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

Statistical Analysis Plan

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Sponsor: BioNTech RNA Pharmaceuticals GmbH

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1 List of Obbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemical classification
CoV	Corona Virus
COVID-19	Corona Virus Disease
CT	Computed Tomography
DLT	Dose Limited Toxicity
eCRF	electronical Case Report Form
EDC	Electronic Data Collection
ELISA	Enzyme-Linked Immunosorbent Assay
[redacted]	[redacted]
FDA	Food and Drug Administration
GMT	Geometric Mean Titer
GMFI	Geometric Mean Fold Increase
HIV	Human Immunodeficiency Virus
[redacted]	[redacted]
IFN	Interferon
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IM	Intramuscular Injection
IRT	Interractive Response Technology
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
NMPA	National Medical Products Administration
pH	Pondus Hydrogenii
PPS	Per Protocol Set
PT	Preferred Term
RNA	Ribonucleic Acid
SAE	Serious Adverse event
SARS	Severe Acute Respiratory Syndrome
SCR	Seroconversion Rate
SD	Standard Deviation
SOC	System Organ Class

SRC	Safety Review Committee
SS	Safety Set
TEAE	Treatment Emergent Adverse Event
TNF	Tumor Necrosis Factor
TVC	Total Vaccinated Cohort
WHODD	World Health Organization Drug Dictionaries

2 Introduction

2.1 Preface

This document presents the statistical analysis plan (SAP) for "Safety and Immunogenicity of SARS-CoV-2 mRNA Vaccine (BNT162b1) in Chinese Healthy Population: A Phase I, Randomized, Placebo-controlled, Observer-blind Study", which will provide the details and methods for analysis and reporting of the patient characteristics, immunegencity and safety. These results of this study might be included in a regulatory submission.

The SAP will be finalized and approved prior to database lock. Statistical programming may occur as study data accumulate in order to have analysis programs in place at the time of database lock.

Mockup table/figure/listing of this SAP will be seperately provided as an attachment.

Relevant Documents

Study Document	Approval/Effective Date
Protocol Version 3.0 (BNT162-03)	August 5, 2020
Blank eCRF V1.1 (BNT162b1 phase I Blank eCRF)	August 3, 2020
Data Management Plan V2.0 (BNT162b1 phase I DMP)	September 10, 2020

2.2 Purpose of Analyses

The purposes of the planned analyses described in this SAP are to assess the safety and tolerability profile, immunogenicity of prime/boost (P/B) immunization given 21 days apart from different dosages in SARS-CoV-2 naïve Chinese healthy population through 28 days after boost vaccination. Results from the analyses will be included in the final Statistical Analysis Report and Clinical Study Report and also be utilized for regulatory submissions, manuscripts, or other clinical development activities.

Post-hoc exploratory analyses not identified in this SAP may be performed to further examine the study data. These analyses will be clearly identified, where appropriate, in the final clinical study report. Additional analyses not prospectively identified in this SAP may also be performed for publications, regulatory or funding inquiries. These analyses, if performed, may not be reported in the final clinical study report, but will be fully documented in the document containing these additional analyses.

2.3 Summary of Statistical Analysis Changes to the Protocol

The analyses described in this analysis plan are consistent with the analyses described in the study protocol.

3 Objectives

3.1 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.

3.2 Secondary Objective

- 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 (including placebo and BNT162b1 subgroups), and observe the sustainability of the immune response to BNT162b1.

3.3 Exploratory Objectives

- [redacted]

4 Trial Design

4.1 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 1** and **Figure 2**.

This study will be implement by Jiangsu Provincial Center for Disease Control and Prevention.

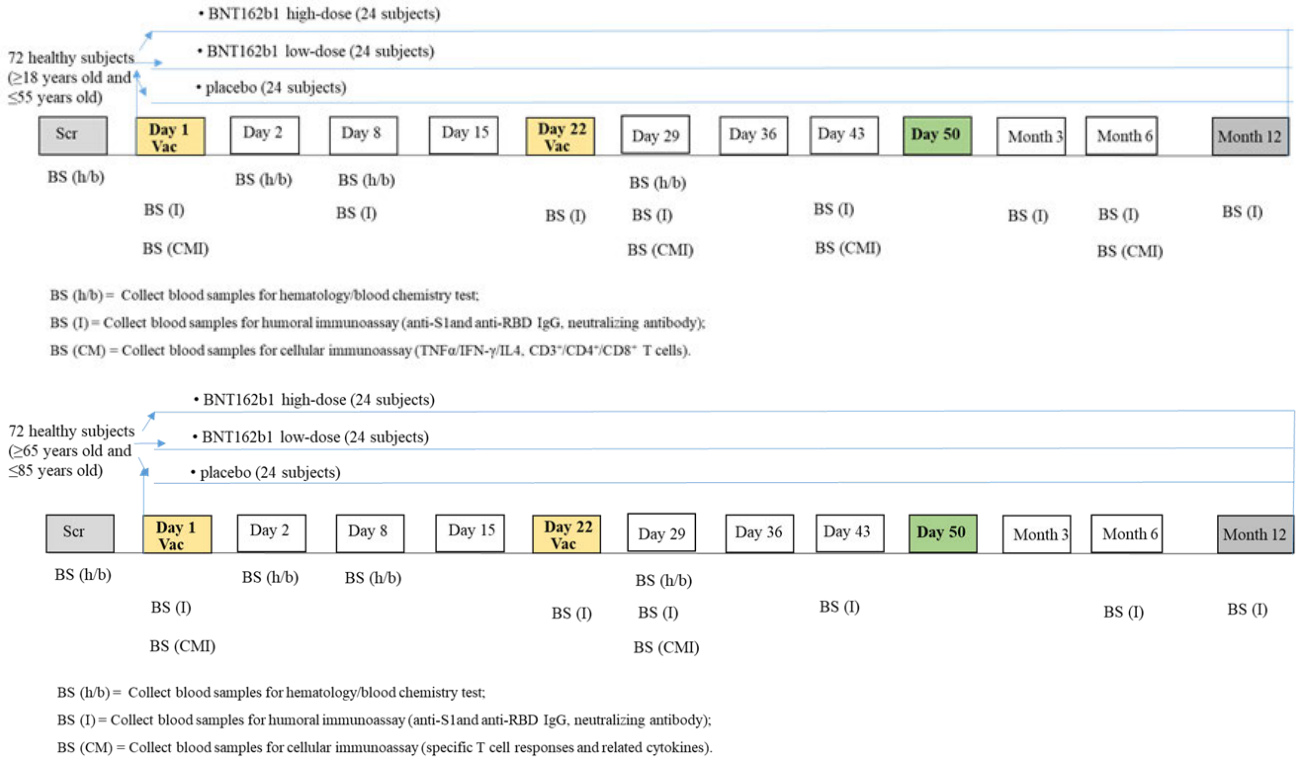

Figure 1 Overall study design: adult subjects (below) and elderly subjects (above)

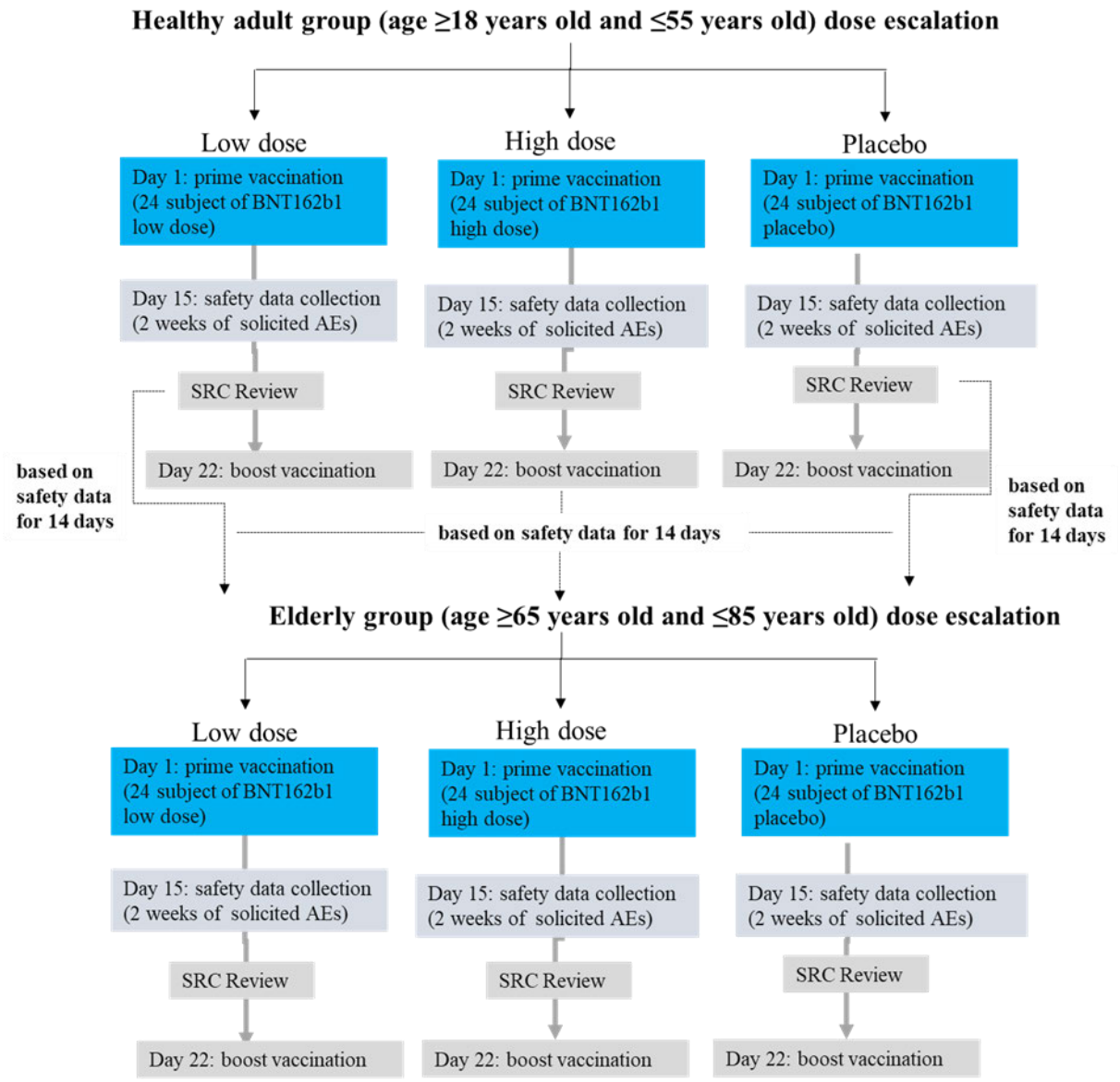

Figure 2 Schematic diagram of dose parallel design

4.1.1 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**).

4.1.2 Dose Modification

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

4.1.3 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 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 serious adverse event (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.

4.2 Randomization and Blinding

4.2.1 Randomization

Block randomization method will be used in this study. An independent randomization professional will generate the randomization table of subjects through SAS9.4 or above, which will be imported into the interactive response technology (IRT) system and 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 screening subjects will be assigned a screening number. Once screened successfully, the subject will be randomized by the IRT system and assigned a randomization number (the randomization number will be used as the unique subject ID number). The randomization parameters and their settings are described in detail in the randomization specification.

4.2.2 Blinding

The trial is a blinding study for subjects and observers. The subjects, data collectors (eg, investigator), and data evaluators (eg, study statisticians) are blinded. The Investigational Medicinal Product (IMP) assignment will be maintained by the unblinded site staff designee. Investigational products will not be blinded in this study.

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

The investigational vaccine/placebo blind should not be broken by the investigator unless the allocation group is necessary for the medical treatment of the subject. Once medical emergency occurs, as far as possible, the medical monitor should be contacted before IMP blinding is broken in order to discuss the need for urgent unblinding.

The Fosun’s Pharmacovigilance Department MUST be notified as soon as possible if IMP blinding is broken by the investigator; and if the unblinding is due to medical reasons (SAE), the completed SAE form must be sent within 24 hours according to the standard process for reporting of SAEs. The emergency unblinding date, time, and reason MUST be recorded in the source document, and the same information (except the time) MUST be recorded in the eCRF.

Unblinding will be conduct at the preliminary analysis of safety and immunogenicity at 28 days after boost vaccination, but the subjects will be kept blinded.

4.3 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.

5 Endpoints

5.1 Immunogenicity Endpoints

The Immunogenicy endpoints at Day 7, Day 21 after prime immunization, at Day 7, Day 21 after boost immunization, Month 3, 6 and 12 after prime immunization are defined as follows：

(1) Geometric mean titer (GMT) of anti-S1 IgG antibody.
(2) GMT of anti-RBD IgG antibody.
(3) GMT of SARS-CoV-2 neutralizing antibody (based on true virus' SARS-CoV-2 neutralizing test).
(4) Geometric mean fold increase (GMFI) in anti-S1 IgG antibody, as compared to baseline.
(5) GMFI in anti- RBD IgG antibody, as compared to baseline.
(6) GMFI in SARS-CoV-2 neutralizing antibody, as compared to baseline.
(7) Seroconversion rate (SCR) of anti-S1 IgG antibody. Seronegative is defined as titers below the starting dilution (1:100) and assigned a titer of 50. Seroconversion after vaccination is defined as a minimum of 4-fold increase of antibody titers, as compared to baseline.
(8) SCR of anti-RBD IgG antibody. Seronegative is defined as titers below the starting dilution (1:100) and assigned a titer of 50. Seroconversion after vaccination is defined as a minimum of 4-fold increase of antibody titers, as compared to baseline.
(9) SCR of SARS-CoV-2 neutralizing antibody. Seronegative is defined as titers below the starting dilution (1:10) and assigned a titer of 5. Seroconversion after vaccination is defined as a minimum of 4-fold increase of antibody titers, as compared to baseline.

The immunogencity endpoints at Month 3, 6 and 12 after prime imunizaton are to assess the immunogencity persisence of BNT162b1.

5.2 Exploratory Endpoints

[redacted]

5.3 Safety Endpoints

(1) **Adverse Events (AEs)**

(2) **Solicited AEs**: including systemic AEs and local AEs (injection site) collected actively within 14 days after each vaccination. Systemic AEs include fever, nausea, vomiting, diarrhea, headache, fatigue, myalgia, arthralgia, chills, loss of appetite, malaise, and local aes include pain, tenderness, erythema/redness, induration/swelling.

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

- ✓ Results in death
- ✓ Is life-threatening
- ✓ Requires hospitalization or prolongation of existing hospitalization
- ✓ Results in persistent or significant disability/incapacity
- ✓ Caused a congenital anomaly/birth defect of offspring
- ✓ Other significant medical events

(4) **Adverse Event of Special Interest (AESI)**: 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 as adverse events of special interest (AESI).

(5) **Laboratory Assessments**, including

(4.1)**Hematology**: including hemoglobin, hematocrit, red blood cell count, white blood cell count and differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count.

(4.2)**Blood chemistry**: including 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

(4.3)**Urinalysis**: including 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.

(4.4)**Thyroid function**: including triiodothyronine (T3), thyroxine (T4), thyroid stimulating hormone.

(4.5)**Coagulation function**: including prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT)), fibrinogen (FIB).

(6) **Vital Signs:** including systolic/diastolic blood pressure, pulse, respiratory rate, and body temperature.

(7) **Physical Examination**: including general, skin and mucosa, lymph gland, head, neck, spine, extremities, nervous system, and other.

6 Analysis Sets

(1) Total Vaccinated Cohort (TVC)

According to intention-to-treat principle, TVC is defined as all randomized subjects who have received at least one dose of IMP and have at least one post-baseline functional antibody titer immunogenicity assessment.

(2) Per Protocol Set (PPS)

PPS is defined as all subjects included in TVC who have no major protocol deviations and receive boost vaccination. The protocol deviation criteria are a part of the blinding data review. Major protocol deviations include:

- ✓ Violation of major inclusion or exclusion criteria,
- ✓ Assignment to incorrect vaccine/dose,
- ✓ Intake of prohibited concomitant medication
- ✓ Other major protocol deviations identified during blinding data review.

Immunogenicity analysis at Day 7 and Day 21 after prime and boost immunization will be based on both TVC and PPS. Immunogenicity persistence analysis for Month 3, 6 and 12 after prime immunization will be based on the evaluable subjects in TVC. The analysis of exploratory endpoints will be only based on TVC subjects.

(3) **Safety Set (SS):** is defined as all subjects who received at least one dose of IMP.

SS consists of total SS, SS for prime immunization (referred to as SS1), and SS for boost immunization (referred to as SS2). Safety analysis for each dose will be based on the vaccinated subjects of each

dose, respectively. SS1 is defined as all subjects received the prime immunization. SS2 is defined as all subjects received the boost immunization.

All above analysis sets will be determined after the discussion of pricinple investigator, project manager, statistician and data manager in data blind review meeting before database lock.

7 Statistical Methods

7.1 General Considerations

No formal statistical testing will be conduct in this study.

7.1.1 General Analysis Method

- **Descriptive Statistics**

Unless otherwise specified, the following descriptive statistics will be provided according to the type of variable:

- ✓ Continuous variables will be summarized by mean, standard deviation (SD), median, minimum (min) and maximum (max).
- ✓ Category or ordinal variables will be summarried by the number and percentage, where the percentage will be calculated based on the number of subjects in the corresponding analysis set as denominator and may be presented with exact 95% Clopper-Pearson CIs.

Additionally, descriptive statistics of titer and fold increase of titer will include geometric mean and its two-sided 95% confidence interval (CI). The geometric mean titer (GMT) is calculated as the mean of the logarithm of the functional antibody titers, back-transformed into the original scale. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean of the logarithmically transformed assay results and transforming the limits back to the original scale.

Geometric mean fold rise (GMFR) is calculated as the mean of the difference of logarithmically transformed assay results (post vaccination time point – pre vaccination time point) and back-transformed into the original scale. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and transforming the limits back to the original scale.

- **Decimal Places**

Unless otherwise specified, the decimal places will follow the following rules:

- ✓ The decimal places of min, max, median, Q1 and Q3 are consistent with the original data.
- ✓ The decimal places of mean, GM, SD and 95% CI are 1 more than the original data.
- ✓ Keep 2 decimal places in the percentage.

- ✓ Keep 2 decimal places in coefficient of variation (CV) and geometric coefficient of variation (GCV).
- ✓ Keep 4 decimal places if the p value is no less than 0.0001, and present as "<0.0001" if the p value is less than 0.0001.
- ✓ Keep 3 decimal places for all testing statistics.
- ✓ Keep 2 decimal places for the derived data.

7.1.2 Definitions and Derivations

- **Baseline**

Unless otherwise specified, baseline is defined as the last available value prior to the prime immunization.

- **Conversion among day, month and year**

Month = day/30.4375, and year = day/365.25, rounded to a decimal place.

- **Study Day**

Taking the date of first dosing as the start date,

- ✓ If study date < date of first dosing, then study day = study date – date of first dosing
- ✓ If study date >= date of first dosing, then study day = study date – date of first dosing + 1

- **Adverse Events Times**

Occurrence time of AE (day) = AE onset date – the corresponding immunization date.

Duration of AE = end date of AE – AE onset date + 1.

- **Treatment Emergent Adverse Event (TEAE)**

Treatment Emergent Adverse Event (TEAE), which is defined as any AE with an onset after the first immunization (if the AE was absent before the first immunization) or worsened after the first immunization (if the AE was present before the first immunization). The implementation of TEAE complies with the following rules: AE with missing start time or AE occurs after or on the day of the prime immunization will be regarded as TEAE, and otherwise will be regarded as non-TEAE.

- **The Severity of related TEAE**

If the severity of related TEAE under China NMPA Guidance is at least grade 1, which under FDA Guidance is less than grade 1 (ie. NULL in EDC), the corresponding event will not be regarded as adverse event under FDA Guidance.

Similarly, if the severity of related TEAE under FDA Guidance is at least grade 1, which under China NMPA Guidance is less than grade 1 (ie. NULL in EDC), the corresponding event will not be regarded as adverse event under China NMPA Guidance.

7.1.3 The Window of Analysis

For visits after baseline, all analyses will be conduct based on the scheduled visit in the protocol, and the unscheduled visits will not be included in the summary tables but be included in the listings.

7.1.4 Analysis Software

All statistical analysis will be conduct by SAS 9.4 or later version.

7.1.5 Tables and listings

- **Tables**

In general, data will be summarized by group (i.e., low dose, high dose and placebo). The groups will be presented in columns.

- **Listings**

Unless otherwise specified, dose level and subject number will always be included in listings. The EDC original data will be displayed in priority. All listings will be sorted first by dose level, then by subject number and finally, if applicable, by visit number and/or a relevant date (e.g. date of onset of AE).

7.2 Subejct Dispositions

The number and percentage of subjects randomized and subjects in the FAS/PPS/SS will be presented by group.

The number and percentage of subjects discontinued from the study with a summary of the primary reason will be presented by group. The number and percentage of subjects in all of the analysis sets will be summarized by group.

The subjects, who fail screening, discontinue and excluded from analysis sets will be listed, respectively.

The compliance (including whether complete the whole course of immunization, whether complete the immunogenicity and CMI blood collection according to the protocol requirements, and whether complete follow-up as required by the protocol) will be summarized by group.

7.3 Demographics and baseline Characteristics

Descriptive statistics will be used to summarize demographics and baseline variables as follows:

- Demographics: including age, gender, race, Chinese nationality, height and weight,
- Clinical characteristics: including travel history and contact history,
- Blood Virus Screening (HIV), nasopharyngeal swabs for SARS-CoV-2 testing,、Blood for SARS-CoV-2 Testing,

- Baseline of physical examinations,
- Baseline of vital signs,
- Baseline of 12-lead ECG and chest CT scan,

Baseline is defined as the last available value prior to the prime immunization.

Prior and/or concomitant diseases and surgery history will be coded using Medical Dictionary for Regulatory Activities Version 23.0 (MedDRA 23.0), and they will be classified and summarized by System Organ Classification (SOC) and Preferred Term (PT). Prior medication, vaccination in the past 4 weeks and concomitant medication will be coded using World Health Organization Drug Dictionaries Version Q1 2020 (WHO-DD Q1 2020), and summarized and presented by ATC2 and drugname.

Listing of prior and/or concomitant diseases, surgery history, prior medication, vaccination and concomitant medication will be provided.

7.4 Immunogenicity Analyses

Descriptive statistics, including geometric mean and 95% confidence intervals (CIs), for GMT and GMFI of anti-S1 IgG antibody at all post-baseline time points will be presented by group.

The number and percentage of subjects with seroconversion of anti-S1 IgG antibody will be summarized by group for all post-baseline time points. The 95 % confidence interval of percentage will be calculated by Clopper-Pearson method.

The geometric mean of anti-S1 IgG antibody at each time points will be plotted in log-scale. The reverse cumulative distribution plot is to display S1 IgG antibody distribution at each time points by group.

The same statistical methods as anti-S1 IgG antibody and seroconversion rate will be conducted to analyze anti-RBD IgG antibody and SARS-CoV-2 neutralizing antibody (based on true virus' SARS-CoV-2 neutralizing test).

7.5 Exploratory analyses

[redacted].

[redacted]

7.6 Safety Analyses

7.6.1 Adverse Events

All AEs will be coded using the recent version of MedDRA Version 23.0, and be summarized by SOC and PT. Additionally, solicited AEs, including systematic AEs and local AEs predefined in the protocol, will be summarized. The severity of AEs will be analyzed under China NMPA Guidance (Refer to Appendix B in the protocol: *NMPA Guidance for Adverse Events Grading Scale for Preventive Vaccine Clinical Trials in China*), and that of adverse reactions will also be analyzed under US Food and Drug Administration (FDA) Guidance (Refer to Appedix C in the protocol: *FDA Toxicity Grading Scale in Preventive Vaccine Clinical Trials*) in addition to China NMPA guidance.

This study is mainly to analyze Treatment Emergent Adverse Events (TEAEs), which are defined as any AEs with an onset on or after the first immunization (if the AE was absent before the first immunization) or worsened after the first immunization (if the AE was present before the first immunization). The Non-TEAEs occur before the first immunization will not be included in the analysis, but will be listed. Unless particularly stated, AEs mentioned in below text are TEAEs.

All solicited AEs, including systematic and local AEs, will be graded based on the criteria given in "NMPA Guidance for Adverse Events Grading Scale for Preventive Vaccine Clinical Trials in China". And all related systematic and local reactions will be graded at the same time according to "US FDA Guidance for Industry. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials". The solicited systematic and local reactions will be analyzed based on both NMPA and US FDA guidance.

The episodes of AEs, number and percentages of subjects who experience at least one TEAE as follows will be presented by group:

- Overall Summary of Adverse Events
- Any TEAEs by SOC and PT
- Related TEAEs by SOC and PT
- Unrelated TEAEs by SOC and PT
- Any TEAEs by Solicited and Unsolicited AEs
- Related TEAEs by Solicited and Unsolicited AEs
- Unrelated TEAEs by Solicited and Unsolicited AEs
- Grade≥3 TEAEs by SOC and PT, according to China NMPA guidance

- Grade≥3 related TEAEs by SOC and PT, according to China NMPA guidance
- Grade≥3 Solicited Systematic and Local Reactions, according to China NMPA guidance
- Grade≥3 Solicited Systematic and Local Reactions, according to US FDA guidance
- TEAEs leading to discontinuation by SOC and PT
- Related TEAEs leading to discontinuation by SOC and PT
- Unrelated TEAEs leading to discontinuation by SOC and PT
- AESIs by SOC and PT
- Related AESIs by SOC and PT
- Unrelated AESIs by SOC and PT
- TESAEs by SOC and PT
- Related TESAEs by SOC and PT
- Unrelated TESAEs by SOC and PT

The DLT AE and related DLT AE will be summaried by group. The distribution of severity, injection stage, occurrence will be provided for TEAEs and related TEAEs. The episodes of AEs, number and percentage of subjects with TEAEs will be summarized by worst grade by PT nested within SOC.

For each solicited reaction (including fever), the number and percentage of subjects with TEAEs within 14 days after each immunization will be summarized by severity and overall.

TEAE after each immunization will be summarized based on Safety Set for prime and boost immunization, respectively.

The following TEAEs will be listed by subject: related TEAEs, unrelated TEAEs, TEAEs leading to discontinuation, AESIs and SAEs.

7.6.2 Laboratory Assessments

Descriptive statistics for quantitive laboratory parameters at each time point and change from baseline will be provided by group.

Shift tables from baseline to the worst intensity grade will be provided by group for each gradable laboratory parameter, where low/normal/high or abnormal not clinically significant/ abnormal clinically significant /normal status had been ascertained.

Also, shift tables from baseline to the worst laboratory abnormality grade will be provided by group for each gradable laboratory parameter (if applicable), where laboratory abnormality grade is calculated according to the Appendix C Table 4: *Laboratory abnormality grading scale*.

Additionally, the occurrence of clinically significant abnormal laboratory results will be provided for each parameter and visit by group.

All of laboratory assessments will be listed by subject along with the normal ranges. Values that are below or above the normal ranges will be flagged.

7.6.3 Vital Signs

Descriptive statistics for each vital sign parameters at each time point and change from baseline will be provided by group.
All of vital sign data will be listed by subject.

7.6.4 Physical Examination

Shift tables from baseline to the worst intensity grade will be provided by group for each gradable physical examination parameter, where normal/abnormal not clinically significant/ abnormal clinically significant status had been ascertained.
All of physical examination will be listed by subject. Abnormal not clinically significant/ abnormal clinically significant status will be flagged.

7.7 Multiplicity

No multiplicity adjustment will be implemented in this Phase I dose-exploratory study.

7.8 Subgroup Analyses

In addition to the analyses on pooled adult and elderly population, immunogenicity, exploratory and safety analyses will be conducted separately on adult subjects and elderly subjects, respectively.

7.9 Handling of Missing Data

This study is Phase I dose-exploratory study, therefore the missing data in this study will not be handled.

7.10Timing of Statistics Analyses

Prime analyses will be conduct based on all available safety and immunogenicity data when all subjects in each age group complete Visit 9 (Day 50, 28 days after boost vaccination). Update analyses will be conduct when all subjects in each age group complete Visit 11 (Month 6 after prime immunization), Visit 12 (Month 12 after prime immunization).
Unblinding will be conduct along with the prime analysis of immunogenicity and safety at 28 days after boost immunization, but the subjects will be kept blinded.

Version History

Version	Date	Author	Changes & Rationale
V1.0	2020-08-28	[redacted]	Initial version.
V1.1	2020-10-29	[redacted]	Add laboratory analysis according to the Appendix C Table 4: Laboratory abnormality grading scale