Title page BNT162-14

EudraCT number:	2021-002387-50
Trial title:	A Phase II, open-label, rollover trial to evaluate the safety and immunogenicity of one or two boosting doses of Comirnaty or one dose of BNT162b2s01 in BNT162-01 trial subjects, or two boosting doses of Comirnaty in BNT162-04 trial subjects
Protocol version:	4.0
Protocol date:	20JAN2022
Investigational medicinal products:	BNT162b2 (Comirnaty®), BNT162b2s01/BNT162b2 (B.1.351)
SAP version:	Final 4.0
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Version history

Table 1: SAP version history summary

SAP version	Approval date	Change	Rationale
1	25APR2022	Not Applicable	Not applicable
2	22JUN2022	Minor formal corrections/typos throughout the document	
		Clarification of immunogenicity set	Adaptation to available study data
		The immunogenicity per-protocol set was updated for group B to only include subjects who received two doses of IMP.	Adaptation to study design
		AE analysis: AEs will be analyzed in three time intervals: 'Up to 28 days after the first IMP injection', 'Up to 28 days after the second IMP injection' and all TEAEs. All AESIs will be analyzed Additional TEAE categories will be analyzed	Adjusting the analysis to two IMP injections Important analyses
3	15JUL2022	Minor formal corrections/typos throughout the document	
		Updated definition of solicited AEs Minor updates in AE analysis	Clarification Adaptation to available study data
		Immunogenicity analysis:	Clarification

		SARS-CoV-2 infection will not be handled as concurrent event	
4	03APR2023	Author and reviewer changed	
		Added tables for results reporting in ClinicalTrials.gov andEudraCT	
		Minor formal corrections/typos throughout the document	
		Minor updates in AE analysis	Clarifications

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1. Introduction

This document presents the statistical analysis plan (SAP) for BNT162-14, a rollover trial investigating the safety and immunogenicity of one or two additional doses of Comirnaty® or one dose of BNT162b2s01 in healthy volunteers and immunocompromised subjects who received one or two previous injections of a BNT162 candidate vaccine in either the BNT162-01 trial or BNT162-04 trial.

This SAP describes the detailed procedures for the planned statistical analyses for the BNT162-14 protocol version 4.0, dated 20 January 2022 (**hereinafter referred to as "the protocol"**) except for the exploratory endpoints. Exploratory analyses are out of scope of this SAP and may be described in a different document. Changes from the protocol are documented in Section 7.1 Appendix 1.

The statistical analyses described in this document will be conducted by Staburo GmbH using SAS® software version 9.4 or higher.

This study will evaluate safety, adverse events, and immunogenicity assessments data.

1.1. Objectives and endpoints

Table 2: Objectives and endpoints

Objectives	Endpoints
Primary	
To determine the safety and tolerability of one or two boosting doses of Comirnaty or one dose of BNT162b2s01 in BNT162-01 trial subjects, or two boosting doses of Comirnaty in BNT162-04 trial subjects.	For all Group A and Group B subjects: • The proportion of subjects in each treatment group with at least one SAE or the proportion of AESIs occurring up to 26 weeks after the first IMP injection. For Group A and a selected subset of Group B subjects: • The frequency of solicited local reactions (pain, tenderness, erythema/redness, induration/swelling) at the injection site recorded up to 7 days after each IMP injection. • The frequency of solicited systemic reactions (vomiting, diarrhea, headache, fatigue/tiredness, fever, chills, nausea, new or worsened muscle pain, new or worsening joint pain) recorded up to 7 days after each IMP injection. • The proportion of subjects with at least one unsolicited TEAE occurring up to 28 days after IMP injection in each treatment group.

Objectives	Endpoints
Secondary	
To describe changes in SARS-CoV-2 neutralizing antibody titers from baseline to reference and SARS-CoV-2 variant B.1.351.	For Group A and Group B subjects (except transplant subjects): • Antibody titers to recombinant S1 and RBD protein derived from reference and SARS-CoV-2 variant B.1.351** will be assessed at baseline (Day 1) and then Day 8, Weeks 3*, 4, 7*, 12, and 26: o Neutralizing antibody titers. o Antibody titers (ELISA). • SARS-CoV-2 functional cross-neutralization of variant B.1.351** to reference strain. * Group B only ** Group A only For Group B transplant subjects only: • Antibody titers to recombinant S1 and RBD protein derived from SARS-CoV-2 will be assessed at baseline (Day 1) and then Day 8, Weeks 4, 12, and 26 post Dose 1, and at Dose 2 (Day 1) and then Day 8, Weeks 4, 12 and, 26 post Dose 2: ○ Neutralizing antibody titers ○ Antibody titers (ELISA)
Exploratory	
To describe B- and T-cell responses to SARS-CoV-2 S and RBD antigens after injection of Comirnaty or BNT162b2s01	For Group A subjects: • Baseline (Day 1) and then at Day 8, and Weeks12 and 26, CMI responses including B cell, CD4 and CD8 T-cell responses to S and RBD antigens of interest. For a selected subset of Group B subjects (except transplant subjects): • Baseline (Day 1) and then at Day 8 and Weeks 4, 12, and 26, CMI responses including B cell, CD4 and CD8 T-cell responses to S and RBD antigens of interest. For Group B transplant subjects only: • Baseline (Day 1) and then at Day 8, Weeks 4 and 12 post Dose 1 and at Dose 2 (Day 1) and then Day 8, Weeks 4, 12, and 26 post Dose 2 CMI responses

	including B cell, CD4 and CD8 T-cell responses to S and RBD antigens of interest.
To evaluate SARS-CoV-2 viral sequences in trial subjects who become infected (with or without symptoms).	In subjects who become SARS-CoV-2 infected: • SARS-CoV-2 S antigen sequences or whole genome sequencing of interest.
To describe time course changes in antibody titers after IMP injection in this trial in relationship to titer time from the last IMP injection in the BNT162-01 or BNT162-04 trials.	In a selected subset of subjects in Groups A and B (except transplant subjects): • SARS-CoV-2 antibody titers to recombinant S1 assessed at baseline (Day 1), and then at Day 8 and Weeks 12 and 26 to describe any potential time dependency immune responses that may include data from BNT162-01 and BNT162-04 trials for: o Neutralizing antibody titers. o Antibody binding (ELISA titers) to SARS-CoV-2 antigens. For Group B transplant subjects only: • SARS-CoV-2 antibody titers to recombinant S1 assessed at baseline (Day 1), and then at Day 8 and Weeks 12 and 26 post Dose 1 and Dose 2 (Day 1) and then Day 8, Weeks 4, 12, and 26 post Dose 2 to describe any potential time dependency immune responses that may include data from BNT162-01trial for: o Neutralizing antibody titers. o Antibody binding (ELISA titers) to SARS-CoV-2 antigens.
To evaluate cross-neutralization of vaccine-induced antibodies to emerging SARS-CoV-2 variants.	In select subjects in Groups A and B: • Measure cross-neutralization of other SARS-CoV-2 VOCs (e.g., using pVNT).

Abbreviations: AE = adverse event; AESI = adverse event of special interest; CD = cluster of differentiation; CMI = cell mediated immune response; d = day(s); ELISA = enzyme-linked immunosorbent assay; IMP = investigational medicinal product; pVNT = pseudovirus neutralization test; RBD = receptor binding domain; SAE = serious adverse event; S protein = SARS-CoV-2 spike protein; S1 = the subunit produced after the SARS-CoV-2 S protein is cleaved by host proteases; TEAE = treatment emergent adverse event; VOCs = variants of concern.

1.2. Trial design

Trial design	This is a Phase II, open-label, rollover trial to evaluate the safety and immunogenicity of one or two boost injections of Comirnaty or one dose of BNT162b2s01 in BNT162-01 trial subjects or two boosting doses of Comirnaty in BNT162-04 trial subjects. There will be two groups.
Trial population	**Group A:** Trial subjects from BNT162-01 who received two injections of 30 µg Comirnaty will be randomized 2:1 to one booster injection (BNT162b2s01:Comirnaty). Day 1 (baseline in this trial) must occur ≥24 weeks after the last Comirnaty injection in the BNT162-01 trial. Note: Transplant subjects from Cohort 13 of the BNT162-01 trial are excluded. **Group B:** Trial subjects in either the trial BNT162-01 or BNT162-04 who did not receive the full two vaccinations of 30 µg Comirnaty will be offered two injections of 30 µg Comirnaty as per the conditional marketing authorization. Day 1 (baseline in this trial) must occur ≥12 weeks after receiving the last BNT162 candidate vaccine in the BNT162-01 or BNT162-04 trial. Transplant subjects will receive one injection of Comirnaty which will be followed 3 to 7 months afterwards by a second injection of Comirnaty. An immunology subset of Group B consenting subjects will participate in more detailed tolerability (reactogenicity) and immunogenicity assessments. Consenting BNT162-01 Cohort 13 transplant recipients will also be included in the immunology subset of Group B. A detailed description of the inclusion and exclusion criteria can be found in Section 5.1 and 5.2 of the protocol.
Trial sites	Multiple sites in Germany that participated in the trials BNT162-01 and BNT162-04
Investigational medicinal products	**Name**: BNT162b2 (Comirnaty®) and BNT162b2s01, RNA based vaccines for prevention of COVID-19 **Type**: BNT162 RNA-LNP vaccines utilizing modRNA For Group A, the vaccine will be administered as booster injection. For Group B, the vaccine will be offered as per the conditional marketing authorization (except for transplant subjects). Consenting transplant subjects will be enrolled into

	Group B immunology subset and will receive one injection of Comirnaty® which could be potentially followed 3 to 7 months afterwards by a second injection of Comirnaty®. This group will be referred to as Group B transplants. Subjects not eligible during this period due to any medical reason (e.g., breakthrough infection causing investigational medicinal product delay decision from the investigator) will not receive the 4th dose in this trial. **Dose**: 30 µg of Comirnaty® or BNT162b2s01 **Dosing regimen:** Group A: One (at Day 1) intramuscular injection with 30 µg of either Comirnaty or BNT162b2s01. Group B: Two (at Day 1 and Day 21) intramuscular injections with 30 µg of Comirnaty, except Group B transplant subjects. Group B transplant subjects: Two intramuscular injections of 30 µg of Comirnaty, with injection 2 administered 3 to 7 months after injection 1 (Day 1). The planned time points for injection of the investigational medicinal product for Groups A and B are provided in the Schedule of Activities in the protocol (Section 1.3) **Administration route:** Intramuscular
Treatment and study duration	In total, the planned trial duration for a subject in this trial is approximately 30 weeks (≤4 weeks of screening and ~26 weeks follow-up).
Planned number of subjects	The maximum number of subjects in Group A will be 90 (including up to 15 HIV-positive subjects) and in Group B will be 459 (including up to15 transplant subjects). A subset of Group B (n=129) will be asked to participate in an immunology subset evaluation.
Randomization and blinding	Subjects in Group A will be randomized in a 2:1 ratio to either BNT162b2s01 or Comirnaty®. All subjects in Group B will receive at least one injection of Comirnaty®. They will not be randomized. The study is open-label.

1.3. Schedule of visits and procedures

The schedule of visits and procedures can be found in the protocol in Tables 1 (Group A), 2 (immunology subset of Group B, with two injections), 2a (immunology subset of Group B transplant subjects, injection 2), and 3 (Group B without immunologic assessments).

2. Statistical hypotheses

There is no formal statistical hypothesis under test.

3. Interim analyses

No formal interim statistical analysis will be performed. However, preliminary analyses may be performed after completion of Visit 5 for any group (i.e., Group A or Group B).

3.1. Data Monitoring Committee (DMC)

No DMC is planned.

There will be a Safety Review Committee (SRC). For details see protocol Section 10.1.5.

4. Sample size determination

No formal sample size calculations were performed as this rollover trial is based on the trials BNT162-01 and BNT162-04.

5. Analysis sets, protocol deviations and subgroups

5.1. Definition of analysis sets

Screened set (SCR)
The screened set is defined as all subjects who signed informed consent.

Safety set (SAF)

The safety set is defined as all subjects who received at least one dose of investigational medicinal product (IMP).

Safety boost set (SAFB)

The safety boost set is defined as all subjects who received two doses of IMP (first injection (Dose 1) and second injection (Dose 2)).

Note: Group A will be excluded from the SAFB as they receive only a single injection according to protocol.

Immunogenicity set (IMM)

The immunogenicity set is defined as all subjects who received at least one dose of IMP and have at least one post-baseline functional antibody titer (e.g., VNT or an equivalent assay) immunogenicity assessment.

Note: The expression 'have at least one post-baseline functional antibody titer immunogenicity assessment' refers to having either at least one post-baseline neutralizing antibody titer or one post-baseline ELISA titer immunogenicity assessment.

Immunogenicity per-protocol set (IMMPP)

The immunogenicity per-protocol set is defined as all subjects included in the immunogenicity set that have no major protocol deviations as determined by the clinician and who received two doses of IMP (first injection (Dose 1) (for Group A and B) and second injection (Dose 2) (only for Group B)).

Note: Subjects with any major protocol deviation thought to interfere with either the mechanism of action or immunogenicity test measurements will be excluded from IMMPP set.

Note: The definitions of all analysis sets apply within the BNT162-14 trial. In all analysis sets, subjects will be assigned to the treatment groups (i.e., vaccine type) according to the actual treatment they received ("as treated"). The condition of receiving two doses of IMP will not apply to Group A.

5.2. Protocol deviations

Protocol deviations are failures to adhere to the inclusion/exclusion criteria and protocol requirements and will be classified into major and minor protocol deviations. They will include, but are not limited to, protocol deviations from the site and process deviations tracked by the sponsor.

Major protocol deviations will be identified by medical review prior to database snapshot for main analysis.

The following criteria must be considered as major protocol deviations:

1. Violation of major inclusion or exclusion criteria
2. Assignment to incorrect vaccine/dose (i.e., actual vaccine/dose taken differs from the scheduled)
3. Non-compliance (e.g., no vaccine was administered)
4. Intake of prohibited concomitant medication
5. Missing primary endpoint data
6. Delayed safety reporting
7. Study assessments prior to signing informed consent form
8. Signing a non-approved version of the informed consent form.

PDs related to COVID-19 will be reported.

Major protocol deviations will be presented in a listing including information on treatment group, site, description of protocol deviation, classification, reason for deviation, coded term, date of occurrence and subject exclusion. For each group, vaccine and subgroup, the number and percentage of subjects with major protocol deviations will be summarized in total, by site and by protocol deviation type.

5.3. Subgroups

Subgroup analyses of HIV-positive subjects in Group A, of transplant subjects within Group B and of the immunology subset within Group B may be conducted as appropriate.

6. Statistical analyses

6.1. General considerations

No formal statistical testing will be done.

Unless otherwise specified, analyses will be based on data pooled across all study sites within the BNT162-14 trial.

Data assessed after a vaccination with a non-trial SARS-CoV-2 vaccine will be excluded from all statistical analyses (tables and listings) accordingly.

Notes:

- Data assessed on the same day as the non-trial vaccination will remain in the analysis.
- If the date of non-trial vaccination is missing, but month and year information is available, data assessed after the last day of the respective month will be excluded from statistical analysis.

6.1.1. Tables and listings

Tables

In general, data will be summarized as follows:

- Group A by vaccine [Comirnaty®, BNT162b2s01], and total
- Group A subjects having received Comirnaty® by HIV infection status
- Group A subjects having received BNT162b2s01 by HIV infection status
- Group B by transplant status, and total
- Group B immunology subset by transplant status, and total

Descriptive summary tables and figures will be based on scheduled visits.

Continuous variables will be summarized using the following descriptive statistics: number of subjects with non-missing data (n), mean, standard deviation (SD), median, minimum (min) and maximum (max).

Descriptive statistics of titer and fold rise of titer will additionally 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 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.

Categorical variables will be summarized presenting absolute and relative frequencies (n and %) of subjects in each category (including the category 'missing' if applicable). Percentages will be calculated based on the number of subjects in the respective analysis set (N) as denominator if not stated differently. Percentages may be presented with exact 95% Clopper-Pearson CIs.

SDs and CIs will only be calculated if values from at least 3 subjects are available.

Listings

Important Case Report Form (CRF) data and all relevant generated and transformed variables together with the original data items will be listed. Separate listings will be provided for Group A and B and immunology subset of Group B. Listings will be sorted first by vaccine (for Group A), subgroup (HIV-positive subjects for Group A, transplant subjects for Group B or immunology subset of Group B), site ID and by subject number and finally, if applicable, by visit number and/or a relevant date (e.g., date of onset of AE).

Programming

SAS® (version 9.4 or higher) programming will be performed according to Staburo GmbH standards as defined in SOP001_PROGRAMMING [1] and related work instructions. Special attention will be paid to planning and performance of quality control measures as documented in the quality control plan for the analysis of this study (see also SOP002_PROGRAM_QC [2]).

Analysis sets

The SCR will be used for disposition. The SAF will be used for analysis of safety and adverse events data. Some analyses of the adverse events will be repeated for Group B using the SAFB if the SAF and the SAFB sets differ. The IMM will be used for the analysis of immunogenicity data. The immunogenicity analyses may be repeated using the IMMPP if the two analysis sets differ significantly. This will be decided at the data review meeting.

Data of subjects who failed to complete all visits of the trial (dropout or withdrawal) will be reported as far as their data is available.

6.1.2. Definitions and derivations

Unscheduled visits

Unscheduled visits will not be included in the summary tables but will be included in the listings.

Variables

Unless otherwise specified, **baseline** is defined as last value prior to first injection of IMP (Dose 1) given in this BNT162-14 trial on Day 1, including unscheduled visits.

Change from baseline will be calculated as follows:

- Change from baseline = post-baseline assessment value – baseline assessment value.

Duration [days] will be calculated as follows:

- Duration [days] = last observation date – first observation date + 1

Time from first injection (Dose 1) to first reaction will be calculated as follows:
Time from first injection to first reaction [days] = first reaction date – date of first injection (Dose 1) + 1

Time from first reaction to last reaction will be calculated as follows:
Time from first to last reaction [days] = last reaction date – first reaction date + 1

Days since last injection will be calculated as follows:

Days since last injection = onset date of AE – date of last injection +1

For conversion of days to months or years the following rules will be applied:

- 1 month = 30.25 days
- 1 year = 365.25 days

Study Day and are defined as follows:

- Study day:
  - If study date < date of first injection (Dose 1), then study day = study date – date of first injection
  - If study date >= date of first injection (Dose 1), then study day = study date – date of first injection + 1

Fold rise will be calculated as follows:

- Fold rise = post-dose value / baseline value

6.1.3. Missing data

As a general rule, missing data will not be imputed (i.e., missing data will not be replaced but will be handled as “missing” in the statistical evaluation), with the following exceptions for summary analyses:

Clinical safety laboratory variables given as “<xx” will be evaluated as 0.5*xx in the summary tables. In the listings they will be displayed as “<xx” or similar.

Data values below lower limit of quantification (LLOQ) or detection (LLOD) will be imputed with 0.5*LLOQ or 0.5*LLOD, respectively, for the analysis of continuous data. Values above the upper limit of quantification (ULOQ) or detection (ULOD) will be imputed with 2*ULOQ or 2*ULOD, respectively, for the analysis of continuous data. In the listings they will be displayed as “<xx” or “>yy” as appropriate. In the tables they will be displayed as “<LLOQ”/“<LLOD” or “>ULOQ”/“>ULOD” in descriptive statistics (e.g., in mean, median, min, max) as appropriate. A footnote will be added to show the value of LLOQ or LLOD or ULOQ or ULOD.

6.2. Subject dispositions

All potential rollover volunteers must enroll in this trial within less than 18 months of their last injection of a BNT162 candidate vaccine in the parent BNT162-01 or BNT162-04 trials.

Subjects of the BNT162-01 and BNT162-04 will undergo a full complete screening for this rollover trial. For example, screening clinical laboratory tests will be performed to assess the new baseline values for the BNT162-14 trial.

Depending on the timing of follow-up in the parent trial, data from the parent trial may be used to determine eligibility in this rollover trial after the trial subject has consented. Once the trial subject has enrolled into this rollover trial, all safety reporting will occur through this rollover trial, this includes the reporting of non-vaccine related AEs that are unresolved from the parent trial, SAEs, and adverse events of special interest. All events occurred earlier (within screening) will be captured into the parent trial databases. All events that occurred between the trials will be captured as medical history events. For subjects who receive a non-trial SARS-CoV-2 vaccination, events will be collected until the date when the subject was vaccinated with the non-trial SARS-CoV-2 vaccine.

For the SCR, a listing of subjects having failed screening for BNT162-14 will be presented. This listing will include subjects having failed first screening and, if applicable, re-screening.

Subject disposition will be listed with date of informed consent, date of screening, date of injection and date of trial completion/discontinuation.
The number and percentage of subjects in the analysis sets will be summarized for the subjects in the SAF.

For the SAF, number and percentage of subjects having prematurely discontinued the trial with a summary of the primary reason (e.g., adverse events, death, withdrawal by subject, lost to follow-up) and of subjects who completed the trial will be presented.

Subjects having prematurely discontinued will be listed with date and reason for premature discontinuation.

Subjects in the SCR but excluded from the SAF, subjects in the SAF but excluded from the SAFB/IMM/IMMPP will be listed with reason for exclusion.

6.3. Baseline characteristics

6.3.1. Demographics

Demographic and baseline variables will be summarized for subjects in the SAF analysis set. Age (calculated as age [years] + age_months [months] /12) and weight [kg] will be summarized as continuous data.

Additionally, age will be summarized with the following categories:

- 18 to <= 64 years

- 65 to <= 84 years
- >=85 years

Gender (male or female), ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown), race (White, Black, or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Not reported, Unknown, Other) and country will be summarized as categorical data.

A listing of demographic data will be provided.

6.3.2. Concomitant medication

For Group A, prior and concomitant medications will be defined using start and stop dates recorded, relative to the first and last injection of trial medication. Any medication taken before 28 days prior to the start date of IMP injection will not be classified as prior or concomitant medication unless a SARS-CoV-2 vaccination was received outside of the parent trial (outside the booster phase). A prior medication will be defined as any therapy taken 28 days prior to (but not including) the start date of IMP injection. A concomitant medication will be defined as any medication either:

- Taken prior to (but not including) the start date of IMP injection and
    - Ongoing at the first vaccination
    - Or with a missing end date
- Or with a start date on or after the date of the first injection (Dose 1) up to Visit 4 (Group A and Immunology subset of Group B) or up to Visit 10 (Immunology subset of Group B transplant subjects)
- Or with a start date on or after the date of the first injection (Dose 1) until the last trial visit for any non-trial SARS-CoV-2 vaccinations

If a medication cannot be clearly assigned to prior medication due to missing dates, it will be evaluated as concomitant medication.

Medications will be coded using the WHO Global (Drug Insight) March 2021 B3 standard drug codes resulting in Anatomical Therapeutic Chemical (ATC) codes indicating therapeutic classification. This also includes COVID-19 vaccine adaptations in WHO Global (Drug insight) March 2021.

Listings of prior and concomitant medications will be provided.

Concomitant therapy recording is not required for Group B but will be recorded in the SAE or AESI report.

6.3.3. Medical history

Medical history data will be coded using the Version Medical Dictionary for Regulatory Activities (MedDRA®) coding system 24.0.

A summary table of type of transplant and number of transplants will be provided for the transplant subjects.

A listing of medical history data will be provided. A listing of transplant information and HIV information will be provided.

6.4. Primary endpoint analyses

The primary endpoints are solicited local reactions at the injection site occurring up to 7 days after each injection, solicited systemic reactions occurring up to 7 days after each injection, the proportion of subjects with at least one serious adverse event (SAE) occurring up to 26 weeks after the first injection, the proportion of subjects with at least one adverse event of special interest (AESI) occurring up to 26 weeks after the first injection and the proportion of subjects with at least one unsolicited treatment emergent adverse event (TEAE) occurring up to 28 days after each injection.

All primary analyses will be performed using the SAF and analyses of adverse events for Group B will possibly be repeated using the SAFB.

6.4.1. Solicited local reactions

Definition
Solicited local reactions at the injection site consist of pain, tenderness, erythema/redness, and induration/swelling. These are assessed by the subject in a diary as stated in the protocol Section 8.2.4.

Local reactions will be graded based on the criteria given in the United States (US)Food and Drug Administration (FDA) Guidance for Industry 'Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials' for 'Local Reaction to Injectable Products'. The grading of local reactions to injectable product is detailed in Section 10.3.2.1 (Table 5) of the protocol. The grades are Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), and Grade 4 (potentially life threatening).

The solicited local reactions will be evaluated for each injection, i.e.

- First injection (Dose 1) up to day 7 (inclusive) after first injection (Group A, immunology subset of Group B)
- Second injection (Dose 2) up to day 7 (inclusive) after second injection (Dose 2) (immunology subset of Group B)
- Both intervals combined (immunology subset of Group B)

The intervals will start with the date and time of the injection.

Note: The interval 'first injection (Dose 1) up to day 7 after first injection (Dose 1)' includes study day 1 to study day 7. This applies to the other intervals accordingly.

All analyses are based on local reactions independent of their relatedness to IMP.

Analysis

All analyses will only be performed for Group A and immunology subset of Group B.

Local reactions with missing time and occurring on the day of first injection (Dose 1) will be assigned to all intervals starting with the first injection (Dose 1). Local reactions with missing time and occurring on the day of the second injection (Dose 2) will be assigned

to all intervals including the second injection. Local reactions with missing date will be assigned to each of the applicable intervals if it cannot be ruled out, that it belongs to the time interval.

The number and percentage of subjects reporting at least one local reaction in each applicable time interval will be summarized for any local reaction and by worst grade.

The denominator of the percentages will be the number of subjects with any information on local reactions in the diary available in the respective time interval.

The number and percentage of subjects reporting at least one local reaction will be summarized by local reaction type (pain, tenderness, erythema/redness, and induration/swelling) and by worst grade for each time interval. The denominator of the percentages will be the number of subjects with any information on local reactions in the diary available in the respective time interval. This analysis will be repeated for local reactions of Grade ≥3.

Additionally, the following analyses will be done for local reactions and for any reaction (local or systemic):

Time after first injection (Dose 1) (Group A and immunology subset of Group B) and after second injection (Dose 2) (immunology subset of Group B) from

- First injection (Dose 1) to first reaction
- First injection (Dose 1) to first reaction of Grade ≥3
- First reaction to last reaction and
- First reaction of Grade ≥3 to last reaction of Grade ≥3

will be determined per subject and will be summarized descriptively overall and by local reaction term.

Moreover, the frequency of subjects with any solicited local reactions and solicited reactions within 7 days after each dose per day and the frequency of subjects with solicited local reactions within 7 days after each dose by term per day will be analyzed. This analysis will be analyzed additionally for solicited local reactions of Grade ≥3.

The compliance with the diary from each injection up to 7 days after each injection will be presented. A table giving the number and percentage of subjects with any information on local reactions in the diary (overall and by local reaction term) available per day will be given. The compliance with the diary based on any information on any reaction (local or systemic) will also be given.

All local reactions from the trial will be listed. Additionally, all days with information on local reactions in the diary will be listed.

For Group A (by randomization) and immunology subset of Group B (by transplant status yes/no), local reactions assessed by subject will be presented graphically using a bar plot. The following plot will be provided:

- Local reactions within 7 days after each dose by worst grade

6.4.2. Solicited systemic reactions

Definition

Solicited systemic reactions consist of vomiting, diarrhea, headache, fatigue/tiredness, fever, chills, nausea, new or worsened muscle pain, and new or worsening joint pain. These are assessed by the subject in a diary.

Solicited systemic reactions will be graded based on the criteria given in the US FDA Guidance for Industry 'Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials'. The grades are Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), and Grade 4 (potentially life threatening). Fever is graded as mild (38.0 to 38.4°C), moderate (38.5 to 38.9°C), severe (39.0 to 40.0°C, and potentially life threatening (>40.0°C).

The solicited systemic reactions will be evaluated for each injection, i.e.

- First injection (Dose 1) up to day 7 (inclusive) after first injection (Group A, immunology subset of Group B)
- Second injection (Dose 2) up to day 7 (inclusive) after second injection (Dose 2) (immunology subset of Group B)
- Both intervals combined (immunology subset of Group B)

The intervals will start with the date and time of the injection.

Note: The interval 'first injection (Dose 1) up to day 7 after first injection' includes study day 1 to study day 7. This applies to the other intervals accordingly. All analyses are based on systemic reactions independent of their relatedness to IMP.

Analysis

Solicited systemic reactions will be analyzed in the same way as solicited local reactions (see Section 6.4.1).

6.4.3. Adverse events

Definition

For detailed information on adverse events see Section 10.3 of the protocol. Solicited AEs that are recorded from the subject diaries on the reactogenicity CRFs will not be reported as AEs unless the solicited AE meets criteria for SAE or begins after Day 8 or started before Day 8 and continues past Day 8.

Adverse events (AEs) will be coded using the Version MedDRA® 24.0 to get a system organ class (SOC) and preferred term (PT) for each AE.

A TEAE is defined as any AE with an onset after the first injection (Dose 1) (if the AE was absent before the first injection) or worsened after the first injection (Dose 1) (if the AE was present before the first injection (Dose 1)). AEs with an onset date more than 28 days after the last injection will be considered as treatment emergent only if

assessed as related to IMP by the investigator. AEs that cannot be determined to not be treatment emergent due to missing date or time will be defined as TEAE.

Note: To clarify the definition in the protocol, AEs with an onset date at the date of the first injection (Dose 1) will only be considered as treatment emergent if the AE occurred after the first injection (Dose 1). AEs with missing time and occurring on the day of Dose 1 or AEs with missing date will be analyzed as treatment emergent.

TEAEs will be evaluated for following time interval and groups:

- Up to 28 days after the first IMP injection (Group A and immunology subset of Group B)
- After the first IMP injection up to 28 days after the second IMP injection (immunology subset of Group B non-transplant)
- After the second IMP up to 28 days after the second IMP injection (immunology subset of Group B transplant)
- All TEAEs (Group A and immunology subset of Group B)

AEs are assigned to the time interval according to their start date and time. AEs with missing date will be assigned to each of the respective intervals if it cannot be ruled out, that it belongs to the time interval.

Adverse events of special interest (AESIs)

The following events will be reported as AESIs: myocarditis, pericarditis, anaphylaxis, thromboembolic events (e.g., deep vein thrombosis, stroke, myocardial infarction), immune thrombocytopenia and immune based neurologic events (e.g., optic neuropathy, Guillain-Barré syndrome). AESIs are recorded in the CRF.

AESIs and SAEs will be evaluated up to 26 weeks after the ICF was signed for all groups.

Analysis

The following TEAE types will be analyzed for Group A and the immunology subset of Group B:

- Any TEAE
- Related TEAE, i.e., suspected unexpected serious adverse reactions (SUSARs) which will be described in safety reports
- Any Grade ≥3 TEAE
- Any related Grade ≥3 TEAE
- Any treatment emergent serious adverse event (TESAE)
- Related TESAE
- TEAESI

- TEAEs linked to confirmed COVID-19 cases (TEAEs with preferred term = ‘COVID-19’)
- Deaths

The following AE types will be analyzed for all groups if applicable:

- Any AE
- Related AE
- Any Grade ≥3 AE
- Any related Grade ≥3 AE
- Any serious adverse event (SAE)
- Related SAE
- AESI
- Related AESI
- Any AEs linked to confirmed COVID-19 cases (AEs with preferred term = ‘COVID-19’)
- Deaths

Overall summary of TEAEs

For Group A and the immunology subset of Group B, the number and percentage of subjects reporting at least one TEAE and the number of TEAEs will be summarized for all TEAE types defined above overall.

For Group B, the number and percentage of subjects reporting at least one

- SAE
- AESIs

will be summarized.

For Group A and the immunology subset of Group B, the number and percentage of subjects reporting at least one TEAE and the number of TEAEs will be summarized by PT nested within SOC for each of the following AE types: Any TEAE, Related TEAE, Any TESAE, Related TESAE, TEAEs leading to treatment discontinuation, solicited TEAEs and fatal TEAE.

For Group B, the number and percentage of subjects reporting at least one TESAE will be summarized by PT nested within SOC.

If a SOC and PT is reported more than once for a subject, the subject will only be counted once for this SOC and PT at the worst grade level. All TEAE summary tables will be sorted alphabetically by SOC and PT within SOC.

TEAE by grade

For Group A and the immunology subset of Group B, the number and percentage of subjects with TEAEs and TESAEs will be summarized by worst grade by PT nested within SOC by time interval.

For Group B, the number and percentage of subjects with TESAEs will be summarized by worst grade by PT nested within SOC.

The worst grade will be counted if a TEAE is reported more than once by the same subject for this SOC and PT.

AEs

The number and percentage of subjects reporting at least one AE and the number of AEs will be summarized for the above defined AE types for all groups.

SAEs

The number and percentage of subjects reporting at least one SAE and the number of SAEs will be summarized by PT nested within SOC for each of the following AE types: Any SAE, Related SAE, fatal SAE and related fatal SAE.

Non-SAEs

The number and percentage of subjects reporting at least one non-SAE and the number of non-SAEs with >5% within any arm or reporting group will be summarized by PT nested within SOC.

AE listings

All TEAEs of subjects that withdrew due to AE, SAEs, and AESIs will be listed. The duration of an AE will be calculated in hours. If for an AE the time is missing then the duration will be calculated in days.

6.5. Secondary endpoint analyses

Secondary endpoints are neutralizing antibody titers and antibody titers (ELISA) to recombinant S1 and RBD protein derived from reference and SARS-CoV-2 variant B.1.351 (B.1.351 for Group A only) and SARS-CoV-2 functional cross-neutralization of variant B.1.351 to reference strain (for Group A only). All secondary analyses will be performed using the IMM and possibly additionally the IMMPP population, see Section 5.1.

Any COVID-19 vaccination that a subject received outside of this trial will be considered as concurrent event and all immunogenicity data assessed beyond this event will be excluded from the immunogenicity analyses.

6.5.1. Neutralizing antibody titers and antibody titers (ELISA)

Definition

For each subject and each time point two titers for each variant will be determined, as each sample will be measured in replicate. The response per subject and timepoint is defined as the geometric mean of the two titers.

Analysis

Antibody titers (ELISA) derived from reference will be summarized using descriptive statistics for all time points for Group A, Group B and the immunology subset. Additionally, GMT with 95% CI will be presented.

The same analysis will be performed for antibody titers (ELISA) derived from SARS-CoV-2 variant B.1.351 for Group A only.

The antibody response will be listed.

Figures: For each vaccine type, antibody titers (ELISA) will be presented graphically displaying GMT with 95% CI at all time points (two line plots, one with linear and one with log scaled y-axis). For group A, additionally, the same plot will be created by treatment group.

The same analysis will be repeated for neutralizing antibody titers.

6.5.2. Neutralizing antibody titers and antibody titers (ELISA) fold rise

Definition

The fold rise of the antibody response will be calculated for all post-baseline time points as post-dose value divided by baseline value. The baseline value will be the BNT162-14 baseline, i.e., the last value prior (predose V1) to first injection of IMP (Dose 1) given in this BNT162-14 trial on Day 1, including unscheduled visits.

Analysis

The fold rise in antibody titers (ELISA) derived from reference will be summarized using descriptive statistics for all time points for Group A, Group B and the immunology subset. Additionally, GMFR with 95% CI will be presented.

The same analysis will be performed for antibody titers (ELISA) derived from SARS-CoV-2 variant B.1.351 for Group A only.

Antibody titers (ELISA) fold rise will be listed.

Figures: The fold rise of antibody titers (ELISA) will be presented graphically displaying GMFR with 95% CI at all time points (line plot).

The same analysis will be repeated for neutralizing antibody titers

6.5.3. Seroconversion

Definition

Seroconversion is defined as a minimum of 4-fold rise of antibody titers as compared to

- parent trial (BNT162-01 or BNT162-04) baseline (only for titers derived from reference strain;baseline refers to pre-dose V1 in BNT162-01 or pre-dose V1 in BNT162-04)
- BNT162-14 baseline, i.e., the last value prior to first injection of IMP (Dose 1) given in this BNT162-14 trial on Day 1, including unscheduled visits (for both titers derived from reference strain and from SARS-CoV-2 variant B.1.351)

Analysis

The number of subjects with seroconversion in antibody titers (ELISA) derived from reference will be summarized by number and percentage with 95% confidence interval for all post-baseline time points for Group A, Group B and the immunology subset. The denominator of the percentages will be the number of subjects with data available at the respective visit.

The analysis based on BNT162-14 baseline, will be performed for antibody titers (ELISA) derived from SARS-CoV-2 variant B.1.351 for Group A only.

Seroconversion data of the antibody titer (ELISA) will be listed.

The same analysis will be repeated for neutralizing antibody titers

6.5.4. SARS-CoV-2 functional cross-neutralization of variant B.1.351 to reference strain

Definition

The SARS-CoV-2 functional cross-neutralization of variant B.1.351 to reference strain is defined as the ratio of the GMT (reference / variant B.1.351). The geometric mean titer ratio is calculated as the GMT of reference divided by the GMT of variant B.1.351.

Analysis

For subjects of Group A, GMTs with 95% CI for all time points will be presented for variant B.1.351 and reference strain (see Section 6.5.1). Moreover, the GMT ratio between reference and variant will be presented.

6.6. Sensitivity analyses

Sensitivity analyses of immunogenicity endpoints (see Section 6.5) may be conducted as appropriate by excluding subjects with a SARS-CoV-2 infection during the BNT162-14 trial.

6.7. Exploratory analyses

Exploratory analyses are out of scope of this SAP and may be described in a different document.

6.8. Further safety analyses

All analyses will be performed in the SAF for Group A and the immunology subset of Group B.

Safety data that will be presented includes IMP compliance, clinical laboratory assessments and vital signs.

6.8.1. Compliance

IMP compliance will be summarized.

Time of first injection after receiving the last BNT162 candidate vaccine in the BNT162-01 or BNT162-04 trial and Time of second injection after receiving the first injection will be summarized.

Drug exposure will be listed.

6.8.2. Laboratory assessments

Definition

Clinical laboratory data to be summarized includes hematology, clinical chemistry, and urinalysis and will be assessed at the time-points indicated in Tables 1, 2, 2a, and 3 of the protocol.

The following clinical laboratory variables will be assessed:

Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count and differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count.

Clinical chemistry

Alkaline phosphatase, creatinine, ferritin, C-reactive protein, albumin, alanine aminotransferase, amylase, aspartate aminotransferase, gamma glutamyl transpeptidase, total bilirubin, blood urea nitrogen, glucose, lipase, sodium, potassium, calcium.

Follicle-stimulating hormone: In women only.

Urinalysis

Dipstick: glucose, bilirubin, ketone, specific gravity (1 mL ≙ 1 g), blood, pH, protein, urobilinogen, nitrite, and leukocytes.

Microscopic urinalysis: If warranted by dipstick results, urine sediment will be microscopically examined for presence of red blood cells, white blood cells, casts, crystals, epithelial cells, and bacteria.

All laboratory tests are classified as normal or lower or higher than reference range (abnormal). All abnormal laboratory tests will be classified by the investigator as clinically significant (CS) or not clinically significant (NCS).

Abnormal lymphocytes data will be categorized as defined in table 7 in the protocol as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), and Grade 4 (potentially life-threatening).

Analysis

Clinical laboratory variables at each time-point and its change from baseline to each post-baseline time-point (for continuous variables and if applicable) will be summarized using descriptive summary statistics for each parameter.

Number and percentage of subjects with low, normal and high clinical laboratory values at each time-point will be summarized for each parameter. The same table will be provided for the grading scheme (grades mild, moderate, severe and life threatening) for lymphocytes.

The number and percentage of subjects with CS abnormal, abnormal (NCS), normal and missing values will be summarized for each parameter.

Clinical laboratory values for each parameter will be summarized using shift tables from baseline to worst post-baseline value with respect to reference range values (low, normal, high), if applicable. Worst post-baseline might be in both directions. Each subject may be counted in the parameter high and in the parameter low category. A subject will only be counted in the normal category if all post-baseline values are normal. If several post-baseline values are considered as worst post-baseline value, the first one is taken.

All clinical laboratory data will be presented in the data listings along with normal ranges abnormal clinical laboratory values will be flagged in the listing.

6.8.3. Vital signs

Definition

Vital sign parameters to be summarized include body temperature [°C], pulse rate [bpm], respiratory rate [breaths per minute], and systolic and diastolic blood pressure [mmHg] and will be assessed at the time-points indicated in Tables 1, 2, 2a, and 3 of the protocol. Only body temperature assessed at the vital signs assessments will be shown (body temperature will also be assessed in the subject diary but will not be considered for the descriptive analysis of body temperature). Normal ranges of the vital sign parameters are given in Table 3. If a value is out of range, it is categorized as CS or NCS in the CRF.

Table 3: Normal ranges for vital signs

Parameter	Range
Systolic blood pressure	90 to 140 mmHg
Diastolic blood pressure	<= 90 mmHg
Pulse rate	50 to 100 beats per minute (bpm)

Respiration rate	8 to 20 breaths per minute
Temperature (where applicable)	35.5 to 37.5°C

Analysis

Vital sign variables at each time-point, and its change from baseline to each post-baseline time-point will be summarized using descriptive summary statistics for each parameter.

Vital sign values for each parameter will be classified as normal/abnormal according to whether the value is within or outside of the reference range for that parameter (see Table 3). The number and percentage of subjects with CS abnormal, abnormal (NCS), normal and missing values will be summarized for each parameter.

All vital sign data will be presented in the data listings. Abnormal vital signs values and clinically significant vital sign abnormalities will be flagged in the listing.

6.8.4. Further safety data

Physical examination and the SARS-CoV-2 testing results will be listed.

7. Supporting documentation

7.1. Appendix 1: Changes to protocol-planned analyses

Instead of AEs by grade, the overall AE table will include AEs with Grade ≥3.

7.2. Appendix 2: List of abbreviations

Abbreviation/Term	Explanation
AE	Adverse event
AESI	Adverse event of special interest
ATC	Anatomical Therapeutic Chemical
bpm	Beats per minute
C	Celsius
CD	Cluster of differentiation
CI	Confidence interval
CMI	Cell-mediated immune testing
CRF	Case Report Form
COVID-19	Coronavirus Disease 2019
CS	Clinically significant
DMC	Data Monitoring Committee
ELISA	Enzyme-linked immunosorbent assay
FDA	Food and drug administration
GMFR	Geometric mean fold rise
GMT	Geometric mean titer
h	Hour(s)
IMP	Investigational medicinal product
LLOD	Lower limit of detection
LLOQ	Lower Limit of quantification
max	Maximum
MedDRA®	Medical Dictionary for Regulatory Activities
min	Minimum
min	Minute
mL	Millilitre
mmHg	Millimeter of mercury

modRNA	Nucleoside-modified messenger RNA
N	Number of subjects
n	Number of observations
NCS	Not clinically significant
PT	Preferred term
pVNT	Pseudovirus neutralization test
RBD	Receptor binding domain
SAF	Safety analysis set
SAP	Statistical analysis plan
SARS-CoV-2	The virus leading to COVID-19
SAS	Statistical analysis software
SCR	Screened set
SD	Standard deviation
SOC	System organ class
SOP	Standard operating procedures
S protein	SARS-CoV-2 spike protein
S1	Subunit produced after the SARS-CoV-2 S protein is cleaved by host proteases
SRC	Safety Review Committee
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment emergent adverse event
TESAE	Treatment emergent serious adverse event
ULOD	Upper limit of detection
ULOQ	Upper limit of quantification
VNT	Virus neutralization test
WHO	World Health Organization Drug Dictionary

7.3. Appendix 3: Reporting conventions

SAS version 9.4, or higher, will be used to produce all tables, listings, and figures.

For summary statistics, the mean, median, and SD will be displayed to one decimal place greater than the original value. Minimum and maximum will be reported to the same decimal places as the original value. Percentages will be presented with no decimal places. Rounding will be done as follows:

Numbers with first digit after the decimal point ≥ 5 will be rounded up to the next integer. All others will be rounded down to the next integer.

The antibody response is defined as the geometric mean of the antibody titer replicates. Therefore, summary statistics and minimum and maximum are displayed with the same number of decimals for antibody response and its fold rise.

8. References

PPD