for conventional symptoms as described in Section 10.5. Treatment of these events is dependent on the discretion of the investigators.

This study adopts placebo control parallel design to ensure the safety of trial subjects during the trial. In order to further ensure the safety of subjects, the protocol specifies:

- Compared with the recently completed FIH clinical trial on RNA vaccine, the on-site observation time of this study is longer. For example, in two trials of Moderna on mRNA vaccines for H10N8 and H7N9 influenza viruses in healthy adults, subjects were observed in the field for only 1 hour after each immunization [12].
- On-site visits after immunization were considered day 2 and 8 after vaccination and were more frequent in this study compared to the recently completed FIH clinical trial investigating RNA vaccine. For example, in the two Moderna trials of H10N8 and H7N9 influenza virus mRNA vaccines in healthy adults, only subjects were

visited on-site on day 8 post-vaccination after each immunization [12].

- If an event occurs in a single subject or the frequency or pattern of AEs in the study is of concern, the investigator may request a special review by the IDMC before administering more subjects

To ensure the safety of subjects during the trial, the safety of subjects will be monitored from visit 0 (screening) to about 12 months after the second-dose vaccination.

In nonclinical studies of different vaccine formulations for the prevention of diseases caused by various coronaviruses, vaccine-associated enhanced disease (VED) has been reported in the literature. So far, no such effect has been found regarding SARS-CoV-2. There are currently no data to rule out that BNT162 may cause VED in vaccinated subjects.

Risks associated with COVID-19 pandemic will be managed through the following requirements for subjects:

- Avoid contact with persons tested positive for SARS-CoV-2 antibodies or at an increased risk for infection during their participation in the trial.
- During participation in the trial, maintain social distance and follow good practices to reduce chances of infection or transmission of COVID-19.
- Complete health status checks which include symptom-directed physical examinations, vital signs assessments, and clinical laboratory assessments at the planned visit days.
- During trial participation, contact the investigator if instruction is needed or if any symptoms of illness occur. Reports of any symptoms of illness, such as exacerbation of respiratory illness or influenza-like symptoms, may require medical consultation at the discretion of the investigator.

To minimize the risk to trial subjects in this trial, an IDMC will review and evaluate the safety and immunogenicity data as needed." See Section 11.0.

4.3.2 Benefit assessment

According to the immunization regimen, some trial subjects should be immune against SARS-CoV-2 after participating in this trial.

There is an urgent need for the development of a new prophylactic vaccine given the threat posed by the increasing number of globally distributed outbreaks of SARS-CoV-2 infection. The BioNTech platform of RNA-based vaccines being tested in this trial is especially attractive because it has the ability to deliver high numbers of vaccine doses rapidly in a single production campaign. This platform has the added advantage of not employing live virus and could therefore potentially be used for immuno-compromised populations.

By participating in this trial, trial subjects will contribute to the marketing of these vaccines to prevent SARS-CoV-2 infection.

4.3.3 Overall benefit/risk conclusion

Overall, Fosun Pharma considers the benefit/risk ratio to be acceptable.

5.0 Objectives, Estimands, and Endpoints

Objectives	Estimands	Endpoints
	Primary Efficacy	
To describe the humoral immune responses to BNT162b2 prophylactic vaccine in Chinese healthy participants at 1-month post Dose 2.	• Seroconversion rates (SCR) of SARS-CoV-2 serum neutralizing titers at 1-month after Dose 2. Seroconversion is defined as ⩾4-fold rise from before vaccination to 1-month post Dose 2. Seronegative is defined as titers below the starting dilution (1:10). • The geometric mean titer (GMT) of SARS-CoV-2 serum neutralizing titers at 1 month after dose 2.	SARS-CoV-2 serum neutralizing titers.
	Secondary Efficacy	
To observe the humoral immune response in Chinese healthy participants vaccinated with BNT162b2 until the end of study.	• Compared with baseline before Vaccination 1, SCR of SARS-CoV-2 serum neutralizing titers at 1 week, 6 and 12 months after dose 2. • The geometric mean titer (GMT) of SARS-CoV-2 serum neutralizing titers at 1 week, 6 and 12 months after dose 2. • Compared with baseline before Vaccination 1, SCR of SARS-CoV-2 anti-S1 IgG antibody level at 1 week, 1, 6 and 12 months after dose 2. • GMT of SARS-CoV-2 anti-S1 IgG antibody level at 1 week, 1, 6 and 12 months after dose 2.	• SARS-CoV-2 serum neutralizing titers. • SARS-CoV-2 anti-S1 IgG antibody level.

	• Compared with baseline before Vaccination 1, the geometric mean fold rise (GMFR) of SARS-CoV-2 serum neutralizing antibody titers at 1 week, 1, 6 and 12 months after dose 2. • Compared with baseline before Vaccination 1, GMFR of SARS-CoV-2 anti-S1 IgG antibody level at 1 week, 1, 6 and 12 months after dose 2.	
	Secondary Safety	
Within 7 days and 14 days post each vaccination, to observe the safety and tolerability profile of BNT162b2 or placebo given 21 days apart.	• Local reactions occur in subjects within 7 days and 14 days after each vaccination. • Systemic events occur in subjects within 7 days and 14 days after each vaccination. • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1, before Dose 2, 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.	• 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). • Hematology and chemistry laboratory assessments.
To observe the safety of BNT162b2 vaccination in Chinese healthy participants until the end of study.	• Adverse events (AEs) from Dose 1 to 1 month after the last dose. • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose.	• Adverse events (AEs). • Serious AEs (SAEs).
	Exploratory Efficacy	
To evaluate the efficacy of prophylactic BNT162b2 vaccine against confirmed COVID-19 in Chinese healthy participants.	Compare the number of confirmed COVID-19 cases (including COVID-19 severity categorization).	Confirmed COVID-19 cases.
To evaluate the efficacy of	Comparison of severe and	Confirmed severe and critical

prophylactic BNT162b2 vaccine against confirmed severe COVID-19 in Chinese healthy participants.	critical cases of COVID-19 suggesting enhanced respiratory disease.	COVID-19 cases.
To describe the cellular immune response of healthy Chinese participants after 2 doses of BNT162b2 prophylactic vaccine.	Cellular immune response determined by ELISpot etc.	IFNγ etc.
To explore the humoral immune response in Chinese healthy participants vaccinated with BNT162b2.	GMT of anti-S1 subtype IgG antibodies.	Anti-S1 subtype IgG antibodies.
The comparative study of neutralization ability of epidemic strains.	To compare the neutralization ability of serum of subjects before and after vaccination against different SARS-Cov-2 epidemic strains.	Cross protection neutralization test.

6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Overall Trial Design

This is a phase II, randomized, placebo-controlled, observer-blind, safety and immunogenicity study of SARS-CoV-2 mRNA vaccine (BNT162b2) in Chinese healthy people. The trial lasted approximately 13 months for each participant after randomization. The screening period, 2 weeks prior to randomization (Day -14 to Day 1), was followed by treatment with two intramuscular (IM) injections of SARS-CoV-2 vaccine (BNT162b2) or placebo given 21 days apart. Preliminary analysis of safety and immunogenicity data 1 month after Dose 2 was conducted and submitted to regulatory authorities Safety and immunogenicity analysis data at 6 and 12 months after Dose 2 was also analyzed and submitted. See Figure 1 for a schematic diagram of parallel design.

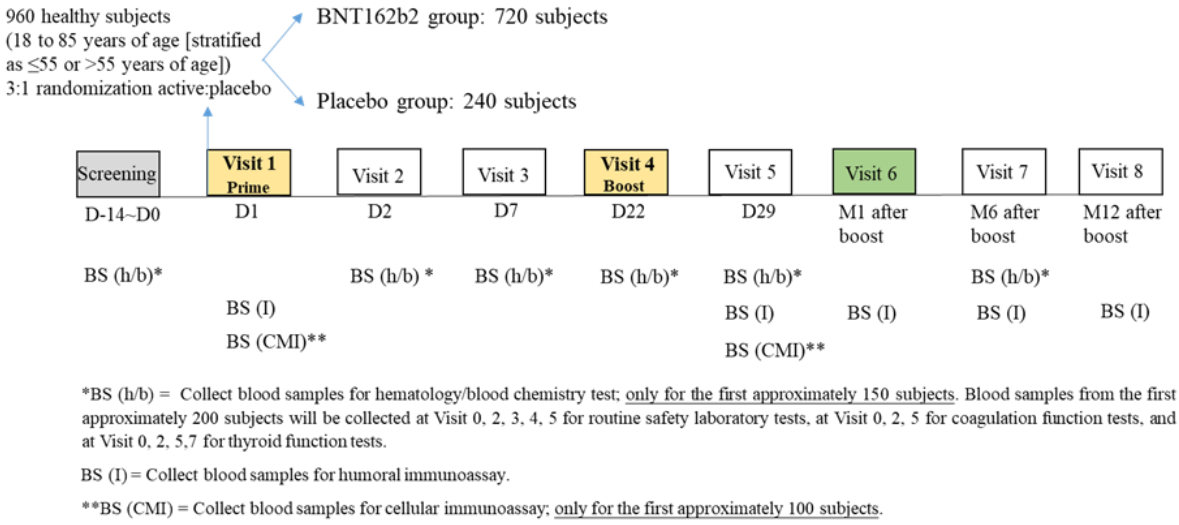


Figure 1 Schematic Diagram of Study Design

The two age stratifications of 18~55 and 56~85 years will be enrolled at the same time; however the Elderly subjects (56~85 years) will follow the sentinel design: 40 subjects (30 of BNT162b2 and 10 of placebo) served as sentinels will be randomized, and followed for 48 hours for safety observation. The SRC composed of principle investigators and Fosun Pharma's medical delegates reviewed the safety data of the sentinels and decide if the random enrollment of elderly subjects could be continued.

When the first approximately 150 subjects (including the elderly sentinels of 40 subjects) have completed the visit 2, SRC will review the safety data (including lab tests) of these subjects and make decision if the random enrollment of remaining subjects could be continued.

For the planned assessments and visits, see Table 2 the schedule of activities.If BNT162b2 is approved by Chinese regulatory authority and the vaccine is available in the region, subjects may request to be unblinded after the 6 months visit after Dose 2 (Visit 7) on an individual basis. Subjects, who based on unblinding have got placebo within BNT 162-06 study, will be withdrawn from the study and will have the opportunity to be vaccinated with BNT162b2 or with other available on market vaccine via the government program. Subjects who receive BNT162b2 vaccination will enter the post-marketing safety observation.

6.2 Enrollment of subjects

Healthy (medically stable) subjects 18 to 85 years of age, inclusive, (stratified as ≤55 or >55 years of age) are enrolled. Approximately 960 subjects will be randomized (3:1) into two groups: 720 subjects in BNT162b2 group and 240 subjects in placebo group.

6.3 Justification for Trial Design, Dose, and Endpoints

The trial design and the collection of solicited or unsolicited AEs following vaccination followed the guidelines for vaccine assessment trials.

As such, the study design, objectives and endpoints were defined so as to assess the safety and reactogenicity of the vaccine candidate, obtain information on its immunogenicity, and provide useful data for the design of further clinical studies. The dose-ranging design adopted is in line with the ICH guidance. The use of placebo as control for the investigational vaccine is justified in the absence of a proven intervention, ie, as no prophylactic vaccine against SARS-CoV-2 infection is available to date.

See section 4.2.6 for rationale for the test protocol.

Please also refer to the IB.

6.4 Duration of Subject’s Expected Participation in the Entire Trial

There was a 2-week screening period prior to randomization (Visit 1), and each subject's participation in the trial lasted approximately 13 months after randomization.

6.5 Criteria for Delayed and/or Stopped Dose 2 Vaccination

After enrollment, subjects may experience clinical conditions that require a delay in the administration of a subsequent dose of study vaccine/placebo vaccination. These situations are listed below:

- Individuals with a clinically significant active infection (as assessed by the investigator) or axillary temperature ≥37.3°C, within 3 days of intended investigational vaccine/placebo administration.“ Within 3 days before the planned study vaccine/placebo vaccination, the subject had a clinically significant active infection (assessed by the investigator) or axillary temperature ≥37.3°C or oral temperature ≥38.0°C, or other clinical symptoms/disease judged by the investigator to be unsuitable for vaccination.

- Subjects received other vaccinations within 21 days prior to the planned vaccination.

If a subject meets the criteria for delayed vaccination beyond the window of the vaccination visit and the subject is still eligible for the trial, the trial vaccination can be administered. The decision to vaccinate in those situations will be taken by the investigator.

In this trial, a second vaccination may be stopped in some cases. These include systemic allergic reactions or serious hypersensitivity reactions after the initial administration of the vaccine/placebo. If these reactions occur, the subject must not receive additional vaccinations; however, the subject is encouraged to continue in trial participation for safety reasons.

6.6 Criteria for Early Study Termination of a Subject

Under some circumstances, a subject's trial participation may be terminated early. This means that no further trial procedures (including data collection) will be performed on that subject beyond the specific date of early termination. The primary reason for early termination of the subject from the trial should be recorded in the electronic Case Report Form (eCRF "end of study visit" page) using the following categories. "For screen failure subjects, refer to Section 9.1.11."

1. Safety termination criteria: refer to section 6.8.1 for Criteria for Premature Termination or Suspension of the Trial. IDMC will review and evaluate the collected safety data as required during the test. A decision to stop treatment for an individual subject or to terminate the trial may be taken if safety concerns are identified by the IDMC.
2. Adverse event: The subject has experienced an AE (irrespective of being related / unrelated to the investigational vaccine or trial-related procedures) that requires early termination because continued participation imposes an unacceptable risk to the subject's health and / or the subject is unwilling to continue participation because of the AE. "If the subject is unwilling to continue because of the AE the primary reason for early termination in this case will be 'withdrawal due to AE' and not 'withdrawal of consent', see below." Any ongoing AEs leading to early termination will be followed by the investigator until resolution or stabilization.
3. Lost to follow-up: The subject did not return to the research center and multiple attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
4. Withdrawal of consent: The subject wishes to withdraw from the trial. The primary reason for early termination will be 'withdrawal of consent" if the subject withdraws from participation due to a non-medical reason (ie, reason other than AE). "The reason for withdrawal, if provided, should be recorded in the eCRF."

Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded.

5. Early termination of the study by Fosun, a regulatory authority, an IEC/IRB, or any

other authority. If Fosun prematurely terminates the clinical study, the Investigator will promptly inform the subject and the local EC/IRB and will ensure appropriate follow-up of the subject. The primary reason for early termination in this case will be ‘trial termination”.

6. Subject′s death during trial participation.
7. Other.

Note: The specific reasons should be recorded in the “specify” field of the eCRF.

6.7 Criteria for Premature Discontinuation of Investigational Vaccine Application

Early (premature) study termination of a subject will by default prevent the subject from continued Trial Vaccine administration, as the subject will no longer be participating in the study."

In addition to early termination of subjects (refer to section 6.6), other circumstances may apply in which a subject may continue in the trial (e.g., providing safety data according to the protocol) but optionally discontinue investigational vaccine. "Regardless of the reasons for discontinuation of Trial Vaccine application, this must be documented as protocol deviation." "Even if the subject is deemed ineligible to continue to receive Trial Vaccine, all efforts should be made to continue the collection of safety data according to protocol." In addition, one primary reason for early discontinuation of Trial Vaccine application should be recorded in “end of Trial Vaccine application” page in the eCRF using the following categories.

1. Adverse Event: The subject develops an AE (irrespective of being related to the study vaccine or the study related procedure), and the subsequent use of the study vaccine will cause unacceptable risk to the subject's health; however, for safety reasons, the subject will continue to participate in the study or other study procedures.
2. Loss to follow-up: The subject did not return to the clinic and multiple attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
3. Withdrawal of consent: The subject wishes to withdraw from the trial. The primary reason for early termination will be ‘withdrawal of consent” if the subject withdraws from participation due to a non-medical reason (ie, reason other than AE). The reason for withdrawal, if provided, should be recorded in the eCRF.
4. Early termination of the study by Fosun, a regulatory authority, an IEC/IRB, or any other authority.

If the clinical study is prematurely terminated by the Fosun, the investigator should be promptly inform the study subjects and local EC/IRB and should assure appropriate follow up for the subjects. The primary reason for early termination in this case will be ‘trial termination”.

5. Subject′s death during trial participation.

6. Protocol deviations: A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. The subject may remain in the trial unless continuation in the trial jeopardizes the subject's health, safety or rights (see Section 7.4).
7. Gestation: Any subject who, despite the requirement for adequate contraception, becomes pregnant during the trial will not receive further Trial Vaccine applications. Pregnant subjects should, however, be asked to continue participating in the trial contributing data to the safety follow-up according to protocol. In addition, the site should maintain contact with the pregnant subject and complete a "Clinical Trial Pregnancy Form" as soon as possible. The subject should be followed-up until the birth of the child, or spontaneous or voluntary termination; when pregnancy outcome information becomes available, the information should be captured using the same form. Data obtained from the "Clinical Trial Pregnancy Form" will be recorded in the safety database.
8. Other.

Note: The specific reasons should be recorded in the "specify" field of the eCRF.

6.8 Premature Termination or Suspension of Trial

6.8.1 Criteria for Premature Termination or Suspension of the Trial

During the enrollment period, the investigators will collect AE up to 14 days after vaccination and reported newly emerging grade ≥3 AE and SAE to the IDMC on a weekly basis. The IDMC evaluates the safety of subjects after vaccination based on the reported data. If one of the following situations occurs, the trial enrollment will be evaluated for possible suspension, and Fosun Pharma will convene an expert panel meeting involving investigators and IDMC, to determine whether to early terminate the clinical trial:

1. Any subject experience an SAE that is considered possibly related to the vaccination by investigators;

2. Any subject experience a Grade 4 adverse event resulting in death or potentially life threatening that is considered related to vaccination by investigators;

3. Occurrence of grade ≥3 adverse events that lasts for at least 48 hours and unresolved (Grade 1 or 2) in more than 15% of subjects.

6.8.2 Procedures for Premature Termination or Suspension of the Trial

If Fosun, an Institutional Review Board (IRB)/Independent Ethics Committee (IEC), or a regulatory authority choose to terminate or discontinue the trial or the participation of an investigational site, trial specific procedures provided by Fosun will be used to early terminate or discontinue the trial.

7.0 Inclusion Criteria and Exclusion Criteria

All entry criteria, including test results, need to be confirmed prior to randomization.

7.1 Inclusion criteria

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

Age and Gender

1. Male or female participants between the ages of 18 and 85 years, inclusive, at randomization.

• Please refer to 9.1.8 for reproductive criteria for male and female participants.

Type of Participant and Disease Characteristics

2. Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures.
3. Healthy participants who are determined by medical history, physical examination (if required), 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, can be included.

Informed consent

4. Capable of giving personal signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form and this protocol.

SARS-CoV-2 Screening

5. SARS-CoV-2 antibody test screening is negative.
6. Negative SARS-CoV-2 test in throat swabs by RT-PCR (only for the first approximately 150 subjects).
7. Normal in chest CT scans (no imaging features of COVID-19, only for the first approximately 150 subjects).

7.2 Exclusion Criteria

Participants are 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.
5. Immunocompromised individuals with known or suspected immunodeficiency, determined by history and/or laboratory/physical examination.
6. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.
7. Women who are pregnant or breastfeeding.

Prior and Concomitant Treatment

8. Previous vaccination with any coronavirus vaccine.
9. Individuals who receive 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 have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.
10. Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.

Prior/contemporaneous clinical study experience

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

Epidemiological history screening

13. Have had contact with confirmed COVID-19 patients or persons tested positive for SARS-CoV-2 within the 30 days prior to Screening Visit.
14. Travel or live in any country or region with a high SARS-CoV-2 infection risk (as defined at Screening Visit) within the 14 days prior to Screening Visit.
15. Symptoms of COVID-19, e.g., respiratory symptoms, fever, cough, shortness of breath and breathing difficulties.
16. Fever, defined as axillary temperature $\geqslant$37.3°C or oral temperature $\geqslant$38.0°C
17. History of SARS, SARS-CoV-2 or MERS infection. Suspected SARS patients should be screened for SARS antibodies.

Other Exclusions

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

8.0 Vaccination and Management

This section contains information on the study medication as required by the protocol, including vaccination and management.

8.1 Vaccination

8.1.1 Investigational Vaccine/Placebo

Investigational Vaccine:

This drug product is a preservative-free, sterile dispersion of RNA formulated in lipid nanoparticles (LNP) in aqueous cryoprotectant buffer for intramuscular administration. The RNA drug substance is the only active ingredient in the drug product. Refer to the Pharmacy Manual for dispensing and operating procedures. Refer to the Pharmacy Manual for the specific preparation and use regimen.

Vaccination frequency:	Twice (21 days apart).
Route of vaccination:	Intramuscular (IM); upper arm, musculus deltoideus; the P/B regimens.

Placebo:

0.9% NaCl solution is being used as placebo. The placebo is a sterile, clear, colorless liquid sodium chloride solution without preservative designed for parenteral use only. The placebo is commercially packaged and stored according to the label conditions. The placebo was vaccinated by IM at 21 days intervals.

8.1.2 Preparation/Handling/Storage/Accountability

The preparation of the solution for injection will be performed by the pharmaceutical professionals or other trained personnel at the trial site according to the aseptic operation procedure.

Refer to the Pharmacy Manual for instructions on preparation, handling, and storage of the investigational medicinal product (IMP, BNT162b2 vaccine).

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all IMP received and any discrepancies are reported and resolved before use of the IMP.

Only subjects participating in the trial should receive the IMP and only authorized unblinded study site personnel should inject the IMP. All IMP (and any components thereof) must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study site personnel.

The investigator, the study site or the head of the study site (if applicable), is responsible for the maintenance, reconciliation and record maintenance (i.e. receipt, reconciliation and final disposition records) of the IMP (and any components thereof).

Further guidance and information for the final disposition of unused IMP (and any components thereof) is provided in the Pharmacy Manual.

8.1.3 Dose and Regimen

Each randomized subject will receive two intramuscular (IM) injections of BNT162b2 or placebo - one at Visit 1 (Day 1) and one at Visit 4 (Day 22), in the third of the deltoid muscle. Additional doses may be explored, see Pharmacy Manual for details

Dose groups: BNT162b2 (30 µg) and placebo.

8.2 Assignment, Preparation and Injection Procedures of Investigational Vaccine/Placebo

The investigational vaccine/placebo will be administered, prepared, and injected by designated, qualified, unblinded personnel as directed in the Pharmacy Manual. All investigational vaccine/placebo preparation will be documented.

The investigator or designee will be responsible for overseeing the administration of investigational vaccine/placebo to subjects enrolled in the trial according to the procedures stipulated in this trial protocol.

Standard immunization practices are to be observed and care should be taken to administer the injection intramuscularly. Before administering the vaccine, the vaccination site is to be disinfected with a skin disinfectant (eg, 70% alcohol). Allow the skin to dry.

As with all injectable vaccines, trained medical personnel and appropriate medical treatment should be readily available in case of anaphylactic reactions following vaccination.

8.3 Randomization Code Creation and Storage

The study adopts the block randomization method. The independent randomization professional generates the subject randomization table through SAS 9.4 or above and imports it into the interactive response technology (IRT) system, which is only accessible by the authorized personnel. Subjects, investigators, and the sponsor's study management team were blinded throughout the trial. Authorized unblinded study site personnel may obtain subject grouping information through IRT system and use the investigational vaccine/placebo for corresponding group according to the grouping information.

All subjects entering screening will be assigned a screening number. For subjects who are screened successfully, randomization will be performed by IRT system and the

randomization number will be obtained (the randomization number will be used as the unique subject ID number). Random parameters and settings are described in detail in the randomization instructions.

8.4 Maintenance of Blindness

The trial is a study where subjects and observers are blinded. Subjects, data collectors (e.g., investigators), and data assessors (e.g., trial statisticians) are all blinded. The investigational product assignment will be maintained by the unblinded statistician and available in the IRT.

All care must be taken to ensure that the unblinded reports and documents are shared only with unblinded personnel and properly stored in a secured area, accessible only by authorized personnel. All unblinded personnel, including dispensing personnel and vaccinating nurses, are required to sign confidentiality agreements.

8.5 Blinding and Unblinding

The IRT will be programmed with blind-breaking instructions.

The investigational vaccine/placebo blind shall not be broken by the investigator unless information concerning the investigational vaccine/placebo is necessary for the medical treatment of the subject. In the event of a medical emergency, if possible, the medical monitor should be contacted before the investigational vaccine/placebo blind is broken to discuss the need for emergency unblinding.

The Fosun's Pharmacovigilance Department must be notified as soon as possible if the investigational vaccine/placebo blind is broken by the investigator; and if the unblinding was for medical reasons (SAE), the completed SAE form must be sent within 24 hours (ie, following the standard process for reporting of SAEs). The date, time, and reason the blind is broken must be recorded in the source document and the same information (except the time) must be recorded on the eCRF.

Unblinding will be carried out when the safety and immunogenicity data are collected 1 month after the Dose 2, but the subject's blinding will be maintained. Details will be provided in the blinding report.

8.6 Concomitant Medications

The following concomitant medications and vaccinations were recorded:

- All vaccinations received during the follow-up period from 28 days before study enrollment to 6 months after the second vaccination.
- Record the concomitant medication, including start and stop dates, drug name, dose, unit, route and frequency.
- All medications taken at baseline were recorded, including start date, medication name, dose, unit, route, and frequency.

8.6.1 Prohibited Medications during Study

Do not administer any vaccine (except for emergency inoculation of rabies and tetanus vaccines) other than the study intervention within 28 days before and 28 days after each study dose unless deemed medically necessary. With the exception of seasonal influenza and pandemic influenza vaccines, which may have been administered at least 14 days after or at least 14 days before the study intervention.

Subject has received chronic systemic therapy with known immunosuppressive drugs or radiation therapy 60 years prior to enrollment and during the study.

Received ≥ 14 days of systemic corticosteroids (prednisone ≥ 20 mg/day or equivalent) from 28 days prior to enrollment through 6 months after the second vaccination.

Received blood/plasma products or immunoglobulins 60 prior to enrollment and during the study.

Receipt of any other (non-study) coronavirus vaccine prior to or during study participation.

The use of prophylactic antipyretics and other pain medications to prevent symptoms related to the study intervention is not permitted. However, if a subject is receiving a drug for another condition, even if the drug may have antipyretic or analgesic effects, it should not be discontinued before the study vaccination.

8.6.2 Permitted Concomitant Medications During the Study

Antipyretics and other pain medications are allowed to treat symptoms or ongoing conditions related to the study intervention.

Medications other than those prohibited in Section 6.5.1 are permitted for treatment of pre-existing stable disease.

Inhaled, local, or local injections of corticosteroids (e.g., intra-articular or intra-osseous injections) are permitted.

All concomitant medications will be coded using the most recent version of World Health Organization Drug Dictionaries (WHODrug) coding system.

9.0 Trial Plan

9.1 Trial Procedures

The following sections describe the trial procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The schedule of trial procedures is located in Table **2**.

9.1.1 Informed consent

Informed consent must be obtained at Screening Visit, prior to the subject entering into the trial and before any protocol-directed procedures are performed.

A screening number will be assigned at screening visit to each subject after informed consent is obtained. If all eligibility criteria are fulfilled, a randomization number will be assigned (the randomization number will be used as the unique subject ID number) and will be used throughout the trial. Subject screening numbers assigned to subjects who fail screening should not be reused (Section 9.1.10).

9.1.2 Demographics, Medical History, Travel History, Prior/Concomitant Medications/Vaccinations, and Blood Donation

Demographic information, to be obtained at Screening Visit, will include age (date of birth), sex, race, and ethnicity as provided by the subject. Refer to Section 6.1 for more details about enrollment.

Medical history will also be collected at Screening Visit and prior to vaccination at Visit 1 (Day 1) pre-dose and will include any medical history that may be relevant to subject eligibility for trial participation such as prior vaccinations, concomitant medications, and previous and ongoing illnesses or injuries. Relevant medical history can also include any medical history that contributes to the understanding of an AE that occurs during trial participation, if it represents an exacerbation of an underlying disease/preexisting problem.

Medical occurrences before administration of the first dose of investigational vaccine/placebo are considered medical history. Including recent (within the past year) or current suicidal ideation / behavior.

Travel history to SARS-CoV-2 endemic countries and SARS-CoV-2 endemic regions of China within 2 weeks prior to screening will be collected at Screening Visit. Travel history to SARS-CoV-2 endemic countries and SARS-CoV-2 endemic regions of China will be collected at each visit.

Subjects were asked about their medication history, and the following medications were recorded: whether they had received coronavirus vaccine, immunoglobulins and/or blood products used within 2 months. All medications, vaccines, and blood products taken or received by the subject within 1 month prior to the start of the trial were recorded in the source documents (patient records) and entered on the Prior and Concomitant

Medications eCRF. The use of antipyretics and/or analgesic medications within 24 hours prior to vaccination must be identified and the reason for their use (prophylaxis versus treatment) must be described in the source documents and the eCRF.

Prohibited Medications/Therapies (Refer to Section 7.0)

- Receiving medications to prevent COVID-19.
- Those receiving immunosuppressive therapy, including cytotoxic drugs or systemic corticosteroids, such as treatment for cancer or autoimmune diseases, or planning to receive treatment throughout the study. If systemic corticosteroids are used for a short period of time (< 14 days) for the treatment of acute illness, the subject should not be admitted to the study until corticosteroid therapy has been discontinued for at least 28 days before study vaccination. Inhaled/spray, intra-articular, intra-osseous or topical (skin or eye) corticosteroids are allowed.
- Received blood/plasma products or immunoglobulins 60 days prior to study vaccination or is scheduled to receive them throughout the study.

Subjects should not donate blood during the main study (starting with the screening visit and continuing until at least 28 days after receiving the last immunization).

Medical history (including corresponding medication) to be obtained will include any significant conditions or diseases that have disappeared or resolved at or prior to signing of informed consent.

9.1.3 SARS-CoV-2 Testing

All subjects will complete SARS-CoV-2 testing at the screening visit. RT-PCR test of nasopharyngeal swabs and chest CT scan will also be performed at the screening visit for the first approximately 150 subjects. SARS-CoV-2 testing, including RT-PCR for throat swab testing as well as SARS-CoV-2 antibody test. This should be done at an unscheduled visit after potential COVID-19. The sample will be collected in accordance with national CDC standards of practice.

Anti-SARS-CoV-2 antibody testing will use a commercial antibody test that can be used during the study to test subjects with worsening respiratory disease or influenza-like symptoms, such as non-remission of symptoms after 7 days, inconsistent relationship of symptom development to RNA immunity, and possible association with COVID-19 disease.

9.1.4 Physical Examination

The physical examination must be performed by a qualified health professional in accordance with applicable regulations and the licensing requirements specified in the Site Authorization Form. Complete physical examination, including height, will be performed at Screening Visit according to the investigator’s standard practice. Measurement of height is only required at Screening Visit. BMI will be calculated using standard BMI calculator.

"Additional symptom-directed physical examinations may be performed at following visits if deemed necessary or indicated by review of the subject's medical history, and should assess clinically significant changes from the baseline examination."

The following should be documented in the subject's source document and transcribed into the eCRF:

- The findings of complete physical examinations;
- the findings of symptom-directed physical examinations.

9.1.5 Vital Signs, 12-lead ECG

Vital signs include systolic pressure/diastolic blood pressure, pulse rate, respiratory rate, and body temperature. Weight was measured at the screening visit only. Follow standard of care for trial population and operational feasibility.

12-lead ECG will be performed at Screening Visit.

"In the event of abnormal ECG, heart rate or blood pressure due to physiological variation or activity, the subject may rest for 10 minutes in a quiet room, and then ECG, blood pressure and/or heart rate may be re-measured." Repeated ECG or vital signs may be used to determine eligibility.

9.1.6 Blood Sample and Urine Sample Collection

Each subject attend 9 clinical visits:

All immunized subjects will attend the screening visit (0 ~ 14 days before Visit 1), Visit 1 (Dose 1), Visit 2 (1 ~ 3 days after Dose 1), Visit 3 (1 week after Dose 1), Visit 4 (2nd dose), Visit 5 (1 week after 2nd dose), Visit 6 (1 month after 2nd dose), Visit 7 (6 months after 2nd dose), Visit 8 (12 months after 2nd dose).

Blood samples from the first approximately 150 subjects will be collected for different tests at the following visits: for eligibility screening (including clinical laboratory tests) at Screening Visit, and for routine safety laboratory tests at Visit 2, 3, 4, 5 (Visit 2, 5 for coagulation function tests and Visit 2, 5,7 for thyroid function tests). Blood samples from all subjects will be collected for detecting the humoral immune response (antibody) at Visit 1 (before Vaccination 1) and Visit 5, 6, 7 and 8. Blood samples from the first up to 150 subjects will be collected for detecting the cellular immune response (specific T cells) at Visit 1 (before Vaccination 1) and Visit 5. Blood samples from about 80 subjects will be collected at visit 1 (before the first dose inoculation) and visit 5 for the comparative study of neutralization ability of epidemic strains. For these subjects, immunogenic blood samples collected at Visit 6 will also be used for the cross neutralization protection study against SARS-COV-2 epidemic strains to evaluate the neutralization ability of BNT162b2 against circulating epidemic strains at the additional time point of 1 month post Dose 2. Urine samples from the first approximately 100 subjects will be collected at Screening Visit (Visit 0) for eligibility screening and will be collected at Visit 2, 3, 4 and 5 for routine safety laboratory examination. Blood samples of women of childbearing potential

(WOCBP) will be collected at Screening Visit (Visit 0), and urine samples at Visit 4 (before Vaccination 2) for pregnancy tests. Blood samples will be collected from all subjects for SARS-COV-2 antibody screening. Each subject will receive a diary card to collect the local reactions, systemic events and antipyretic medication usage for 14 days post each vaccination (including the day of vaccine/placebo vaccination). These data are collected independently in CRF. The ongoing local reactions, systemic events and antipyretic medication usage after 14 days post each vaccination are also collected, and the stop time needs to be reported. Oral temperature is recorded if axillary temperature is ≥37.3ºC.

9.1.6.1 Screening Laboratory Tests

Screening Laboratory Test, laboratory tests that will be performed on blood and urine samples at Screening Visit are outlined in **Table 3**.

If a laboratory test result is outside the acceptable range, repeat screening tests may be allowed, provided that the results outside the normal range can be interpreted.

Should the respective repeated test results be within the screening period, no new subject screening numbers will be required; the repeated screening tests will be recorded in the appropriate CRF (unscheduled lab form). Should the respective repeated test results not be available within the screening period, the subject would need to be screen failed and all screening procedures and tests would need to be repeated with a new subject screening number.

Blood samples for screening laboratory testing will be approximately 15 mL.

Table 3 Clinical Laboratory Assessments

Sample		Tests
Blood	Hematology	Hemoglobin, hematocrit, red blood cell count, white blood cell count and differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count
	Blood Chemistry	Alkaline phosphatase, creatinine, ferritin, C-reactive protein, albumin, alanine aminotransferase, amylase, aspartate aminotransferase, gamma glutamyl transpeptidase, total bilirubin, blood urea, fasting glucose, lipase, sodium, potassium, calcium
	Thyroid function	Triiodothyronine (T3), thyroxine (T4), thyrotropin
	Coagulation function	Prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen (FIB)
	Pregnancy test	Blood β-hCG test
Urine	Urinalysis	Glucose, bilirubin, ketone, specific gravity, occult blood, pH, protein, urobilinogen, nitrite, and leukocytes. Microscopic

		urinalysis if warranted by dipstick results, urine sediment will be microscopically examined for the presence of red blood cells, white blood cells, casts, crystals, epithelial cells, and bacteria.
	Pregnancy test	Urine β-hCG test

9.1.6.2 Safety Laboratory Tests

Routine safety laboratory tests include hematology, blood chemistry, and urinalysis, as well as thyroid function and coagulation function, and laboratory tests are listed in.**Table 3**. Each blood sample will be about: blood routine of 2 mL, blood chemistry of 4 mL, ferritin of 4 mL, thyroid function of 3 mL and coagulation function of 2 mL

For abnormal laboratory test values, the grading of abnormal values should be recorded according to the grading table in Appendix B and Appendix C.

9.1.6.3 Immunogenicity Assessments

Serological immunogenicity (humoral immunity/antibody) was detected by ELISA method. Each blood sample was approximately 10 mL for IgG antibody testing and 7.5 mL for neutralizing antibody testing.

Each blood sample was approximately 33 mL for CMI testing.

Each blood sample was approximately 10 mL for the comparative study of neutralization ability of epidemic strains.

If blood samples are collected during the vaccination visit, it must be done before administration of the investigational vaccine or placebo.

SARS-CoV-2 neutralizing antibody titer will be evaluated using a cytopathic effect (CPE)-based microneutralization (MN) assay. Serum samples (at pre-determined dilutions) will be incubated with live SARS-CoV-2 virus to determine the potential of antibodies present in the serum to neutralize the infection of a cell line (Vero E6). The microneutralization titre (MNt) is calculated by determining the reciprocal of the highest serum dilution multiple that protects at least 50% of cells from virus-induced CPE. Positive (high titer monoclonal antibody with known MNt) and negative (normal human serum without IgA/IgM/IgG) controls will be included in each run to ensure assay quality.

9.1.6.4 SARS-CoV-2 Antibody Testing

Blood samples will be collected from all subjects for SARS-COV-2 antibody screening. SARS-CoV-2 antibody testing should be performed at an unscheduled visit after the potential occurrence of COVID-19.

9.1.7 Safety Assessments

During the trial, safety assessments included the collection and recording of solicited local events (injection site) and solicited systemic events (including fever), unsolicited

AEs (serious and non-serious). Refer to Section 10.1 for safety definitions. Refer to Section 10.2 for details on collection and reporting of solicited reactions and adverse events. "Refer to Section 9.3.4 for details about the diary cards distribution, review and collection processes."

9.1.8 Reproductive Inclusion Criteria and Contraceptive Guidelines

Subjects will be given guidance on contraception.

Male subject reproductive inclusion criteria

Male subjects were eligible if they agreed to meet the following requirements during the vaccination period and for 1 year after vaccination:

- Avoid donating sperm. Plus any of the following,
- Stay abstinent for long periods of time (not having sex with WOCBP). or
- When having sex, a male condom must be used before ejaculation. In addition to male condom use, partners of WOCBP who are male subjects should consider a highly effective method of contraception.

Female Participant Reproductive Inclusion Criteria

Female subjects who are not pregnant or breastfeeding are eligible for the study and should meet at least one of the following conditions:

- Not a WOCBP. or
- WOCBP who agrees to use a medically acceptable method of contraception during the vaccination period and for 1 year after vaccination. The investigator should evaluate the efficacy of contraception to understand the relationship with the first vaccination.

The investigator is responsible for reviewing medical history, menstrual history, and recent sexual activity to reduce the risk of including the risk of undetected women in early pregnancy.

WOCBP Criteria

Unless permanently sterile, after menarche until premenopausal, women are considered fertile.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and menstrual cycle cannot be determined.

Additional assessments should be considered before the first vaccination.

Women in the following categories are not considered WOCBP

1. Premenopausal women with one of the following:

- Documented hysterectomy;
- Documented bilateral salpingectomy;
- Documented bilateral ovarian resection.

In addition to the above, individuals with permanent infertility due to other medical reasons (e.g., mullerian agenesis, androgen insensitivity) should be treated at the discretion of the investigator to meet the inclusion criteria.

2. Postmenopausal women:

- Menopausal status was defined as no menstrual period for 12 months, excluding drug causes. In addition.
- In women under 60 years of age who are not using hormones, high postmenopausal FSH levels may be used to confirm postmenopausal status
- Use of female hormone replacement therapy and unknown menopause requires use of a highly effective method of contraception that is not estrogen hormones. Otherwise, hormone replacement therapy should be discontinued and menopause should be clarified before enrollment.

Contraceptive Methods

Contraceptives and contraceptive methods used by male or female subjects should be consistent with local availability/regulations.

1 Implantable progestogen-only contraception associated with ovulation inhibition;

2 Intrauterine devices;

3 intrauterine hormone-releasing system;

4 Bilateral Tubal obstruction;

5 Vasectomized partners:

- A vasectomized partner is a highly effective method of contraception provided that the partner is the sole sexual partner of a woman of childbearing potential and that the absence of sperm has been confirmed. If not, another highly effective method of contraception should be used. The spermiogenesis cycle is approximately 90 days.

6 Combined (estrogen- and progestogen-containing) hormonal contraception associated with ovulation inhibition:

- Oral;
- Intravaginal;
- Transdermal;
- Injectable.

7 Progestogen-only contraception associated with ovulation inhibition.

- Oral;
- Injectable.

8 Sexual abstinence:

- Sexual abstinence is considered an efficient method only if it is defined as the avoidance of heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be assessed in relation to the duration of the study as well as the subject's preference and lifestyle of daily life.

9 Pure progestogen oral hormone contraception in which ovulation inhibition is not the main mode of action.

10 Male or female condoms with or without spermicide.

11 Cervical caps, diaphragms, or sponges containing spermicide.

12 Combination of male condom and cervical cap, diaphragm, or sponge with spermicide (double-barrier method).

9.1.9 Pregnancy and breastfeeding

For WOCBP, a blood pregnancy test will be performed at the Screening Visit, and a urine pregnancy test prior to administration of Dose 2 of investigational vaccine/placebo.

Subjects must have a negative β-hCG pregnancy test at screening and prior to receiving the 2nd dose.

In order to ensure the safety of subjects, if a female subject or female partner of a male subject becomes pregnant during the study vaccination period, the Pregnancy Report Form A shall be completed and reported to Fosun within 24 hours after being informed. Meanwhile, the pregnancy must be followed up to determine the pregnancy outcome (if the female partner of the male subject agrees to collect the information), including spontaneous or induced abortion, delivery details, congenital malformation, or maternal or neonatal complications, etc., and the Pregnancy Report Form B shall be completed and reported.

Those who deliver normally should continue to be followed up for at least one year after the birth of the fetus. Elective abortions without complications were not considered adverse event, and the Pregnancy Report Form is to be completed. Other pregnancy outcomes must be reported as SAEs. The Pregnancy Report Form is to be completed and reported along with the SAE form. If other SAEs occur during pregnancy, an SAE form must also be completed and reported.

If a participant becomes pregnant during the trial, they will not receive any more of the investigational vaccine/placebo. If the pregnancy occurs after the injection of the study vaccine/placebo under blind conditions, the investigator must inform the subjects of their right to be informed of the information about the study vaccine/placebo injected. If the

subject chooses to be unblinded, the investigator should perform the individual unblinding and must follow the procedure described in Section 8.5.

Exposure during breastfeeding should also be reported to Fosun within 24 hours after being informed.

9.1.10 Documentation of Trial Enrollment/Randomization

Only subjects who have signed an ICF at Screening Visit, meet all of the inclusion criteria and none of the exclusion criteria, are eligible for randomization into the vaccination phase.

At the screening visit, each subject will be assigned a subject screening number.

960 healthy (medically stable) subjects 18 to 85 years of age (stratified as ≤55 or >55 years of age) are randomized 3:1 into 2 groups: approximately 720 subjects in the BNT162b2 (30 µg) group and approximately 240 subjects in the placebo group. The subjects are stratified by age.

9.1.11 Documentation of subjects who are enrolled but not randomized

If a subject who signs the ICF is found to be ineligible during the screening period, the subject is considered a screen failure, the investigator should complete the eCRF and explain the reason.

The primary reason for not being enrolled/randomized will be recorded in the eCRF using the following categories:

- Screen failure: does not meet one or more inclusion criteria; meets one or more exclusion criteria;
- Withdrawal by subject;
- Fosun Pharmaceutical terminated the trial.

A subject could have been a temporary screen failure under the following circumstances: transient conditions (see exclusion criteria) due to receiving immunosuppressive or immunomodulatory therapy, blood products, immunoglobulins, or vaccines during the respective prohibited period; or the subject had an indeterminate pregnancy test result prior to the start of the study. Subjects screen failed for the above-mentioned reasons may be rescreened once they cease to meet the respective exclusion criteria. Should the respective repeated test results be within the initial screening period, no new subject screening numbers will be required; the repeated screening tests will be recorded in the appropriate CRF (unscheduled Visit form). Should the respective repeated test results not be available within the initial screening period, the subject would need to be screen failed and all screening procedures and tests would need to be repeated with a new subject screening number.

Subject screening numbers assigned to subjects who fail screening should not be reused.

9.2 Subject Treatment Compliance

The investigator records all injections of investigational vaccine/placebo given to the subject in the eCRF.

9.3 Schedule of Observations and Procedures

The schedule for all trial-related procedures for all evaluations is shown in Table **2**. Assessments should be completed at the designated visit(s)/time point(s).

9.3.1 Screening Procedures (Screening Visit)

Refer to Section 6.1 for more details about enrollment.

The following screening procedures will be performed at Screening Visit:

1. Confirm informed consent, and complete and collect ICF (see Section 9.1.1). Before performing any other trial procedure, the signed ICF needs to be obtained. Only applicable for newly screened subjects.
2. Assign subject ID number (see Section 6.1 for more details about the enrollment).
3. Assess eligibility criteria (see Sections 7.1 and 7.2).
4. Collect demographics (see Section 9.1.2).
5. Collect medical history, travel history (to SARS-CoV-2 endemic countries and SARS-CoV-2 endemic regions of China), and prior/concomitant medications/vaccinations (see Section 9.1.2).
6. Perform “complete” physical examination (see Section 9.1.4).
7. Check vital signs (see Section 9.1.5).
8. Check 12-lead ECG (only for the first approximately 150 subjects, see Section 9.1.5).
9. Collect blood sample for eligibility screening tests (only for the first approximately 150 subjects, see Section 9.1.6).
10. Collect urine sample for eligibility screening urinalysis (only for the first approximately 150 subjects, see Section 9.1.6)
11. For WOCBP, perform a urine pregnancy test at the Screening Visit (see Section 9.1.6 for pregnancy test) and provide guidance on contraception (see Sections 9.1.8 and 9.1.9).
12. Collected samples for SARS-COV-2 antibody screening. Collect throat swab (only for the first approximately 150 subjects) for SARS-CoV-2 testing.
13. Perform chest CT test (only for the first approximately 150 subjects).

9.3.2 Procedures Before Vaccination

The following procedures will be performed at Visit 1 and Visit 4:

1. Collect medical history, travel history (to SARS-CoV-2 endemic countries and SARS-CoV-2 endemic regions of China), and concomitant medications/vaccinations (see Section 9.1.2).
2. Perform symptom-directed physical examination (if deemed necessary, see Section 9.1.4).
3. Assess eligibility criteria (see Sections 7.1 and 7.2) at Visit 1 (Day 1).
4. Check vital signs (see Section 9.1.5).
5. For randomized subjects (only at Visit 1 on Day 1), the randomized subject was assigned a randomization number (the randomization number was used as the unique subject ID number) (see Section 9.1.10).
6. Collect blood sample for clinical laboratory and immunogenicity assessment (see Section 9.1.6).
7. Blood samples are collected for comparative study of the neutralization capacity of epidemic strains (only from about 80 subjects, see Section 9.1.6).
8. For WOCBP, a urine pregnancy test was performed before Dose 2 (see Section 9.1.9).

9.3.3 Vaccination Procedures

The following procedures will be performed at Visit 1 and Visit 4:

1. Check contraindications to vaccination and criteria for the development of toxicity (see Sections 7.2 and 7.3).
2. The investigational vaccine/placebo was prepared according to the Pharmacy Manual (see Section 8.2).
3. Inject the investigational vaccine or placebo (see Section 8.2).

9.3.4 Procedures After Vaccination

The following procedures, will be performed at Visit 1 and Visit 4:

1. All subjects will complete vital signs (systolic pressure/diastolic blood pressure, pulse rate, respiratory rate, and body temperature) at the screening visits. At each immunization visit, for the first approximately 150 subjects, vital signs will be performed at 1, 3, and 6 h post each immunization, including systolic pressure/diastolic blood pressure, pulse rate, respiratory rate, and body temperature. Abnormal body temperature at other times on the day of vaccination will also be recorded. For the first approximately 150 subjects, vital signs will be performed at each on site visit, and including systolic pressure/diastolic blood pressure, pulse rate,

respiratory rate, and body temperature. The remaining subjects will stay on site for 30 min, vital will performed at each on site visit, and including only body temperature. The investigator or delegate will take the opportunity to remind the subject how to measure solicited reactions and body temperature as part of this observation period. All safety data will be collected in the subject's source documents.

2. Provide the subject with a diary card, and train the subject on how to use it.

   Careful training of the subject on how to record concomitant medications, how to measure solicited reactions and body temperature, how to complete the diary card and how often to complete the diary card. Training should be directed at the individual(s) who will perform the measurements of solicited AEs and those who will enter the information into the diary card. This individual may or may not be the subject, but if a person other than the subject enters information into the diary card, this person's identity must be documented in the trial file and this person must receive training on the diary card. Training of the subject on how to measure an vaccination site AE should be performed while the subject is under observation after vaccination.

   The instructions on the diary card must include the following: The subject must understand that timely completion of the diary card on a daily basis is a key component of participation in the trial. The subject was instructed to write clearly and complete the diary card with a signed pen. Any corrections to the diary card that are performed by the person completing the diary card should include a single strikethrough line with a brief explanation for any change and be signed and dated.

   Please note:

   Diary cards will be the only source document allowed for remote collection of solicited local and systemic events (including body temperature measurements). The following additional rules apply to the documentation of safety information collected by diary card:

   - Diary cards should be reviewed with the subject.
   - No corrections or additions to the diary card will be allowed after it is reviewed with the investigator/designee.
   - Any data that are identified as implausible or incorrect, and confirmed by the subject as recording error should be corrected by the subject on the diary card (the correction should include a single strikethrough line and should be signed and dated by the subject). If the subject has difficulty in recording, the diary card can be modified or added after review by the investigator/ designee, but the date should be signed and the reason for the modification should be recorded if necessary.
   - Any blank or illegible fields on the diary card not otherwise corrected as above will be missing in the eCRF.
   - The study site must enter all readable entries on the diary card into the eCRF.

- Any newly described solicited safety information should be added to the diary card by the subject and signed and dated. Any new unsolicited safety information would be recorded in the subject source document as a verbally reported event and therefore captured as an AE and recorded in the AE eCRF.
- Starting on the day of vaccine/placebo administration, the subject will check for specific types of events at the vaccination site (solicited local events), any specific follow (solicited systemic events), body temperature (axillary), any other symptoms or change in the subject's health status, and any medications taken. These solicited response and body temperature were recorded in diaries. Assessments should preferably take place in the evening at day's end using the same method of measurement every day.
- Temperature measurement is to be performed using the thermometer provided by the study site. If the subject feels unusually hot or cold during the day, the subject should check his/her temperature. The highest body temperature measured that day should be recorded on the diary card.
- Solicited local events (pain at the injection site, redness, swelling) should be measured using a ruler provided by the site. If multiple measurements are taken during the day, the highest measured value should be recorded on the diary card.
- Body temperature, solicited local events and solicited systemic events recorded on the diary cards should be collected for 14 consecutive days after each vaccine/placebo injection. Unsolicited AEs and medications recorded on diary cards will be collected continuously from the Dose 1 until 1 month after the 2nd dose.
- The healthcare professional reviewing the data on the diary cards will discuss the AEs (if any) reported by the subject and will determine if any additional diagnoses and/or AEs are present and/or concomitant medications have been used.

3. At Visit 4 (Day 22), review the previous diary card with the subject and collect it.
4. Provide contraception guidance (see Section 9.1.8).
5. Provide the subject with a written reminder of the next planned trial activity. The subject will be reminded to complete the diary card daily and to contact the site if there are any questions and to contact the study site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit or is otherwise perceived as serious. Provide subjects with available contact information.
6. Schedule the next site visit with the subject.

If subject experiences any of the following from day 1 to day 7 (where day 1 is the day of vaccination) after vaccination, please contact the site staff or investigator immediately to determine if an unscheduled safety visit is required:

- Fever ≥ 39.0 ° C (≥ 102.1 ° F).
- Redness or swelling at the injection site measuring greater than 10 cm.
- Severe pain at the injection site.
- Any serious systemic event.

If the subject experiences a medical event (eg, a visit, emergency) or is hospitalized, contact the site staff or the investigator. If the subject experiences any COVID-19 symptoms, please contact the site staff or the investigator immediately.

9.3.5 Main Visits After Vaccination

The following procedures will be performed at the main visit after vaccination:

1. Collect travel history (to SARS-CoV-2 endemic countries and SARS-CoV-2 endemic regions of China) and concomitant medications/vaccinations (see Section 9.1.2).
2. Check vital signs (see Section 9.1.5).
3. Blood samples were collected for routine safety laboratory tests (only for the first approximately 150 subjects, see Section 9.1.6).
4. Blood samples were collected for immunogenicity assessment and CMI testing (CMI only for the first approximately 100 subjects, see Section 9.1.6).
5. Blood samples are collected for comparative study of the neutralization capacity of epidemic strains (only from about 80 subjects, see Section 9.1.6).
6. Urine samples were collected for routine safety laboratory tests (urinalysis, see Section 9.1.6).
7. Review the previous diary card with the subject and collect it (see Section 9.3.4).
8. Provide the subject with a new diary card, and remind the subject on how to use it (see Section 9.3.4).
9. Provide contraception guidance (see Section 9.1.8).
10. Provide the subject with a written reminder of the next planned trial activity. The subject will be reminded to complete the diary card daily. The subject will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit or is otherwise perceived as serious. All contact details will be provided to the subject.
11. Schedule the next site visit with the subject.

9.3.6 Extended Visit Period

An extension visit will occur 3 month after the 2nd dose through 12 months. If a subject terminates earlier, a final Visit procedure should be performed, if possible.

The following procedures will be performed:

1. Collect travel history (to SARS-CoV-2 endemic countries and SARS-CoV-2 endemic regions of China) and concomitant medications/vaccinations (see Section 9.1.2).
2. Check vital signs (see Section 9.1.5).
3. Collect blood sample for thyroid function tests (only for the first approximately 150 subjects, see Section 9.1.6).
4. Collect blood sample for immunogenicity assessment (CMI only for the first approximately 150 subjects, see Section 9.1.6).
5. Schedule the next site visit with the subject.

9.3.7 Unscheduled Visits for Grade 3 or Suspected Grade 4 Reactions

If a subject reports a Grade 3 local event, systemic event, or fever, additional details should be asked and a determination made as to whether an unscheduled site visit is required. If a subject reports a suspected Grade 4 local event, systemic event, or fever, additional details should be asked and a determination made as to whether the Grade 4 criteria are met and whether an unscheduled site visit is required.

If confirmed, schedule a site visit as soon as possible to assess the subject, unless either of the following occurs:

Subject is unable to attend an unscheduled visit.

- Local events/systemic events are no longer present at the time of telephone contact.
- Incorrect values were recorded by the subject.
- Not required as determined by the PI or authorized designee.

Details of the enquiries were recorded in the subject's source documents and CRFs.

If a subject is unable to attend an unscheduled visit, or if the investigator determines it is not necessary, any ongoing local/systemic events must be assessed at the next study visit.

9.3.8 COVID-19 Monitoring

Subjects will be instructed to contact the site immediately if they experience symptoms of COVID-19 and, if confirmed, should be seen in person or telemedicine as soon as possible, preferably within 3 days of symptom onset. Potential COVID-19 disease visits should not be triggered when potential COVID-19 symptoms overlap with a resultant

systemic event (i.e., fever, chills, new or worsening myalgias, diarrhea, vomiting) within 7 days after each vaccination unless, in the opinion of the investigator, the clinical presentation is more indicative of a possible COVID-19 disease than the reactogenicity of the vaccine. Please note that this is not a substitute for the subject's usual medical care. Therefore, participants should be encouraged to seek care through the usual pathway.

- Diagnosis of COVID-19;
- Fever;
- New or worsening cough;
- New or worsening shortness of breath;
- Chills;
- New or worsening myalgia;
- New onset of loss of taste or smell;
- Pharyngolaryngeal pain;
- Diarrhea;
- Vomiting.

After enrollment, if subjects have epidemiological exposure history or clinical manifestations of COVID-19 during the study period, they should immediately conduct epidemiological investigation and relevant nucleic acid test, take chest CT if necessary, and conduct quarantine observation according to local prevention and control requirements. If the subject is diagnosed with COVID-19, the drug will be stopped (if the full-course vaccination is not completed), and the subject will receive treatment and appropriate medication from the local CDC as required.

9.3.8.1 Visit for potential COVID-19 disease (preferably within 3 days after onset of potential COVID-19 disease)

It is expected that medical information and services will be shared at this visit so that subjects and investigators can communicate regarding clinical care.

Since a subject's COVID-19 disease may develop over time, several contacts may be required to obtain the following information:

- Documented AEs.
- Documented details of any prohibited medication taken by the subject.
- Instruct and encourage participants to seek care through the usual pathway
- Collect standard of care clinical and laboratory information related to COVID-19. This included, but may not have been limited to:
- Symptoms and signs, including:

- Clinical symptoms at rest indicating severe systemic disease (RR ≥ 30 bpm, HR ≥ 125 bpm, SpO2 ≤ 93% on sea-level room air, or PaO2/FiO2 < 300 mmHg).
- Evidence of shock (SBP < 90 mmHg, DBP < 60 mmHg or need for vasopressors).
- Severe acute renal, hepatic or neurological disturbances.
- Respiratory failure (defined as requiring high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO).
- Clinical diagnosis
- Local lab COVID-19 test results
- Complete blood count
- Blood chemistry, particularly creatinine, urea, liver function tests, and C-reactive protein
- Documentation of imaging findings of neurological disturbances (e.g., CT or MRI scans)
- Number and type of any medical contact; length of stay and ICU length of hospital stay
- Death
- Schedule the subject for a potential COVID-19 rehabilitation visit when he/she will return for rehabilitation.
- Complete the source document.
- The investigator or authorized designee completed the CRF.

9.3.8.2 Potential COVID-19 Rehabilitation Visit (28 to 35 days after potential COVID-19 Illness Visit)

- Documented AEs.
- Documented details of any prohibited medication taken by the subject.
- Collect blood samples for immunogenicity testing.
- Collect/update clinical and laboratory information on COVID-19.
- Complete the source document.
- The investigator or authorized designee completed the CRF.

9.4 Biological Sample Retention and Destruction

In this trial, specimens for testing will be collected as described in Section 9.1.6. After blood draw and serum processing, the serum samples will be preserved and retained as required by applicable regulations. Fosun Pharma has put into place a system to protect the subjects' personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

10.0 Adverse Events

10.1 Definitions

10.1.1 Adverse Events (AEs)

Adverse event (AE): refers to any adverse medical event that occurs in patients or drug clinical study subjects. It does not necessarily have a causal relationship with drug treatment. An adverse event can be an adverse sign, symptom or disease that is not related to the purpose of the medication (including abnormal laboratory tests, etc.), in spite of the causal relationship with the drug.

This includes any new occurrence or worsening in severity or frequency compared to baseline conditions, including laboratory abnormalities with clinical manifestations.

AE does not include:

- Medical or surgical procedures, such as surgery, endoscopy, tooth extraction, and transfusion (operations should not be collected as AEs, but diseases that cause these operations should be reported as AEs);
- Pre-existing diseases or conditions, including abnormal laboratory findings, that were present or detected but not exacerbated before the start of the study vaccine.

Transient laboratory abnormalities due to the known mechanism of action of the drug without evidence of clinical risk or potential permanent impairment as judged by the investigator.

A treatment-emergent AE (TEAE) was defined as any AE that occurred after the first administration of IMP (if the AE was not present prior to the prime vaccination) or that worsened after the first administration of IMP (if the AE was present prior to the prime vaccination). AEs with an onset date more than 1 month after the last vaccination of IMP will be considered as treatment emergent only if assessed as related to IMP by the investigator.

10.1.2 Solicited Reactions

Selected safety parameters were measured/collected within 14 days after each vaccination (including the days of vaccination) as described below **Table 4**.

Table 4 Solicited local events systemic events

Local events (injection site):	Pain Redness Swelling
Systemic events:	Fever [(a)] Fatigue

	Headache
	Chills
	Vomiting
	Diarrhea
	New or worsening muscle pain
	New or worsening joint pain

(a) Based on recorded body temperature, fever is defined as axillary temperature ≥37.3°C.

Assess the grade of solicited safety parameters separately as described in the Grading Tables in Appendix B and Appendix C.

Solicited adverse reactions: There is at least a reasonable possibility that the investigational vaccine is associated with adverse events, i.e., a causal relationship cannot be ruled out.

10.1.3 Serious Adverse Events (SAEs)

Serious Adverse Event (SAE): Serious adverse events refer to the following adverse medical events (at any dose):

- Results in death
- Life-threatening

(Refers to the fact that the subject was at risk of death at the time of the event. Does not include an event that could theoretically have caused death if it were more severe)

- Requires or prolongs inpatient hospitalization

Note: Generally speaking, hospitalization refers to patients staying in the hospital or emergency ward for observation （usually at least one overnight） and/or receiving treatment that is not suitable to be conducted in the doctor's office or outpatient department. The complication occurring during hospitalization is considered as an AE. If the complication leads to prolonged hospitalization or any other severity criteria are met, it will be considered as an serious adverse event. This AE should also be regarded as a serious event when it is uncertain whether "hospitalization” is conducted or whether "hospitalization” is required. Hospitalization due to elective treatment or pre-existing disease that has not worsened since baseline is not considered as AE.

- Leading to permanent or significant disability/loss of function

Note: The term of disability refers to that the ability to perform normal life functions is severely affected. It does not include the events with relatively small clinical significance,

such as simple headache, nausea, vomiting, diarrhea, flu, and accidental trauma (such as achilles rupture). These events may affect daily function, but do not cause a significant loss of function.

- Leading to congenital anomaly/birth defects in offspring
- Other important medical event

Other important medical events: Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in certain situations. Such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may also be considered serious if medical action is necessary to prevent one of the above situations.

Note: The following hospitalizations are not considered serious adverse events because there is no "adverse event" associated with the hospitalization (i.e., there is no adverse medical occurrence):

- Admission for respite care;
- Hospitalisation for social reasons, for example, hospitalisation for easy care;
- Planned hospitalizations required by the protocol, e.g., for study vaccine administration or for insertion of a study vaccine or protocol-required tests;
- Hospitalization, elective surgery, or examination planned before informed consent for a pre-existing condition (in which case the condition requiring hospitalisation did not worsen or develop into a new disease after administration of the study vaccine, as evidenced by archiving of source documents);
- Hospitalization for routine maintenance (e.g., battery replacement) of equipment in place prior to study participation.

Any confirmed case of COVID-19 disease occurring during the observation period should be reported as an SAE, where the intensity of the respective AE is rated as "moderate" or "severe" (according to the criteria provided in Appendix B and Appendix C), and isolation or hospitalization is necessary according to the diagnosis and treatment plan for coronavirus pneumonia (Trial version 8). If no other SAE definition is deemed appropriate, the criterion of "medically important event" should be applied. An SAE form should be completed, including follow-up information, as detailed in Section 10.2.3 for the preparation and distribution of SAE reports and instructions.

10.1.4 Adverse Events of Special Interest

Exacerbation of respiratory disease or influenza-like symptoms, without resolution at 7 days, or development of symptoms with inconsistent relationship to RNA immunization as judged by the investigator, will be considered an adverse event of special interest (AESI).

All AESI, no matter whether they are serious or not, and no matter whether they are causally related to the study drug, need to notify Fosun within 24 hours, fill in the Serious Adverse Event Report Form, and send it to the Pharmacovigilance Department of Beijing Fosun Pharmaceutical Technology Development Co., Ltd. within 24 hours after being informed. If the adverse events of special interest meet the criteria for SAEs, they need to be handled and reported as SAEs.

10.1.5 AEs Associated with Overdose or Incorrect Administration

If a subject experiences symptom as a result of an overdose or incorrect administration of the vaccine, the overdose or incorrect administration and all associated symptoms should be recorded on the AE page of the eCRF and reported to Fosun according to the procedures for SAEs. Asymptomatic vaccine overdose also requires rapid notification within 24 hours. In case of serious consequences or symptoms after vaccine overdose that meet the assessment criteria for SAE, the overdose should be reported as SAE.

10.2 Collection and Recording of Adverse Events

10.2.1 Collection and Reporting of Solicited Reactions

The occurrence of selected indicators of safety will be collected on diary cards by the subjects for 14 days following each investigational vaccine/placebo vaccination (ie, the day of vaccination +13 subsequent days) and will be recorded on the “Solicited Local and Systemic events” eCRF, as applicable. These will be summarized under the category "solicited reactions" in the final report to distinguish them from other unsolicited AEs. Any solicited local or systemic adverse events observed 14 days after vaccination will be recorded as unsolicited AEs on the adverse event eCRF. Any solicited local (injection site) or systemic event that persists after 14 days following each investigational vaccine will be recorded on the Adverse Event eCRF for follow-up. For these ongoing/prolonged solicited reactions, an end date will be recorded on the Adverse Event eCRF to allow a differential analysis between unsolicited AEs.

10.2.2 Collection and Reporting of Unsolicited AEs

Unsolicited AEs were collected from the first dose of vaccine/placebo through 1 month after the 2nd dose via diary cards. After 1 month and till 12 months post 2nd dose only the IMP related AEs need to be reported. All SAE and AEs leading to withdrawal or discontinuation will be collected throughout the trial. The Investigator should collect and report signs and symptoms that are diagnostic of AEs, such as "flu-like symptoms" or "injection site reactions".

The following information will be documented for each event:

- Reported term for the Adverse Event,
- Start and end date,

- Serious (Y/N),
- The investigator should make clinical judgment on severity according to the grading criteria in 10.3.1. For the specific events listed in Appendices B and C, please refer to the grading criteria of corresponding guidelines.
- Investigator's opinion of the causality (relationship) between the event and administration of investigational vaccine(s) ("related" or "not related"),
- Investigator's opinion of the causality (relationship) to trial procedure(s), including the details of the suspected procedure,
- Action to be Taken,
- Outcome of the event.

10.2.3 Collection and Reporting of SAEs

For any SAE during the trial, whether related to the study vaccine or not, the investigator should take active measures to ensure the safety of subjects. The investigator should report to Fosun within 24 hours of becoming aware of the SAE.

For the reporting of death events, the investigator should provide the Fosun and the Ethics Committee with other required data, such as autopsy report and final medical report.

The investigator should timely sign and read the relevant safety information of the clinical trial provided by the sponsor, consider whether the treatment of the subject is adjusted accordingly, communicate with the subject as soon as possible when necessary, and report the suspected unexpected serious adverse reaction (SUSAR) provided by the sponsor to the Ethics Committee.

The investigator should follow up the SAE according to the requirements of the protocol and provide a detailed written follow-up report within 24 hours after being informed of the follow-up information. The reporting method is the same as above.

The sponsor or its representative evaluated and reported SAEs (including SUSARs) from clinical trials in accordance with the latest applicable regulatory requirements for drug clinical trials.

Contact information for serious adverse event reporting

Table 5 Contact information for serious adverse event reporting

Unit	**Tel**	**Reporting ways**
Pharmacovigilance Department of Beijing Fosun Pharmaceutical		Email：[redacted]

Technology Development Co., Ltd.		
Jiangsu Provincial Center for Disease Control and Prevention		

10.3 Assessment of Safety Parameters

10.3.1 Severity Assessment

The investigators will grade the vaccination reactions and symptoms involved in the grading table according to the NMPA "Guidelines for Grading Criteria for Adverse Events in Clinical Trials of Preventive Vaccines" (Appendix B) and the FDA Toxicity Grading Table for Clinical Trials of Preventive Vaccines (Appendix C). AEs not mentioned in the grading table will be graded clinically by the investigator according to the following criteria. Grading and seriousness need to be assessed separately for each AE recorded on the CRF.

Mild	Grade 1	Short-term (< 48h) or mild discomfort, no influence on activities, no treatment required.
Moderate S	Grade 2	Mild or moderate limitation of motion, which may require medical attention and may not require or require only mild treatment.
Severe	Grade 3	Marked limitation in activity requiring medical attention and treatment and hospitalization.
Critical	Grade 4	May be life-threatening, severely restricted in activity, requires monitoring for treatment
Dead	Grade 5	

10.3.2 Relationship to Investigational Product

Relatedness (causality) to vaccine will also be assessed by the investigator. The relationship of each adverse event to the investigational vaccine will be assessed using the following categories:

- Definitely related: There is a reasonable temporal relationship between the drug administration and the occurrence of adverse events; the reaction disappears or rapidly reduces and improves after drug withdrawal (i.e., positive dechallenge); the adverse event reappears after re-administration (i.e., positive rechallenge) and may

be significantly aggravated; it is supported by the investigator's brochure or literature data; and the influence of other confounding factors such as primary disease has been excluded.

- Probably related: There was no history of repeated medication. And the rest were "definitely related", or although there was concomitant medication, the possibility of adverse reactions caused by concomitant medication could be basically excluded.
- Possibly related: There was close relationship between the medication and the occurrence time of adverse events, which was supported by literatures. However, there was more than one drug causing adverse events, or progressive factors of primary disease could not be excluded.
- Unlikely related: The adverse event is not closely related to the medication time. The clinical manifestations are inconsistent with the known adverse reactions of the drug. The development of primary disease may have similar clinical manifestations.
- Definitely unrelated: The absence of drug administration, or the absence of correlation between drug administration.

The occurrence time of adverse events, or the presence of another clear cause for adverse events.

10.3.3 Relationship to Trial Procedures

Relationship (causality) to trial procedures should be determined for all AEs.

The relationship should be assessed as “Yes” if the investigator considers that there is reasonable possibility that an event is due to a trial procedure. Otherwise, the relationship should be assessed as “No”.

10.3.4 Anticipatory Evaluation of Adverse Events

Unexpected adverse reactions refer to the nature, severity, consequences or frequency of adverse reactions, which are different from the expected risks described in the current relevant data of investigational vaccine (such as Investigator's Brochure, etc.). The Investigator's Brochure provides the reference safety information used as the primary document to determine whether an adverse reaction is expected or unexpected.

Suspected Unexpected Serious Adverse Reaction (SUSAR): Suspected Unexpected Serious Adverse Reaction (SUSAR) refers to a suspected unexpected serious adverse reaction whose nature and severity of clinical manifestations exceed the existing information such as the Investigator's Brochure of the investigational vaccine, the package insert of the marketed drug or the summary of product characteristics.

10.4 Follow-up of Adverse Events

The investigator should follow up on each adverse event. Re-test and close follow-up should be performed in time for laboratory tests of clinical indicators if there are

abnormalities ≥ Grade 1 and judged as clinically significant by the investigator. All SAEs and related AEs still present at the end of the AE/SAEs collection record should be followed up to:

- The event resolves or returns to baseline status or stabilizes;
- The investigator determines that there will be no further improvement;
- Impossible to obtain more information (the subject refuses to provide more information, or there is evidence that the subject is still lost to follow) up after best efforts have been made).

The recovery time of the adverse event (with dates) should be recorded on the adverse event eCRF and in the patient's medical record during the study to facilitate source data verification.

For serious adverse events, adverse events of special interest, and pregnancy events, Fosun or other designee may obtain additional case information by telephone, fax, email, and/or monitoring to enable an independent medical assessment of these reported cases.

The updated AE original data after database lock should be recorded for future use. For SAE information, it is required to fill in Serious Adverse Event Report Form as detailed as possible and submit it to the PV department.

10.5 Treatment of Vaccination Reactions and Adverse Events

Treatment of any vaccination reactions and AE is at the sole discretion of the Investigator and according to local standard of care.

Mitigation plans for specific Vaccination Reactions

Based on experience with other RNA-based vaccines at BioNTech, it is expected that following injection of an RNA vaccine, subjects may experience TEAEs, flu-like symptoms, and/or injection site reactions due to the mechanism of action of the RNA vaccine. This may include fever, chills, rigors, tachycardia, arthralgia, myalgia, headache, nausea. Treatment of these events is dependent on the discretion of the investigators, however the following management suggestions are provided:

- Treat fever with acetaminophen or nonsteroidal anti-inflammatory drug (NSAIDs) with a dose per study site recommendation.
- After the first occurrence of flu-like symptomatology, subjects can be treated with standard therapeutic dose of acetaminophen, or NSAIDs, starting at least 2 h after the immunization.
- Corticosteroids should be avoided as either prophylaxis or treatment as it counteracts the effects of immunization.

- Local injection site reactions can be managed by simple measures, such as cooling, defervescence, and analgesia.

Ensure adequate hydration of subjects on the day of immunization. Consider administration of fluids (e.g., 0.5-1.0 L of drinking water) within approximately 2 hours of immunization, per study site standard.

If the subject experiences progression of enhanced respiratory disease or influenza-like symptomatology, if symptoms are not resolved after 7 days and the relationship between symptom changes and RNA immunity is inconsistent, additional diagnostic measures should be considered and the medical monitor should be informed.

10.6 Outcomes of Adverse Events

The investigator should determine the outcome of the adverse event based on the outcome of the adverse event. The outcome of the adverse event are as follows:

- Recovered: The subject fully recovered from the AE without any residual effects or harm.
- Recovering: Signs and symptoms associated with the event have abated but have not completely disappeared.
- Recovered with sequelae: The subject has recovered but with residual effect or injury. These residual effects may be temporary but were still present at the time of the report. If the sequelae are not considered permanent, additional information will be required at follow-up when the event changes.
- Unchanged: The signs and symptoms associated with the event did not abate. The subject's condition remained unchanged.
- Disease worsening: There was no decrease in signs and symptoms associated with the event. The subject's condition worsened.
- Death: Only SAEs leading to death may choose "death" as the outcome. All other AEs/SAEs present at the time of death should be reported.
- Unknown: when the subject is lost to follow-up and the study staff cannot determine the outcome.

11.0 Monitoring Committee

11.1 Safety Review Committee (SRC)

SRC will be established, consisting Investigators and Fosun Medical Representative.

- When the elderly sentinels of 40 subjects are dosed and followed up for 48 hours after the first dose for safety observation, SRC will review the safety data (including lab tests) for safety and make decision if the random enrollment of remaining elderly subjects could be continued.
- When the first approximately 150 subjects (including the elderly sentinel of 40 subjects) have completed the visit 2, SRC will review the safety data (including lab tests) of these subjects for safety and make decision if the random enrollment of remaining subjects could be continued.
- AE of special interest (AESI) will be evaluated. This includes enhanced respiratory disease (ERD) cases.

Detail information will be provided in the SRC charter.

11.2 Independent Data Monitoring Committee (IDMC)

This study is supervised by the independent data monitoring committee. IDMC will consist of 3 independent members (including a chair/statistician, an epidemiologist and a clinical expert) and 1 non-voting independent statistician. IDMC will be requested by Fosun Pharma in the event of suspicious significant events and risks that may lead to study suspension.

Unblinded data will be provided by unblinded statistician who is not Fosun employee or consultant. The IDMC will review blinded and unblinded safety data in the event of risks that may lead to suspension. The IDMC could request suspension of the study based on review results of safety data. If no recommendation for suspension or modification is received from the IDMC, the study may proceed per the protocol.

The IDMC meetings will consist of open and closed sessions, either a face-to-face meetings or teleconference calls will be scheduled by Fosun Pharma. The type and frequency of scheduled meetings will depend on the subject enrollment and safety event rates. Unscheduled ad hoc meetings will occur if a stopping rule occurs, or at any time IDMC is requested by the Pharmacovigilance Study Team.

The IDMC reviews safety data on an ongoing basis.

Further information will be provided in the IDMC charter, which will be finalized and signed off prior to the first subject receives study drug.

12.0 Data Management

This project is based on the requirements in Technical Guidelines for Data Management of Clinical Trials issued by NMPA in 2016, Guidelines for Planning and Reporting of Data Management and Statistical Analysis of Drug Clinical Trials and Technical Guidelines for Electronic Data Collection of Clinical Trials.

12.1 Data collection and management

An electronic data capture system (EDC) was used for data collection and management in this study. Subject data will be entered into the designated eCRF. The eCRF will be retained by Fosun and copies will be sent to the investigator as a copy of the study.

The investigator or authorized staff shall be responsible for completing the eCRF, and carefully and thoroughly record the items in the eCRF, without blank or missing items (UK/NA/ND should be filled in for the blank space without record according to the actual situation); all the data in the eCRF must be checked with the data in the original data of the subject to ensure accuracy.

The investigator should keep all the original laboratory test sheets or copies; for abnormal laboratory or test data, the investigator must verify and explain whether there is clinical significance; the investigator should fill in the eCRF in strict accordance with the instructions for completing the eCRF.

12.2 Database Lock

The data can be locked when the following conditions are met.

- All data have been entered into the database.
- All queries have been resolved;
- The statistical analysis population was determined and judged.

The locked data file will not be unlocked and changed without the authorization.

Specific data management processes will be detailed in the Data Management Plan (DMP).

13.0 Statistical Approach

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be finalized prior to database lock. SAP will provide further details regarding the definition of analysis variables and analysis methodology to address all trial objectives.

A blinded data review will be conducted regularly prior to unblinding of subject's randomization assignment. This review will assess the accuracy and quality of the data.

13.1.1 Analysis Population

- *Safety analysis population*: The safety analysis set will include all randomized subjects who receive at least one dose of the investigational vaccine/placebo.
- *Intention-to-treat population (ITT)*: The ITT will include all randomized subjects who received at least one dose of the investigational vaccine/placebo and could provide a valid baseline according to the Intention-To-Treat principle.
- *Per protocol set (PPS)*: The PPS will include subjects in the ITT except those who have major protocol violations and do not complete the two vaccinations. Protocol violations review is a part of the blinded data review. The categories of major protocol violations include:
    - Do not meet inclusion criteria, or meet exclusion criteria,
    - receiving a wrong investigational vaccine/placebo,
    - receiving prohibited therapies,
    - and major protocol violations influencing the evaluation of immunogenicity identified during blinded data reviews.
- *Dose 2 evaluable immunogenicity population:* All eligible randomized participants who receive 2 doses of the vaccine to which they are randomly assigned, within the predefined window, have at least 1 valid and determinate immunogenicity result after Dose 2, have blood collection within an appropriate window after Dose 2, and have no other important protocol deviations as determined by the clinician.
- *Dose 2 all-available immunogenicity population:* All randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 2.

All summaries and analyses of safety data will be based on subjects in the Safety population.

Analyses of the primary immunogenicity endpoint will be based on ITT, with sensitivity analysis based on PPS, and analyses of other immunogenicity endpoints will be based on ITT.

13.1.2 General Considerations

In general, data will be summarized by groups and groups may be combined as appropriate.

Continuous variables will be summarized by group using the following descriptive statistics: number of subjects (n), mean, standard deviation, median, minimum and maximum.

Categorical variables will be summarized by group presenting count and percentage (n and %) of subjects in each category.

Baseline is defined as last non-missing value prior to first dose.

13.1.3 Analysis of Demographics and Other Baseline Characteristics

Summaries of age, gender, race, and other baseline characteristics will be presented by groups.

13.1.4 Immunogenicity Analysis

Primary Immunogenicity Analysis

Number and percentage of SCR will be summarized by group and compared for the treatment differences. 95% CI will be provided using the Clopper-Pearson method, assuming binomial distribution. Primary analysis will be performed, when all randomized subjects complete 1-month visit post Dose 2.

GMT will be summarized by group and compared for the treatment differences. 95% CI will be provided. Primary analysis will be performed, when all randomized subjects complete 1-month visit post Dose 2.

Secondary Immunogenicity Analysis

Descriptive statistics for the secondary immunogenicity endpoints will be provided for GMT/GMC, GMFR, and GMR, by visit and by group, the BNT162b2 group and placebo group. The BNT162b2 group and placebo group will be compared to calculate the point estimate and 2-sided 95% CI for the difference in GMT/GMC, GMFR, and GMR by group. Subgroup analysis by age will be summarized. Missing serology data will be described in the SAP.

13.1.5 Safety Analysis

Descriptive statistics will be provided for the reactogenicity endpoints by time point, the BNT162b2 group and placebo group. Within 7 and 14 days after each vaccination (including the day of vaccine/placebo administration), collected local and systemic events

will be presented cumulatively by severity to assess reactogenicity. Descriptive summary statistics will include the number and percentage of subjects with the specified endpoint.

All AEs and SAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA v. 23.0) and summarized by system organ class (SOC) and preferred term (PT) for each group (BNT162b2 and placebo), including exacerbations after primary vaccination and new onset medical conditions.

Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CI) will be provided for any AE in the BNT162b2 group and placebo group. SAEs will be classified according to MedDRA terminology. The number and percentage of SAEs from Dose 1 to 6 months and 12 months after Dose 2 will be provided for the BNT162b2 group and placebo group.

Shifts in grade of hematology and chemistry laboratory assessments at baseline and 1 and 7 days after Dose 1, and before and 7 days after Dose 2 of BNT162b2 were tabulated and summarized.

AE

All AEs will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA23.0) coding system to get a SOC and PT for each AE.

AEs and solicited reactions will be summarized using the Safety Analysis Set. Generally, safety measures will be analyzed by group and by each immunization.

For each analysis, the number and percentage of subjects reporting at least one AE will be summarized by PT nested within SOC for each of the following AE types using the Safety Set:

- Any AE
- Related AE
- Grade ≥ 3 AEs
- Related ≥ Grade 3 AEs
- AEs Leading to Withdrawal
- Any SAE
- Related SAE

Moreover, the number and percentage of subjects with any AE will be summarized by worst grade by PT nested within SOC.

Solicited Events

Reactogenicity was assessed within 14 days after each vaccination (including the day of BNT162b2/placebo vaccination) by collecting solicited reactions daily, including local events (injection site pain, redness, and swelling) and systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsening muscle pain, and new or worsening joint pain), as well as unsolicited AEs.

For each solicited reaction (including fever), the percentage of subjects will be summarized by severity of the event and overall for each within 7 and 14 days following each vaccine/placebo administration.

Solicited local events and systemic events within 7 and 14 days after each vaccination, and unsolicited TEAEs from Dose 1 up to 1 month after Dose 2, and AEs related to the study vaccine after 1 month after Dose 1 will be graded separately using the grading criteria for adverse reactions given in Appendix B and Appendix C. During the study, investigators will perform clinical grading according to the criteria in Section 10.3.1 for AEs not mentioned in the appendix grading table.

For each immunization, the number and percentage of subjects reporting at least 1 local event or systemic event will be summarized for each of the following categories using the Safety Analysis Set:

- Any local event or systemic event
- Related local events or systemic events
- Grade ≥ 3 local events or systemic events
- Related ≥ Grade 3 local events or systemic events

In addition, the number and percentage of subjects reporting at least 1 local event will be summarized by worst grade using the Safety Analysis Set.

Clinical Laboratory Parameters

Clinical laboratory parameters at each timepoint and change from baseline to each post-baseline time point will be summarized using descriptive summary statistics for each parameter by group.

Shift tables from baseline to worst intensity grade will be provided for each laboratory parameter by group. From normal at baseline to abnormal after vaccination, or from abnormal at baseline to increase in severity after vaccination were tabulated and summarized descriptively

"Additionally, the occurrence of clinically significant abnormal laboratory results within a trial subject will be analyzed using descriptive summary statistics for each parameter and visit by group."

Laboratory parameter results will be listed along with the normal ranges. Values that are below or above the normal ranges will be flagged.

VITAL SIGNS

Vital sign parameters at each time point and change from baseline to each post-baseline time point will be summarized using descriptive summary statistics for each parameter by group.

ECG

ECGs will be judged by the investigator as clinically significant (yes/no). The number and percentage of trial subjects with clinically significant ECG findings will be summarized by group for each visit.

A safety summary will be given by different age stratification and different dose cohorts/placebo groups.

13.1.6 Exploratory Analyses

Analyses for exploratory endpoints will be described in the SAP and will include:

- Cellular immune responses measured by ELIspot assay etc.
- GMT of anti-S1 subtype IgG antibodies.
- Compare the number of confirmed COVID-19 cases (including COVID-19 classification, see the appendix for classification criteria).
- Compare the severe and critical cases of COVID-19 suggestive of enhanced respiratory disease.
- Compare the neutralization ability of serum of subjects before and after vaccination against different SARS-Cov-2 epidemic strains.

13.2 Statistical Analysis Time Points

Initial analysis: safety and immunogenicity data at 1 month after the 2nd dose.

Unblinding will occur at the completion of the initial analysis, but the subject's blindness will be maintained. Refer to the Statistical Analysis Plan (SAP) for further details of the analyses and for the bridging analyses from the China study and foreign studies.

An analytical report for this phase will be written after each analysis and an overall study report will be written at the end of the study.

13.3 Statistical Hypotheses

The objectives part of this study is to confirm the vaccine efficacy through 2 primary efficacy endpoints evaluating immunogenicity, which is defined as Seroconversion rate (SCR) and GMT (geometric mean titer), compared to placebo, in participants in China at 1 month after Dose 2. Dose 2 evaluable immunogenicity population will be used for the following hypothesis testing:

Hypothesis for GMT

H_0: $\ln(\mu 2) = \ln(\mu 1)$

H_a: $\ln(\mu 2) \neq \ln(\mu 1)$

Hypothesis for SRC

H_0: $\pi 2 = \pi 1$

H_a: $\pi 2 \neq \pi 1$

ln(μ2) and ln(μ1) are the natural log of the geometric mean of SARS-CoV-2 neutralizing titers from BNT162b2 and placebo recipients, respectively, measured 1 month after Dose 2. $\pi 2$ and $\pi 1$ are the seroconversion rate of SARS-CoV-2 neutralizing titers from BNT162b2 and placebo recipients, respectively, measured 1 month after Dose 2. SCR and GMT will be evaluated sequentially, first with SCR and then by GMT, to control the overall type I error to the desired level of 5%, 2-sided. 95% CI will be calculated using Pearson-Clopper and t-distribution, respectively, for SCR and GMT.

An additional analysis may be performed based on the Dose 2 all-available immunogenicity population if needed.

13.4 Determination of Sample Size

Several factors are considered in the evaluation of sample size determination.

From efficacy perspective, this is a phase II, randomized, placebo-controlled study. Superiority comparison will be performed between the BNT162b2 vaccinated group and the placebo group in a 3:1 randomization ratio. [redacted] be needed to test the significant difference between groups for both age stratifications.

From safety perspective, as per the requirement of vaccine clinical development guidance (2004) in China, a minimal sample size of 300 subjects in the vaccine groups is required for phase 2 trials. [redacted] The sample size of approximately 960 subjects is sufficient for bridging evaluation.

In summary, a total of approximately 960 subjects will be enrolled in the study. Subjects will be randomly allocated to one of the two groups, including 720 subjects in the BNT162b2 group and 240 subjects in the placebo group in a 3:1 randomization ratio.

14.0 Study Management

14.1 Ethical Considerations

This study will be conducted in compliance with the ethical requirements in the Declaration of Helsinki (Fortaleza, 2013), International Council for Harmonization (ICH) E6 GCP, Chinese laws and regulations related to clinical studies as well as this protocol.

The study protocol, informed consent form, medical record report and some other materials, etc. must be submitted to the ethics committee for -approval before the study begins. The ethics committee will review and approve these materials in strict accordance with the provisions of relevant laws and regulations. Only after receiving the approval from the ethics committee, can the study be started.

During the study, any changes to the protocol must be reviewed and approved by the ethics committee before implementation.

In addition, the ethics committee will approve all amendments to clinical trial protocol (except for administrative changes approved by the Fosun), informed consent form and updates, subject recruitment procedures, written information provided to subjects, available safety information, information about the remuneration and subsidies available to the subject, the resume and/or other qualification certificates of the investigator, and any other documents required by the ethics committee and regulatory agency (if applicable).

14.2 Informed Consent

The investigator or designated representative will be responsible for explaining the study background, pharmacological characteristics of study drug, study protocol and benefits and risks of participating in the study to each subject, the subject's legal representative or independent witness, and must give the subject sufficient time and opportunity to inquire about the details of the trial, answer their questions satisfactorily and decide whether to participate in the study. Written informed consent was obtained from the subject or the subject's legal representative and from the investigator or study physician on his/her behalf before the subject entered the study (before screening examination).

The text of the final ICF should contain the following contents: study background, study purpose, study process, subjects' cooperation matters, risks and discomforts of participating in the study, damage possibly caused by trial-related operation, storage and treatment of biological samples, benefits of participating in the study, alternative treatment, costs related to participating in the study; treatment available to the subjects and appropriate insurance compensation in case of study-related damage; access to study data and confidentiality of subject information. The informed consent form should be written in non-technical language and approved by the IRB/IEC.

The consent form must be signed and dated by subjects or their legal representatives, and the investigator who performs the informed consent process or the representative.

The investigator and subject should keep one copy of informed consent form respectively. If important new data involving the study vaccine or new information that will affect the subject's willingness to continue to participate in the study are found, the subject or his/her legal representative should be informed in a timely manner, and the subject's informed consent should be obtained again.

14.3 Protocol Amendments

Any important modifications to this protocol require a written amendment approved by Fosun and the investigator before implementation, which needs to be reported to the ethics committee for approval and sent to the regulatory agency for record.

Any changes to the protocol will require a written protocol amendment, which must be approved by Fosun prior to implementation of administrative changes. If the changes have special impacts on the safety of the subject, the scope of the study or the scientific quality of the study, an application needs to be submitted to the regulatory agency, and approved by the appropriate ethics committee of each research institution. The above requirements shall not preclude the immediate action of the Investigator or Fosun to protect the safety and interests of all subjects. If the investigator believes that for safety reasons, it is necessary to immediately change or deviate from the protocol to eliminate the harm to the subject, the medical monitor and the ethics committee of the research institution should be notified immediately. Fosun must notify the regulatory authorities in accordance with local regulations.

There is no need to submit an application to the regulatory agency or the ethics committee for amendments only involving study management or administrative aspects, but the regulatory agency or the ethics committee should be notified in accordance with local regulations.

14.4 Protocol Deviations

If no formal amendment to the clinical trial protocol is identified and approved by the appropriate ethics committee, the investigator should not deviate from the study protocol, except to eliminate an immediate hazard to subjects or when the change involves only management or administrative aspects of the study and is approved by the medical monitor and/or Fosun.

All requirements specified in the study protocol must be strictly implemented. Any intentional or unintentional deviations or violations of the study protocol and GCP principles can be classified as protocol deviations or violations. The investigator or the designated personnel must record and explain the details and reasons for protocol deviations or violations and notify the regulatory agency or the ethics committee in accordance with local regulations.

See the medical monitoring plan for specific protocol deviations or violations.

14.5 Confidentiality and Privacy of Subjects

The personal information and privacy of the subject will be kept strictly confidential. During the study, the subject's name and other personal data will be replaced with a code or number. The personal data collection and processing in this study will be limited to those necessary to investigate the efficacy, safety, tolerability, quality, and effectiveness of the study vaccine. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. These subject records will be made available to the monitor, other authorized representatives of Fosun, Ethics Committee, and regulatory agency representatives. The results of the study may be published in the journal, but any personal information of subjects will not be disclosed.

14.6 Monitoring

The investigator should allow the clinical monitor to inspect the clinic, laboratory, and pharmacy facilities, and to access the case report forms, informed consent forms, and all source documents to ensure that the study is compliant with Good Clinical Practice and local regulatory requirements.

A designated clinical monitor will conduct monitoring visits to each study site in accordance with the monitoring plan. An on-site visit will be conducted before the study begins. Regular visits are required during the study. If necessary, telephone, fax or e-mail can be used for contact as a supplementation to on-site visit.

Before the start of the study, the investigator will be notified of the expected frequency of monitoring visits. In addition, the investigator will be notified in advance before each monitoring visit during the study. The purpose of the visit is to ensure that clinical study is conducted strictly in accordance with the study protocol, and to ensure the completeness, accuracy of the case report forms which can be verified through original documents.

The clinical monitor verifies that all case report forms are correctly and completely filled out and are consistent with the original data. After any errors or omissions have been corrected or noted, they will be signed and dated by the investigator. At each visit, the investigator and the clinical monitor are required to work closely to review and verify case report forms, vaccine supply and inventory records, vaccine distribution and recovery records and any additional records scheduled.

14.7 Quality Assurance and Quality Control

Fosun, investigator and CRO shall all perform their respective responsibilities in accordance with the requirements of GCP, strictly follow the trial protocol and adopt corresponding standard operating procedures to ensure the implementation of quality control and quality assurance system in the processes of clinical trial, sample test and data statistical calculation etc.

In order to ensure the quality of the study, all investigators must be trained on the trial protocol before the trial is initiated. All SOPs should be strictly implemented during the trial. Fosun should send qualified monitors to supervise the trial process and check the trial data.

Fosun may entrust auditors to conduct systematic audit of trial-related activities and documents to review whether the trial is conducted in accordance with the trial protocol, standard operating procedures and relevant regulations and technical guidelines, and whether the trial data are timely, true, accurate and complete recorded and reported. The auditor performed by a person independent of the clinical trial.

Relevant materials and documents (including medical records) of study sites and laboratories participating in clinical trials shall be inspected and verified by drug regulatory authorities.

14.8 Direct Access

The Principal Investigator will provide direct access to source data and documents to Ethics Committee personnel, monitors, and other Fosun designees performing study-related monitoring and/or review. The purpose of monitoring or auditing is to systematically and independently examine all study-related activities and documents, determine whether these activities were conducted, and record, analyze, and accurately report data in accordance with the protocol, GCP, ICH guidelines, and any appropriate regulatory requirements. If the regulatory authority contacts the Institution and/or Principal Investigator for an audit, the Principal Investigator will notify Fosun immediately.

The investigator must inform the subject that his/her study-related records may be reviewed by the above individual without violating the privacy of the subject's personal health information.

14.9 Data Recording and Storage

In order to ensure the evaluation and supervision by regulatory authorities and Fosun, the investigator should agree to preserve all study data, including the confirmed records of all subjects (which can effectively check all the recorded materials, such as case report form and hospital original records), all the original signed ICFs of subjects, all case report forms, detailed records of vaccine distribution, etc. The retention period is 5 years after the end of the study or until the time limit is agreed in the clinical contract and the notice of destruction by Fosun is obtained.

All the data of this clinical study are proprietary to Fosun. Except for the requirements of regulatory authorities, the investigator shall not provide them to a third party in any form without the written consent of Fosun.

14.10 Subject Insurance and Indemnity

The sponsor will provide insurance to the study in accordance with applicable law and regulations.

If the subject suffers any injury causally related to the study due to participation in this study, Fosun will bear the treatment cost and corresponding economic compensation, except for those caused by medical malpractice.

14.11 Storage and Use of Biological Specimens

The biological samples of this study will be stored in a designated place for this clinical study only. The test blood samples will be destroyed after testing. The backup blood samples will be stored according to the requirements of national regulations until the specified time after the study vaccine is approved for marketing.

14.12 Study Interruption and Early Termination

The sponsor and Fosun reserves the right to stop the study at any time due to medical reasons or any other reasons. If the study is terminated or discontinued early, Fosun should immediately notify the investigator that the study has been terminated or discontinued and give the reasons for the termination or discontinuation. According to the requirements of relevant laws and regulations, Fosun or the Investigator should also immediately notify the Ethics Committee that the study has been terminated or suspended, and explain the reasons.

The investigator reserves the right to decide whether to stop the study. If the investigator terminates or suspends the study without obtaining Fosun's consent in advance, the investigator should immediately notify Fosun and the Ethics Committee and provide Fosun and the Ethics Committee with a detailed written explanation of the termination or discontinuation. Study records must be kept.

14.13 Study Summary Report

After the end of the study, the investigator and Fosun objectively summarized the study results and statistically analyzed the study data with appropriate statistical methods. The safety of the study vaccine was objectively evaluated according to the results. After review and approval by the sponsor and Fosun, a written summary report of this clinical study was made.

14.14 Information Disclosure and Data Publication Policy

The investigator shall keep confidential the information and data related to this study, and shall not cite or publish relevant study results or data without the consent of the sponsor and Fosun.

The sponsor and Fosun have the right to publish the information or data related to this study to regulatory authorities. If the name of the investigator needs to appear in the publication or advertisement by the sponsor and Fosun, the consent of the investigator should be obtained.

Appendix A Websites of WHO and CDC

- World map with risk areas for COVID-19: https://www.who.int/emergencies/diseases/novel-coronavirus-2019
- COVID-19 Map of China: http://2019ncov.chinacdc.cn/2019-nCoV/

Appendix B NMPA Adverse Event Grading Scale for Preventive Vaccine Clinical Trial Guidelines

Appendix B Table1 Vaccination Site (Local) Adverse Event Grading Table

Symptoms/ Signs	Grade 1	Grade 2	Grade 3	Grade 4
Pain, tenderness (optionally used; palpation for subjects unable to autonomously express pain)				
Pain	Does not or slightly influence limb movement	Influence on limb movement	Influence on daily life	Loss of basic self-care ability, or hospitalization
Tenderness	Resistant to touch or shrink	Cry after touching, but can soothe	Constant crying does not soothe	Require emergency room visit or hospitalization
Induration *, swelling ** #	2.5 to < 5 cm in diameter or 6.25 to < 25 cm^2 in area, with no or slight influence on daily life	5 to < 10 cm in diameter or 25 to < 100 cm^2 in area or interfere with daily life	≥ 10 cm in diameter or ≥ 100 cm^2 in area or ulceration or secondary infection or phlebitis or aseptic abscess or wound drainage or significant impact on daily life	Abscess, exfoliative dermatitis, necrosis of dermis or deep tissue
Rash *, blush ** #	2.5 to < 5 cm in diameter or 6.25 to < 25 cm^2 in area, with no or slight influence on daily life	5 to < 10 cm in diameter or 25 to < 100 cm^2 in area or interfere with daily life	≥ 10 cm in diameter or ≥ 100 cm^2 in area or ulceration or secondary infection or phlebitis or aseptic abscess or	Abscess, exfoliative dermatitis, necrosis of dermis or deep tissue

Symptoms/ Signs	Grade 1	Grade 2	Grade 3	Grade 4
			wound drainage or significant impact on daily life	
Other				
Pruritus	Vaccination site pruritus, which resolved spontaneously or within 48 h after treatment	Vaccination site pruritus, which did not resolve within 48 h after treatment	Influence on daily life	NA
Cellulitis	NA	Need for non-injectable treatment (e.g., oral anti-bacterial, antifungal, antiviral therapy)	Need for intravenous therapy (e.g., intravenous antibacterials, antifungals, antivirals)	Sepsis, or tissue necrosis, etc.

Note: * In addition to directly measuring the diameter to grade the evaluation, record the progressive change of measurement results.

** The largest measured diameter or area shall be used.

Induration and swelling, rash, and blush should be evaluated and graded based on functional class and actual measurement, and the index with the higher grade should be selected.

Appendix B Table 2 Vital Signs Grading Scale

Signs	Grade 1	Grade 2	Grade 3	Grade 4
Fever * [Axillary temperature (℃)]	37.3~<38.0	38.0~<38.5	38.5~<39.5	≥39.5 for more than 3 days
Electrocardiogram PR interval prolonged or AV block	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds or 2nd degree atrioventricu	2nd degree atrioventricu-lar block type II or intermittent	Complete atrioventricular block

Signs	Grade 1	Grade 2	Grade 3	Grade 4
		l-ar block type I	≥ 3 seconds	
Signs	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Heart rate				
Tachycardia (bpm)	101~115	116~130	>130	Arrhythmia requiring emergency treatment or hospitalization
Bradycardia (bpm)	50~54	45~49	<45	Arrhythmia requiring emergency treatment or hospitalization
Blood Pressure				
Hypertension (mmHg)	Systolic blood pressure: 140 to < 160 or diastolic blood pressure: 90 to < 100	Systolic blood pressure: ≥ 160 to < 180 or diastolic blood pressure: ≥ 100 to < 110	Systolic blood pressure: ≥ 180 or diastolic blood pressure: ≥ 110	Life-threatening complications not previously diagnosed (eg, malignant hypertension) or hospitalization
Hypotension (systolic blood pressure) (mmHg)	85~<89	80~<85	<80	Shock or hospitalization
Respiratory rate (bpm)	17~20	21~25	>25	Need for tracheal intubation

Appendix B Table 3 Non-vaccination site (systemic) adverse event grading table

Organ system symptom/sign	Grade 1	Grade 2	Grade 3	Grade 4
Gastrointestinal system				

Organ system symptom/sign	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	Mild or transient, 3-4 times/day, abnormal stool appearance, or mild diarrhea lasting less than 1 week	Moderate or persistent, 5-7 times/day, abnormal stool appearance, or diarrhea for > 1 week	> 7 times/day, abnormal stool appearance, or hemorrhagic diarrhea, orthostatic hypotension, electrolyte imbalance, requiring > 2 L intravenous fluids	Hypotensive shock, Need to be hospitalized
Constipation*	Requires stool softener and dietary modification	Need for laxatives	Stubborn constipation requires manual dredging or the use of enemas	Toxic megacolon or ileus
Dysphagia	Mild discomfort while swallowing	Dietary restrictions	Eating, talking very limited; unable to eat solid foods	Cannot eat liquid food; requires parenteral nutrition
Anorexia	Decreased appetite without decreased food intake	Decreased appetite, decreased food intake without significant weight loss	Decreased appetite with significant weight loss	Intervention Required (e.g. tube feeding, parenteral nutrition)
Vomiting	1-2 times/24 h without influence on activities	3-5 times/24 h or limited activities	> 6 episodes in 24 h or need for intravenous hydration	Shock due to hypotension requiring hospitalization or other routes of nutrition

Organ system symptom/sign	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	Transient (< 24 h) or intermittent and essentially normal food intake	Sustained nausea leading to reduced food intake (24-48 h)	Persistent nausea resulting in little to no food intake (> 48 h) or need for intravenous hydration	Life-threatening (e.g. hypotensive shock)
Musculoskeletal and connective tissue				
Myalgia (non-vaccination site)	No influence on daily activities	Slight influence on daily activities	Severe muscle pain, severe interference with daily activities	Emergency or hospitalization
Arthritis	Mild pain with inflammation, erythema, or joint swelling; does not interfere with function	Moderate pain with inflammation, erythema, or joint swelling; preventing function but not interfering with daily activities	Severe pain with inflammation, erythema, or joint swelling; interference with daily activities	Permanent and/or disabling joint damage
Arthralgia	Mild pain, no interference with function	Moderate pain; pain requiring analgesics and/or pain preventing function but not influencing on daily activities	Severe pain; requiring analgesics and/or pain influencing on daily activities	Disabling pain
Nervous System				
Headache	No influence on daily	Transient, slight influence on daily activities,	Significant disruption of daily activity	Intractable requiring emergency

Organ system symptom/sign	Grade 1	Grade 2	Grade 3	Grade 4
	activities, no treatment required	may require treatment or intervention	requiring treatment or intervention	room visit or hospitalization
Syncope	Close to syncope without loss of consciousness (e.g. pre-syncope)	Loss of consciousness without treatment	Loss of consciousness requiring treatment or hospitalization	NA
New convulsions	NA	NA	1-3 times convulsions	Prolonged and repeated convulsions (e.g. status convulsion) or difficult to control (e.g. intractable epilepsy)
Respiratory System				
Cough	Transient, no treatment required	Persistent cough, effective treatment	Paroxysmal cough that cannot be controlled by treatment	Emergency or hospitalization
Acute bronchospasm	Transient; no treatment required; FEV_1% 70-80%	Requires treatment; bronchodilator therapy normalized; FEV_1% 50-70%	Bronchodilator treatment does not return to normal; FEV_1% 25% to 50% or persistent depression in the intercostal space	Cyanosis; FEV_1% < 25%; or intubation required
Dyspnea	Dyspnea on exercise	Dyspnea with normal activity	Dyspnea at rest	Dyspnea requiring oxygen therapy,

Organ system symptom/sign	Grade 1	Grade 2	Grade 3	Grade 4
				hospitalization or assisted breathing
Organ system symptom/sign	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Skin and subcutaneous tissue				
Non-vaccination site pruritus (no skin lesions)	Slight itching, no or slight influence on daily life	Pruritus influencing on daily life	Itching prevents daily life	NA
Mucocutaneous disorder	Erythema/ Itching/Color Altered	Diffuse rash/maculopapular rash/dryness/desquamation	Herpes/oozing/desquamation/ulceration	Exfoliative dermatitis involving mucosa, erythema multiforme, or suspected Stevens-Johnsons syndrome
Psychiatric system				
Insomnia*	Mild difficulty falling asleep, no or slight influence on daily life	Moderate difficulty falling asleep,influence on daily life	Severe difficulty falling asleep, severe influence on daily life, treatment or hospitalization required	NA
Irritation or depression	Mild irritability or mild	Irritability or somnolence	Unable to soothe or become hyporesponsive	NA

Organ system symptom/sign	Grade 1	Grade 2	Grade 3	Grade 4
	depression			
Mental disorder (includes anxiety, depression, mania, and insanity) Detailed symptoms to be reported	Minor symptoms that do not require medical attention or behavior do not influence or slightly influence daily life	Clinical symptoms requiring medical attention or behavior influencing on daily life	Requires hospitalization or inability to perform daily life	Have a tendency to hurt yourself or others or acute insanity or loss of basic self-care ability
Immune system				
Acute allergic reactions **	Localized urticaria (blistering) not requiring treatment	Localized urticaria requiring treatment or mild angioedema not requiring treatment	Extensive urticaria or angioedema requiring treatment or mild bronchospasm	Anaphylactic shock or life-threatening bronchospasm or laryngeal oedema
Other				
Fatigue, asthenia	No influence on daily activities	Influence normal daily activities	Seriously influence daily activities and cannot work	Emergency or hospitalization
Non-vaccination site pain (Identify location when reporting)	Mild pain, no or slight influence on daily life	Pain influencing on daily life	Pain incapacitating for daily life	Disabling pain, loss of basic self-care ability

Note: FEV_1% refers to forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC)

* For constipation and insomnia, attention should be paid to changes before and after vaccination.

* Refers to type I hypersensitivity.

Refers to non-vaccination site pain other than myalgia, arthralgia, headache.

Appendix B Table 4 Blood chemistry grading table

Test indicators	Grade 1	Grade 2	Grade 3	Grade 4
Hepatic function (ALT, AST increased)	1.25~<2.5 ×ULN	2.5~<5.0×ULN	5.0~<10×ULN	≥10×ULN
Total bilirubin increase (mg/dL; μmol/L)	1.1~<1.6×ULN	1.6~<2.6×ULN	2.6~5.0×ULN	≥5.0×ULN
Pancreatic enzymes (amylase, lipase)	1.1~<1.5×ULN	1.5~<3.0×ULN	3.0~<5.0×ULN	≥5.0×ULN
Creatine phosphokinase (CPK)	1.25~<1.5×ULN	1.5~<3.0×ULN	3.0~<10×ULN	≥10×ULN
Hypernatremia (Na, mmol/L)	146~<150	150~<154	154~<160	≥160
Hyponatremia (Na, mmol/L)	130~<135	125~<130	121~<125	≤120
Hyperkalemia (K, mmol/L)	5.6~<6.0	6.0~<6.5	6.5~<7.0	≥7.0
Hypokalemia (K, mmol/L)	3.0~<3.4	2.5~<3.0	2.0~<2.5	<2.0
Hypercalcemia (Ca, mmol/L)	2.65~<2.88	2.88~<3.13	3.13~<3.38	≥3.38
Hypocalcemia (Ca, mmol/L)	1.95~<2.10	1.75~<1.95	1.53~<1.75	<1.53
Hyperglycemia (Glu, mmol/L)				
Fasted	6.11~<6.95	6.95~<13.89	13.89~<27.75	≥27.75
Non-fasting	6.44~<8.89	8.89~<13.89	13.89~<27.75	≥27.75

Test indicators	Grade 1	Grade 2	Grade 3	Grade 4
Hypoglycemia (Glu, mmol/L)	3.05~<3.55	2.22~<3.05	1.67~<2.22	<1.67

Note: ULN refers to the upper limit of the normal range.

Appendix B Table 5 Grading table for routine blood examination

Test Indicators/Grading	Grade 1	Grade 2	Grade 3	Grade 4
Increased white blood cells (WBC, 10^9/L)	11~<13	13~<15	15~<30	≥30
Leukopenia (WBC, 10^9/L)	2.000~2.499	1.500~1.999	1.000~1.499	<1.000
Lymphopenia (LY，10^9/L)	0.75~1.00	0.5~0.749	0.25~0.49	<0.25
Neutrophils decreased (ANC, 10^9/L)	0.800~1.000	0.600~0.799	0.400~0.599	<0.400
Eosinophils (Eos, 10^9/L)	0.65~1.5	1.51~5.0	>5.0	Hypereosinophilic syndrome
Thrombocytopenia (PLT, 10^9/L)	125~140	100~124	25~99	<25
Low Hemoglobin (g/dL)				
Male	10.0~10.9	9.0~<10.0	7.0~<9.0	<7.0
Female	9.5~10.4	8.5~<9.5	6.5~<8.5	<6.5

Appendix B Table 6 Grading table for routine examination of urine

Test indicators	Grade 1	Grade 2	Grade 3	Grade 4
Urine protein (PRO) (Urine dipstick test)	1+	2+	3 + or higher	NA
Urine glucose (Urine dipstick test)	Trace ~ 1 + Or ≤ 250 mg	2+ Or > 250 to ≤ 500 mg	>2+ Or＞500 mg	NA
Red blood cells (microscopic) [Number of red blood cells per high-power field (rbc/hpf) (excluding menses in females)]	6~<10	≥10	Gross hematuria with or without blood clots; or urine red blood cell cylinders; or treatment required	Emergency or hospitalization

Appendix B Table 7 Other general principles for adverse event grading

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mild: Short-term (< 48 h) or slight discomfort, no influence on activities, no treatment required	Moderate: mild or moderate limitation of motion, may require medical attention, no or mild treatment required	Severe: marked limitation of motion, Requires medical attention and treatment, may require hospitalization	Critical: May be life threatening, severely limited mobility, requires monitoring and treatment	Dead

Note: For thyroid function (T3, T4, thyrotropin) and coagulation (PT, APTT, TT, FIB), the grading can refer to Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0.

Appendix C FDA Toxicity Grading Tables for Prophylactic Vaccine Clinical Trials

The guidelines for these toxicity grading scales are designed primarily for healthy adult and adolescent volunteers.

Assessment of Severity

The intensity of AEs or SAEs will be graded by the investigator. For additional guidance, see the FDA Guidance for Industry. Criteria for grading of adverse reactions in healthy adult and adolescent volunteers included in clinical trials of prophylactic vaccines ". If no specific guidance on adverse event terms is provided, the following general approach should be followed:

- Grade 1 – Mild; it does not interfere with the subject's normal function.
- Grade 2 - Moderate; to some extent interfere with the subject's normal function.
- Grade 3 - Severe; interfere significantly with the subject's normal function.
- Grade 4 – Potentially life-threatening; life-threatening consequences requiring urgent intervention.

Please also refer to the intensity tables given in the intensity guidelines for clinical and laboratory abnormalities reported as AEs:

- Guidance Section III.A – Assessing Clinical Abnormalities (Local and Systemic)

Local reaction

Redness and swelling were measured and recorded in centimeters and then classified as none, mild, moderate, or severe according to the grading criteria in Table 1.

Test subjects assessed injection site pain as none, mild, moderate, or severe according to the grading criteria in Table 1.

Appendix C Table 1 Local reaction grading table

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Injection site pain	Does not interfere with daily activities	Interfere with daily activities	Hinder daily activities	Severe pain requiring emergency room visit or hospitalization
Redness	2.5 cm to 5.0 cm	>5.0 cm to 10.0 cm	>10 cm	Necrosis or exfoliative dermatitis
Swollen	2.5 cm to 5.0 cm	>5.0 cm to 10.0 cm	>10 cm	Necrosis

Systemic reactions

Subjects assessed vomiting, diarrhea, headache, asthenia, chills, new or worsening myalgia, and new or worsening arthralgia as none, mild, moderate, or severe according to the grading criteria in Table 2.

Appendix C Table 2 Grading scale for systemic reactions

	Mild (Grade 1)	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Vomiting	1-2 times within 24 h	> 2 times within 24 h	IV infusion required	Hypotensive shock requiring emergency room visit or hospitalization
Diarrhea	2-3 times loose stools within 24 h	4-5 times within 24 h Loose stools	> 6 loose stools within 24 h	Severe diarrhea requiring emergency room visit or hospitalization
Headache	Does not interfere with daily activities	Slight interference with usual activities	Prevents routine daily activities	Severe headache, Emergency room visit required or hospitalization
Fatigue/ asthenia	Does not interfere with daily activities	Slight interference with usual activities	Prevents routine daily activities	Severe fatigue requiring emergency room visit or hospitalization
Chills	Does not interfere with daily activities	Slight interference with usual activities	Prevents routine daily activities	Severe chills requiring emergency room visit or hospitalization
New or worseni ng myalgia	Does not interfere with daily activities	Slight interference with usual activities	Prevents routine daily activities	Severe new or worsening myalgia requiring emergency room visit or hospitalization
New or worsening arthralgia	Does not interfere with daily activities	Slight interference with usual activities	Prevents routine daily activities	Severe new or worsening joint pain requiring emergency room visit or hospitalization

Fever

Fever was defined as an oral temperature ≥ 38.0°C. Measure the temperature to 1 decimal place and classify according to the criteria in Table 3 during the analysis.

Appendix C Table 3 Fever Grading Table

	Mild (Grade 1)	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Fever	38.0-38.4°C	38.5-38.9°C	39.0-40.0°C	>40.0°C

Laboratory Abnormality

Laboratory abnormalities were graded according to the grading scheme in Table 4.

Appendix C Table 4 Laboratory abnormality grading table

Hematology	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**May be life threatening (Grade 4)**
Hemoglobin (female) -g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Change from baseline in hemoglobin (females) – g/dL	Any reduction - 1.5	1.6 – 2.0	2.1 – 5.0	>5.0
Hemoglobin (male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
Hemoglobin Change from Baseline (male) – g/dL	Any reduction - 1.5	1.6 – 2.0	2.1 – 5.0	>5.0
WBC increase - cells/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	>25,000
WBC decreased - cells/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Lymphopenia - cells/mm^3	750 – 1,000	500 – 749	250 – 499	<250
Neutropenia- cells/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	<500
Eosinophils/mm^3	650 – 1500	1501 - 5000	>5000	Hypereosinophilic

Hematology	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**May be life threatening (Grade 4)**
Thrombocytopenia – cells/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000
BIOCHEMISTRY	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**May be life threatening (Grade 4)**
BUN-mg/dL	23 – 26	27 – 31	> 31	Need for dialysis
Creatinine - mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requiring dialysis
Alkaline phosphatase - increase due to contributing factors	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN
Liver function tests - elevations of ALT, AST due to contributing factors	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
Hematology	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**May be life threatening (Grade 4)**
Bilirubin - elevations due to contributing factors accompanied by elevations in liver function tests	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	>1.75 x ULN
Bilirubin - elevation due to contributing	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN

Hematology	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**May be life threatening (Grade 4)**
factors but with normal liver function tests				

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = above upper limit of normal; WBC = white blood cell.

Appendix D Clinical Classification of COVID-19

From the latest Diagnosis and Treatment Protocol for COVID-19 (Trial Version 8)

1. Mild cases

The clinical symptoms are mild, and there are no radiological findings of pneumonia.

2. Moderate cases

Showing fever and respiratory symptoms with radiological findings of pneumonia.

3. Severe cases

Adult cases meeting any of the following criteria:

(1) Respiratory distress (≥30 breaths/ min);

(2) Oxygen saturation≤93% at rest;

(3) Arterial partial pressure of oxygen (PaO_2)/ fraction of inspired oxygen (FiO_2)≤ 300mmHg (l mmHg=0.133kPa).

In high-altitude areas (at an altitude of over 1,000 meters above the sea level), PaO_2/ FiO_2 shall be corrected by the following formula: PaO_2/FiO_2 ×[760/atmospheric pressure (mmHg)].

4. Cases with progressive severe clinical symptoms and chest imaging that shows obvious lesion progression within 24～48 hours >50% shall be managed as severe cases.

Child cases meeting any of the following criteria:

(2) Continued hyperthermia for more than 3 days

(2) Tachypnea (RR ≥ 60 breaths/min for infants aged below 2 months; RR ≥ 50 BPM for infants aged 2～12 months; RR ≥ 40 BPM for children aged 1～5 years, and RR ≥ 30 BPM for children above 5 years old) independent of fever and crying;

(3) Oxygen saturation≤93% at rest;

(4) Labored breathing (nasal fluttering, and infrasternal, supraclavicular and intercostal retraction);

(4) Lethargy and convulsion;

(5) Difficulty feeding and signs of dehydration.

4. Critical cases

Cases meeting any of the following criteria:

1. Respiratory failure and requiring mechanical ventilation;

2. Shock;

3. With other organ failure that requires ICU care.

Appendix E Severity categorization for SARS-CoV infection diseases

FDA Guidelines on COVID-19: Developing Drugs and Biological Products for Treatment or Prevention Guidance for Industry.

SARS-CoV-2 infection without symptoms:

- Positive testing by standard reverse transcription polymerase chain reaction (RT-PCR) assay or equivalent test
- No symptoms.

Mild COVID-19

- Positive testing by standard RT-PCR assay or equivalent testing
- Symptoms of mild illness with COVID-19 that could include fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, without shortness of breath or dyspnea;
- No clinical signs indicative of Moderate, Severe, or Critical Severity

Moderate COVID-19

- Positive testing by standard RT-PCR assay or equivalent testing
- Symptoms of moderate illness with COVID-19, which could include any symptom of mild illness or shortness of breath with exertion;
- Clinical signs suggestive of moderate illness with COVID-19, such as respiratory rate ≥ 20 breaths per minute, saturation of oxygen (SpO_2) > 93% on room air at sea level, heart rate ≥ 90 beats per minute
- No clinical signs indicative of Severe or Critical Illness Severity

Severe COVID-19

- Positive testing by standard RT-PCR assay or equivalent testing
- Symptoms suggestive of severe systemic illness with COVID-19, which could include any symptom of moderate illness or shortness of breath at rest, or respiratory distress
- Clinical signs indicative of severe systemic illness with COVID-19, such as respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, SpO_2 ≤ 93% on room air at sea level or PaO_2/FiO_2 < 300
- No criteria for Critical Severity

Critical COVID-19:

- Positive testing by standard RT-PCR assay or equivalent testing
- Evidence of critical illness, defined by at least one of the following:

- Respiratory failure defined based on resource utilization requiring at least one of the following:
  - Endotracheal intubation and mechanical ventilation, oxygen delivered by high-flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates > 20 L/min with fraction of delivered oxygen ≥ 0.5), noninvasive positive pressure ventilation, ECMO, or clinical diagnosis of respiratory failure (i.e., clinical need for one of the preceding therapies, but preceding therapies not able to be administered in setting of resource limitation)
- Shock (defined by systolic blood pressure < 90 mm Hg, or diastolic blood pressure < 60 mm Hg or requiring vasopressors)
- Multi-organ dysfunction/failure

NOTE: A clinical diagnosis of respiratory failure (in the setting of resource limitation) in which the management deviates from standard of care should be recorded as part of formal data collection.

Appendix F Protocol amendments

V1.1 change:

In-text location (Section)	**Before**	**After**	**Rationale**
Page header, the first page, synopsis (P2, P3, P21)	Version: V1.0 Date: 7 November 2020	Version: **V1.1** Date: 14 November 2020	Version change
Synopsis (P12)		Add： **Subjects aged between 56-85 years account for about 40% of the total subjects, which should be adjusted appropriately when necessary, to keep the proportion of the elderly population consistent with the global Phase 2 study.**	Clarify the proportion of subjects in each age stratification.
Synopsis (P12，20), main text (P45, 83)	When the first approximately 150 subjects have completed the visit 2, SRC will review the safety data (including lab tests) of these subjects	When the first approximately 150 subjects have completed the visit 2, SRC will review the safety data (including lab tests) of these subjects **and make decision if the random enrollment of remaining subjects could be continued**	Increase SRC approval for subsequent subjects after the first 150.
Synopsis (P13)	Blood samples will be collected from all subjects for SARS-COV-2 antibody screening (venous blood will be collected from the first approximately 150 subjects, fingertip blood will be collected from other subjects).	Blood samples will be collected from all subjects **at Screening Visit** for SARS-COV-2 antibody screening ~~(venous blood will be collected from the first approximately 150 subjects, fingertip blood will be collected from other subjects)~~.	Clarify the visit for SARS-COV-2 antibody screening.
Synopsis (P13), main text (P42)		Primary Efficacy, add: **The geometric mean titer (GMT) of SARS-CoV-2 serum neutralizing titers at 1 month after dose 2.**	CDE recommends the inclusion of neutralizing antibody

			GMT as the primary endpoint.
Synopsis (P17), main text (P51)		Exclusion criteria, add: **16. Fever, defined as axillary temperature ⩾37.3℃ or oral temperature.**	Clarify exclusion definition of fever.
Synopsis (P18), main text (P85)		Analysis Population, add the detailed description of the following two analysis population: • **Dose 2 evaluable immunogenicity** • **Dose 2 all-available immunogenicity**	Add the detailed description of immunogenicity analysis population
Synopsis (P19), main text (P90)		Sample Size Determination, add: [redacted]	CDE recommends a study hypothesis for the neutralizing antibodies by GMT.
Table 2 Schedule of Activities (P25), main text (P68)	At each immunization visit, the first approximately 150 subjects will stay on site for 24 h, and the other subjects will stay on site for 30 min. For the first approximately 150 subjects, For the remaining subjects, vital will performed at each on site visit, and including only body temperature.	At each immunization visit, ~~the first approximately 150 subjects will stay on site for 24 h,~~ and the other subjects will stay on site for 30 min. For the first approximately 150 subjects, For the remaining subjects **will stay on site for 30 min**, vital will performed at each on site visit, and including only body temperature.	Modify according to actual clinical practice.
Main text *9.1.6.3 Immunogenicity Assessments* (P61)		Add: **detailed description of the neutralizing antibody detection method.**	CDE recommends detailed description of the neutralizing antibody detection.

Main text 9.1.8 Reproductive Inclusion Criteria and Contraceptive Guidelines *(*P62)	Male subjects were eligible if they agreed to meet the following requirements during the vaccination period and for at least 28 days after vaccination	Male subjects were eligible if they agreed to meet the following requirements during the vaccination period and for **1 year** ~~at least 28 days~~ after vaccination	Consistent with the time requirements of exclusion criteria no.7
Main text 13.1.4 Immunogenicity Analysis (P86)		Primary Immunogenicity Analysis, add: **GMT will be summarized by group and compared for the treatment differences. 95% CI will be provided. Primary analysis will be performed, when all randomized subjects complete 1-month visit.**	Due to change of primary endpoint.
Main text 13.2 Statistical Analysis Time Points (P89)	Initial analysis: safety and immunogenicity data at 1 month after the 2nd dose. Analysis of safety and immunogenicity data at 6, 12 months after the 2nd dose, updated statistical analysis will be performed.	Initial analysis: safety and immunogenicity data at 1 month after the 2nd dose. ~~Analysis of safety and immunogenicity data at 6, 12 months after the 2nd dose, updated statistical analysis will be performed.~~	Change the text to be more accurate.
Main text 13.3 Statistical Hypotheses (P89)		Add: **detailed description of the statistical hypotheses.**	CDE recommends detailed description of the statistical hypotheses.

V1.2 change:

In-text location (Section)	**Before**	**After**	**Rationale**
Page header, the first page, synopsis (P2, P3, P21)	Version: V1.1 Date: 14 November 2020	Version: **V1.2** Date: 26 November 2020	Version change

Main text 13.1.5 Safety Analysis (P74)	The number and percentage of SAEs from Dose 1 to 6 months after Dose 2 will be provided for the BNT162b2 group and placebo group.	The number and percentage of SAEs from Dose 1 to 6 months **and 12 months** after Dose 2 will be provided for the BNT162b2 group and placebo group.	Adjust the time for the safety analysis based on the SAE collection.

V1.3 change:

In-text location (Section)	**Before**	**After**	**Rationale**
Page header, the first page, synopsis (P2, P3, P21)	Version: V1.2 Date: 26 November 2020	Version: **V1.3** Date: 8 December2020	Version change
Synopsis (P13), table 2, main text (P27, 59, 61, 67, 70)		Add：**Blood samples from about 80 subjects will be collected at visit 1 (before the first dose inoculation) and visit 5 for the comparative study of neutralization ability of epidemic strains.**	Add the comparative study of neutralization ability of epidemic strains.
Synopsis (P15), main text (P44, 89)		Add： **The comparative study of neutralization ability of epidemic strains.**	Add the comparative study of neutralization ability of epidemic strains.
Main text (P54, 69)	Visit 5 (Day 22)	Visit **4** (Day 22)	Typo erro
Main text (P27)	90.5 mL	**92.5** mL	Typo erro

V1.4 change:

In-text location (Section)	**Before**	**After**	**Rationale**

Page header, the first page, synopsis (P2, P3, P21)	Version: V1.3 Date: 8 December2020	Version: **V1.4** Date: **21 June 2021**	Version change
Synopsis (P20)	Unblinding will be carried out before the initial analysis is conducted.	**Unblinding will be carried out for the initial analysis, but the subjects will remain blinded throughout the study.**	Describe the maintenance of the subjects' blindness clearly.
Synopsis (P12), main text (P45)		Add: **If BNT162b2 is approved by Chinese regulatory authority and the vaccine is available in the region, subjects may request to be unblinded after the 6 months visit after Dose 2 (Visit 7) on an individual basis. Subjects, who based on unblinding have got placebo within BNT 162-06 study, will be withdrawn from the study and will have the opportunity to be vaccinated with BNT162b2 or with other available on market vaccine via the government program. Subjects who receive BNT162b2 vaccination will enter the post-marketing safety observation.**	Subjects who were initially given a placebo may have the opportunity to receive BNT162b2.
Table 2 Schedule of Activities (P26)		Add: **All SAEs will be collected throughout the study, and only the AEs related to the study vaccine will be reported after Visit 6 (1 month post Dose 2).**	Clarify SAEs and AEs reporting period and categories.
Table 2 Schedule of Activities (P22, P27)	154~168	**175~189**	Recalculate the time window of Visit 7 (6 months post the Dose 2) accurately.
Main text (P77)	AEs and SAEs reported by	**After 1 month and till 12 moths post 2nd dose only the IMP**	Clarify SAEs and AEs

	the subjects after 1 month post the 2nd dose, should also be collected. AEs leading to withdrawal or discontinuation will be collected throughout the trial.	**related AEs need to be reported. All SAE and AEs leading to withdrawal or discontinuation will be collected throughout the trial.**	reporting period and categories.
Main text (P20, 21, 49, 83)	the sponsor	**the Fosun Pharma**	Revised when a task or responsibility is assigned to the Fosun Pharma.

V1.5 change:

In-text location (Section)	**Before**	**After**	**Rationale**
Page header, the first page, synopsis (P2, P3, P21)	Version: V1.4 Date: 21 June 2021	Version: **V1.5** Date: **23 July 2021**	Version change
Synopsis (P13), table 2 (P26, 27), main text (P59)		Add: **For these subjects, immunogenic blood samples collected at Visit 6 will also be used for the cross neutralization protection study against SARS-COV-2 epidemic strains to evaluate the neutralization ability of BNT162b2 against circulating epidemic strains at the additional time point of 1 month post Dose 2.**	To further explore the neutralization ability of BNT162b2 against epidemic strains

15.0 References

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