FOSUN PHARMA
Innovation for Good Health

Clinical Protocol

Safety and Immunogenicity of SARS-CoV-2 mRNA Vaccine (BNT162b1) in Chinese Healthy Subjects: A Phase I, Randomized, Placebo-controlled, Observer-blind Study

Protocol No.: BNT162-03

Clinical Phase: Phase I

Authorized Representative (Signature)

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Signed by: _____ Date: _____

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Execution Organization

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Sponsor

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Germany

Version: Protocol Amendment 3-Version 3.0

Date: 5 AUG 2020

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

Confidentiality Statement

The information in this document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by applicable law or regulations. In any event, persons to whom the information is disclosed must be informed that the information is *privileged* or *confidential* and may not be further disclosed by them. These restrictions on disclosure will apply equally to *all* future information supplied to you that is indicated as privileged or *confidential*.

Confidential

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

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

The Fosun will provide investigators with site-specific emergency medical contact information cards to be carried by each subject.

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

Table 1 Contact information

Issue	Contact
Serious adverse event and pregnancy reporting	Fosun Pharma [redacted] Telephone numbers for serious adverse event and pregnancy reporting will be provided to the site
Medical Monitor (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 No. and Version No.	Valid Range
Initial version	20 APR 2020	BNT162-03-CN, Version 1.0	China
Initial submitted version	20 MAY 2020	BNT162-03, Version 1.0	China
Amendment 1	10 JUL 2020	BNT162-03, Version 2.0	China
Amendment 2	26 JUL 2020	BNT162-03, Version 2.1	China
Amendment 3	5 AUG 2020	BNT162-03, Version 3.0	China

1.3 Approval

Signature Page for Investigator

We have read this clinical study protocol, protocol number: BNT162-03, version number: V3.0 (version date AUG 5, 2020). I agree to perform relevant duties in accordance with Chinese laws, *Declaration of Helsinki*, NMPA GCP and this study protocol. This study can only be carried out after obtaining the approval from the ethics committee.

During the implementation of the study, I will strictly follow the requirements of this protocol. In case of need to modify this protocol, it can only be implemented after notification to the Fosun for agreement and the approval or filing agreement of the ethics committee, unless measures that must be taken to protect the safety, rights, and interests of the subjects.

I will provide copies of this protocol to all the study personnel participating in this study under my responsibility, and discuss the protocol and related information with them to ensure that they fully understand the investigational vacccine and how to conduct this study.

I will keep this protocol and related content confidential.

Clinical study institution: **Jiangsu Provincial Center for Disease Control and Prevention**

Principal investigator (printing): [redacted]

(Signature): _____ Date of signature: _____

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2.0 TRIAL SUMMARY

BioNTech RNA Pharmaceuticals GmbH An der Goldgrube 12, 55131 Mainz, Germany	**Product Name:** SARS-CoV-2 mRNA Vaccine (BNT162b1)
Trial Title: Safety and Immunogenicity of SARS-CoV-2 mRNA Vaccine (BNT162b1) in Chinese Healthy Subjects: A Phase I, Randomized, Placebo-controlled, Observer-blind Study	
IND No.: 2020L00032/ 2020L00033	**EudraCT No.:** NA
Study Identifier: BNT162-03 **Phase:** I	**Trial Blinding Schema:** 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 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 attacks of autoimmunity on pulmonary alveoli. Since the beginning of these outbreaks and up to mid-May 2020, there has been more than 4,580,000 confirmed COVID-19 associated with SARS-CoV-2 infection with over 310,000 deaths in over 200 countries, areas, or territories worldwide. [4]

SARS-CoV-2 is a respiratory virus that can cause disease of the respiratory system. 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 supportive and focuses on symptoms. The main recommendations to prevent outbreaks are through social distancing (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 the

virus has not yet been epidemic. 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 (BNT162b1), 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.

Two Phase I/II clinical studies of BNT162b1 are currently being conducted in Germany and the United States; at the same time, the 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 efficacy and safety of BNT162b1 at animal level and human body level. Interim Report of the United States Phase I/II clinical study has been published. Results of data analyses for pre-clinical studies and clinical studies will be provided by continuously updating in the Investigator's Brochure (IB). The clinical studies conducted in Germany and the United States are first-in-human trials, so dose escalation mode is adopted and sentinel subjects are added for both. The maximum dose examined in these two studies is 100μg, and the safety result shows that the local reaction of vaccination site and systemic event 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 booster 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. Above results will support the further evaluation of the mRNA candidate vaccine. Currently, the optimal dose range is predicted as 10~30 μg according to safety and efficacy data of foreign subjects. Since the preliminary safety and immunology data are obtained, and clinical studies conducted in Germany and the United States will continue to support studies in China, so China plans to conduct bridging trial to confirm foreign study results among Chinese subjects.

BNT162-03 is a phase I, dose confirmation study in China, which adopts a parallel two-dose cohort design in adult healthy subjects (adult group) and elderly healthy subjects (senior group); and the trial in adult group is conducted firstly and followed by the trial in the elderly group. And the study is intended to confirm that the response (safety/immunogenicity) seen in foreign subjects is comparable to that in Chinese subjects. Healthy adults who are ≥18 years old and ≤55 years old will be enrolled in the adult group and healthy elderly subjects who are ≥65 years old and ≤85 years old will be enrolled in the elderly group. To ensure the enrollment of healthy subjects, screening tests (hematology, biochemistry, and urinalysis) will be performed prior to vaccine/placebo vaccination. In each age group of subjects, the trial will be conducted by the parallel two-dose and placebo cohort allocation. The design of this study, including the selection of two optimal dose levels referred to the safety and immunogenicity data from the ongoing or completed foreign studies of BNT162b1. In this study, a Safety Review Committee (SRC) will be comprised of investigators, Fosun medical representative and medical monitor, and SRC will review the safety data in a blinded manner. SRC will review the available safety and tolerability data of all subjects in a dose cohort (including at least safety laboratory test results and safety events collected from diary cards within 14 days after the prime vaccination) before starting the boost vaccination for each cohort to suggest whether the boost vaccination of BNT162b1 vaccine can be conducted. 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 a significant event or risk occurs in the study that might cause the study to be suspended.

Due to the ongoing threat of SARS-CoV-2 disease and the urgent need of a vaccine, this study will be accelerated to assess the bridging data for BNT162b1, in addition to confirm that the response (safety/immunogenicity) seen in foreign subjects is comparable to that observed in Chinese subjects.

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 trial is justified. 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 receive two doses of either SARS-CoV-2 vaccine (BNT162b1) or placebo intramuscularly (IM) on Day 1 and on Day 22. The objective of the study BNT162-03 is to assess the safety and immunogenicity of BNT162b1 in the Chinese healthy subjects.

The primary rationale for selection of the vaccine dose levels can be summarized as follows:

Based on the clinical data from the overseas clinical studies, and the non-clinical data of the RNA components (modRNA), with other liposomes or in conjunction with the lipid nanoparticles as will be tested clinically in this trial, we expect that doses in the 1 to 5 μg range will be immunogenic and induce neutralizing antibodies. The dose range of 1~100 μg has been identified in foreign subjects, based on safety and efficacy data. Accordingly, a degree of reactogenicity is anticipated with BNT162b1 with mild or moderate local or systemic reactions common amongst subjects.

Two predicted optimal doses are selected according to the safety and immunogenicity data of global clinical trials in Germany and the United States as available at present to confirm the comparability of safety and efficacy for BNT162b1 in China.

- The low-dose level (10 μg);
- The high-dose level (30 μg);

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 I, randomized, placebo-controlled, observer-blind, safety and immunogenicity study of SARS-CoV-2 mRNA vaccine (BNT162b1) in Chinese healthy subjects. After randomization, the trial for each subject will last for approximately 12 months. Screening period is 2 weeks prior to randomization (Day -14 to Day 0), and each dose of either SARS-CoV-2 vaccine (BNT162b1) or placebo will be given intramuscularly (IM) on Day 1 and on Day 22. After each age group completes the follow-up 28 days after boost vaccination (Day 50), initial analysis will be conducted.

Subjects who are ≥18 years old and ≤ 55 years old will be enrolled in adult group, and healthy elderly subjects who are ≥65 years old and ≤85 years old will be enrolled in elderly group. Approximately 72 subjects for each age group will be allocated to three cohorts (BNT162b1 high-, low-dose groups and placebo group) in parallel, with approximately 24 subjects at each BNT162b1 dose level, including 24 placebo group subjects, the subjects will be randomized in a 1:1:1 ratio.

After the 14-day safety observation post the prime vaccination of the subjects in adult group, the prime vaccination for the subjects in the elderly group will start. SRC will review the available safety and tolerability data of all subjects in a cohort (including safety observation 14 days after the prime vaccination for all subjects in this cohort) before starting the boost vaccination for each cohort, to decide whether the BNT162b1 vaccine can be boosted.

For dose allocation design, see schematic diagram in **Figure 1**. For the planned assessments and visits, see schedule of activities in **Table 2**.

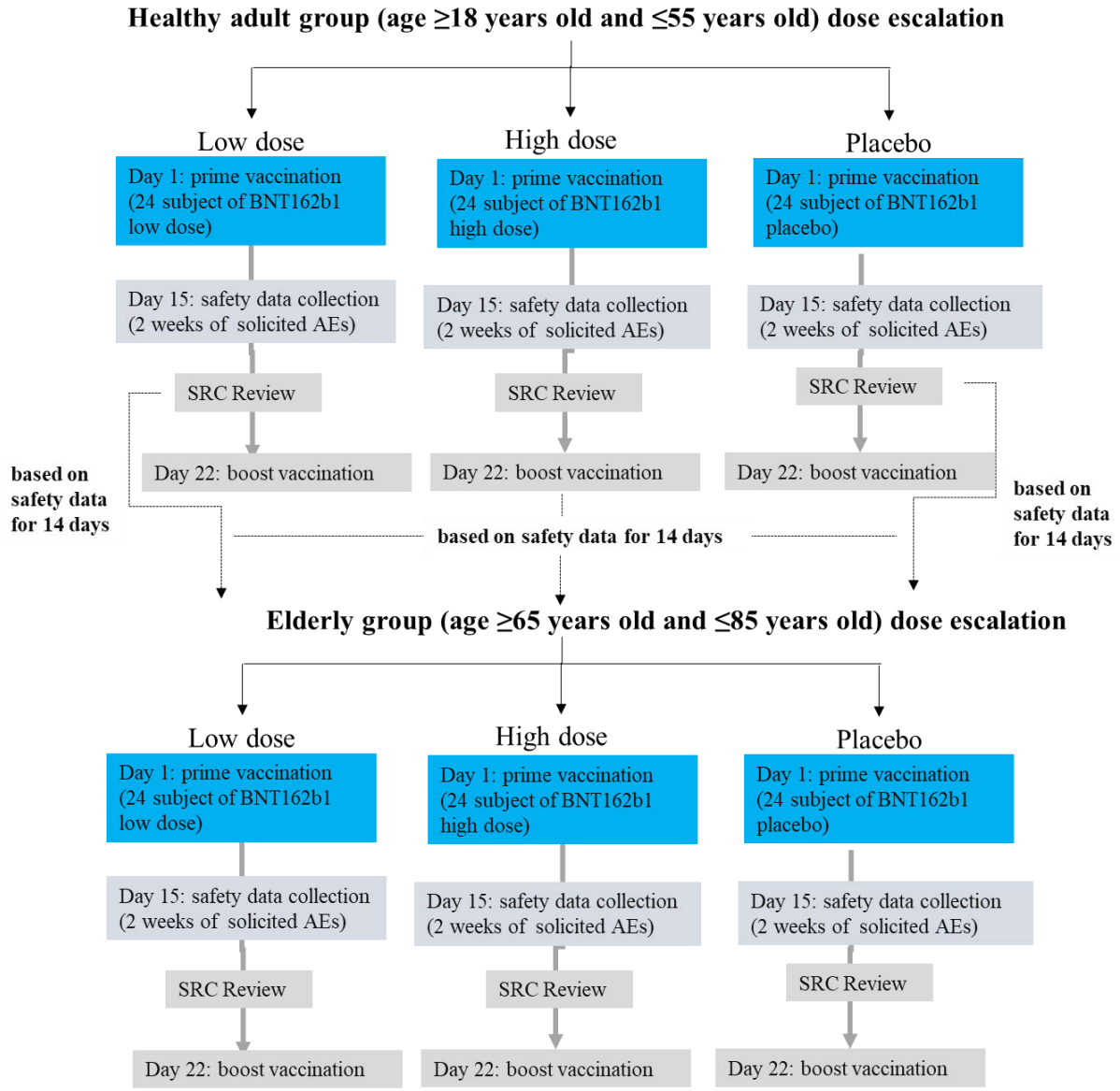

Figure 1 Schematic diagram of dose parallel design

Subjects enrollment and dose cohorts:

The study will be aimed at enrolling SARS-CoV-2 naïve subjects. All subjects who sign the informed consent form (ICF) and have confirmed basic eligibility at Screening will be tested for SARS-CoV-2 antibodies (qualitative), virus nucleic acid and chest computed tomography (CT). Within 2 weeks after the screening visit, naïve subjects selected in each cohort at Screening will be randomized at visit 1.

The study will follow a parallel dose cohort design, as shown in **Figure 1**.

The enrollment process of subjects in adult group is as follows:

- The planned low-dose cohort, high-dose cohort and placebo group. 72 subjects will be randomized in a 1:1:1 ratio to inject BNT162b1 or placebo on Day 1.
- If the SRC considers that the subjects are safe with good tolerance after 14 days of observation, boost vaccination will be conducted on Day 22.
- When the subjects in the adult group completed safety visits up to 14 days post prime vaccination, the available safety data for all subjects were summarized. If approved by the SRC,
  - The planned dose cohorts of elderly group will be initiated (see **Figure 1**).
    The data assessed by the SRC comprises: vital signs, TEAEs, local reactions, blood/clinical laboratory data and brief physical examination outcome.
  - The parallel dose cohort study is conducted in the elderly group with consistent methods as those in the adult group (see **Figure 1**).

Vaccination protocol and visit schedule

Each randomized subject will be given two doses of either BNT162b1 (10 or 30 μg) or placebo intramuscularly (IM) – one vaccination at Visit 1 (on Day 1) and one vaccination at Visit 5 (on Day 22), into one third of the deltoid muscle, preferably in the non-dominant arm.

From the treatment randomization, each subject will be required to attend 12 clinical visits:

All immunized subjects will attend Visit 1 (prime vaccination) on Day 1, Visit 2 on Day 2 (24 hours after prime vaccination), Visit 3 on Day 8 (7 days after prime vaccination), Visit 4 on Day 15 (14 days after prime vaccination), Visit 5 on Day 22 (boost vaccination), Visit 6 on Day 29 (7 days after boost vaccination), Visit 7 on Day 36 (14 days after boost vaccination), Visit 8 on Day 43 (21 days after boost vaccination), Visit 9 on Day 50 (28 days after boost vaccination), Visit 10 at Month 3, Visit 11 at Month 6 and Visit 12 at Month 12.

Blood samples of subjects in adult group will be collected at the following visits for different tests: at Screening Visit (Visit 0) for eligibility screening tests (including clinical laboratory), at Visits 2, 3, 6 for routine safety laboratory testing (visits 2, 6 coagulation function test, visit 2, 6, 11 thyroid function test), at Visit 1 (prior to prime vaccination) and Visits 5 (prior to boost vaccination), 6, 8, 10, 11, 12 for humoral immunity (antibody). Blood sample will be collected at Visit 1 (prior to prime vaccination) and Visits 6, 8, 11 for cell-mediated immunity (CMI). Urine samples will be collected at Screening Visit (Visit 0) for eligibility screening and collected at Visits 2, 3, 6 for regular safety laboratory testing; serum samples of women of childbearing potential will be collected at Screening Visits (Visit 0) and Visit 5 (prior to boost vaccination) for pregnancy test. Fingertip blood will be collected during the screening visit (visit 0) for detection of SARS-CoV-2 antibody and HIV antibody.

Blood samples of subjects in elderly group will be collected at the following site visit for different tests: at Screening Visit (Visit 0) for eligibility screening tests (including clinical laboratory), at Visits 2, 3, 6 for regular safety laboratory testing, at Visit 1 (prior to prime vaccination) and Visit 5 (prior to boost vaccination), 6, 8, 11, 12 for humoral immunity (antibody). Blood sample will be collected at Visit 1 (prior to prime vaccination) and Visit 6 for cell-mediated immunity (CMI). Urine samples will be collected at Screening Visit (Visit 0) for eligibility screening and collected at Visits 2, 3, 6 for regular safety laboratory testing; serum samples of women

of childbearing potential will be collected at Screening Visits (Visit 0) and Visit 5 for pregnancy test. Fingertip blood will be collected during the screening visit (visit 0) for detection of SARS-CoV-2 antibody and HIV antibody.

Each subject will receive diary cards to collect solicited reaction for 14 days after each vaccination (including the days of vaccine/placebo vaccination), and unsolicited AE for 21 days after prime vaccination and 28 days after boost vaccination (including the days of vaccine/placebo vaccination). Additional safety assessments will include vaccine related adverse events (AEs) collection for the rest of the entire trial.

Primary objective

- To evaluate the safety and tolerability profiles of BNT162b1 prime/boost (P/B) immunization given 21 days apart from different doses in SARS-CoV-2 naïve Chinese healthy subjects through 28 days after boost vaccination.

Secondary objectives

- To observe the immunogenicity (anti-S1 and anti-RBD IgG antibody) of two doses of BNT162b1 given 21 days apart measured by enzyme-linked immunosorbent assay (ELISA).
- To observe the immunoreactivity of healthy subjects after BNT162b1 P/B immunization by the true virus-based SARS-CoV-2 neutralizing antibody assay.
- To observe the safety of BNT162b1 vaccination in Chinese healthy subjects until the end of the study.
- To conduct 12-month follow-up for healthy subjects in the BNT162b1 vaccination dose cohorts, and observe the sustainability of the immune response to BNT162b1.

Exploratory objective

[redacted]

Subject subjects:

Healthy subjects: SARS-CoV-2 naïve

Planned age range: Adults (age ≥18 and ≤55 years old) and elderly (age ≥65 years old and ≤85 years old)

Planned subjects: a total of 144 subjects will be randomized, including approximately 72 in each of 2 age groups (including 2 dose cohorts and 1 placebo group, 24 in each group).

Planned number of cohorts:

Subjects will be allocated to receive 2 BNT162b1 dose cohorts or placebo group (in each group: n=24 subjects).

- Cohort 1: BNT162b1 low-dose;
- Cohort 2: BNT162b1 high-dose;
- Cohort 3: placebo.

For adult subjects (age ≥18 and ≤55)

Inclusion criteria:

1. Male or female subjects of ⩾18 years old and ⩽55 years old with body mass index (BMI) ⩾18 and ⩽30 at the Screening Visit.

2. Individuals who are in good health condition at the time of entry into the trial as determined by medical history, physical examination (including vital signs, ECG) and eligibility screening test (hematology, blood chemistry and urine analysis) and clinical judgment of the investigator at Screening Visit.
3. The subject can provide with informed consent and signs and dates a written informed consent form (ICF) prior to the initiation of any trial procedures.
4. They must be able to understand and follow trial-related instructions.
5. They must be willing and able to comply with planned visits, treatment schedule, laboratory tests and other requirements of the trial.
6. Negative in antibodies screening of SARS-CoV-2 (fingerstick).
7. Normal in chest CT scans (no imaging features of COVID-19).
8. Axillary temperature$\leqslant$37.0^{o} C.
9. Negative SARS-CoV-2 test in throat swabs by RT-PCR.
10. Women of childbearing potential (WOCBP) must have a negative beta-human chorionic gonadotropin (β-hCG) in serum sample at Screening Visit. Women that are postmenopausal (Menopause$\geqslant$12 consecutive months) or permanently sterilized will be considered as not having reproductive potential.
11. WOCBP must have used effective contraception 14 days prior to screening and agree to use effective contraception continuously during the trial period, from 14 days prior to Screening Visit to 60 days after the last immunization.
12. WOCBP must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during trial, starting from Screening Visit and continuously until 60 days after be given the last immunization.
13. Men who are sexually active with a WOCBP and have not had a vasectomy must agree to practice a effective form of contraception with their female partner of childbearing potential during the trial, starting from Screening Visit and continuously until 60 days after be given the last immunization.
14. Men must be willing to refrain from sperm donation, starting from Screening Visit and continuously until 60 days after receiving the last immunization.

Exclusion criteria:

1. Have had any acute illness, as determined by the investigator, with or without fever, within 72 h prior to the prime vaccination. An acute illness which is nearly resolved with only minor residual symptoms remaining is allowable if, in the opinion of the investigator, the residual symptoms will not compromise their well-being if they participate as trial subjects in the trial, or that could prevent, limit, or confound the protocol-specified assessments.
2. Are breastfeeding on the day of Screening Visit or who plan to breastfeed during the trial, starting from Screening Visit and continuously until at least 90 days after the last immunization. Women or partners who plan to become pregnant within 1 year post the screening visit.
3. Have a known allergy, hypersensitivity, or intolerance to the planned vaccine for trial including any excipients.
4. Used to have a history of hypersensitivity or serious reactions to vaccination.
5. Received any vaccination within 4 weeks prior to Visit 1.
6. Don't agree to not be vaccinated during the trial, starting from Screening Visit and continuously until 28 days after receiving the last immunization, except emergency vaccination (e.g. rabies vaccine, tetanus vaccine).
7. Had any medical condition (e.g., autoimmune disease) or any major surgery (e.g., requiring general

anesthesia) within the past 5 years, which in the opinion of the investigator, could compromise their well-being if they participate as trial subjects in the trial, or that could prevent, limit, or confound the protocol-specified assessments.

8. Have any surgery planned during the trial, starting from Screening Visit and continuously until at least 90 days after the last immunization.
9. Had any chronic use (more than 14 continuous days) of any systemic medications that affects immune function, including immunosuppressant or other immune-modifying drugs, within 6 months prior to Screening Visit unless in the opinion of the investigator, the medication would not prevent, limit, or confound the protocol-specified assessments or could compromise safety of subjects.
10. Had administration of any immunoglobulins and/or any blood products within the 3 months prior to Screening Visit.
11. Had administration of another investigational product including vaccines within 60 days or 5 half-lives (whichever is longer), prior to Screening Visit.
12. With known history of AIDS or HIV test positive.
13. History of HBV or HCV infection, through medical inquiry.
14. History of SARS, SARS-CoV-2 or MERS infection. Suspected SARS patients should be screened for SARS antibodies.
15. Previously participated in a clinical trial involving lipid nanoparticles.
16. Are subject to exclusion periods of other clinical trials or simultaneous participation in another clinical trial.
17. Have any affiliation with the study site (e.g., are close relative of the investigator or dependent person, such as an employee or student of the study site).
18. Have a history of drug abuse or known medical, psychological, or social conditions within the past 5 years. In the opinion of the investigator, could comprise their well-being if they participate as trial subjects in the trial, or that could prevent, limit, or confound the protocol-specified assessments.
19. Have a history of narcolepsy.
20. Have history of alcohol abuse or drug addiction within 1 year prior to Screening Visit.
21. Have a history of or suspected immunosuppressive condition, acquired or congenital, as determined by medical history and/or physical examination at Screening Visit.
22. Have any abnormality or permanent body art (e.g., tattoo), in the opinion of the investigator, would obstruct the ability to observe local reactions at the vaccination site.
23. Have had any blood loss >400 mL, e.g., due to donation of blood or blood products or injury, within the 28 days prior to Screening Visit or plan to donate blood or plasma during the trial, starting from Screening Visit and continuously until at least 28 days after be given the last immunization.
24. 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.
25. They plan to visit any country or region with a high SARS-CoV-2 infection risk (as defined at Screening Visit), from Screening Visit until 14 days after be given the last immunization.
26. Symptoms of COVID-19, e.g., respiratory symptoms, fever, cough, shortness of breath and breathing difficulties.
27. Have had contact with confirmed COVID-19 patients or persons tested positive for SARS-CoV-2 within the 30 days prior to Screening Visit.

28. Are vulnerable persons, e.g., soldiers, subjects in detention, CRO or Fosun staffs or their family members.

For the elderly subjects (age ≥65 years old and ≤85 years old)

Inclusion criteria:

1. Male or female subjects ≥65 years old and ≤85 years old at Screening Visit.
2. Individuals who are in a health condition that can receive the investigational vaccine, at the time of entry into the trial as determined by medical history, physical examination (including vital signs, ECG) and eligibility screening tests (hematology, biochemistry and urinalysis) and clinical judgment of the investigator at Screening Visit.
3. The subject can provide with informed consent and signs and dates a written informed consent form (ICF) prior to the initiation of any trial procedures.
4. They must be able to understand and follow trial-related instructions.
5. They must be willing and able to comply with planned visits, treatment schedule, laboratory tests and other requirements of the trial.
6. Negative in antibodies screening of SARS-CoV-2 (blood samples from fingertip).
7. No imaging features of COVID-19 in chest CT.
8. Axillary temperature≤37.0^{o} C.
9. Negative SARS-CoV-2 test in throat swabs by RT-PCR.
10. Women of childbearing potential (WOCBP) must have a negative serum β-hCG at Screening Visit. Women that are postmenopausal (Menopause⩾12 consecutive months) or permanently sterilized will be considered as not having reproductive potential.
11. WOCBP must have used effective contraception 14 days prior to screening and agree to use effective contraception continuously during the trial period, from 14 days prior to Screening Visit to 60 days after the last immunization.
12. WOCBP must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during trial, starting from Screening Visit and continuously until 60 days after be given the last immunization.
13. Men who are sexually active with a WOCBP and have not had a vasectomy must agree to practice a effective form of contraception with their female partner of childbearing potential during the trial, starting from Screening Visit and continuously until 60 days after be given the last immunization.
14. Men must be willing to refrain from sperm donation, starting from Screening Visit and continuously until 60 days after receiving the last immunization.

Exclusion criteria:

1. Baseline laboratory abnormalities with Grade ≥3 (for hematology abnormalities with Grade ≥2, according to the grading criteria in appendix B) during screening visits, by physical examination and eligibility screening.
2. Have had any acute illness, as determined by the investigator, with or without fever, within 72 h prior to the prime vaccination. An acute illness which is nearly resolved with only minor residual symptoms remaining is allowable if, in the opinion of the investigator, the residual symptoms will not compromise their well-being if they participate as trial subjects in the trial, or that will not prevent, limit, or confound the protocol-specified assessments.
3. Have a known allergy, hypersensitivity, or intolerance to the planned vaccine for trial including any excipients.

4. Used to have a history of hypersensitivity or serious reactions to vaccination.
5. Received any vaccination within 4 weeks prior to Visit 1.
6. Don't agree to not be vaccinated during the trial, starting from Screening Visit and continuously until 28 days after receiving the last immunization, except emergency vaccination (e.g. rabies vaccine, tetanus vaccine).
7. Had administration of any immunoglobulins and/or any blood products within the 3 months prior to Screening Visit.
8. Had any serious or life-threatening medical condition (e.g., autoimmune disease, cardiovascular disease) within the past 5 years, which in the opinion of the investigator, could compromise their well-being if they participate as trial subjects in the trial, or that could prevent, limit, or confound the protocol-specified assessments.
9. Have any surgery planned during the trial, starting from Screening Visit and continuously until at least 90 days after the last immunization.
10. Had any chronic use (more than 14 continuous days) of any systemic medications that affects immune function, including immunosuppressant or other immune-modifying drugs, within 6 months prior to Screening Visit unless in the opinion of the investigator, the medication would not prevent, limit, or confound the protocol-specified assessments or could compromise safety of subjects.
11. Had administration of another investigational product including vaccines within 60 days or 5 half-lives (whichever is longer), prior to Screening Visit.
12. With known history of AIDS or HIV test positive.
13. History of HBV or HCV infection.
14. History of SARS, SARS-CoV-2 or MERS infection. Suspected SARS patients should be screened for SARS antibodies.
15. Previously participated in a clinical trial involving lipid nanoparticles.
16. Are subject to exclusion periods of other clinical trials or simultaneous participation in another clinical trial.
17. Have any affiliation with the study site (e.g., are close relative of the investigator or dependent person, such as an employee or student of the study site).
18. Have a history of drug abuse or known medical, psychological, or social conditions within the past 5 years. In the opinion of the investigator, could comprise their well-being if they participate as trial subjects in the trial, or that could prevent, limit, or confound the protocol-specified assessments.
19. Have a history of narcolepsy.
20. Have history of alcohol abuse or drug addiction within 1 year prior to Screening Visit.
21. Have a history of or suspected immunosuppressive condition, acquired or congenital, as determined by medical history and/or physical examination at Screening Visit.
22. Have any abnormality or permanent body art (e.g., tattoo), in the opinion of the investigator, would obstruct the ability to observe local reactions at the vaccination site.
23. Have had any blood loss >400 mL, e.g., due to donation of blood or blood products or injury, within the 28 days prior to Screening Visit or plan to donate blood or plasma during the trial, starting from Screening Visit and continuously until at least 28 days after be given the last immunization.
24. 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.
25. They plan to visit any country or region with a high SARS-CoV-2 infection risk (as defined at Screening

Visit), from Screening Visit until 14 days after be given the last immunization.

26. Symptoms of COVID-19, e.g., respiratory symptoms, fever, cough, shortness of breath and breathing difficulties.
27. Have had contact with confirmed COVID-19 patients or persons tested positive for SARS-CoV-2 within the 30 days prior to Screening Visit.
28. Are vulnerable persons, e.g., soldiers, subjects in detention, CRO or Fosun staffs or their family members.

Trial Vaccines:

Investigational Vaccine:

The 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. For dispensing and operation protocol, see Pharmacy Manual.

Frequency of vaccination:	Two injections (21 days apart).
Route of vaccination:	Intramuscular (IM); upper arm, musculus deltoideus; the P/B regimens. The same arm may be used for both immunizations. The non-dominant arm is preferred.

Placebo:

NaCl 0.9% solution is being used as placebo. It is a sterile, clear, colorless liquid solution of sodium chloride without preservative designed for parenteral use only. Placebos are commercially packaged and stored according to the labeling. The placebo is vaccinated by IM at 21-day intervals.

Duration of the trial/Evaluation period:

Approximately 12 months (after screening period).

Primary endpoints

Safety and tolerability of BNT162b1, as determined by:

- Occurrence of solicited local reactions in the subjects (eg, vaccination sites: pain/tenderness, erythema/redness, induration/swelling) during the 14-day after each dose of BNT162b1 or placebo.
- Occurrence of solicited systematic reactions (eg, nausea, vomiting, diarrhea, headache, fatigue, myalgia, arthralgia, chills, loss of appetite, malaise and fever) during 14-day after each dose of BNT162b1 or placebo.
- Occurrence of AE associated with vaccination in subjects during the 21-day period after prime vaccination and the 28-day period after boost dose of BNT162b1 or placebo.

Secondary endpoints

Safety and tolerability of BNT162b1, as determined by:

- The proportion of subjects experiencing SAEs, occuring up to Day 21 after prime vaccination and Day 28 after boost vaccination, up to Month 3, 6 and 12.
- The proportion of subjects experiencing AE associated with BNT162b1, occuring up to Month 3, 6 and 12.
- The proportion of of subjects experiencing abnormal markers of hematology, blood chemistry and urine analysis, occuring at Hour 24 and Day 7 after prime vaccination and at Day 7 after boost dose of BNT162b1 or placebo.

Immunogenicity of BNT162b1, as determined by:

- Geometric mean titer (GMT) of anti-S1 IgG antibody at Day 7, Day 21 after prime vaccination, at Day 7, Day 21 after boost vaccination, and at Month 3, 6 and 12.

- Geometric mean titer (GMT) of anti-RBD IgG antibody at Day 7, Day 21 after prime vaccination, at Day 7, Day 21 after boost vaccination, and at Month 3, 6 and 12.
- GMT of SARS-CoV-2 neutralizing antibody (including true virus-based SARS-CoV-2 neutralizing antibody assay) at Day 7, Day 21 after prime vaccination, at Day 7, Day 21 after boost vaccination, and at Month 3, 6 and 12.
- Fold increase in antibody anti-S1 IgG antibody titers, as compared to baseline, at Day 7, Day 21 after prime vaccination, at Day 7, Day 21 after boost vaccination, and at Month 3, 6 and 12.
- Fold increase in antibody anti-RBD IgG antibody titers, as compared to baseline, at Day 7, Day 21 after prime vaccination, at Day 7, Day 21 after boost vaccination, and at Month 3, 6 and 12.
- Fold increase in SARS-CoV-2 neutralizing antibody titers (virus neutralizing test), as compared to baseline, at Day 7, Day 21 after prime vaccination, at Day 7, Day 21 after boost vaccination, and at Month 3, 6 and 12.
- Seroconversion rates (SCR), defined as a minimum of 4-fold increase of antibody titers, as compared to baseline, at Day 7, Day 21 after prime vaccination, and at Day 7, Day 21 after boost vaccination.

Exploratory endpoints

- [redacted]

Statistical Considerations:

Analysis sets:

- *Safety Set*: Safety Set will consist of all randomized subjects who receive at least one dose of the investigational vaccine/placebo and at least one safety evaluation.
- *Total Vaccinated Cohort (TVC)*: According to intention-to-treat analysis set principle, the TCV will include all randomized subjects who have received at least one dose of the investigational vaccine/placebo and provided valid baseline.
- *Per protocol set (PPS)*: The PPS will include all subjects in the TVC who have no major protocol violations and complete boost vaccination. The protocol violation criteria will be defined as part of the blinded data review. The categories of major protocol violations include:
  1 not meeting inclusion criteria, or meeting exclusion criteria,
  2 receiving a wrong investigational vaccine/placebo,
  3 receiving prohibited therapies,
  4 other major protocol violations that be identified during blinded data reviews.

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

The primary immunogenicity endpoint analyses will be based on the PPS and TVC, and additional immunogenicity endpoint analyses will be based on the TVC.

Demographics and other baseline characteristic analysis: Summaries of age, gender, race, and other baseline characteristics will be presented by groups of BNT162b1 and placebo.

Immunogenicity analysis: Descriptive statistics for the primary and secondary immunogenicity endpoints, including estimates and 95% confidence intervals (95% CI) for GMT and SCR, will be provided by time point and by different age's groups, different dose cohorts of BNT162b1 and placebo group. Different BNT162b1 dose cohorts will be compared in pairs, and the GMT ratio of each two dose cohorts as well as the point estimate value of SCR difference and 95% CI will be calculated. Generally, immunogenicity will be summarized and analyzed based on age groups and dose cohorts.

- *Seronegative subjects:* subjects with no detectable serum antibodies (test results are below Lower Limit of Detection) as measured by ELISA/neutralization assay.
- *Seroconverted subjects*: By ELISA/neutralization detection, the subject whose serum antibodies titers after vaccination of subjects are at least 4 times higher than baseline. If the baseline did not reach the lower limit of titer detection, the positive conversion is defined as the antibody titer reaching at least 4 times of the lower limit.

Safety analysis: Within 14 days after each vaccination (Including the day of vaccination of vaccine/placebo), by collecting soliciting AE, including local reactions (Vaccination site: pain/tenderness, erythema/redness, induration/swelling) and general reactions (nausea, vomiting, diarrhea, headache, fatigue/tiredness, myalgia, arthralgia, chills loss of appetite, malaise and fever), to evaluate reactogenicity. In addition, body temperature (axillary) as indicator of reactogenicity will be collected (with fever defined as axillary temperature ≥37.3ºC, oral temperature ≥38.0 ºC).

For each solicited reaction, including fever, the percentage of subjects will be summarized by event severity for each day within 14 days after each vaccine/placebo vaccination and overall.

All AEs and SAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 23.0) and summarized by system organ class (SOC) and preferred term (PT) for each group (BNT162b1 and placebo) including aggravation after vaccination and new medical conditions.

Safety summaries will be provided by different age groups and different dose cohorts/placebo groups.

Sample Size Justification:

This study is a phase 1 exploratory clinical trial.

In the study, approximately 24 subjects will be included in each dose cohort of each age group, another 24 subjects vaccinated with placebo. If the occurrence of TEAE is 8%, the probability of observation of at least one TEAE in 24 subjects in each dose group is 86.5%, which is sufficient to perform safety evaluation for investigational vaccine at each dose level.

Timepoint of Statistical Analysis:

Initial analysis:

In the study, all available safety and immunogenicity data will be included when all subjects in each age group complete Visit 9 (Day 50, 28 days after boost vaccination) to perform initial analysis. When all subjects in each age group complete Visit 11 (visit at Month 6 after prime vaccination), Viisit 12 (visit at Month 12 after prime vaccination), and an overall analysis will be performed.

Unblinding will be occurred at the initial analysis of safety and immunogenicity 28 days after boost inoculation, but the subjects will be kept blinded. More details regarding the analyses will be provided in the Statistical Analysis Plan (SAP).

The analysis report will be prepared after each phase of analysis and the overall study report will be prepared at the end of study.

Safety Review Committee (SRC):

Safety Review Committee (SRC) will be established comprising investigators, Fosun medical representatives, and medical monitor, etc.

Key roles of the SRC are as follows:

- Before progression to the next age group (elderly group), assess the safety and tolerability data of the subjects completed safety visits up to 14 days after prime vaccination, and decide whether to approve initiation of the dose cohort of elderly group. Data collected include vital signs, TEAEs, local reactions, blood/clinical laboratory data, and brief physical examination outcome.
- Before each dose cohort begins boost vaccination, for each dose cohort, assess the safety and tolerability data of the prime vaccination of subjects (including data collected at least up to 14 days post-vaccination) and, decide whether to approve initiation of boost vaccination of this dose cohort. Data collected include vital signs, TEAEs, local reactions, blood/clinical laboratory data, and brief physical examination outcome.
- Throughout the trial, assess whether to replace trial subjects permanently discontinued due to safety issues.
- Throughout the trial, the SRC may specific additional dose levels to be tested and an appropriate regime for enrollment and safety oversight.

See SRC charter for more information. The SRC will act according to written procedures described in SRC charter.

Independent Data Monitoring Committee:

The study will be overseen by an Independent Data Monitoring Committee (IDMC). IDMC will consist of 3 or 5 independent members (including epidemiologist, clinical experts, and statistical expert) and 1 independent non-voting statistician.

The IDMC is required to review the unblinded data when a significant event or risk that could cause the study to be suspended occurs. Based on the results of the safety data review, IDMC can request the suspension of investigation in a certain dose group/age group, or suspension of boost vaccination, and can also provide recommendations for subsequent development based on the periodical study data. This study will proceed in accordance with the protocol-specified procedures if no IDMC recommendation for suspension or modification is received.

The IDMC meetings will consist of open and closed face-to-face meetings or teleconference calls. 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 consultation is requested by the Pharmacovigilance Study Team.

The IDMC will review safety data on an ongoing basis, when the reported AEs meet with the dose-limiting toxicity (DLT) criteria, the IDMC will review all relevant safety data and consider a possible pause of the study, if it deems necessary:

See IDMC charter for more information. The IDMC will act according to written procedures described in IDMC charter.

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Table 2 Schedule of activities

1-1 Schedule of activities of adult subjects

Procedure/Assessment	Visit 0	Visit 1 Before prime vaccination	Visit 1 Prime vaccination & after vaccination	Visit 2	Visit 3 7 days after prime vaccination	Visit 4 14 days after prime vaccination	Visit 5 Before boost vaccination	Visit 5 Boost vaccination & after vaccination	Visit 6 7 days after boost vaccination	Visit 7 14 days after boost vaccination	Visit 8 21 days after boost vaccination	Visit 9 28 days after boost	Visit 10	Visit 11	Visit 12
Time Points	Screening D -14~D 0	Day 1	Day 1	24 h (±2 h)	Day 8 (±1 d)	Day 15 (±1 d)	Day 22 (±2 d)	Day 22 (±2 d)	Day 29 (±3 d)	Day 36 (±3 d)	Day 43 (±4 d)	Day 50 (±4 d)	Month 3 (D 85 ±7d)	Month 6 (D 184 ±9d)	Month 12 (D 366 ±9d)
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	x	x
Physical Examination[c]	x	x	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	x	x
12-lead ECG	x														
Chest CT scan	x														
WOCBP serum pregnancy test[e]	x						x								
Clinical laboratory tests (urine routine)[f]	x			x	x				x						
Clinical laboratory tests (blood routine, blood chemistry)[g]	x			x	x				x						
Clinical laboratory tests (thyroid function)[h]	x			x					x					x	
Clinical laboratory tests (coagulation function)[i]	x			x					x						
HIV test (fingertip blood)	x														

Procedure/Assessment	Visit 0	Visit 1 Before prime vaccination	Visit 1 Prime vaccination & after vaccination	Visit 2	Visit 3 7 days after prime vaccination	Visit 4 14 days after prime vaccination	Visit 5 Before boost vaccination	Visit 5 Boost vaccination & after vaccination	Visit 6 7 days after boost vaccination	Visit 7 14 days after boost vaccination	Visit 8 21 days after boost vaccination	Visit 9 28 days after boost	Visit 10	Visit 11	Visit 12
Time Points	Screening D -14~D 0	Day 1	Day 1	24 h (±2 h)	Day 8 (±1 d)	Day 15 (±1 d)	Day 22 (±2 d)	Day 22 (±2 d)	Day 29 (±3 d)	Day 36 (±3 d)	Day 43 (±4 d)	Day 50 (±4 d)	Month 3 (D 85 ±7d)	Month 6 (D 184 ±9d)	Month 12 (D 366 ±9d)
SARS-CoV-2 testing[j]	x														
Treatment Randomization[k]		x													
Immunization[l]			x					x							
Collect blood samples for IgG antibody		x					x		x		x		x	x	x
Collect blood samples for neutralizing antibody		x					x		x		x		x	x	x
Collect blood samples for CMI test[m]		x							x		x			x	
Issue subject diaries[n]			x		x	x		x	x	x	x				
Collect subject diaries				x	x	x	x		x	x	x	x			
Record AEs since last visit	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Local reaction assessment[o]			x	x	x	x	x	x	x	x	x	x			
Record concomitant medications/ products/ vaccinations		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Ask about the health condition of subject	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

[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. Adverse occurrences before the prime vaccination of investigational vaccine/placebo are considered medical history.

[c] Complete physical examination (including 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 site, the investigator shall follow his/her standard practice.

[d] Vital signs will be performed at each on site visit, and at 1, 3, and 6 h (±15 min) post each immunization. Vital signs include systolic/diastolic blood pressure, pulse rate, respiratory rate, and body temperature.

[e] In WOCBP women only: collect blood sample for testing β-hCG.

[f] Urine analysis: glucose, bilirubin, ketone, specific gravity, blood, pH, protein, urobilinogen, nitrite, and leukocytes. Microscopic urinalysis (based 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.

[g] Clinical laboratory: (Chemistry) alkaline phosphatase, creatinine, ferritin, C-reactive protein, albumin, alanine aminotransferase, amylase, aspartate aminotransferase, gamma glutamyl transpeptidase, total bilirubin, blood urea, fasting blood sugar, lipase, sodium, potassium, calcium; (Hematology) hemoglobin, hematocrit, red blood cell count, white blood cell count and differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count.

[h] Clinical laboratory tests (thyroid function): triiodothyronine (T3), thyroxine (T4), thyroid stimulating hormone.

[i] Clinical laboratory tests (coagulation function): prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT)), fibrinogen (FIB).

[j] SARS-CoV-2 testing, including RT-PCR test of nasopharyngeal swabs and SARS-CoV-2 antibodies screening. See Appendix C for procedures of collecting and handling specimens of nasopharyngeal swabs.

[k] Eligible virus naïve subjects with normal chest CT image enrolled at Screening will enter each cohortwill be randomized to vaccination of BNT162b1 or placebo at Visit 1, within 7 days after Screening Visit 0.

[l] Each randomized subject will receive two doses of either BNT162b1 (10 or 30 µg) or placebo intramuscularly (IM) – one vaccination each at Visit 1 (on Day 1) and at Visit 5 (on Day 22), conduct injections at one third of the deltoid muscle (preferably in the non-dominant arm).

[m] [redacted]

[n] Each subject will receive diary cards to collect solicited reactions for 14 days after each vaccination (including the days of vaccine/placebo vaccination), and unsolicited AEs for 21 days after prime vaccination and 28 days after boost (including the days of vaccine/placebo vaccination).

[o] From the beginning of prime vaccination to 28 days after boost, local reaction assessment should be conducted at 1, 3 and 6 h (±15 min) after each vaccination and at each site visit after vaccination.

1-2 Schedule of blood collection of adult subjects

Visit times	Visit 0	Visit 1 Before prime vaccination	Visit 1 Prime vaccination & after vaccination	Visit 2	Visit 3 7 days after prime vaccination	Visit 4 14 days after prime vaccination	Visit 5 Before boost vaccination	Visit 5 Boost vaccination & after vaccination	Visit 6 7 days after boost vaccination	Visit 7 14 days after boost vaccination	Visit 8 21 days after boost vaccination	Visit 9 28 days after boost vaccination	Visit 10	Visit 11	Visit 12
Time Points	Screening D -14~D 0	Day 1	Day 1	24 h (±2 h)	Day 8 (±1 d)	Day 15 (±1 d)	Day 22 (±2 d)	Day 22 (±2 d)	Day 29 (±3 d)	Day 36 (±3 d)	Day 43 (±4 d)	Day 50 (±4 d)	Month 3 (D 85 ±7d)	Month 6 (D 184 ±9d)	Month 12 (D 366 ±9d)
Blood routine (anticoagulant)	2 ml	---	---	2 ml	2 ml	---	---	---	2 ml	---		---	---	---	---
Blood chemistry (procoagulant)	4 ml	---	---	4 ml	4 ml	---	---	---	4 ml	---		---	---	---	---
Ferritin (procoagulant)	4 ml	---	---	4 ml	4 ml	---	---	---	4 ml	---	---	---	---	---	---
Thyroid function (procoagulant)	3 ml	---	---	3 ml	---	---	---	---	3 ml	---	---	---	---	3 ml	---
Coagulation function (anticoagulant)	2 ml	---	---	2 ml	---	---	---	---	2 ml	---	---	---	---	---	---
Pregnancy test (procoagulant)	3 ml	---	---	---	---	---	3 ml	---	---	---	---	---	---	---	---
IgG antibody (procoagulant)	---	7.5 ml	---	---		---	7.5 ml	---	7.5 ml	---	7.5 ml	---	7.5 ml	7.5 ml	7.5 ml
Neutralizing antibody (procoagulant)	---	7.5 ml	---	---		---	7.5 ml	---	7.5 ml	---	7.5 ml	---	7.5 ml	7.5 ml	7.5 ml
[redacted]															
ICS (anticoagulant)	---	25 ml	---	---	---	---	---	---	25 ml	---	25 ml	---	---	25 ml	---
Total volume of blood collected	18 ml	48 ml	---	15 ml	10 ml	---	18 ml	---	63 ml	---	48 ml	---	15 ml	51 ml	15 ml

Total volume of blood collected: 301 mL

2-1 Schedule of activities of elderly subjects

Procedure/Assessment	Visit 0	Visit 1 Before prime vaccination	Visit 1 Prime vaccination & after vaccination	Visit 2	Visit 3 7 days after prime vaccination	Visit 4 14 days after prime vaccination	Visit 5 Before boost vaccination	Visit 5 Boost vaccination & after vaccination	Visit 6 7 days after boost vaccination	Visit 7 14 days after boost vaccination	Visit 8 21 days after boost vaccination	Visit 9 28 days after boost vaccination	Visit 10	Visit 11	Visit 12
Time Points	Screening D -14~D 0	Day 1	Day 1	24 h (±2 h)	Day 8 (±1 d)	Day 15 (±1 d)	Day 22 (±2 d)	Day 22 (±2 d)	Day 29 (±3 d)	Day 36 (±3 d)	Day 43 (±4 d)	Day 50 (±4 d)	Month 3 (D 85 ±7d)	Month 6 (D 184 ±9d)	Month 12 (D 366 ±9d)
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	x	x
Physical Examination[c]	x	x	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	x	x
12-lead ECG	x														
Chest CT scan	x														
WOCBP serum pregnancy test[e]	x						x								
Clinical laboratory tests (urine routine)[f]	x			x	x				x						
Clinical laboratory tests (blood routine, blood chemistry)[g]	x			x	x				x						
Clinical laboratory tests (thyroid function)[h]	x			x					x					x	
Clinical laboratory tests (coagulation function)[i]	x			x					x						

Procedure/Assessment	Visit 0	Visit 1 Before prime vaccination	Visit 1 Prime vaccination & after vaccination	Visit 2	Visit 3 7 days after prime vaccination	Visit 4 14 days after prime vaccination	Visit 5 Before boost vaccination	Visit 5 Boost vaccination & after vaccination	Visit 6 7 days after boost vaccination	Visit 7 14 days after boost vaccination	Visit 8 21 days after boost vaccination	Visit 9 28 days after boost vaccination	Visit 10	Visit 11	Visit 12
Time Points	Screening D -14–D 0	Day 1	Day 1	24 h (±2 h)	Day 8 (±1 d)	Day 15 (±1 d)	Day 22 (±2 d)	Day 22 (±2 d)	Day 29 (±3 d)	Day 36 (±3 d)	Day 43 (±4 d)	Day 50 (±4 d)	Month 3 (D 85 ±7d)	Month 6 (D 184 ±9d)	Month 12 (D 366 ±9d)
HIV test (fingertip blood)	x														
SARS-CoV-2 testing[j]	x														
Treatment Randomization[k]		x													
Immunization[l]			x					x							
Collect blood samples for IgG antibody		x					x		x		x			x	x
Collect blood samples for neutralizing antibody		x					x		x		x			x	x
Collect blood samples for CMI test[m]		x							x						
Issue subject diaries[n]			x		x	x		x	x	x	x				
Collect subject diaries				x	x	x	x		x	x	x	x			
Record AEs since last visit	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Local reaction assessment[o]			x	x	x	x	x	x	x	x	x	x			
Record concomitant medications/ products/ vaccinations		x	x	x	x	x	x	x	x	x	x	x	x	x	x

Procedure/Assessment	Visit 0	Visit 1 Before prime vaccination	Visit 1 Prime vaccination & after vaccination	Visit 2	Visit 3 7 days after prime vaccination	Visit 4 14 days after prime vaccination	Visit 5 Before boost vaccination	Visit 5 Boost vaccination & after vaccination	Visit 6 7 days after boost vaccination	Visit 7 14 days after boost vaccination	Visit 8 21 days after boost vaccination	Visit 9 28 days after boost vaccination	Visit 10	Visit 11	Visit 12
Time Points	Screening D -14–D 0	Day 1	Day 1	24 h (±2 h)	Day 8 (±1 d)	Day 15 (±1 d)	Day 22 (±2 d)	Day 22 (±2 d)	Day 29 (±3 d)	Day 36 (±3 d)	Day 43 (±4 d)	Day 50 (±4 d)	Month 3 (D 85 ±7d)	Month 6 (D 184 ±9d)	Month 12 (D 366 ±9d)
Ask about the health condition of subject	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

[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. smoke and 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. Adverse occurrences before the prime vaccination of investigational vaccine/placebo are considered medical history.

[c] Complete physical examination (including 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 site, the investigator shall follow his/her standard practice.

[d] Vital signs will performed at each on site visit, and at 1, 3, and 6 h (±15 min) post each immunization. Vital signs include systolic/diastolic blood pressure, pulse rate, respiratory rate, and body temperature.

[e] In WOCBP women only: collect blood sample for testing β-hCG.

[f] Urine analysis: glucose, bilirubin, ketone, specific gravity, blood, pH, protein, urobilinogen, nitrite, and leukocytes. Microscopic urinalysis (based 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.

[g] Clinical laboratory: (Chemistry) alkaline phosphatase, creatinine, ferritin, C-reactive protein, albumin, alanine aminotransferase, amylase, aspartate aminotransferase, gamma glutamyl transpeptidase, total bilirubin, blood urea, fasting blood sugar, lipase, sodium, potassium, calcium; (Hematology) hemoglobin, hematocrit, red blood cell count, white blood cell count and differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count.

[h] Clinical laboratory tests (thyroid function): triiodothyronine (T3), thyroxine (T4), thyroid stimulating hormone.

[i] Clinical laboratory tests (coagulation function): prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT)), fibrinogen (FIB).

[j] SARS-CoV-2 testing, including RT-PCR test of nasopharyngeal swabs and SARS-CoV-2 antibodies screening (fingertip blood). See Appendix C for procedures of collecting and handling specimens of nasopharyngeal swabs.

[k] Eligible virus naïve subjects with normal chest CT image enrolled at Screening will enter each cohort, and will be randomized to vaccination of BNT162b1 or placebo at Visit 1, within 7 days after Screening Visit 0.

[l] Each randomized subject will receive two doses of either BNT162b1 (10 or 30 µg) or placebo intramuscularly (IM) – one vaccination each at Visit 1 (on Day 1) and at Visit 5 (on Day 22), conduct injections at one third of the deltoid muscle (preferably in the non-dominant arm).

[m] [redacted]

[n] Each subject will receive diary cards to collect solicited reactions for 14 days after each vaccination (including the days of vaccine/placebo vaccination), and unsolicited AEs for 21 days after prime vaccination and 28 days after boost vaccination (including the days of vaccine/placebo vaccination).

[o] From the beginning of prime vaccination to 28 days after boost vaccination, local reaction assessment should be conducted at 1, 3 and 6 h (±15 min) after each vaccination and at each site visit after vaccination.

2-2 Schedule of blood collection of elderly subjects

Visit times	Visit 0	Visit 1 Before prime vaccination	Visit 1 Prime vaccination & after vaccination	Visit 2	Visit 3 7 days after prime vaccination	Visit 4 14 days after prime vaccination	Visit 5 Before boost vaccination	Visit 5 Boost vaccination & after vaccination	Visit 6 7 days after boost vaccination	Visit 7 14 days after boost vaccination	Visit 8 21 days after boost vaccination	Visit 9 28 days after boost vaccination	Visit 10	Visit 11	Visit 12
Time Points	Screening D -14~D 0	Day 1	Day 1	24 h (±2 h)	Day 8 (±1 d)	Day 15 (±1 d)	Day 22 (±2 d)	Day 22 (±2 d)	Day 29 (±3 d)	Day 36 (±3 d)	Day 43 (±4 d)	Day 50 (±4 d)	Month 3 (D 85 ±7d)	Month 6 (D 184 ±9d)	Month 12 (D 366 ±9d)
Blood routine (anticoagulant)	2 ml	---	---	2 ml	2 ml	---	---	---	2 ml	---		---	---	---	
Blood chemistry (procoagulant)	4 ml	---	---	4 ml	4 ml	---	---	---	4 ml	---		---	---	---	
Ferritin (procoagulant)	4 ml	---	---	4 ml	4 ml	---	---		4 ml	---	---	---	---	---	
Thyroid function (procoagulant)	3 ml			3 ml					3 ml					3 ml	
Coagulation function (anticoagulant)	2 ml			2 ml					2 ml						
Pregnancy test (procoagulant)	3 ml	---	---	---	---	---	3 ml	---	---	---	---	---	---	---	---
IgG antibody (procoagulant)	---	7.5 ml	---	---	---	---	7.5 ml	---	7.5 ml	---	7.5 ml	---	---	7.5 ml	7.5 ml
Neutralizing antibody (procoagulant)	---	7.5 ml	---	---	---	---	7.5 ml	---	7.5 ml	---	7.5 ml	---	---	7.5 ml	7.5 ml
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICS (anticoagulant)	---	25 ml	---	---	---	---	---	---	25 ml	---	---	---	---	---	---
Total volume of blood collected	18 ml	48 ml	---	15 ml	10 ml	---	18 ml	---	63 ml	---	15 ml	---	---	18 ml	15 ml

Total volume of blood collected: 220 mL

3.0 LIST OF ABBREVIATIONS

AE	Adverse Events
AESI	Adverse Event of Special Interest
BMI	Body Mass Index
BNT162b1	BNT162 RNA-LNP vaccine utilizing nucleoside modified messenger RNA (the variants BNT162b1 will be tested in this trial)
CI	Confidence Interval
CMI	Cell-mediated Immunity
CRO	Contract Research Organization
CoV	Corona Virus
COVID-19	Coronavirus Disease 2019
CT	Computed Tomography
DLT	Dose Limit Toxicity (ies)
DMC	Data Monitoring Committee
eCRF	electronic Case Report Form
EDC	Electronic Data Capture system
ELISA	Enzyme-linked Immunosorbent Assay
[redacted]	[redacted]
EMA	European Medicines Agency
GBS	Guillain-Barré Syndrome
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMT	Geometric Mean Titres
β-hCG	Beta Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICS	Intracellular Cytokine Staining
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IM	Intramuscular Injection
IMP	Investigational Medicinal Product; in this trial, BNT162b1 vaccines
IRB	Institutional Review Board
ISF	Investigator's Site File

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, ie, water-based salt solution containing potassium dihydrogen phosphate (KH_2PO_4), sodium hydrogen phosphate (Na_2HPO_4), and sodium chloride
PEI	Paul-Ehrlich-Institute
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 Events
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
SRC	Safety Review Committee (SRC)
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Event
TMF	Trial Master File
TVC	Total Vaccinated Cohort
uRNA	Non-modified Uridine Containing Messenger RNA
VED	Vaccine Enhances 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. It is rarely for animal coronaviruses to infect people and then spread among infected people just like SARS-CoV-2. [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 was 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. Like 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. 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 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 attacks of autoimmunity on pulmonary alveoli. Since the beginning of these outbreaks and up to mid-May, there has been more than 4,580,000 confirmed COVID-19 associated with SARS-CoV-2 infection with over 310,000 deaths in over 200 countries, areas or territories worldwide. [4]

SARS-CoV-2 is a respiratory virus that can cause disease of the respiratory system. 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 social distancing (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 Rationale of trial plan

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 epidemic. 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 vaccine (BNT162b1), 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 control 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.

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 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 this study's sponsor, 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 administered IM reported a consistent pattern of reactogenicity but overall good safety and tolerability. [12]

4.2.3 Summary of available non-clinical data

4.2.3.1 Non-clinical pharmacology studies

The primary pharmacodynamics of the BNT162 vaccine was investigated in a range of non-clinical pharmacology studies *in vitro* and *in vivo*. Expression of RNA-encoded antigens was investigated *in vitro*. The mode of action of BNT162b1 vaccine was investigated with immunogenicity data in mice. The antibody response induced by RNA-encoded antigens was investigated by enzyme-linked immunosorbent assay (ELISA) and pseudovirus neutralization assay (pVNT).

To assess the potency of the LNP-formulated modRNA vaccine candidate BNT162b1, which encodes RBD V5, BALB/c mice were immunized IM once. ELISA data from sera obtained 7, 14 and 21 d after immunization show an early, dose-dependent IgG response recognizing S1 and the RBD (**Figure** 2).

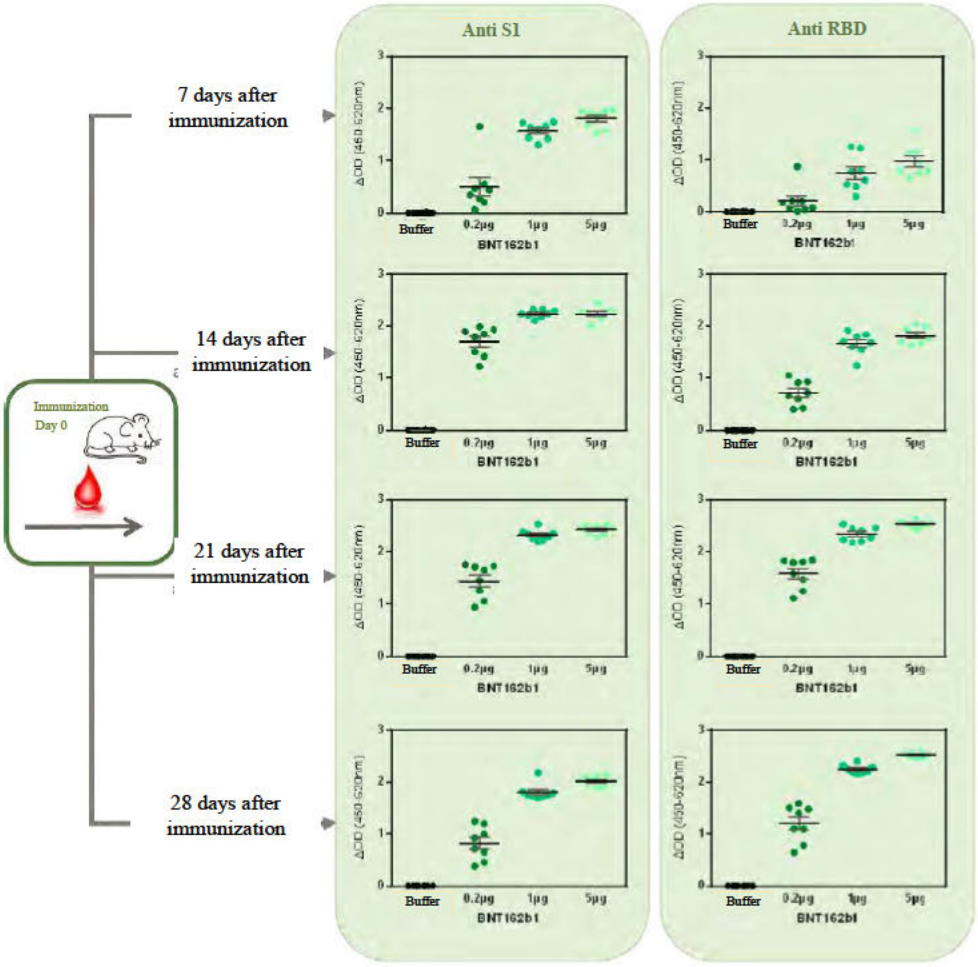


Figure 2 Anti-S IgG response 7, 14, 21 and 28 days after immunization with BNT162b1

BALB/c mice were immunized IM once with 0.2, 1 or 5 µg of LNP-formulated modRNA vaccine candidate encoding the RBD (BNT162b1). On 7, 14, 21 and 28 days after immunization, animals were bled, and the serum samples were analyzed for anti-S1 (left) and anti-RBD (right) antigen-specific IgG by ELISA. For day 7 (1:100), day 14 (1:100), day 21 (1:900) and day 28 (1:2700), data from different serum dilutions were included on the graphs. One point on the graphs stands for one mouse. Every serum sample was measured in duplicate. Group size n=8. Mean ± SEM is depicted by a horizontal line with whiskers for each group.

Antibody concentrations in the serum samples were calculated for the individual sampling days and the kinetics of IgGs against S1 and RBD proteins is shown in **Figure** 3. Antibody concentrations against S1 (**Figure** 3A) and RBD (**Figure** 3B) increased in a dose-dependent manner over time.

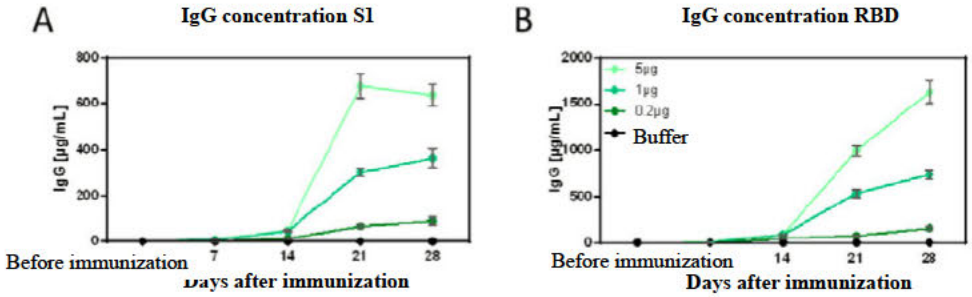


Figure 3 Kinetics of the antibody concentration against the viral antigen

For individual ΔOD values, the antibody concentrations in the serum samples were calculated based on each. The serum samples were tested against (A) the S1 protein and (B) RBD. Group mean antibody was shown (±SEM). Note that for the S1 and the RBD, 1mg/mL protein were coated onto a 96 well plate. BNT162b1 encodes for the receptor binding domain only. As the RBD has a smaller size than the S1, more antibody binding sites are available within 1 mg/mL of RBD compared to S1 which could explain the higher antibody concentration calculated against RBD.

Sera obtained 14, 21, and 28 d after immunization show high SARS-CoV-2 pseudovirus neutralization, especially sera from mice immunized with 1 or 5 µg BNT162b1 and correlating with the strong increase of IgG antibody titers (Figure 4).

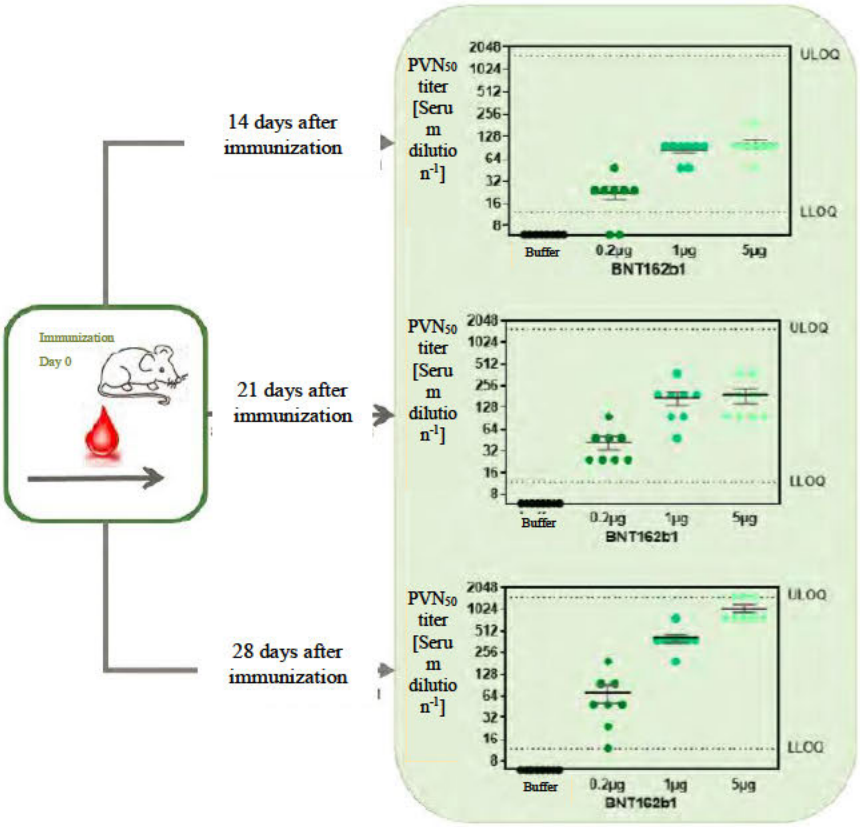


Figure 4 Neutralization of SARS CoV-2 pseudovirus 14, 21 and 28 d after immunization with BNT162b1

BALB/c mice were immunized IM once with 0.2, 1 or 5 µg of BNT162b1. On 14, 21 and 28 d after immunization, animals were bled, and the sera were tested for SARS CoV-2 pseudovirus neutralization. Graphs depict pVN50 serum dilutions (50% reduction of infectious events, compared to positive controls without serum). One point on the graphs stands for one mouse. Every mouse sample was measured in duplicate. Group size n=8. Mean ± SEM is depicted by a horizontal line with whiskers for each group. LLOQ, lower limit of quantification. ULOQ, upper limit of quantification.

4.2.3.2 Non-clinical pharmacokinetic studies

Pharmacokinetic studies were conducted using a luciferase reporter RNA, and protein expression after IM injection was demonstrated in vivo. The luciferase biodistribution profile resembles that of similar RNA products developed by BioNTech, some of which have been tested for safety at higher doses non-clinically and clinically using IV administration. Prior clinical experience with similar RNA products developed by BioNTech indicates that the distribution of vaccines in the liver does not pose a safety risk. But the liver parameters still will be carefully monitored during the clinical development of the BNT162b1 vaccines.

4.2.3.3 Toxicologic study

Through the study on GLP compliance repeat-dose toxicity in Wistar Han rats and, until data cut-off date, through the recovery phase of the repeat-dose toxicity study, there were no clinical signs or mortalities observed. As expected, the BNT162b1 vaccines induce a pro-inflammatory response, which manifests in a reduction in body weight (up to approximately 13%) 24 h post immunization without affecting body weight gain overall. The temporary weight loss is probably caused by shortly reduced food and water consumption after administration, which also leads to less urine production immediately after immunization. The observed increases in typical inflammatory blood parameters (such as fibrinogen and acute phase proteins) support this hypothesis. The transient and reversible elevation of GGT activity in serum in the absence of elevation of liver specific inflammation markers, such as ALAT or ASAT is considered a general inflammation marker.

Few hematological changes were observed: an increase in large unclassified cell and leukocyte (monocyte and neutrophil) counts, as well as a transient, dose-dependent reduction in reticulocytes after first immunization. The reduction in reticulocytes was reversed under continued immunizations and did not affect erythrocyte or hemoglobin levels and is species-specific. These changes have been observed in rats treated with the licensed LNP-small interfering RNA (siRNA) pharmaceutical Onpattro™ (FDA assessment report of Onpattro™ 2018), but have not been observed in patients treated with this compound. After the last immunization, a slight reduction in platelet numbers was observed. This effect is most likely attributable to inflammation specific platelet consumption and though it mediates a slight prolongation of aPTT in Groups 3, 4, 5, 6 and 7 of 2-3 seconds, it is not considered a safety concern but rather a pharmacodynamics attribute.

As an induction of a local pro-inflammatory environment within the muscle, which promotes potent immune responses, can be considered a mode of action of BNT162b1 vaccines, local

reactions were anticipated. The only local reactions observed after the first immunization were very slight to slight (grade 1 - 2) edema. Of note, no grade 3 or 4 local reactions occurred after the first immunization. The occurrence of higher grade of local reactions after boost immunizations is considered to be attributable to the undiluted status of the vaccines and to the - in relation to body weight of the rat - high vaccine dose (approximately up to 0.5 mg/kg), in addition to the short interval of 7 d between immunizations. It is not anticipated to occur in the clinical trial, in which boost immunizations of a maximum dose of 0.002 mg/kg (e.g., for the highest dose of 100 µg in a participant weighing 50 kg) will be administered 21 d apart.

Macroscopic observations of indurated injection sites and - in some animals - enlarged spleens and/or draining lymph nodes together with a tendency of increased spleen weights in vaccinated animals, support the hypothesis that the vaccine candidates generate a pro-inflammatory environment. In rats, the potent immune response observed can already be detected 17 d post first immunization.

Taking together the previous non-clinical and clinical experience with the preliminary results of the BNT162b1 vaccine toxicity study, a benign clinical safety profile is anticipated.

4.2.4 Summary of available clinical data

Two Phase I/II clinical studies of BNT162b1 are currently being conducted in Germany and the United States; at the same time, the 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 efficacy and safety of BNT162b1 at animal level and human body level. Interim Report of the United States Phase I/II clinical study has been published [5]. Results of data analyses for pre-clinical studies and clinical studies will be provided by continuously updating in the Investigator's Brochure (IB). The clinical studies conducted in Germany and the United States are first-in-human trials, so dose escalation mode is adopted and sentinel subjects are added for both. The maximum dose examined in these two studies is 100µg, and the safety result shows that the local reaction of vaccination site and systemic event 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 booster 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. Above results will support the further evaluation of the mRNA candidate vaccine. Currently, the optimal dose range is predicted as 10~30 µg according to safety and efficacy data of foreign subjects. Since the preliminary safety and immunology data are obtained, and clinical studies conducted in Germany and the United States will continue to support studies in China, so China plans to conduct bridging trial to confirm foreign study results among Chinese subjects.

4.2.4.1 Safety summary

According to the periodic summary of the United States Phase I/Ⅱ clinical study, pain at the injection site was the most common local reaction within 7 days of the first dose and the second

dose of vaccine; after the first vaccination, probability of pain in 10 μg group was 58.3% (7/12), in 30 μg group and 100 μg group were 100.0% (12/12), and in placebo group was 22.2% (2/9). After the second vaccination, there were 83.3% and 100.0% of subjects got pain respectively in the dose level of 10 μg and 30 μg, while 16.7% subjects in placebo group got pain. All local reactions were mild or moderate except the 100 μg group reported severe pain after inoculation of BNT162b1.

Within 7 days of each vaccination, the most common systemic events reported in BNT162b1 and placebo groups were mild to moderate fatigue and headache. Fatigue and headache were more common in BNT162b1 than that in placebo group. Furthermore, chills, muscle pain and joint pain were reported in the BNT162b1 group, but not in the placebo group. Systemic events increased with dose levels, and there were an increased number of subjects reporting systemic events after the second vaccination (10 μg and 30 μg groups). After the first vaccination, there were 8.3% (1/12) of subjects respectively in 10 μg group and 30 μg group, and 50.0% (6/12) of subjects in 100 μg group got fever (defined as ≥38.0° C). Based on the reactogenicity reported after the first dose of 100 μg and the second dose of 30 μg, subjects initially received 100 μg of vaccination will no longer receive the second vaccination. After the second vaccination, 8.3% (1/12) of subjects in 10 μg group and 75.0% (9/12) of subjects in 30 μg group got fever ≥38.0° C. The fever usually got resolved within 1 day of onset. There was no systemic event or fever of grade 4. Most local reactions and systemic events peaked 2 days after vaccination and resolved at day 7.

Subjects received 10 μg or 30 μg BNT162b1 reported 50.0% (6/12) of adverse events, subjects received 100 μg BNT162b1 reported 58.3% (7/12), and placebo group reported 11.1% (1/9). 2 subjects reported severe adverse events: fever of grade 3 was reported 2 days after vaccination in the 30 μg group, and sleep disturbances was reported 1 day after vaccination in the 100 μg group. Rate of related adverse events reported in BNT162b1 group was 25% (10 μg group was 3/12) tp 50% (30 μg and 100 μg groups each was 6/12), placebo group was 11.1% (1/9). No serious adverse event.

After BNT162b1 vaccination, most subjects had no change in routine clinical laboratory values or laboratory abnormalities of level 1 or above. Among patients with changes in laboratory values, the biggest change was a decrease in lymphocyte count after the first dose of vaccine, 10 μg, 30 μg and 100 μg were respectively 8.3% (1/12), 45.5% (5/11) and 50.0% (6/12). There was 1 each in the dose level of 10 μg group (8.3% [1/12]) and 30 μg group (9.1% [1/11]), and 4 in 100 μg group (33.3% [4/12]) that reported lymphopenia of grade 3. The decrease in lymphocyte count after the first vaccination was transient and it returned to normal 6-8 days after vaccination. In addition, 1 subject each in the 10 μg group or 30 μg group was reported to have neutropenia of grade 2 6-8 days after BNT162b1 boost injection. Both subjects were followed up in the study, and no adverse events or clinical manifestations of neutropenia have been reported to date. All of the observed post-vaccination abnormalities were unrelated to clinical findings.

4.2.4.2 Immunogenicity summaries

According to the periodic summary of the United States Phase I/Ⅱ clinical study, geometric mean concentration (GMC) of RBD specific IgG was 534-1,778 U/mL 21 days after prime vaccination. In contrast, RBD specific IgG GMC was 602 U/mL in 38 samples of sarS-COV-2 infection /COVID-19 convalescent human serum taken from patients aged 18-83 years old and at least 14 days after PCR confirmation. 7 days after the second vaccination (at dose levels of 10 μg and 30 μg), the GMC of RBD specific IgG antibody increased to 4,813-27,872 U/mL. 21 days after prime vaccination, RBD specific antibody concentrations were not increased in subjects who received the first dose of 100 μg BNT162b1. In subjects receiving doses of 10 μg and 30 μg BNT162b1, high concentrations of RBD specific antibodies persisted until the last time point so far assessed (day 35 of the trial, 14 days after the second vaccination). These RBD-binding antibodies were present at concentrations of 5,880-16,166 U/mL.

For all dose groups, a moderate increase in SARS-COV-2 neutralizing geometric mean titer (GMT) was observed 21 days after the first vaccination. 7 days after the second dose of 10 μg or 30 μg vaccine, the GMT of serum neutralizing antibody was significantly increased to 168-267, while the GMT of human serum during recovery was 94.

4.2.5 BioNTech RNA-based vaccine candidate

BioNTech has 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, modRNA, and saRNA formulated with different nanoparticles for various administration routes including for intravenous (IV) injection. The favorable safety profile after IV dosing is notable because it results in a higher systemic exposure than the planned IM dosing in this trial. Overall, the findings were mild adverse events and mostly related to the mode-of-action and the RNA-intrinsic stimulation of innate immune sensors. 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.
Phase I/II clinical study of BNT162b1 is currently conducted in Germany and the United States, and the effect and safety of BNT162b1 has been persistently observedat the animal level and human body level in a Good Laboratory Practice (GLP)-compliant, immunogenicity, repeat-dose toxicological study and virus challenge study in BALB/c mice. Data analysis results will be provided in the Investigator Brochure (IB) in a form of continuous updates. An optimal dose range of 10~30 μg has been identified in foreign subjects, based on safety and efficacy data.

4.2.6 Rationale for BNT162-03 trial

BNT162-03 is a phase I, dose confirmation study, which adopts a parallel two-dose cohort and placebo design in adult healthy subjects (adult group) and elderly healthy subjects (elderly group); and the trial in adult group is conducted firstly and followed by the trial in the elderly group. And the study is intended to confirm that the response (safety/immunogenicity) seen in foreign subjects is comparable to that observed in Chinese subjects. Healthy adults who are ≥18 years old and ≤55 years old will be enrolled in adult group, and healthy elderly subjects who are ≥65 years old and ≤85 years old will be enrolled in elderly group. To ensure the enrollment of healthy subjects, screening tests (hematology, biochemistry, and urinalysis) will be performed prior to vaccine/placebo vaccination. In each age group of subjects, the testing is conducted according to the parallel two-dose cohort and placebo allocation. The design of this study, including the selection of two optimal dose levels are informed by safety and immunogenicity data from the ongoing or completed foreign studies of BNT162b1.In this study, a Safety Review Committee (SRC) will be comprised of investigators, Fosun medical representative and medical monitor, and SRC will review the safety data in a blinded way. SRC will review the available safety and tolerability data of all subjects in this cohort (including at least safety laboratory test results and safety events collected in diary cards within 14 days after the prime vaccination) before starting the boost vaccination for each cohort to suggest whether the boost vaccination of BNT162b1 vaccine can be conducted. Data from the ongoing foreign clinical studies may be used to help select optimal doses for testing in this study. 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 a significant event or risk occurs in the study that could cause the study to be suspended.

Due to the ongoing threat of SARS-CoV-2 disease and the urgent need of a vaccine, this study will be accelerated to assess the bridging data for BNT162b1, in addition to confirm that the response (safety/immunogenicity) seen in foreign subjects is comparable to that observed in Chinese subjects.

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 trial is justified. 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 receive two doses of either SARS-CoV-2 vaccine (BNT162b1) or placebo intramuscularly (IM) on Day 1 and on Day 22. The objective of the study BNT162-03 is to assess the safety and immunogenicity of BNT162b1 in the Chinese healthy subjects.

The primary rationale for selection of the two-vaccine dose levels can be summarized as follows:

Based on the clinical data from the overseas clinical studies, and the non-clinical data of the RNA components (modRNA), with other liposomes or in conjunction with the lipid nanoparticles as will be tested clinically in this trial, we expects that doses at the 1~5 μg range will be immunogenic and induce neutralizing antibodies. The dose range of 1~100 μg has been identified in foreign

subjects, based on safety and efficacy data. Accordingly, a degree of reactogenicity is anticipated with BNT162b1 with mild or moderate local or systemic reactions common amongst subjects.

Based on currently available data on safety and immunogenicity of global clinical trials in Germany and the United States, two predicted optimal doses are selected to confirm the comparability of safety and efficacy for BNT162b1 in China.

- the low-dose level (10 μg);
- the high-dose level (30 μg).

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

4.3 Benefit/risk assessment

4.3.1 Risk assessment

The risks linked to the trial-specific procedures and connected mitigations are as follows:

- Throughout the trial period (i.e. approximately 12 months), the volume of blood drawn per subject will be kept to a minimum and will remain less than that drawn when donating blood.
- All trial-specific 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 study studies of BNT162b1 are currently being conducted in Germany and the United States. There are no published clinical data currently available for BNT162b1. 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 BNT162b1 vaccines are as follows:

- Due to the IM route of administration, there is the risk of local reactions at the vaccination site, e.g., flush, pruritus, pain, tenderness, swelling, sweating.
- Due to the immune-modulatory effect, vaccines may cause systemic flu-like reactions such as temporary headache, fatigue, loss of appetite, myalgia, arthralgia, fever. Rarely, with certain prophylactic vaccines (e.g., as seen for vaccines using attenuated viruses) severe allergic reaction or a neurological side effects, such as a seizure, were seen. Although these rare side effects are a concern, the risk of a vaccine causing serious harm or death is extremely small, for BNT162b1 vaccines, which are molecularly defined, highly purified, and based on RNA, which naturally occurs and is metabolized in the human organism.
- Due to the IM route the risk of systemic reactions is considered low.

  An IM vaccine based on modRNA encapsulated into a related but not identical vaccination 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, BNT162b1 administration may cause temporary headache, fatigue, or loss of appetite. Rarely, with certain prophylactic vaccines (e.g., as seen for vaccines using attenuated viruses) severe allergic reaction or a neurological side effects, such as a seizure, were seen. Although these rare side effects are a concern, the risk of a vaccine causing serious harm or death is extremely small, for BNT162b1 vaccines, which are molecularly defined, highly purified, subunit vaccines.
- The available non-clinical data of BNT162b1 suggest a favorable safety profile with events that are mild and mostly related to the mode-of- action and the RNA-intrinsic stimulation of innate immune sensors.

  Based on the available clinical and non-clinical data on the RNA component (uRNA) and individual components of the related RNA platform (modRNA, saRNA), that are combined within the BNT162 products, a favorable safety profile of BNT162b1 products is expected with mild and localized effects (see the IB for details on these trials).

  - IV administration to cancer patients of uRNA in a different liposomal formulation (i.e., uRNA-LPX) had a favorable safety profile. In these trials' systemic exposure at doses up to 400 µg to uRNA-LPX IV was tolerated without dose limiting toxicities. In line with the transient secretion of a distinct range of cytokines observed in these patients, the AE profile was found to be dominated by mild to moderate flu-like symptoms, e.g., pyrexia and chills. These immune modulation-related AEs started within 2-6 h after IV injection, resolved within 24 h.
  - Non-formulated uRNA administered in oncological trials intradermally or injected into inguinal lymph nodes was tolerated with only occasional and mild local reactions. Systemic reactions after local application were not observed.
  - Non-formulated modRNA administered in buffer into tumor lesions of cancer patients was tolerated with occasional mild local reactions. Systemic reactions after local application were not observed.
- To date, there is very limited clinical experience with BNT162b1 vaccines in human subjects. Reactogenicity is anticipated and considered to contribute to the mode-of-action of inducing vaccine immune responses. Initial dose-ranging studies have suggested AE profiles consistent with previous usage of similar constructs in cancer patients, with AEs generally dividing into 2 groups: local injection site reactions and systemic flu-like illness. With BNT162b1 vaccines to date most reported AEs have been mild to moderate in intensity and no serious AEs have been reported. Fever of severe intensity has been reported. Most AEs can be managed with simple measures and resolve spontaneously. Short-lived effects can be seen on immune parameter due to the PD effects, such as lowering of lymphocytes due to temporary trafficking in to the lymph system, or raising of CRP. These are only regarded as AEs if there are clinical consequences.

The listed risks can be managed using routine symptom driven standard of care as described in Section 10.5. Treatment of these events is dependent on the discretion of the investigators.

The trial uses placebo control parallel design, to ensure trial subject safety during the trial. To further ensure trial subject safety, the trial protocol foresees that:

- They are much longer than used in recently completed FIH clinical trials investigating related RNA-based vaccines. For example, the two Moderna trials investigating mRNA vaccines against avian H10N8 and H7N9 influenza viruses in healthy adults that observed trial subjects on-site for only 1 h after each immunization before discharge from the trial site.[12]
- More frequent on-site visits after immunization (i.e., on Days 2 and 8) than used in recently completed FIH clinical trials investigating with related RNA-based vaccines, e.g., the two Moderna trials investigating mRNA vaccines against avian H10N8 and H7N9 influenza viruses in healthy adults that used on-site visits on Day 8.[12]
- Additional subject wellbeing calls may be included at the discretion of the SRC.
- In the case that an individual experiences dose limiting toxic events or that the frequency or pattern of AEs within a sub-cohort gives cause for concern, the investigator may request an ad hoc review by the SRC before further doses of a given vaccine construct are administered.
-
- The SRC must assess the safety and tolerability data of the subjects before allowing progression to the next cohort. A 14-day interval was set between the dose cohorts.
- After each assessment, the SRC may request a prolongation of the observation periods. Additional telephone health inquiries may be added.

SRC may make recommendations on increasing observation periods and additional subject wellbeing calls may be included at the discretion of the SRC.

To ensure trial subject safety during the trial, their safety will be monitored from Visit 0 (screening) until approximately 12 months after the last immunization.

Vaccine-related enhanced disease has been reported in the literature from non-clinical studies investigating different vaccine formulations tested to prevent various coronavirus-induced diseases. Such effects have not been documented so far for SARS-CoV-2. No data are currently available to exclude that BNT162 may cause enhanced disease in vaccinated subjects.

The risks linked to the pandemic COVID-19 outbreak will be managed by requiring that the trials subjects:

- Avoid contact with persons tested positive for SARS-CoV-2 antibodies or have an increased risk for infection during their participation in the trial.
- Practice social distancing and follow good practices to reduce their chances of being infected or spreading COVID-19 during their participation in the trial.
- Complete health status checks which include symptom directed physical examinations, vital signs assessments, and clinical laboratory tests at the planned visit days.
- Contact the trial site during their participation in the trial should they require guidance or should they experience any symptoms of illness. The reporting of any symptoms of illness, e.g.,

enhanced respiratory disease or flu-like symptoms, may trigger diagnostic measures at the discretion of the investigator.

To minimize the risk to trial subjects in this trial, SRC and IDMC will regularly review and evaluate the safety and immunogenicity data. For details, see Section 11.0.

4.3.2 Benefit assessment

After participating in this trial, depending on the immunization regimen followed, some trial subjects should be immune against SARS-CoV-2 infection.

There is an urgent need for the development of new prophylactic vaccines 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 can 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, the trial subjects will help to market these prophylactic vaccines against SARS-CoV-2 infection.

4.3.3 Overall benefit/risk conclusion

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

5.0 TRIAL OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary objective

- To assess the safety and tolerability profiles of BNT162b1 prime/boost (P/B) immunization given 21 days apart from different dosages in SARS-CoV-2 naïve Chinese healthy subjects through 28 days after boost vaccination.

5.1.2 Secondary objectives

- To observe the immunogenicity of two doses of BNT162b1 (anti-S1 and anti-RBD IgG antibodies) given 21 days apart measured by enzyme-linked immunosorbent assay (ELISA).
- To observe the immune response of healthy subjects after BNT162b1 P/B immunization by true virus-based SARS-CoV-2 neutralizing antibody detection.
- To observe the safety of BNT162b1 vaccination in Chinese healthy subjects until the end of the study.
- To conduct 12-month follow-up for healthy subjects in the BNT162b1 vaccination dose cohorts, and observe the sustainability of the immune response to BNT162b1.

5.1.3 Exploratory objective

- [redacted]

5.2 Endpoints

5.2.1 Primary endpoints

Safety and tolerability of BNT162b1, as determined by:

- Occurrence of solicited local reactions in the subjects (eg, vaccination sites: pain/tenderness, erythema/redness, induration/swelling) during the 14-day after each dose of BNT162b1 or placebo.
- Occurrence of solicited systematic reactions (eg, nausea, vomiting, diarrhea, headache, fatigue, myalgia, arthralgia, chills, loss of appetite, malaise, and fever) during 14-day after each dose of BNT162b1 or placebo.

- Occurrence of AE associated with vaccination in subjects during the 21-day period after prime vaccination and the 28-day period after boost dose of BNT162b1 or placebo.

5.2.2 Secondary endpoints

Safety and tolerability of BNT162b1, as determined by:

- The proportion of subjects experiencing SAEs, occuring up to Day 21 after prime vaccination and Day 28 after boost vaccination, up to Month 3, 6 and 12.
- The proportion of subjects experiencing AE associated with BNT162b1, occuring up to Month 3, 6 and 12.
- The proportion of of subjects experiencing abnormal markers of hematology, blood chemistry and urine analysis, occuring at Hour 24 and Day 7 after prime vaccination and Day 7 period after boost dose of BNT162b1 or placebo.

Immunogenicity of BNT162b1, as determined by:

- Geometric mean titer (GMT) of anti-S1 IgG antibody at Day 7, Day 21 after prime vaccination, at Day 7, Day 21 after boost vaccination, and at Month 3, 6 and 12.
- Geometric mean titer (GMT) of anti-RBD IgG antibody at Day 7, Day 21 after prime vaccination, at Day 7, Day 21 after boost vaccination, and at Month 3, 6 and 12.
- GMT of SARS-CoV-2 neutralizing antibody (including true virus-based SARS-CoV-2 neutralizing test) at Day 7, Day 21 after prime vaccination, at Day 7, Day 21 after boost vaccination, and at Month 3, 6 and 12.
- Fold increase in antibody anti-S1 IgG antibody titers, as compared to baseline, at Day 7, Day 21 after prime vaccination, at Day 7, Day 21 after boost vaccination, and at Month 3, 6 and 12.
- Fold increase in antibody anti-RBD IgG antibody titers, as compared to baseline, at Day 7, Day 21 after prime vaccination, at Day 7, Day 21 after boost vaccination, and at Month 3, 6 and 12.
- Fold increase in SARS-CoV-2 neutralizing antibody titers (virus neutralizing test), as compared to baseline, at Day 7, Day 21 after prime vaccination, at Day 7, Day 21 after boost vaccination, and at Month 3, 6 and 12.
- Seroconversion rates (SCR) defined as a minimum of 4-fold increase of antibody titers, as compared to baseline, at Day 7, Day 21 after prime vaccination, and at Day 7, Day 21 after boost vaccination.

5.2.3 Exploratory endpoints

- [redacted]

[redacted].

- [redacted]

6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Overall trial design

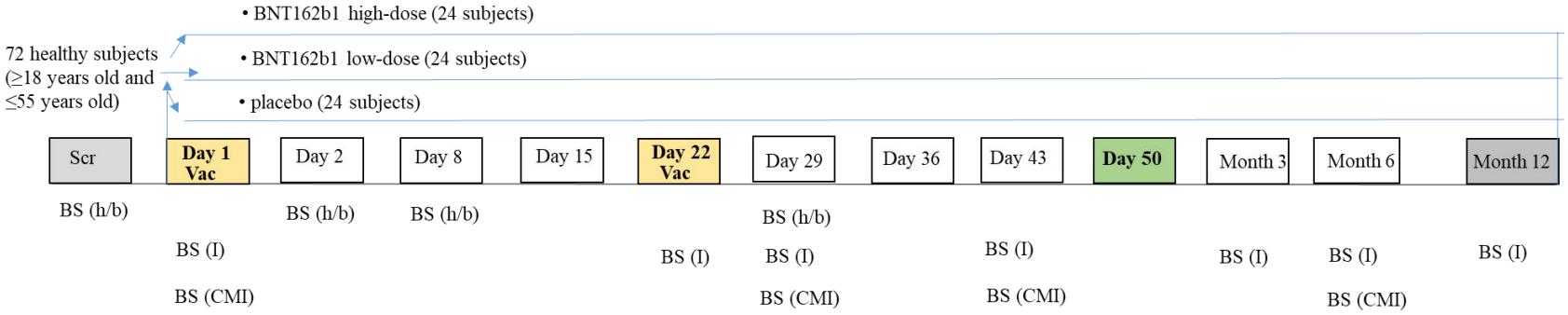
This is a phase I, randomized, placebo-controlled, observer-blind, safety and immunogenicity study of SARS-CoV-2 mRNA vaccine (BNT162b1) in Chinese healthy subjects.

After randomization, the trial for each subject will last for approximately 12 months. Screening period is 2 weeks prior to randomization (Day -14 to Day 0), and two doses of either SARS-CoV-2 vaccine (BNT162b1) or placebo will be given intramuscularly (IM) on Day 1 and on Day 22. After each age group completes the follow-up 28 days after boost vaccination (Day 50), initial analysis will be conducted.

Subjects who are ≥18 years old and ≤55 years old will be enrolled in adult group, and healthy elderly subjects who are ≥65 years old and ≤85 years old will be enrolled in elderly group. Approximately 72 subjects from each age group are allocated to two-dose cohorts (10 μg and 30 μg) in parallel, with approximately 24 subjects at each BNT162b1 dose level, 24 subjects in placebo goup. The subjects will be randomized in a 1:1:1 ratio to inject BNT162b1 or placebo, respectively.

After the 14-day safety observation post the completion of prime vaccination of the subject in the adult group, the prime vaccination for subjects in the elderly group will start. SRC will review the available safety and tolerability data of all subjects in a cohort before starting the boost vaccination for each cohort to suggest whether the boost vaccination of BNT162b1 vaccine can be conducted.

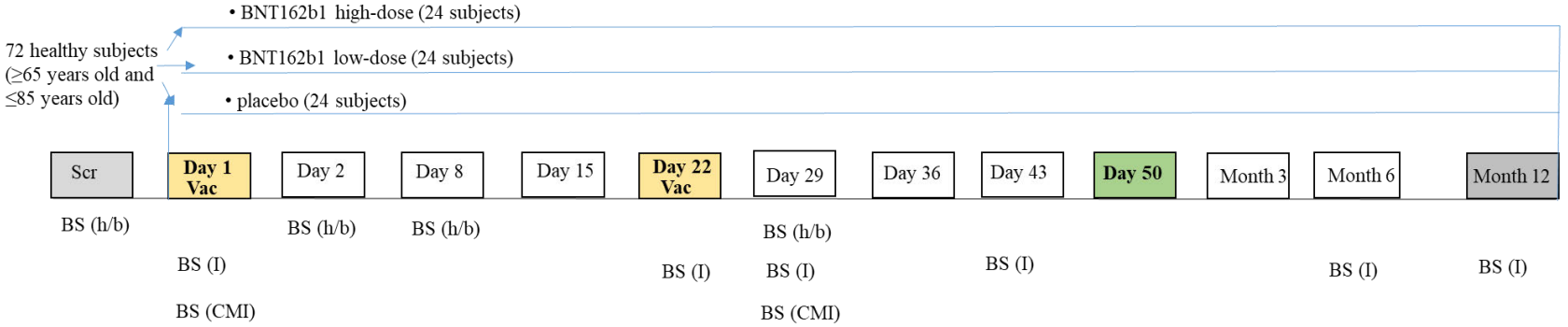
A summary of the dose cohort design can be seen in **Figure 5** General protocol design (adult subjects and elderly subjects), and **Figure 1** Schematic diagram of dose allocation design. For the planned assessments and visits, see Schedule of activities in **Table** 2 (adult subjects, elderly subjects).



BS (h/b) = Collect blood samples for hematology/blood chemistry test;

BS (I) = Collect blood samples for humoral immunoassay (anti-S1and anti-RBD IgG, neutralizing antibody);

BS (CM) = Collect blood samples for cellular immunoassay (specific T cell responses and related cytokines).



BS (h/b) = Collect blood samples for hematology/blood chemistry test;

BS (I) = Collect blood samples for humoral immunoassay (anti-S1and anti-RBD IgG, neutralizing antibody);

BS (CM) = Collect blood samples for cellular immunoassay (specific T cell responses and related cytokines).

Figure 5 Overall study design: adult subjects (below) and elderly subjects (above)

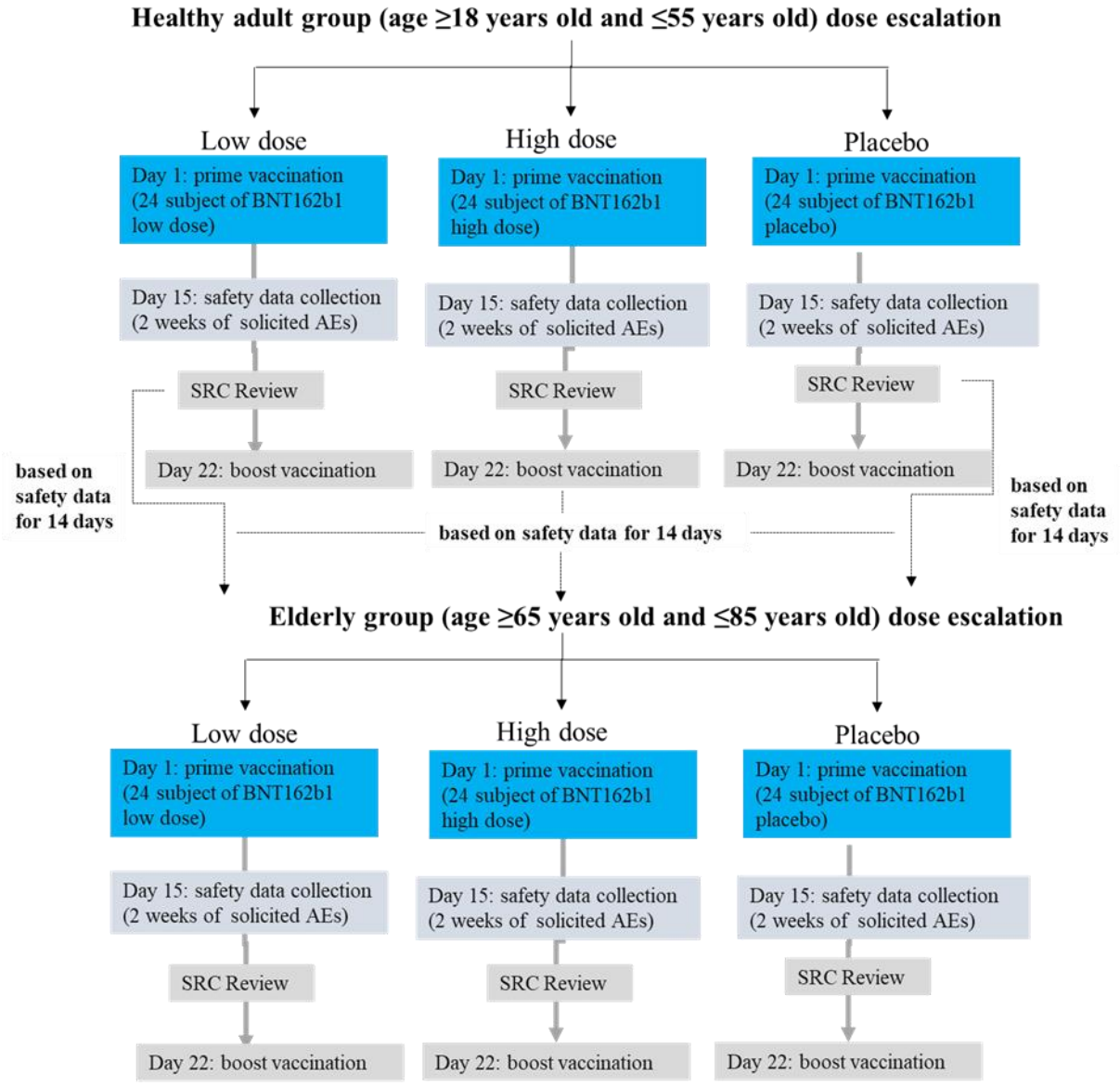


Figure 1 Schematic diagram of dose parallel design

6.2 Subjects enrollment and dose cohorts

The study will follow a parallel two-dose cohort and placebo design.

In the adult group, the enrollment process for subjects is as follows:

- In each planned low-dose cohort, high-dose cohort and placebo group, 72 subjects will be randomized in a 1:1:1 ratio to inject BNT162b1 or placebo vaccinated on Day 1.
- If the SRC considers that the subjects are safe with good tolerance after 14 days of observation, the boost vaccination will be conducted on Day 22.
- When the subjects in the adult group completed safety visits up to 14 days post prime vaccination, the available safety data for all subjects were summarized. If approved by the SRC,
    - the planned dose cohort of elderly group will be initiated (see **Figure 1**).

      The data assessed by the SRC comprises: vital signs, TEAEs, local reactions, blood/clinical laboratory data and brief physical examination outcome.
    - The parallel dose cohort study is conducted in the elderly group with consistent methods as those in the adult group (see **Figure 1**).

6.3 Dose modification

Any change in planned doses or testing of additional doses must be approved by the SRC.

6.4 Justification for trial design, dose, and endpoints

The trial design and the collection of solicited reactions and unsolicited AEs following vaccination follows related guidelines on vaccine evaluation trials.

The design of the study answers to the principles outlined in the ICH Considerations on Clinical Trials E8 and the WHO Guidelines for Evaluation of Vaccines, and more specifically for phase I/II trials. As such, the study design, objectives, and endpoints were defined to assess the safety and reactogenicity of the vaccine candidate, obtain information on its immunogenicity, and provide data useful 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 the rationale of trial protocol.

Please also refer to the IB.

6.5 Duration of subject's expected participation in the entire trial

Each enrolled subject's participation in the trial will last approximately 12 months after randomization, following a two-week screening period prior to randomization (Visit 1).

6.6 Dose limiting toxicity (DLT)

During the time of enrollment into a given cohort, if any of the following events occur and are assessed to be vaccine related, further vaccination in that cohort will be suspended:

- Anaphylaxis reaction considered related;
- Generalized urticaria considered related;
- 1/3 trial subjects in that cohort with any severe unsolicited local reaction, if considered related and not manageable with simple measures (e.g. cooling, analgesia, nonsteroidal anti-inflammatory drugs [NSAID];
- Any possibly related AEs within 7 days of vaccination assessed to be potentially life-threatening (Grade 4);
- Any systemic SAE within 7 days of vaccination considered related;
- Any fever >40.0°C (>104.0°F) within 7 days of vaccination considered related;
- Occurence of grade ≥3 adverse events that lasted at least 48 h and associated with vaccination, and for which there is no alternative feasible explanation, in more than 20% of participants (except local reactions: pain/tenderness, erythema/redness, and induration/swelling) after primary or booster inoculation;
- Occurence of grade ≥3 clinical laboratory abnormality related adverse events with clinical manifestations, that not recovered for at least 8 days and associated with vaccination, and for which there is no alternative feasible explanation, in more than 20% of participants after primary or booster inoculation.

Approval from the SRC will be required prior to any further vaccination in the affected cohort. The SRC may call for the opening of a lower dose level cohort.

The same events will prompt IMP discontinuation for individual subjects as described in Section 6.9 until SRC review is completed.

6.7 Criteria for delay of boost vaccination and/or stop for boost vaccination

After enrollment, subjects may encounter clinical circumstances that warrant a delay in the administration of the subsequent vaccination of investigational vaccine/placebo. These situations are listed below:

- Individuals with a clinically significant active infection (as assessed by the investigator) or axillary temperature ≥37.3°C or oral temperature ≥38.0°C, within 3 days before intended investigational vaccine/placebo vaccination. Or other clinical symptoms/diseases that may be considered inappropriate for vaccination by the investigator
- Individuals who received any other vaccines within 21 days before planned vaccination.

If a subject meets a criterion for delay of vaccination, the subject may receive trial vaccination, if the subject is otherwise eligible for trial participation even if the window period of vaccination visit has passed. The decision to vaccinate in those situations will be taken by the investigator.

In this trial, the second vaccination may be stopped in some circumstances. These circumstances include systemic anaphylaxis or severe hypersensitivity reactions following the prime vaccine/placebo administration. If these reactions occur, the subject must not receive additional vaccinations; however, the subject is encouraged to continue in trial participation for safety reasons.

6.8 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 stopping criteria: The SRC will review and evaluate the collected safety data periodically during the trial. A decision to stop treatment for an individual subject or to terminate the trial may be taken if safety concerns are identified by the SRC. Suspected unexpected serious adverse reactions (SUSARs) will immediately be reviewed by the SRC. They will trigger a temporary stop of IMP administration to new subjects in the respective dose level cohort for that vaccine until the SRC recommendation to continue or to permanently stop IMP administration of new subjects in the respective dose level cohort for that vaccine.
2. Adverse events: the subject has experienced an AE (irrespective of being related to the trial 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 study site and several 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 reasons should be recorded.

5. Premature study termination by Fosun, a regulatory agency, the IEC/IRB, or any other authority.

If the clinical study is early terminated by the Fosun, the investigator is to promptly inform the 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".

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

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

6.9 Criteria for premature discontinuation of trial 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 (see Section 6.8) criteria, other situations may apply in which subjects may continue participating in the trial (eg, contributing safety data according to protocol) but Trial Vaccine application is discontinued selectively. 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, the one primary reason for early discontinuation of Trial Vaccine application should be recorded in the eCRF, "end of Trial Vaccine application" page using the following categories.

1. Adverse events: the subject has experienced an AE (irrespective of being related to the Trial Vaccine or trial-related procedures) for which subsequent Trial Vaccine applications impose an unacceptable risk to the subject's health, but the subject will continue trial participation or other study procedures for safety.
2. Lost to follow up: the subject did not return to the clinical and several 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. Premature study termination by Fosun, a regulatory agency, the IEC/IRB, or any other authority.

   If the clinical study is early terminated by the Fosun, the investigator is to 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 Deviation: 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. Pregnancy: 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 captured in the safety database.

8. Other.

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

6.10. Premature termination or suspension of the trial

6.10.1 Criteria for premature termination or suspension of the trial

The trial will be completed as planned unless one or more of the following criteria are satisfied that require temporary suspension or early termination of the trial.

- New information or other evaluation regarding the safety or efficacy of the investigational vaccine that indicates a change in the known risk/benefit profile, such that the risk/benefit is no longer acceptable for subjects participating in the trial.
- SRC/IDMC recommends that the trial should be suspended or terminated.
- It deviates from Good Clinical Practice (GCP) significantly, so that the primary objective of the trial cannot be achieved or the safety of subjects may be compromised.

6.10.2 Procedures for premature termination or suspension of the trial

If the Fosun, an institutional review board (IRB)/independent ethics committee (IEC) or regulatory authority elects to terminate or suspend the trial or the participation of an investigational site, a trial-specific procedure for early termination or suspension will be provided by the Fosun.

7.0 Inclusion and exclusion criteria

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

7.1 Inclusion and exclusion criteria for adults

Inclusion criteria:

1. Male or female subjects of ≥18 years old and ≤55 years old with body mass index (BMI) ≥18 and ≤30 at the Screening Visit.
2. Individuals who are in good health condition at the time of entry into the trial as determined by medical history, physical examination (including vital signs, ECG) and eligibility screening test (hematology, blood chemistry and urine analysis) and clinical judgment of the investigator at Screening Visit.
3. The subject can provide with imformed consent and signs and dates a written informed consent form (ICF) prior to the initiation of any trial procedures.
4. They must be able to understand and follow trial-related instructions.
5. They must be willing and able to comply with planned visits, treatment schedule, laboratory tests and other requirements of the trial.
6. Negative in antibodies screening of SARS-CoV-2 (fingerstick).
7. Normal in chest CT scans (no imaging features of COVID-19).
8. Axillary temperature≤37.0ºC.
9. Negative SARS-CoV-2 test in throat swabs by RT-PCR.
10. Women of childbearing potential (WOCBP) must have a negative serum β-hCG at Screening Visit. Women that are postmenopausal (Menopause ≥12 consecutive months) or permanently sterilized will be considered as not having reproductive potential.
11. WOCBP must have used effective contraception 14 days prior to screening and agree to use effective contraception continuously during the trial period, from 14 days prior to Screening Visit to 60 days after the last immunization.
12. WOCBP must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during trial, starting from Screening Visit and continuously until 60 days after be given the last immunization.
13. Men who are sexually active with a WOCBP and have not had a vasectomy must agree to practice a effective form of contraception with their female partner of childbearing potential during the trial, starting from Screening Visit and continuously until 60 days after be given the last immunization.
14. Men must be willing to refrain from sperm donation, starting from Screening Visit and continuously until 60 days after receiving the last immunization.

Exclusion criteria:

1. Have had any acute illness, as determined by the investigator, with or without fever, within 72 h prior to the prime vaccination. An acute illness which is nearly resolved with only minor residual symptoms remaining is allowable if, in the opinion of the investigator, the residual symptoms will not compromise their well-being if they participate as trial subjects in the trial, or that could prevent, limit, or confound the protocol-specified assessments.
2. Are breastfeeding on the day of Screening Visit or who plan to breastfeed during the trial, starting from Screening Visit and continuously until at least 90 days after the last immunization. Women or partners who plan to become pregnant within 1 year post the screening visit.
3. Have a known allergy, hypersensitivity, or intolerance to the planned vaccine for trial including any excipients.
4. Used to have a history of hypersensitivity or serious reactions to vaccinations.
5. Received any vaccination within 4 weeks prior to Visit 1.
6. Don't agree to not be vaccinated during the trial, starting from Screening Visit and continuously until 28 days after receiving the last immunization, except emergency vaccination (e.g. rabies vaccine, tetanus vaccine).
7. Had any medical condition (e.g., autoimmune disease) or any major surgery (e.g., requiring general anesthesia) within the past 5 years, which in the opinion of the investigator, could compromise their well-being if they participate as trial subjects in the trial, or that could prevent, limit, or confound the protocol-specified assessments.
8. Have any surgery planned during the trial, starting from Screening Visit and continuously until at least 90 days after the last immunization.
9. Had any chronic use (more than 14 continuous days) of any systemic medications, including immunosuppressant or other immune-modifying drugs, within 6 months prior to Screening Visit unless in the opinion of the investigator, the medication would not prevent, limit, or confound the protocol-specified assessments or could compromise safety of subjects.
10. Had administration of any immunoglobulins and/or any blood products within the 3 months prior to Screening Visit.
11. Had administration of another investigational product including vaccines within 60 days or 5 half-lives (whichever is longer), prior to Screening Visit.
12. With known history of AIDS or HIV test positive.
13. Have active HBV or HCV infection, through medical inquiry.
14. History of SARS, SARS-CoV-2 or MERS infection. Suspected SARS patients should be screened for SARS antibodies.
15. Previously participated in a clinical trial involving lipid nanoparticles.
16. Are subject to exclusion periods of other clinical trials or simultaneous participation in another clinical trial.
17. Have any affiliation with the study site (e.g., are close relative of the investigator or dependent person, such as an employee or student of the study site).

18. Have a history of drug abuse or known medical, psychological or social conditions within the past 5 years. In the opinion of the investigator, could comprise their well-being if they participate as trial subjects in the trial, or that could prevent, limit, or confound the protocol-specified assessments.
19. Have a history of narcolepsy.
20. Have history of alcohol abuse or drug addiction within 1 year prior to Screening Visit.
21. Have a history of or suspected immunosuppressive condition, acquired or congenital, as determined by medical history and/or physical examination at Screening Visit.
22. Have any abnormality or permanent body art (e.g., tattoo), in the opinion of the investigator, would obstruct the ability to observe local reactions at the vaccination site.
23. Have had any blood loss >400 mL, e.g., due to donation of blood or blood products or injury, within the 28 days prior to Screening Visit or plan to donate blood or plasma during the trial, starting from Screening Visit and continuously until at least 28 days after be given the last immunization.
24. 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.
25. They plan to visit any country or region with a high SARS-CoV-2 infection risk (as defined at Screening Visit), from Screening Visit until 14 days after be given the last immunization.
26. Symptoms of COVID-19, e.g., respiratory symptoms, fever, cough, shortness of breath and breathing difficulties.
27. Have had contact with confirmed COVID-19 patients or persons tested positive for SARS-CoV-2 within the 30 days prior to Screening Visit.
28. Are vulnerable persons, e.g., soldiers, subjects in detention, CRO or Fosun staffs or their family members.

7.2 Inclusion and exclusion criteria for the elderly

Inclusion criteria:

1. Male or female subjects ≥65 years old and ≤85 years old at Screening Visit.
2. Individuals who are in a health condition that can receive the investigational vaccine, at the time of entry into the trial as determined by medical history, physical examination (including vital signs, ECG) and eligibility screening tests (hematology, biochemistry and urinalysis) and clinical judgment of the investigator at Screening Visit.
3. The subject can provide with informed consent and signs and dates a written informed consent form (ICF) prior to the initiation of any trial procedures.
4. They must be able to understand and follow trial-related instructions.
5. They must be willing and able to comply with planned visits, treatment schedule, laboratory tests and other requirements of the trial.

6. Negative in antibodies screening of SARS-CoV-2 (blood sample from fingertip).
7. No imaging features of COVID-19 in chest CT scan.
8. Axillary temperature≤37.0ºC.
9. Negative SARS-CoV-2 test in throat swabs by RT-PCR. Women of childbearing potential (WOCBP) must have a negative serum β-hCG at Screening Visit. Women that are postmenopausal (Menopause≥12 consecutive months) or permanently sterilized will be considered as not having reproductive potential.
10. Women of childbearing potential (WOCBP) must have a negative serum β-hCG at Screening Visit. Women that are postmenopausal (Menopause ≥12 consecutive months) or permanently sterilized will be considered as not having reproductive potential.
11. WOCBP must have used effective contraception 14 days prior to screening and agree to use effective contraception continuously during the trial period, from 14 days prior to Screening Visit to 60 days after the last immunization.
12. WOCBP must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during trial, starting from Screening Visit and continuously until 60 days after be given the last immunization.
13. Men who are sexually active with a WOCBP and have not had a vasectomy must agree to practice a effective form of contraception with their female partner of childbearing potential during the trial, starting from Screening Visit and continuously until 60 days after be given the last immunization.
14. Men must be willing to refrain from sperm donation, starting from Screening Visit and continuously until 60 days after receiving the last immunization.

Exclusion criteria:

1. Physical examination and qualifying screening during screening visits, finding baseline laboratory abnormalities ≥grade 3 (for hematology abnormalities with Grade ≥2, according to grading criteria in Appendix B).
2. Have had any acute illness, as determined by the investigator, with or without fever, within 72 h prior to the prime vaccination. An acute illness which is nearly resolved with only minor residual symptoms remaining is allowable if, in the opinion of the investigator, the residual symptoms will not compromise their well-being if they participate as trial subjects in the trial, or that could not prevent, limit, or confound the protocol-specified assessments.
3. Have a known allergy, hypersensitivity, or intolerance to the planned vaccine for trial including any excipients.
4. Used to have a history of hypersensitivity or serious reactions to vaccinations.
5. Received any vaccination within 4 weeks prior to Visit 1.
6. The subject doesn't agree to avoid vaccination during the trial, starting from Screening Visit and continuously until 28 days after receiving the last immunization, except emergency vaccination (e.g. rabies vaccine, tetanus vaccine).

7. Had administration of any immunoglobulins and/or any blood products within the 3 months prior to Screening Visit.
8. Had any serious or life-threatening medical condition (e.g., autoimmune disease, cardiovascular disease) within the past 5 years, which in the opinion of the investigator, could compromise their well-being if they participate as trial subjects in the trial, or that could prevent, limit, or confound the protocol-specified assessments.
9. Have any surgery planned during the trial, starting from Screening Visit and continuously until at least 90 days after the last immunization.
10. Had any chronic use (more than 14 continuous days) of any systemic medications, including immunosuppressant or other immune-modifying drugs, within 6 months prior to Screening Visit unless in the opinion of the investigator, the medication would not prevent, limit, or confound the protocol-specified assessments or could compromise safety of subjects.
11. Had administration of another investigational product including vaccines within 60 days or 5 half-lives (whichever is longer), prior to Screening Visit.
12. With known history of AIDS or HIV test positive.
13. Have infection history of HBV or HCV.
14. History of SARS, SARS-CoV-2 or MERS infection. Suspected SARS patients should be screened for SARS antibodies.
15. Previously participated in a clinical trial involving lipid nanoparticles.
16. Are subject to exclusion periods of other clinical trials or simultaneous participation in another clinical trial.
17. Have any affiliation with the study site (e.g., are close relative of the investigator or dependent person, such as an employee or student of the study site).
18. Have a history of drug abuse or known medical, psychological or social conditions within the past 5 years. In the opinion of the investigator, could comprise their well-being if they participate as trial subjects in the trial, or that could prevent, limit, or confound the protocol-specified assessments.
19. Have a history of narcolepsy.
20. Have history of alcohol abuse or drug addiction within 1 year prior to Screening Visit.
21. Have a history of or suspected immunosuppressive condition, acquired or congenital, as determined by medical history and/or physical examination at Screening Visit.
22. Have any abnormality or permanent body art (e.g., tattoo), in the opinion of the investigator, would obstruct the ability to observe local reactions at the vaccination site.
23. Have had any blood loss >400 mL, e.g., due to donation of blood or blood products or injury, within the 28 days prior to Screening Visit or plan to donate blood or plasma during the trial, starting from Screening Visit and continuously until at least 28 days after be given the last immunization.
24. 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.

25. They plan to visit any country or region with a high SARS-CoV-2 infection risk (as defined at Screening Visit), from Screening Visit until 14 days after be given the last immunization.
26. Symptoms of COVID-19, e.g., respiratory symptoms, fever, cough, shortness of breath and breathing difficulties.
27. Have had contact with confirmed COVID-19 patients or persons tested positive for SARS-CoV-2 nucleic acids or antibodies within the 30 days prior to Screening Visit.
28. Are vulnerable persons, e.g., soldiers, subjects in detention, CRO or Fosun staffs or their family members.

8.0 VACCINATION AND MANAGEMENT OF VACCINE

This section contains the information of the investigational drug needed for the protocol, including vaccination and management of vaccine.

8.1 Vaccination

8.1.1 Investigational vaccine/ placebo

Investigational vaccine:

The 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. For dispensing and operation protocol, see Pharmacy Manual.

Frequency of vaccination:	Two injections (21 days apart).
Route of vaccination:	Intramuscular (IM); upper arm, musculus deltoideus; the P/B regimens. The same arm may be used for both immunizations. The non-dominant arm is preferred.

Placebo:

NaCl 0.9% solution is being used as placebo. It is a sterile, clear, colorless liquid solution of sodium chloride without preservative designed for parenteral use only. The placebo is commercially available packaged and stored according to the labelling. The placebo is vaccinated by IM at 21-day intervals.

8.1.2 Preparation/handling/storage/accountability

The preparation of solution for injection will be carried out by the pharmaceutical professionals or other trained personnel at the trial site according to the sterile operation procedures.

For instructions on preparation, handling and storage of investigational drugs (IMP BNT162b1 vaccine), see the Pharmacy Manual.

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 IMP.

Only subjects enrolled in the trial may receive IMP and only authorized site unblinded personnel may administer IMP. All IMP (and any components thereof) must be stored in a safe, 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, study site, or the head of the site (where applicable) is responsible for storage, checking, and record maintenance (i.e., receipt, check and final disposition records) of 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 BNT162b1 (low-dose and high-dose) or placebo intramuscularly (IM) for two times – one injection at Visit 1 (on Day 1) and one injection at Visit 5 (on Day 22) IM into the one third of the deltoid muscle, preferably in the non-dominant arm.The additional doses may be explored, and the details will be provided in the pharmacy manual

Planned cohorts:

- Cohort 1: BNT162b1 low-dose (10 μg);
- Cohort 2: BNT162b1 high-dose (30 μg);
- Cohort 3: placebo.

8.2 Allocation, preparation and injection procedures of investigational vaccine/placebo

According to the instructions of the Pharmacy Manual, the designated qualified non-blind personnel shall regulate, prepare and inject investigational vaccine/ placebo. 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). And 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 method of block randomization will be used, and the random table of subjects will be generated by an independent randomized professional through SAS9.4 or above, and will be imported to the interactive response technology (IRT) system, which could only be accessed by authorized personnel. Subjects, researchers and sponsor study management will remain blinded throughout the trial. The authorized unblinded staff of the research center can obtain the subject allocation information through the IRT system and allocate the experimental vaccine or placebo of the corresponding group according to the allocation information.

All selected subjects will be assigned a screening number. For the selected subjects, the IRT system was used for randomization and a random number was obtained (the random number was used as the unique subject ID number). The random parameters and Settings are described in detail in the randomization specification.

8.4 Maintain of blinding

The trial is a blinding study for subjects and observers. The subjects, data collectors (eg, investigator), and data evaluators (eg, trial statisticians) are blinded. The investigational product assignment will be maintained by the unblinded site staff designee. It is no need of blinding for investigational products.

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 non-blinded personnel, including dispensers and vaccination nurses, are required to sign confidentiality agreements.

8.5 Unblinding procedures

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 urgent unblinding.

The Fosun’s Pharmacovigilance Department must be notified as soon as possible if the investigational vaccine/placebo blinding 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, follow 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 occurred at the initial analysis of safety and immunogenicity 28 days after boost vaccination, but the subjects will be kept blinded.

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 (the unique subject ID number) will be assigned, and this subject ID number 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. See Section 6.1 for more details about the enrollment.

Medical history will also be collected at Screening Visit and at Visit 1 (Day 1) pre-vaccination 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.

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.

Ask the subject’s medical history, record the following medication of the subject: 4 weeks within the vaccincation, long-term use of systemic medication affecting the immune function within 6 months, immunoglobulin and/or blood products within 3 months, take another kind of study drug (including vaccine) within 60 days or five half-life (will be subject to a long time). And all medications, vaccines and blood products taken or received by the subjects within 1 monthprior to the start of the trial are to be recorded on the source document (patient record) 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.

Contradicted medication/treatment (See Section 7.0)

- Had any chronic use (more than 14 continuous days) of systemic medications affecting immune function, including immunosuppressant or other immune-modifying drugs, within 6 months prior to Screening Visit unless in the opinion of the investigator, the medication would not prevent, limit, or confound the protocol-specified assessments or could compromise safety of subjects.
- Received any vaccine within 4 weeks prior to Visit 1.
- Had administration of any immunoglobulins and/or any blood products within the 3 months prior to Screening Visit.
- Had administration of another investigational product including vaccines within 60 days or 5 half-lives (whichever is longer), prior to Screening Visit.

Subjects should not donate blood during the main study period (starting after screening visit and continuously 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 be tested for SARS-CoV-2 at Screening Visit, including oropharyngeal swabs through RT-PCR and fingertip blood will be collected for SARS-CoV-2 antibodies screening.

The anti-SARS-CoV-2 antibody testing will be performed with a commercially available antibody test. It will be used to test subjects who may have experienced enhanced respiratory disease or progression of flu-like symptomatology, such as non-resolution of the symptoms after 7 d, symptom kinetics that are inconsistent with a relationship to RNA immunization, as might be expected with a COVID-19 disease (See Section 10.5).

9.1.4 Physical examination

The physical examination must be carried out by qualified health professionals in accordance with the relevant regulations and the licensing requirements designated with 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;

- if symptom-directed physical examinations were not required.

9.1.5 Vital signs, 12-lead ECG and chest CT scan

Vital signs include systolic/diastolic blood pressure, pulse rate, respiratory rate, and body temperature. Measurement of body weight is only required at Screening Visit. Follow standard of care for trial population and operational feasibility.

Vital signs must be within normal limits (ie, below Grade 1 as specified in the NMPA Toxicity Grading Scale for Healthy Adult Volunteers, see Appendix B).

12-lead ECG and Chest CT scan will be performed at Screening Visit. Chest CT images must have no imaging features of COVID-19.

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

Blood samples will be collected at each site visit: ie, at Screening Visit for eligibility screening tests (clinical laboratory testing, see Section 9.1.6.3), at Visits 2, 3 and 6 for routine safety laboratory testing (see Section 9.1.6.4 for Visits 2, 6 coagulation function test, Visits 2, 6, 11 thyroid function test). Blood samples for immunogenicity (anti-S1/ anti-RBD IgG and SARS-CoV-2 neutralizing antibody) will be collected at Visits 1, 5, 6, 8, 10, 11 and 12 for adults and at Visits 1, 5, 6, 8, 11 and 12 for the elderly (see Section 9.1.6.5). [redacted] Should a blood sampling be performed during a vaccination visit, this sampling must occur before the injection of the investigational vaccine or placebo. Serum sample will be collected for women of childbearing potential at Screening Visit and Visit 5 before each investigational vaccine/placebo injection for pregnancy testing (see Section 9.1.9). Figertip blood samples will be collected at Screening Visit for SARS-CoV-2 serostatus determination (see Section 9.1.6.1) and HIV serostatus determination (see Section 9.1.6.2).

Urine samples will be collected for all subjects at Screening Visit for eligibility screening (see Section 9.1.6.3), and at Visits 2, 3 and 6 for routine safety laboratory testing (see Section 9.1.6.4).

All samples will be collected in accordance with acceptable laboratory procedures. Samples of immunogenicity and CMI testing will be processed and stored at the study site as described in the provided Laboratory Manual.

9.1.6.1 SARS-CoV-2 antibody test

All subjects who sign the ICF will be tested for SARS-CoV-2 antibody test (fingertip blood) at Screening Visit.

9.1.6.2 HIV test

All subjects who sign the ICF will be tested for HIV antibody at Screening Visit. For screening, the subject's fingertip blood will be collected for anti-HIV antibodies.

9.1.6.3 Screening laboratory testing

Screening laboratory testing that will be performed on blood and urine samples at Screening Visit are outlined in **Table** 4.

Subjects of adults must have laborat ory values within normal limits or not be above Grade 1 as defined in Appendix B within 7 days before enrollment, and Grade 2 for the elderly. If the results of laboratory screening testing are out of acceptable range, repeat of screening tests is permitted once, provided there is an alternative explanation for the out of normal range value.

Should the respective repeated test results be available 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		Test
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 blood sugar, lipase, sodium, potassium, calcium
	Thyroid function	triiodothyronine (T3), thyroxine (T4), thyroid stimulating hormone.
	Coagulation function	prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT)), fibrinogen (FIB).
	Pregnancy test	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.

9.1.6.4 Safety laboratory testing

Routine safety laboratory testing includes hematology, blood chemistry and urine routines, thyroid function and coagulation function and laboratory testing is outlined in **Table 3**. Each blood sample was

approximately: blood routine 2 ml, blood chemistry 4 ml, ferritin 4 ml, thyroid function 3 ml, coagulation function 2ml.

9.1.6.5 Immunogenicity assessment

Serum immunogenicity (humoral immunity / antibody) is detected by ELISA and neutralizing antibody test. Each blood sample for ELISA assessments will be approximately 7.5 mL, and for neutralizing antibody test will be approximately 7.5 mL.

Should a blood sampling be performed during a vaccination visit, this sampling must occur before the vaccination of the investigational vaccine or placebo.

9.1.6.6 CMI assessments

[redacted]

9.1.7 Safety assessments

During the trial, safety assessments will include collection and recording of local (vaccination site) and systemic reactions (including fever), unsolicited AEs (serious and non-serious). Refer to Section 10.1 for safety definitions. Details on collection and reporting of reactions and AEs are in Section 10.2. Refer to Section 9.3.4 for details about the diary cards distribution, review and collection processes.

9.1.8 Contraception guidance

Subjects will be provided with guidelines on acceptable methods of contraception.

Female subject of childbearing potential and sexually active will have to use an “acceptable contraceptive method” from 2 weeks before screening through 2 months after the last dose of trial vaccine, and will be advised not to donate ova during this period.

Male subjects must be advised not to donate sperm during this period.

9.1.9 Pregnancy

For WOCBP, pregnancy testing will be performed at Screening Visit, and blood pregnancy testing will be performed before the boost vaccination of investigational vaccine/placebo.

Subjects must have a negative serum β-hCG pregnancy test at screening and before boost vaccination.

For the sake of the safety of a subject, if a female subject or female partner of a male subject is pregnant during the study vaccination, it must be reported to the Fosun with a pregnancy reporting form A within 24 hours after learning the event. At the same time, the pregnant patient must be followed up to determine the pregnancy outcome (provided that the female partner of a male subject agrees to have the data collected), including spontaneous or induced abortion, details of

childbirth, congenital malformations, or maternal or neonatal comorbidities, etc., and a pregnancy reporting form B will be filled for reporting.

Normal deliveries should be followed up at least one year after birth; other pregnancy results must be reported as serious adverse events (SAE), and the SAE form must be completed and reported, in addition to the pregnancy report form. Selective abortion without complications is not considered as an adverse event. If other SAEs occur during pregnancy, the SAE form must also be completed and reported.

If the subject becomes pregnant during the trial, she will not receive any further doses of any investigational vaccine/placebo. Should the pregnancy occur after administration of investigational vaccine/placebo in a blinded condition, the investigator must inform the subject of their right to receive information on the investigational vaccine/placebo injected. If the subject chooses to know unblinded information, the individual blind should be broken by the investigator and procedures must be followed, as described in Section 8.5.

9.1.10 Documentation of trial entrance/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 allocation/randomization into the vaccination phase.

One single subject screening number will be assigned to each subject at Screening Visit. In the study, subjects will be randomized at 1:1:1 with each cohort of 24 subjects to inject BNT162b1 or placebo.

9.1.11 Documentation of subjects who are not enrolled/randomized

If a subject who signs the ICF is found to be not eligible within the screening period, the investigator should complete the eCRF and explain the reasons.

The primary reason for un-enrollment/non-randomization is recorded in the eCRF using the following categories:

- Screen failure: does not meet one or more inclusion criteria; does meet one or more exclusion criteria;
- Withdrawal by subject;
- Trial terminated by Fosun Phar.

A subject may be a temporary screen failure under the following circumstances: due to temporary conditions such as receipt of immunosuppressive or immunomodulatory therapies, blood products, immunoglobulins, or vaccines, in the respective prohibited periods (see exclusion criteria), or in the event that a subject has an indeterminate pregnancy test result. 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 available within the prime 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 prime 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)

See Section 6.1 for more details about the 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 (including alcohol taken), 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. Perform 12-lead ECG and chest CT test (see Section 9.1.5).
9. Collect blood sample for eligibility screening tests (hematology, biochemistry, see Section 9.1.6).
10. Collect fingertip blood for SARS-CoV-2 and HIV antibody.
11. Collect oropharyngeal swabs for SARS-CoV-2 testing.
12. Collect urine sample for eligibility screening urinalysis.
13. For WOCBP, serum pregnancy testing will be performed at Screening Visit (see Section 9.1.6 for pregnancy test), and contraception guidance will be provided (see Section 9.1.8 and 9.1.9).

9.3.2 Pre-vaccination procedures

The following procedures will be performed at Visit 1 (Day 1) and Visit 5 (Day 22):

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. Randomize subject (only at Visit 1 on Day 1), a random number was obtained (the random 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. For WOCBP, serum pregnancy testing will be performed before boost vaccination (see Section 9.1.9).

9.3.3 Vaccination procedures

The following procedures will be performed at Visit 1 (Day 1) and Visit 5 (Day 22):

1. Check contraindications to vaccination and criteria for encountering toxicities of vaccination (see Sections 7.2 and 7.3).
2. Prepare the investigational vaccine/placebo according to the Pharmacy Manual (see Section 8.2)
3. Inject the investigational vaccine or placebo (see Section 8.2).

9.3.4 Post-vaccination procedures

The following post-vaccination procedures will be performed at Visit 1 (Day 1) and Visit 5 (Day 22):

1. After vaccination, the subject will be observed for at least 6 hours on site, including observation for immediate reactions and body temperature measurement. Vital signs will be performed at 1, 3, and 6 h (±15 min) post each immunization. Information should be recorded in the eCRF as immediate reactions. 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 reactions 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 a vaccination site AE should be performed while the subject is under observation after vaccination.

Diary card instructions must include the following: the subject must understand that timely completion of the diary card on a daily basis is a critical component of trial participation. The subject should also be instructed to write clearly and to complete the diary card with sign 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 primeed and dated.

Please note:

Diary cards will be the only source document allowed for remote collection of solicited local and systemic reactions (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 to be a recording error should be corrected by the subject on the diary card (the correction should include a single strikethrough line and should be primeed and dated by the subject).
- Any blank or illegible fields on the diary card not otherwise corrected as above will be missing in the eCRF.
- The study site should 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 primeed 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 reactions), any specific generalized symptoms (solicited systemic reactions), body temperature (axillary), any other symptoms or change in the subject's health status, and any medications taken. These solicited reactions and body temperature will be recorded in the diary. 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.

- The measurement of solicited local reactions (pain/tenderness, erythema/redness, and induration/swelling) is to be performed using the ruler provided by the study site. If multiple measurements are taken during the day, the highest measured value should be recorded on the diary card.
- The collection on the diary card of body temperature, solicited local reactions, and solicited systemic reactions will continue for a total of 14 days following each vaccine/placebo administration. The collection on the diary card of unsolicited AEs and medications will continue for 21 days following prime vaccination and 28 days following boost vaccination.
- 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 5 (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 study 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. Available contact details will be provided to the subjects.
6. Schedule the next site visit with the subjects.

9.3.5 Main visits post vaccination

The following main visits post vaccination 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. Perform symptom-directed physical examination (if deemed necessary, see Section 9.1.4).
3. Check vital signs (see Section 9.1.5).
4. Collect blood samples for routine safety laboratory testing, immunogenicity assessment and CMI testing (see Section 9.1.6).
5. Collect urine sample for routine safety laboratory testing (urinalysis; see Section 9.1.6).
6. Review the previous diary card with the subject and collect it (see Section 9.3.4).
7. Provide the subject with a new diary card, and remind the subject on how to use it (see Section 9.3.4).
8. Provide contraception guidance (see Section 9.1.8).

9. 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.
10. Schedule the next site visit with the subjects.

9.3.6 Follow-up extension

The extension visits will be performed at Visit 10 (Month 3), Visit 11 (Month 6), and at Month 12 (Visit 12). 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. Perform symptom-directed physical examination (if deemed necessary, see Section 9.1.4).
3. Check vital signs (see Section 9.1.5).
4. Collect blood sample for immunogenicity assessment (see Section 9.1.6.5).

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 laws. The Fosun Phar. 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 subjects in drug clinical study. It does not necessarily have a causal relationship with drug treatment. An adverse event can be an unfavorable 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.

It includes any new occurrence or deterioration in severity or frequency compared to baseline conditions, including abnormal results of laboratory tests (with clinical manifestations).

AE excludes:

- Medical or surgical procedures, such as operation, endoscopy, tooth extraction, infusion (the operation should not be collected as AE, but the diseases leading to these operations should be reported as AE);
- Existing diseases or conditions that exist or have been detected but have not worsened prior to the start of using the study drug, including abnormal results of laboratory tests.
- Transitory effects on laboratory tests due to the known mechanism of action of the drug, where there is no manifest clinical risk or evidence of potential lasting harm, judged by the investigator.

Treatment-emergent AE (TEAE) is defined as any AE with an onset date on or after the first administration of IMP (if the AE was absent before the first vaccination of IMP) or worsened after the first vaccination of IMP (if the AE was present before the first administration of IMP). AEs with an onset date more than 28 d 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

The occurrence of selected indicators of safety will be measured/collected for 14 days after each vaccination (including the days of vaccine vaccination), see details in following**Table** 5.

Table 4 Solicited local and systemic reactions

Local reactions (vaccination site):	Pain/tenderness
	Erythema/redness
	Induration/swelling
Systemic reactions:	Fever [(a)]
	Nausea
	Vomiting
	Diarrhea

	Headache
	Fatigue
	Myalgia
	Arthralgia
	Chills
	Loss of appetite
	Malaise

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

The intensity of solicited safety parameters will be assessed respectively as described in grading scale of Appendix B and C.

Solicitation adverse reactions: there is at least a reasonable possibility of a causal relationship between vaccines and adverse events, that is, causality cannot be ruled out.

10.1.3 Serious adverse events (SAEs)

Serious Adverse Event (SAE): Serious adverse event is defined as any untoward medical occurrence that (at any dose):

- Results in death
- Is life-threatening

(It refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event which hypothetically may have caused death if it is more severe.)

- Requires hospitalization or prolongation of existing hospitalization

Note: In general, hospitalization is defined that the patient stays in the hospital or emergency ward for observation (usually stays for one night at least) and/or receives the treatment which is not suitable to be given in doctor's office or outpatient department. Complications that occur during hospitalization are also considered as AE. If a complication prolongs hospitalization or meets any other criteria of serious event, the event is serious. When it is uncertain whether it is hospitalization or whether hospitalization is needed, the event should also be considered serious. Hospitalization required by selective treatment or due to original disease which does not get worse since baseline does not belong to AE.

- Results in persistent or significant disability/incapacity

Note: Disability is defined that the person's ability to do activity of normal life is significantly influenced. It does not include events with little clinical significance, such as simple headache, nausea, vomiting, diarrhea, flu or accidental trauma (such as ankle sprain). These events may influence daily life function, but they will not result in obvious loss of function.

- Caused a congenital anomaly/birth defect of offspring
- Other significant medical events

Other significant medical events: In some cases, medical and scientific judgment should be made to decide whether expedited report is needed. If the significant events do not immediately threaten life, cause death or require hospitalization, but medical measures are needed to prevent the above situation, then these event are also considered serious.

Note: The following hospitalization treatments are not considered as serious adverse events, since there are no adverse events related to hospitalization (i.e, there are no adverse medical events).

- Temporary care and hospitalization
- Hospitalization due to social reason, for example, hospital admission for convenient care.
- Scheduled hospitalization according to the study protocol, for example, hospitalization for administration of the study vacccine or insertion of study vacccine or laboratory test required by protocol.
- Scheduled hospitalization, selective operation or examination which the patient plans to undertake for pre-existing disease prior to the informed consent (in this case, the disease that requires hospitalization does not get worse or develop into a new disease after the administration of study vacccine, which should be also proved by the original document).
- Hospitalization for daily maintenance of equipment which have been in place before study (such as battery replacement).

Any confirmed cases of COVID-19 disease that occur during observation should be reported as SAE, where the intensity of the corresponding AE is rated as "moderate" or "severe" (according to the criteria provided in appendix B and appendix C), and necessary isolation or hospitalization should be performed in accordance with the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7). If no other SAE definition is deemed appropriate, then "other significant medical events" should be used as the SAE criterion.SAE forms should be completed, including follow-up information, as detailed in section 10.2.3, for the preparation and distribution of SAE reports and notes.

10.1.4 Adverse events of special interest

Enhanced respiratory disease or flu-like symptomatology not-resolved after 7 d or with symptom kinetics that are inconsistent with a relationship to RNA immunization, judged by the investigtors, will be considered adverse events of special interest (AESI).

All AESI, whether or not serious adverse events, whether or not have causal relationship with the investigational product, need to inform Beijing Fosun medicine science and technology development co., LTD. (the Fosun) within 24 hours, and fill out the form of serious adverse events and send to the pharmacovigilance department. If the adverse events of special interest meet the SAE standard, it needs to be handled and reported according to the SAE.

10.1.5 AE associated with an overdose or error in vacccine administration

If the subject presents with symptoms due to overdose or error in vacccine administration, the vacccine administration of overdose and error and all related symptoms should be recorded on AE page of eCRF and should be reported to the Fosun according to the SAE procedure. The overdose which does not cause any symptoms should also be immediately reported within 24 hours. If there are serious consequences or the subject presents with symptoms which meet the assessment criteria of SAE after overdose, this overdose should be reported as SAE.

10.2 Collection and record of safety events

10.2.1 Collection and reporting of solicited reactions

The occurrence of selected symptoms indicative of safety will be collected on diary cards by the subjects for 14 days following each investigational vaccine/placebo administration (i.e, the day of vaccination +13 subsequent days) and will be recorded on the "Local and Systemic reactions" eCRF (if applicable). These will be summarized in the final report under the category "solicited reactions" to differentiate them from unsolicited AE. Any solicited local or systemic reaction observed beyond 14 days after vaccination will be recorded as unsolicited AE on the Adverse Event eCRF. Any solicited continuing local (vaccination site) or systemic reactions observed beyond 14 days following each trial vaccination will be additionally recorded on the Adverse Event eCRF for follow-up. For these persistent/prolonged solicited reactions, the end date will be captured on the Adverse Event eCRF to permit a separate analysis from the unsolicited AE.

10.2.2 Collection and reporting of unsolicited AEs

Unsolicited AE occurring within 21 days after the prime vaccination and within 28 days after boost vaccination of vaccine/placebo will be collected on diary card (ie, day 22 to day 50 of the trial). AEs leading to withdrawal or discontinuation will be collected throughout the trial. Investigators should report collections of signs and symptoms as diagnosis AEs e.g. 'flu-like symptoms' or 'injection site reaction'.

Related AE/SAE occurring after 28 days after boost vaccination should also be collected and reported.

The following information will be documented for each event:

- Reported term for the Adverse Event,
- Start and end date,
- Serious (Y/N),
- Severity should be judged clincially by the investigator according to the grading standard in 10.3.1. For reference to the specific events listed in Appendix B and Appendix C, refer to the grading standards of the corresponding guidelines.
- Investigator's opinion on the causality (relationship) between the event and administration of trial vaccine(s),

- Investigator's opinion of the causality (relationship) to trial procedure(s), including the details of the suspected procedure,
- Actions taken,
- Outcome of event.

10.2.3 Collection and reporting of SAEs

For any SAE during the trial, the investigator should actively take appropriate action to ensure the safety of subject, no matter whether the SAE is related to study vacccine. The investigator should report to Fosun whthin 24 hours of being informed of the SAE.

For reports of deaths, the investigator shall provide the Fosun and the ethics committee with other information as required, such as an autopsy report and a final medical report.

The investigator shall sign and read the clinical trial safety information provided by the sponsor in a timely manner, and shall consider the treatment of the subject, whether to adjust accordingly, communicate with the subject as soon as necessary, and report to the ethics committee the suspicious and unexpected serious adverse reactions (SUSAR) provided by the sponsor.

The investigator shall follow up the SAE according to the protocol requirements, and provide a detailed, written follow-up report within 24 hours after receiving the follow-up information, in the same manner as above.

The sponsor or its representative shall evaluate and report the SAE (including SUSAR) in the clinical trial in accordance with the latest applicable regulatory requirements for the clinical trial of the investigational product.

Contacts of serious adverse event reports:

Table 5 Contact information for serious adverse events reporting

Unit	Phone	Reporting way
Pharmacovigilance Department of Beijing Fosun		Email: FSADEDESK@fosunpharma.com
Jiangsu Center for Disease Control and Prevention		

10.3 Assessment of safety parameters

10.3.1 Assessment of intensity

Reaction signs and symptoms involved in the grading scale will be graded respectively by the investigator according to the *Guidelines for Adverse Event Classification Standards for Clinical*

Trials of Preventive Vaccines of NMPA (Appendix B) and FDA (Appendix C). AEs uninvolved in the grading scale will be graded clinically by the investigator according to following criteria. Grading and seriousness need to be assessed independently for each AE recorded on the CRF.

Mild	Grade 1	Lasting for a short time (<48h) or slight discomfort, which do not influence activity and no treatment is needed.
Moderate	Grade 2	Mild or moderate limitation of activity, which may require hospital visit, does not require or only requires mild treatment.
Severe	Grade 3	Obvious limitation of activity, which requires hospital visit and treatment, possibly requires hospitalization.
Critical	Grade 4	Possibly life-threatening; serious limitation of activity, which requires intensive care
Death	Grade 5	

10.3.2 Relationship to investigational drug

Relatedness (causality) to vaccine will also be assessed by the investigator. The relationship between each AE, including solicited systemic AEs (solicited local AEs are considered as related) to trial vaccine(s) will be assessed using the following categories:

- Definitely related: There is reasonable time relationship between drug administration and the occurrence of adverse event; after drug withdrawal, the adverse reaction disappears or is rapidly relieved and improved (ie, dechallenge positive); when the drug is administrated again, the adverse event appears again (ie, rechallenge positive) and may get worse obviously; meanwhile, there is evidence from investigator brochure or literature data; besides, influence from original disease and other confounding factors are excluded.
- Probably related: There is no history of repeated drug administration. The rest are the same as those for “definitely related”, or even if there is drug combination, the possibility of adverse reaction resulted from drug combination is generally excluded.
- Possibly related: There is close relationship between drug administration and adverse event, which can also be proved by literature data. However, there may be more than one drug which causes adverse event or the original disease progression cannot be excluded.
- Possibly unrelated: The relationship between adverse event and medication time is not close. The clinical manifestation is not consistent with the known adverse events of the drug. If the original disease develops, it may have the similar clinical manifestation.
- Unrelated: No drug is administrated, or there is no association between drug administration and the occurrence time of adverse event or there is other definite reason which results in adverse event.

Related, probably related and possibly related are listed as related to the investigational vaccine.

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 Expectation assessment of adverse events

An unexpected adverse reaction refers to an adverse reaction with the nature, severity, consequence, or frequency different from the expected risks described in the current relevant data of the investigational vacccine (such as investigator brochure or another document). Investigator brochure is used as the main document to provide safety reference information to judge whether an adverse reaction is expected or unexpected.

Suspected unexpected serious adverse reaction (SUSAR): refers to a suspected and unintended serious adverse reaction with the nature and severity of clinical manifestations beyond the existing data and information in investigator brochure of investigational vacccine, package inserts of drugs on market or summary of product characteristics, etc.

10.4 Follow-up of adverse events

The investigator should follow up each adverse event. The laboratory test of clinical indicators shall be retested in time if there are ⩾ Grade 1 or clinically significant abnormal items judged by the investigator. For all SAEs and AEs with relevance which still exist until the end of AE/SAE collection and record, the investigator should follow up to:

- The event is solved or resumes to the status of baseline or is stable;
- The investigator can confirm that there will be no further improvement;
- No more information can be obtained (the subject refuses to provide more information, or there is evidence which proves that the subject is lost to follow-up even if the investigator has tried his/her best).

During the study, the recovery time (with date) of adverse event should be recorded in AE eCRF and the patient's medical record to verify the original data.

For serious adverse events, adverse events of special interest and pregnancy events, the Fosun or other designated personnel can obtain more case information through telephone, fax, e-mail and/or supervising to perform independent medical assessment for these cases.

The AE original data records updated after the lock of database are available for backup. SAE information needs to be filled in the Serious Adverse Event Report Form as detailed as possible, which is reported to PV department.

10.5 Treatment of reactions and adverse events

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

Mitigation plans for specific reactions

Based on experience with other BioNTech RNA-based vaccines, it is anticipated that subjects may experience TEAEs of flu-like symptomatology and/or injection site reactions following the administration of RNA vaccines due to the mechanism of action of RNA-vaccines. 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 recommended by the investigational site.
- 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 treated with simple measures such as cooling, antipyretics, analgesics.

Ensure adequate hydration of trial subjects on the day of immunization. Consider administering fluids (e.g., water for drinking, 0.5 - 1.0 L) within approximately 2 h following the immunization according to the standard of investigational site.

If subjects experience enhanced respiratory disease or progression of flu-like symptomatology, such as non-resolution of the symptoms after 7 d, symptom changes that are inconsistent with a relationship to RNA immunization, additional diagnostic measures should be considered and the medical supervisor should be informed.

10.6 Outcome of adverse events

The investigator should determine the outcome of adverse events according to its prognosis. The outcome of adverse events is as follows:

- Recovered/resolved: The subject is fully recovered from AE, without any residual influence or damage.
- Recovering/resolving: The signs and symptoms related to the event are relieved but have not disappeared completely.
- Recovered/resolved with sequelae: The subject is recovered, still with residual influence or damage. The residual influence may be temporary, but still exists at the time of report. If

these sequelae are not considered permanent, new information should be provided at follow-up when there is change of the event.

- Unchanged: The signs and symptoms related to the event are not relieved. The condition of the subject remains unchanged.
- Aggravated: The signs and symptoms related to the event are not relieved. The condition of the subject is aggravated.
- Fatal: Only when the death is resulted from SAEs, the *fatal* can be chosen as an outcome. All other AEs/SAEs which exist at death should be reported.
- Unknown: It refers to a situation when the subject is lost to follow-up and the investigator cannot confirm the outcome.

11.0 Monitoring Committee

11.1 Safety Review Committee (SRC)

Safety Review Committee (SRC) will be established comprising investigators, Fosun medical representatives, and medical monitor, etc.

Key roles of the SRC are as follows:

- Before progression to the next age group (elderly group), assess the safety and tolerability data of the subjects in the adult group completed safety visits up to 14 days after prime vaccination, and decide whether to approve initiation of the dose cohort of elderly group. Data collected include vital signs, TEAEs, local reactions, blood/clinical laboratory data, and brief physical examination outcome.
- Before each dose cohort begins boost vaccination, for each dose cohort, assess the safety and tolerability data of the prime vaccination of subjects (including data collected at least up to 14 days post-vaccination) and, decide whether to approve initiation of boost vaccination of this dose cohort. Data collected include vital signs, TEAEs, local reactions, blood/clinical laboratory data, and brief physical examination outcome.
- Throughout the trial, assess whether to replace trial subjects permanently discontinued due to safety issues.
- Throughout the trial, the SRC may specific additional dose levels to be tested and an appropriate regime for enrollment and safety oversight.

See SRC charter for more information. The SRC will act according to written procedures described in SRC charter.

11.2 Independent Data Monitoring Committee (IDMC)

The study will be overseen by an Independent Data Monitoring Committee (IDMC). IDMC will consist of 3 or 5 independent members (including epidemiologist, clinical experts, and statistical expert) and 1 independent non-voting statistician.

The IDMC is required to review the unblinded data when a significant event or risk that could cause the study to be suspended occurs. Based on the results of the safety data review, IDMC can request the suspension of investigation in a certain dose group/age group, or suspension of boost vaccination, and can also provide recommendations for subsequent development based on the periodical study data. This study will proceed in accordance with the protocol-specified procedures if no IDMC recommendation for suspension or modification is received.

The IDMC meetings will consist of open and closed face-to-face meetings or teleconference calls. 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 consultation is requested by the Pharmacovigilance Study Team.

The IDMC will review safety data on an ongoing basis, except at regular review time points. When the reported AEs meet with the dose-limiting toxicity (DLT) criteria, the IDMC will review all relevant safety data and consider a possible pause of the study, if it deems necessary:

See IDMC charter for more information. The IDMC will act according to written procedures described in IDMC charter.

12.0 DATA MANAGEMENT

Data management ofthis project is implemented based on the requirement from *Technical Guideline for Data Management of Clinical Trial*, *Guiding Principle for Planning and Reporting of Data Management and Statistical Analysis for Drug Clinical Trial, Technical Guiding Principle for Electronic Data Collection of Clinical trial*, issued in 2016 by NMPA.

12.1 Data collection and management

Data collection and management is conducted with the electronic data collection (EDC) system in this study. The data of subjects will be recorded in the designated eCRF. The eCRF will be preserved by the Fosun and its copy will be sent to the investigator as a research copy.

The investigator or authorized staff is responsible to fill out the eCRF. They should carefully record the items of eCRF in detail. Blank or missing of an item is not permitted (for the blank without record, UK/NA/ND should be filled in according to the fact); all data in eCRF should be verified with the data of original material to guarantee the accuracy.

The investigator must preserve all original laboratory test reports or the copies; in terms of abnormal laboratory or examination data, the investigator should verify these data and explain whether they have clinical significance or not; the investigator should fill in eCRFs strictly following the eCRF instructions.

12.2 Database lock

When the following conditions are met, data can be locked.

- All data are entered into the database.
- All issues are solved.
- Statistical analysis set has been confirmed and judgment is made.

The locked data and document cannot be changed without the Fosun’s authorization.

The detailed process of data management will be described in DMP.

13.0 STATISTICAL METHODS

13.1 Statistical and analytical plans

The statistical analysis plan (SAP) will be finalized prior to unblinding of subject's treatment assignment. SAP will provide further details regarding the definition of analysis variables and analysis methodology to address all trial objectives.

A review of data under blind state will be conducted prior to unblinding of subject's vaccination assignment. This review will assess the accuracy and completeness of the trial database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis sets

- *Safety Set*: Safety Set will consist of all randomized subjects who receive at least one dose of the investigational vaccine/placebo and at least one safety evaluation.
- *Total Vaccinated Cohort (TVC)*: According to intention-to-treat analysis set principle, the TCV will include all randomized subjects who have received at least one dose of the investigational vaccine/placebo and can provide with effective baseline.
- *Per protocol set (PPS)*: The PPS will include all subjects in the TVC who have no major protocol violations and complete boost vaccination. The protocol violation criteria will be defined as part of the blinded data review. The categories of major protocol violations include:
    1 not meeting inclusion criteria, or meeting exclusion criteria,
    2 receiving a wrong investigational vaccine/placebo,
    3 receiving prohibited therapies,
    4 other major protocol violations that be identified during blinded data reviews.

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

The primary immunogenicity endpoint analyses will be based on the PPS and TVC, and secondary immunogenicity endpoint analyses will be based on the TVC.

13.1.2 General principles

Data is usually summarized by groups, and groups can be merged as appropriate.

The following descriptive statistics will be used: number of subjects (n), mean, standard deviation, median, minimum, and maximum will summarize the continuous variables by groups.

The categorical variables are summarized by groups, listing the absolute value and relative frequency (n and %) of the subjects in each category.

Baseline was defined as the last available value before the first administration.

13.1.3 Analysis of demographics and other baseline characteristics

Summaries of age, gender, race, and other baseline characteristics will be presented by groups of BNT162b1 and placebo.

13.1.4 Primary endpoints

All AEs will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA version 23.0) coding system to get a system organ class (SOC) and preferred term (PT) for each AE.

AEs and solicited reactions will be summarized using the Safety Set. In general, safety parameters will be analyzed by grouping and for each immunization, i.e., for:

- Day 1-21 (pre-boost)
- Day 21(post-boost) - 28

Additionally, AEs and reactions will be summarized for all dose levels combined for each type.

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 AE
- Related AE ≥Grade 3
- AE 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.

During 14 days post vaccination (including the day of BNT162b1/placebo vaccination), evaluate reactogenicity by daily solicited reactions, including local reactions (vaccination site: pain/tenderness, erythema/redness, induration/swelling) and systemic reactions (nausea, vomiting, diarrhea, headache, fatigue, myalgia, arthralgia, chills, loss of appetite, malaise, and fever), as well as non solicited AE. In addition, body temperature (axillary) was collected as the indicator of reactogenicity (fever was defined as axillary temperature ≥37.3℃ or oral temperature ≥38℃).

For each solicited reaction (including fever), the percentage of subjects will be aggregated according to the severity of the events and the total number of subjects within 14 days of each vaccination/placebo.

Local and systemic responses were recruited within 14 days after each vaccination, non-solicited TEAE within 21 days after the prime vaccination and 28 days after boost vaccination, and IMP-

related AE were studied after 28 days. Adverse reaction classification criteria given in appendix B and appendix C were used for classification. During the study period, AEs uninvolved in the appendix grading scales will be graded clinically by the investigator according to the criteria in Section 10.3.1.

For each immunization, the number and percentage of subjects reporting at least one local reaction or systemic reaction will be summarized for each of the following types using the Safety Set:

- Any local reactions or systemic reactions
- Related local reactions or systemic reactions
- Grade ≥3 local reactions or systemic reactions
- Related grade ≥3 local reactions or systemic reactions

Moreover, the number and percentage of subjects reporting at least one local reaction will be summarized by worst grade using the Safety Set.

13.1.5 Immunogenicity analysis

Descriptive statistics for the primary and secondary immunogenicity endpoints, including estimates and 95% confidence intervals (95% CI) for GMT and SCR, will be provided by time point and by different age groups, different dose cohort of BNT162b1 and placebo group).

Different BNT162b1 dose cohorts will be compared in pairs, and the GMT ratio of each two dose cohorts as well as the point estimate value of SCR difference and 95% CI will be calculated. Generally, immunogenicity will be summarized and analyzed based on age groups and dose cohorts.

- *Seronegative subjects:* Subjects with no detectable serum antibodies (test results are lower than the lower limit of detection) as measured by ELISA/neutralization assay.
- *Seroconverted subjects*: The serum antibody titer after vaccination of subject is at least 4 times higher than baseline by ELISA/neutralization assay.

13.1.6 Safety analysis

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. Make a list and descriptive summary from normal baseline to post-vaccination abnormality, or from abnormal baseline to post-vaccination enhancement of severity.

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 age groups and dose cohorts/placebo group.

13.2 Periodical Analysis

Initial analysis: all available safety and immunogenicity data will be included when all subjects in each age group complete Visit 9 (Day 50, 28 days after boost vaccination) to perform initial analysis. All available safety and immunogenicity data will be included when all subjects in each age group complete Visit 11 (visit at Month 6 after prime vaccination), Visit 12 (visit at Month 12 after prime vaccination), will update the statistical analysis.

Unblinding will be occurred after the completion of the initial analysis of immunogenicity and safety observation 28 days after boost vaccination, but the subjects will be kept blinded. More details regarding the analyses will be provided in the Statistical Analysis Plan (SAP).

The phase analysis report will be prepared after each time of analysis and the overall study report will be prepared at the end of study.

13.3 Determination of sample size

This study is a phase I exploratory clinical trial.

In the study, approximately 24 subjects will be included in each BNT162b1 dose cohort of each age group, with another 24 subjects vaccinated with placebo. If the occurrence of TEAE is 8%, the probability of observation of at least one TEAE in 24 subjects in each dose group is 86.5%, which is sufficient to perform safety evaluation for investigational vaccine at each dose level.

14.0 STUDY MANAGEMENT

14.1 Ethical considerations

This study will be conducted in accordance with the ethical requirements of the *Declaration of Helsinki* (Fortaleza 2013 edition), the International Conference on Harmonization (ICH) E6 *Good Clinical Practice*, national laws and regulations related to clinical study, and this study protocol.

The study protocol, informed consents, case report forms and other materials must be submitted to the ethics committee for approval before the study begins. The ethics committee will strictly follow the requirements of relevant laws and regulations to review and approve these materials. Only after receiving the approval of the ethics committee can the study be started.

During the study process, any changes to the protocol must be reviewed and approved by the ethics committee before they can be implemented.

In addition, the ethics committee will approve all clinical trial protocol amendments (except for Fosun approved administrative changes), informed consents and updates, subject recruitment procedures, written information to be provided to the subjects, available safety information, information about payment and compensation available to subjects, the Investigator's curriculum vitae and/or other evidence of qualifications, and any other documents requested by the ethics committee and regulatory authority as applicable.

14.2 Informed consent

The investigator or his/her designated representative will be responsible for explaining the study background, the pharmacological characteristics of the investigational medicinal product, the study protocol, and the benefits and risks of participating in the study to each subject, the legal representative of the subject or independent witness, and must give the subjects enough time and opportunity to ask about the details of the trial, allow them to obtain satisfactory answers for their questions and decide whether to participate in the study. Before a subject enter the study (before the screening test), the written informed consent signed by the subject or his/her legal representative and the investigator or his/her representative physician should be obtained.

The final text of the informed consent should include the following: study background, study objectives, study process, matters about subject cooperation, risk and discomfort of study participation, possible damage caused by trial-related operations, storage and handling of biological samples, benefits of study participation, alternative treatment, and related costs of study participation; treatment and appropriate insurance compensation a subject will receive in the event of damage related to the study; access to the study data and the confidentiality of subject information, etc. This informed consent should be written in non-technical language and approved by the institutional review board/independent ethics committee.

The subject or his/her legal representative, investigator who performs the informed consent process, or his/her representative is required to sign and date the informed consent. The informed consent should be kept by the investigator and the subject. If important new data related to the investigational drug or new information that will affect the subject's willingness to continue

participating in the study is found, the subject or his/her legal representative shall be notified in time to obtain the subject's informed consent again.

14.3 Protocol amendments

Any important modification to this protocol requires written amendments approved by the sponsor and Fosun and the investigator before implementation and reported to the ethics committee for approval and sent to the regulatory agency for filing.

Any changes to the protocol require written protocol amendments, and administrative changes must be approved by the sponsor and Fosun before implementation. If the change has a special impact on the safety of subjects, the scope of the study or the scientific quality of the study, an application needs to be submitted to the regulatory agency and the approval of the appropriate ethics committee of each study institution should be obtained. The above requirements shall not prevent the investigator or Fosun from taking immediate actions to protect the safety interests of all subjects. If the investigator believes that, for safety reasons, the protocol needs to be changed or deviated immediately to eliminate the harm to subjects, the medical monitor and the ethics committee of the study site should be notified immediately. The Fosun must notify the regulatory agency in accordance with local regulations.

For protocol amendments that only involve study management or administrative aspects, there is no need to apply to the regulatory agency or ethics committee, but the regulatory agency or ethics committee should be notified in accordance with local regulations.

14.4 Protocol deviations

If no formal clinical trial protocol amendment is determined and approved by the appropriate ethics committee, the investigator must not deviate from the study protocol unless it is to eliminate direct harm to the subject or when the change only involves the management or administrative aspects of the study and is approved by the medical monitor and/or the Fosun.

All requirements specified in the study protocol must be strictly implemented. Any intentional or unintentional deviation or violation of the trial protocol and GCP principles can be classified as deviation from the protocol or violation of the protocol. The investigator or personnel designated by the investigator should record and explain the details and reasons of the deviation/violation of the protocol, and inform the regulatory agency or ethics committee according to local regulations.

For the specific protocol deviation or protocol violation, see the medical monitoring plan.

14.5 Subject confidentiality and privacy

The subjects' personal information and privacy will be kept strictly confidential. During the study period, the subject's name and other personal data will be replaced by code or number. The collection and processing of personal data from subjects enrolled in this study will be limited to data that are essential to investigate the efficacy, safety, tolerability, quality and utility of the investigational drug. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.

The monitor, other authorized representatives of the Fosun, ethics committee, and representatives of the regulatory agency can consult these subject records. The results of the study may be published in a journal, but no personal information of subjects will be disclosed.

14.6 Monitoring

The investigator should allow the clinical research associate to inspect outpatient, laboratory, and pharmacy facilities, and review case report forms, informed consents, and all original data, thereby ensuring that the study complies with the Good Clinical Practice and local regulations.

According to the monitoring plan, the designated clinical research associate will conduct monitoring visits to each study site. Before the study begins, a site visit will be conducted. During the study, regular visits are required. Contact by telephone, fax or email can be used as needed as a supplement to the site visits.

Before the start of this study, the investigator will be notified of the expected frequency of monitoring visits. In addition, during the study, the investigator will be notified in advance before each monitoring visit. The purpose of visits is to ensure that the implementation of clinical study strictly adheres to the study protocol; and ensure the completeness and accuracy of the case report forms, which can be confirmed from the original documents.

The clinical research associate verifies that all case report forms are correctly and completely filled out and are consistent with the original data; all errors or omissions have been corrected or noted, signed and dated by the investigator. At each visit, in order to review and verify the case report forms, drug supply and inventory records, drug release and recovery records, and any additional records arranged, close cooperation between the investigator and clinical research associate is needed.

14.7 Quality assurance and quality control

The Fosun, investigator and contract research organization should perform their respective duties in accordance with the requirements of the GCP, strictly follow the trial protocol, and adopt the corresponding standard operating procedures to ensure the implementation of quality control and quality assurance systems for clinical tests, sample testing, data statistical calculations and other processes.

To ensure the quality of the study, all investigators must be trained for the trial protocol before the start of the trial. The SOPs must be strictly implemented during trial. The Fosun should send qualified monitors to supervise the trial process and verify the trial data.

The Fosun can entrust an inspector to conduct a systematic inspection of the trial-related activities and documents to verify 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 is recorded and reported in a timely, true, accurate and complete manner. Inspection should be performed by personnel independent of the clinical trial.

Relevant materials and documents (including case records) of study sites and laboratories participating in the clinical trial should be inspected and verified by the drug regulatory authority.

14.8 Direct access

The principal investigator will provide direct access to the source data and documents to the ethics committee personnel, monitors, and other designated personnel of the Fosun who conduct the study-related monitoring and/or review. The purpose of the monitoring or inspection is to systematically and independently review all study-related activities and documents, and determine whether these activities have been carried out, and record, analyze, and accurately report data according to the protocol, GCP, ICH guidelines, and any appropriate regulatory requirements. If the regulatory agency contacts the study site and/or the principal investigator for verification, the principal investigator will immediately notify the Fosun.

The investigator must inform the subject that his/her study-related records can be reviewed by the above individuals without infringing on the privacy of the subject's personal health information.

14.9 Data recording and storage

To ensure the evaluation and supervision of the regulatory agency and the Fosun, the investigator should agree to keep all study data, including confirmation records for all subjects (all recorded data, such as case report forms and hospital original records, can be effectively checked), all original signed subject informed consents, all case report forms, detailed records of drug distribution, etc. The storage period is 5 years after the end of the study or until the time limit agreed in the clinical contract and until the notification of destruction by the Fosun is obtained.

All the materials of this clinical study belong to the Fosun. Investigator shall not provide them to third parties in any form without the Fosun's written consent unless required by the regulatory agency.

14.10 Subject insurance and indemnity

The sponsor will provide insurance to every subject participating in the study in accordance with all applicable laws and regulations.

If a subject does suffer from an injury that has a causal relationship with the study due to participation in the study, the Fosun will bear the cost of treatment and corresponding economic compensation, except for those caused by medical accidents.

14.11 Storage and use of biological specimens

The biological samples of this study will be stored at the designated location for the use of this clinical study only. The blood samples will be destroyed after the test is completed, and the backup blood samples will be kept according to the requirements of national laws and regulations until a specified time after the investigational drug is approved for marketing.

14.12 Study interruption and early termination

The sponsor and Fosun reserve the right to stop the study at any time due to medical reasons or any other reasons. If the study is terminated or interrupted early, the Fosun should immediately

notify the investigator that the study has been terminated or interrupted, and explain the reason for the termination or interruption of the study. In accordance with the requirements of relevant regulations, the Fosun or investigator should also immediately notify the ethics committee that the study has been terminated or interrupted, and explain the reason.

The investigator reserves the right to decide whether the study should be stopped or not. If the investigator terminates or interrupts the study without the prior consent of the Fosun, the investigator should immediately notify the Fosun and the ethics committee and provide the Fosun and the ethics committee with detailed written explanations regarding the termination or interruption of the study. Study records must be kept.

14.13 Study summary report

After the end of the study, the investigator and the Fosun should objectively summarize the study results, statistically analyze the study data using appropriate statistical methods, make an objective evaluation of the drug safety based on the results, and prepare a written summary report of this clinical study after review and approval by the sponsor and Fosun.

14.14 Information disclosure and data publishing policy

The investigator should keep the information and data related to this study confidential and do not cite or publish relevant study results or data without the sponsor and Fosun’s consent.

The sponsor and Fosun have the right to publish information or data related to this study, or report it to the regulatory authority. If the sponsor and Fosun need to display the name of the investigator in the publication or advertising content, it should obtain the investigator's consent.

Appendix A WHO and CDC Website

- World Map indicating Areas with Risk of 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 Guidance for Adverse Events Grading Scale for Preventive Vaccine Clinical Trials in China

Appendix B Table 1 Grading scale for vaccination site (local) adverse events

Symptoms/signs	Grade 1	Grade 2	Grade 3	Grade 4
Pain and tenderness (optional; use tenderness for subjects who cannot express pain autonomously)				
Pain	Do not affect or slightly affect physical activity	Affect physical activity	Affect daily life	Loss of basic self-care ability, or hospitalization
Tenderness	Resist or flinch after touching	Cry after touching, but can be soothed	Cry continuously, unable to be soothed	Need emergency treatment or hospitalization
Induration*, swelling** #	2.5 ~ <5 cm in diameter or 6.25 ~ <25 cm^2 in area and do not affect or slightly affect daily life	5 ~ <10 cm in diameter or 25 ~ <100 cm^2 in area or affect daily life	≥10 cm in diameter or ≥100 cm^2 in area or ulceration or secondary infection or phlebitis or sterile abscess or wound drainage or seriously affect daily life	Abscess, exfoliative dermatitis, dermal or deep tissue necrosis
Rash*, blush ** #	2.5 ~ <5 cm in diameter or 6.25 ~ <25 cm^2 in area and do not affect or slightly affect daily life	5 ~ <10 cm in diameter or 25 ~ <100 cm^2 in area or affect daily life	≥10 cm in diameter or ≥100 cm^2 in area or ulceration or secondary infection or phlebitis or sterile abscess or wound drainage or seriously affect daily life	Abscess, exfoliative dermatitis, dermal or deep tissue necrosis
Others				
Pruritus	Pruritus at the vaccination site, resolved by itself or within 48 hours after treatment	Pruritus at the vaccination site, not resolved within 48 hours after treatment	Affect daily life	NA

Symptoms/signs	Grade 1	Grade 2	Grade 3	Grade 4
Cellulitis	NA	Need for treatment other than injection (e.g. oral antibacterial, antifungal, antiviral drugs)	Need for intravenous therapy (e.g. intravenous antibacterial, antifungal, antiviral drugs)	Sepsis, or tissue necrosis, etc.

Note: * In addition to directly measuring the diameter for graded evaluation, the progression changes of the measurement results should also be recorded.

** The maximum measured diameter or area should be used.

#The evaluation and grading of induration and swelling, rash, and blush should be based on the functional level and actual measurement results, and select a higher grading index.

Appendix B. Table 2 Grading scale for vital signs

Signs	Grade 1	Grade 2	Grade 3	Grade 4
Fever* [Axillary temperature (ºC)]	37.3~<38.0	38.0~<38.5	38.5~<39.5	≥39.5 for more than 3 days
ECG PR interval extension or atrioventricular block	PR interval 0.21 ~ <0.25 seconds	PR interval ≥0.25 seconds or second-degree atrioventricular block type Ⅰ	Second-degree atrioventricular block type Ⅱ or ventricular interval ≥ 3 seconds	Complete atrioventricular block
Signs	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Heart rate				
Tachycardia (beats/minute)	101~115	116~130	>130	Arrhythmia requiring emergency treatment or hospitalization
Bradycardia (beats/minute)	50~54	45~49	<45	Arrhythmia requiring emergency treatment or hospitalization
Blood pressure				
Hypertension (mmHg)	Systolic blood pressure: 140 ~ <160 or diastolic blood pressure: 90 ~ <100	Systolic blood pressure: ≥160 ~ <180 or diastolic blood pressure: ≥100 ~ <110	Systolic blood pressure: ≥180 or diastolic blood pressure: ≥110	Occurrence of previously undiagnosed life-threatening complications (eg malignant hypertension) or hospitalization
Hypotension (systolic blood pressure) (mmHg)	85~<89	80~<85	<80	Shock or hospitalization
Respirator rate (times/minute)	17~20	21~25	>25	Intubation required

Note: * Axillary temperature is usually adopted in China, and it can be converted into oral temperature and anal temperature if necessary. Generally, oral temperature = axillary temperature + 0.2 ºC;

Anal temperature = axillary temperature + (0.3 ~ 0.5ºC). When persistent high fever occurs, the cause of high fever should be identified as soon as possible.

Appendix B. Table 3 Grading scale for non-vaccination site (systemic) reactions

Organ system symptoms/signs	Grade 1	Grade 2	Grade 3	Grade 4
Gastrointestinal system				
Diarrhea	Mild or transient, 3 to 4 times/day, abnormal fecal appearance, or mild diarrhea lasting less than 1 week	Moderate or persistent, 5-7 times/day, abnormal fecal appearance, or diarrhea> 1 week	>7 times/day, abnormal fecal appearance, or hemorrhagic diarrhea, orthostatic hypotension, electrolyte imbalance, needing intravenous infusion> 2L	Hypotension shock, needing hospitalization
Constipation*	Stool softener and diet adjustment needed	Laxative medications needed	Stubborn constipation requiring manual defaecation or enema	Toxic megacolon or intestinal obstruction
Dysphagia	Mild discomfort when swallowing	Restricted diet	Diet and conversation are very limited; cannot eat solid food	Cannot eat liquid food; intravenous nutrition needed
Anorexia	Loss of appetite, food intake not reduced	Loss of appetite, reduced food intake, but no significant weight loss	Loss of appetite and significant weight loss	Intervention needed (Such as gastrointestinal feeding, parenteral nutrition)
Vomiting	1 ~ 2 times/24 hours without affecting activities	3 ~ 5 times/24 hours or limited activity	> 6 times within 24 hours or intravenous fluid therapy needed	Due to hypotensive shock, hospitalization or other means of nutrition are required
Nausea	Transient (<24 hours) or intermittent with basically normal food intake	Persistent nausea leading to reduced food intake (24 to 48 hours)	Persistent nausea leading to almost no food intake (> 48 hours) or the need for intravenous fluid therapy	Life threatening (Such as hypotension shock)
Musculoskeletal and connective tissue				

Organ system symptoms/signs	Grade 1	Grade 2	Grade 3	Grade 4
Myalgia (Non-vaccination site)	Do not affect daily activities	Slightly affect daily activities	Severe muscle pain, severely affecting daily activities	Emergency treatment or hospitalization
Arthritis	Mild pain, accompanied by inflammation, erythema, or joint swelling; but not hindering function	Moderate pain, accompanied by inflammation, erythema, or joint swelling; hindering function, but not affecting daily activities	Severe pain, accompanied by inflammation, erythema, or joint swelling; affecting daily activities	Permanent and/or disabling joint damage
Arthralgia	Mild pain, not hindering function	Moderate pain; needing analgesics and/or pain hindering function, but not affecting daily activities	Severe pain; needing analgesics and/or pain affecting daily activities	Disabling pain
Nervous System				
Headache	Not affecting daily activities, no treatment required	Transient, slightly affecting daily activities, possibly requiring treatment or intervention	Seriously affecting daily activities and requiring treatment or intervention	Intractable, requiring emergency treatment or hospitalization
Syncope	Close to syncope, without losing consciousness (e.g., pre-syncope)	Loss of consciousness, but no treatment is needed	Loss of consciousness, requiring treatment or hospitalization	NA
New-onset convulsions	NA	NA	1 ~ 3 occurrences of convulsion	Prolonged and multiple occurrences of convulsion (e.g., convulsion status) or difficult to control (e.g., intractable epilepsy)
Respiratory system				
Cough	Transient, no treatment needed	Continuous cough, effective treatment	Paroxysmal cough, cannot be controlled by treatment	Emergency treatment or hospitalization

Organ system symptoms/signs	Grade 1	Grade 2	Grade 3	Grade 4
Acute bronchospasm	Transient; no treatment required; FEV_1% is 70% to 80%	Treatment required; return to normal after bronchodilator treatment; FEV_1% is 50% to 70%	Cannot return to normal after bronchodilator treatment; FEV_1% is 25% to 50% or continuous intercostal depression	Cyanosis; FEV_1% <25%; or intubation required
Dyspnea	Dyspnea during exercise	Dyspnea in normal activities	Dyspnea at rest	Dyspnea, requiring oxygen therapy, hospitalization or assisted breathing
Organ system symptoms/signs	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Skin and subcutaneous tissue				
Pruritus at the non-vaccination site (No skin damage)	Slight itching, does not affect or slightly affects daily life	Pruritus affecting daily life	Pruritus making daily life impossible	NA
Abnormal skin and mucosa	Erythema/pruritus/color change	Diffuse rash/maculopapular rash/xerosis/desquamation	Blistering/exudation/desquamation/ulceration	Exfoliative dermatitis involving mucosa, or erythema multiforme, or suspected Stevens-Johnsons syndrome
Mental system				
Insomnia*	Mild difficulty falling asleep, not affecting or slightly affecting daily life	Moderate difficulty falling asleep, affecting daily life	Severe difficulty falling asleep, seriously affecting daily life, requiring treatment or hospitalization	NA
Irritation or suppression	Mild irritation or mild suppression	Irritability or drowsiness	Unable to soothe or respond poorly	NA
Mental disorders (Including anxiety, depression, mania, and insanity)	Mild symptoms, no need to see a doctor, or behavior does not affect or slightly	Have clinical symptoms and need medical treatment or behaviors affect daily life	Need to be hospitalized or unable to support daily life	Have a tendency to hurt him/herself or others or acute mental confusion or loss of basic self-care ability

Organ system symptoms/signs	Grade 1	Grade 2	Grade 3	Grade 4
Detailed symptoms should be reported	affects daily life			
Immune system				
Acute allergic reactions**	Local urticaria (blisters), requiring no treatment	Local urticaria requiring treatment or mild angioedema requiring no treatment	Extensive urticaria or angioedema requiring treatment or mild bronchospasm	Allergic shock or life-threatening bronchospasm or laryngeal edema
Others				
Fatigue, asthenia	Do not affect daily activities	Affect normal daily activities	Seriously affect daily activities and cannot work	Emergency treatment or hospitalization
Pain at non-vaccination site (Specify the location when reporting)	Mild pain, not affecting or slightly affecting daily life	Pain affecting daily life	Pain making daily life impossible	Disabling pain, loss of basic self-care ability

Note: FEV1% refers to forced expiratory volume in one second (FEV1) / forced vital capacity (FVC)

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

** Refers to type I hypersensitivity.

Refers to other non-vaccination site pains except muscle pain, arthralgia and headache.

Appendix B. Table 4 Grading scale for blood biochemistry

Testing parameter	Grade 1	Grade 2	Grade 3	Grade 4
Liver function (Elevated ALT, AST)	1.25~<2.5 ×ULN	2.5~<5.0×ULN	5.0~<10×ULN	≥10×ULN
Elevated total bilirubin (mg/dL; µmol/L)	1.1~<1.6×ULN	1.6~<2.6×ULN	2.6~5.0×ULN	≥5.0×ULN
Pancreatin (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

Testing parameter	Grade 1	Grade 2	Grade 3	Grade 4
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)				
Fasting	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
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 scale for blood routine tests

Testing parameter/Grading	Grade 1	Grade 2	Grade 3	Grade 4
Increased white blood cells (WBC, 10^9/L)	11~<13	13~<15	15~<30	≥30
Decreased white blood cells (WBC, 10^9/L)	2.000~2.499	1.500~1.999	1.000~1.499	<1.000
Decreased lymphocytes (LY, 10^9/L)	0.75~1.00	0.5~0.749	0.25~0.49	<0.25
Decreased neutrophils (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 scale for urine routine tests

Testing parameter	Grade 1	Grade 2	Grade 3	Grade 4
Urine protein (PRO) (Urine test strip testing)	1+	2+	3+ or higher	NA
Urine glucose (Urine test strip testing)	Trace ~ 1+ or ≤250mg	2+ or >250~≤500mg	>2+ or >500mg	NA
Red blood cells (microscopic examination) [The number of red blood cells (rbc/hpf) per high-power field of view (excluding female menstrual periods)]	6~<10	≥10	Gross hematuria with or without blood clots; or barrel-type urinary erythrocyte; or in need of treatment	Emergency treatment or hospitalization

Appendix B. Table 7 General principles for grading of other adverse events

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mild: Short-term (<48h) or slight discomfort, which does not affect activity, and no treatment is needed	Moderate: Mild or moderate limitation of activity, which may require medical attention, does not require or only requires mild treatment	Severe: Obviously restricted activity, requiring medical attention and treatment, possibly requiring hospitalization	Critical: Possibly life-threatening; serious limitation of activity, requiring intensive care	Death

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

Appendix C FDA Toxicity Grading Scale in Preventive Vaccine Clinical Trials

These guidelines for toxicity grading scales are primarily intended for healthy adult and adolescent volunteers.

Assessment of intensity

The intensity of AEs or SAEs will be graded by the investigator. For further guidance please refer to guideline "US FDA Guidance for Industry. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials". Where specific guidance for an adverse event term is not provided, the following general approach should be followed:

- Grade 1 - Mild; does not interfere with the subject's usual function.
- Grade 2 - Moderate; interferes to some extend with the subject's usual function.
- Grade 3 - Severe; interferes significantly with the subject's usual function.
- Grade 4 - Potentially Life threatening; life-threatening consequences, urgent intervention required.

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

- Guideline Section III. A for assessment of clinical abnormalities (local and systemic)

Local Reactions

Redness and swelling will be measured and recorded in centimeters and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 1.

Pain at the injection site will be assessed by the trial subject as absent, mild, moderate, or severe according the grading scale in Table 1.

Appendix C. Table 1 Local reaction grading scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Redness	2.5 cm to 5.0 cm	>5.0 cm to 10.0 cm	>10 cm	Necrosis or exfoliative dermatitis
Swelling	2.5 cm to 5.0 cm	>5.0 cm to 10.0 cm	>10 cm	Necrosis

Systemic events

Symptoms of vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 2.

Appendix C. Table 2 Systemic event grading scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)

Vomiting	1-2 times in 24 h	>2 times in 24 h	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 h	4 to 5 loose stools in 24 h	6 or more loose stools in 24 h	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/ tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

Fever

Fever is defined as an oral temperature of ≥38.0°C. Temperature will be measured and recorded to 1 decimal place and then categorized during analysis according to the scale shown in Table 3.

Appendix C. Table 3 Fever grading scale

	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 abnormalities

Laboratory abnormalities will be graded according to the grading scheme given in Table 4.

Appendix C Table 4: Laboratory abnormality grading scale

Hematology	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Hemoglobin (Female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (Female) change from baseline value - g/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	>5.0

Hematology	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Hemoglobin (Male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
Hemoglobin (Male) change from baseline value – g/dL	Any decrease – 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 decrease - cells/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Lymphocytes decrease - cells/mm^3	750 – 1,000	500 – 749	250 – 499	<250
Neutrophils decrease - cells/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	<500
Eosinophils - cells/mm^3	650 – 1500	1501 - 5000	>5000	Hypereosinophilic
Platelets decreased - cells/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000
Chemistry	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
BUN - mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN
Liver function tests – ALT, AST increase by factor	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)**	**Potentially Life Threatening (Grade 4)**
Bilirubin – when accompanied by any increase in liver function test - increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	>1.75 x ULN
Bilirubin – when liver function test is normal - increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN

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

Appendix D Collection and Processing of Throat Swab Specimens

The sampled person gargles with normal saline first, and the sampling person puts the swab in sterile normal saline to moisten it (it is forbidden to put the swab in the virus preserving fluid to avoid allergy caused by antibiotics). The sampled person slightly raises the head, opens the mouth widely and says "ah" to expose the pharyngeal tonsils on both sides. Pass the swab over the root of tongue, and wipe the pharyngeal tonsils on both sides of the sampled person with a little bit strength for at least 3 times back and forth. Then wipe up and down the posterior pharyngeal wall for at least 3 times, immerse the swab head into a tube containing 2 ~ 3 mL of virus preserving fluid (isotonic saline solution, tissue culture solution or phosphate buffer solution can also be used), discard the tail end, and tighten the cap.

Specimens are packed in the biosafety cabinet of a Biological Safety Level 2 laboratory after collection. All specimens should be placed in a freezing-resistant sample collection tube of suitable size with a screw cap and an inner gasket, and tightened. The sample number, type, name and sampling date are indicated on the outside of the container. Specimens should be sent to the laboratory as soon as possible after collection and tested as soon as possible. Specimens that can be tested within 24 hours can be stored at 4 °C; specimens that cannot be tested within 24 hours should be stored at -70 °C or below.

Appendix E Protocol amendments

Main Changes from Version 2.0 to Version 3.0

In-text location (Section)	**Before**	**After**	**Rationale**
Page header, the first page, synopsis	Version 2.0 Date: 10 JUL 2020	Version 3.0 Date: 5 AUG 2020	Version change
Synopsis, Section 10.1.2, 10.2.1, 10.2.2	Solicited **adverse event**	Solicited reaction	Change wording
Synopsis, Section 4.2.6, 6.1, 7.2	Age range for elderly subjects: **>55 years old**	≥65 years old and ≤85 years old	Consistent with the age range of the elderly subjects in Germany and US trials.
Synopsis, Section 9.1.6	Blood samples for humoral immunity (antibody) in adult group will be collected at Visit 1 (prior to prime vaccination) and Visits ~~3~~, 5 (prior to boost vaccination), 6, 8, 10, 11, 12.	Blood samples for humoral immunity (antibody) in adult group will be collected at Visit 1 (prior to prime vaccination) and Visits 5 (prior to boost vaccination), 6, 8, 10, 11, 12.	According to the preliminary immunogenicity data of Germany and US trials.
Synopsis, Section 7.2	Exclusion criteria for elderly subjects: 1. Physical examination and qualifying screening during screening visits, finding baseline laboratory abnormalities ≥grade	1. Physical examination and qualifying screening during screening visits, finding baseline laboratory abnormalities ≥grade 3 (**for hematology abnormalities**	According to the preliminary safety data of Germany and US trials.

	3 (according to grading criteria in Appendix B).	**with Grade ⩾2**, according to grading criteria in Appendix B).	
Synopsis, Table 2	Screening period: **7 days.**	Screening period: **14 days.**	Delay for IMP import
Section 6.6	During the time of enrollment into a given cohort, if any of the following events occur and are assessed to be vaccine related, further vaccination in that cohort will be **stopped**: • Anaphylaxis reaction considered related; • Generalized urticaria considered related; • 1/3 trial subjects in that cohort with any severe unsolicited local reaction, if considered related and not manageable with simple measures (e.g. cooling, analgesia, nonsteroidal anti-inflammatory drugs [NSAID]; • Any possibly related AEs within 7 days of vaccination assessed to be potentially life-threatening (Grade 4); • Any systemic SAE within 7 days of vaccination considered related; • Any fever >40.0°C (>104.0°F) within 7 days of vaccination considered related;	During the time of enrollment into a given cohort, if any of the following events occur and are assessed to be vaccine related, further vaccination in that cohort will be **suspended**: • Anaphylaxis reaction considered related; • Generalized urticaria considered related; • 1/3 trial subjects in that cohort with any severe unsolicited local reaction, if considered related and not manageable with simple measures (e.g. cooling, analgesia, nonsteroidal anti-inflammatory drugs [NSAID]; • Any possibly related AEs within 7 days of vaccination assessed to be potentially life-threatening (Grade 4);	According to the preliminary safety data of Germany and US trials.

	• ~~15% trial subjects with the severe (Grade 3) AE (including laboratory abnormalities with clinical manifestations) within 7 days of vaccination, considered vaccine related.~~	• Any systemic SAE within 7 days of vaccination considered related; • Any fever >40.0°C (>104.0°F) within 7 days of vaccination considered related; • **Occurence of grade ≥3 adverse events that lasted at least 48 h and associated with vaccination, and for which there is no alternative feasible explanation, in more than 20% of participants (except local reactions: pain/tenderness, erythema/redness, and induration/swelling) after primary or booster inoculation;** • **Occurence of grade ≥3 clinical laboratory abnormality related adverse events with clinical manifestations, that not recovered for at least 8 days and associated with vaccination, and for which there is no alternative feasible explanation, in more than 20% of participants after**	

		primary or booster inoculation.	
Section 6.7	Individuals with a clinically significant active infection (as assessed by the investigator) or axillary temperature ≥37.3°C or oral temperature ≥38.0°C, within 3 days **after** intended investigational vaccine/placebo vaccination.	Individuals with a clinically significant active infection (as assessed by the investigator) or axillary temperature ≥37.3°C or oral temperature ≥38.0°C, within 3 days **before** intended investigational vaccine/placebo vaccination.	Typo
Synopsis, Section 5.2.1, 10.1.2	pain, tenderness	pain/tenderness	According to the Guidance for Adverse Events Grading Scale
Synopsis, Section 5.1.3, 5.2.3	Exploratory endpoints: [redacted]	Exploratory endpoints: [redacted]	The lab test item change

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