Title Page

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Version History

This Statistical Analysis Plan for study BNT162-01 is based on the protocol dated 28OCT2020.

Table 1 SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	08JUN2020	Not Applicable	Original version
2	04SEP2020	• BNT162c2 also P/B • Additional time points to evaluate endpoints • Older subjects included in the trial	Adaptation to version 8 of the protocol
		• Analyses added for local and systemic reactions • Analyses added for TEAEs	Additional analyses required
		• IMM set based on data of functional antibody titer • SD and CIs will only be calculated if data of at least 3 subjects is available • Days since last immunization was harmonized with the rules for duration • Functional antibody titers with values below LLOD or above ULOD will not be imputed, as this is already implemented in the received SDTM data • No overall tables will be created, as the tables will be created per vaccine • Clarification of definition of concomitant medication • Analysis of local and systemic reactions only based on data assessed in the diary • Local and systemic reactions: denominator changed in the tables • Clarification of definition of TEAEs • Change in interval of the TEAE analysis • Denominator changed in analysis of seroconversion • Change in reporting convention for functional antibody response	Clarifications

3	16NOV2020	• Expansion cohorts • Part B will no longer be conducted • Changed wording: ‘dose level’ to ‘cohort’ • Specification of analysis of older subjects	Adaptation to version 10 of the protocol
		• Listing for completers sets added • Analyses added for local and systemic reactions • New functional antibody responses	Additional analyses required
		• Clarification of AE table by worst severity	Clarification
4	18NOV2020	• Changed ‘elderly’ to ‘older’ • Clarified definition of concomitant medication	Clarification

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1. Introduction

This document presents the statistical analysis plan (SAP) for BNT162-01, a dose-escalation phase I/II study in healthy and immunocompromised subjects. The results of this study might be included in a regulatory submission.

This SAP describes the detailed procedures for the planned statistical analyses for protocol version 10.0, dated 28 October 2020 (hereinafter referred to as "the protocol"). Changes from the protocol are documented in Section 7.1 Appendix 1.

The study consists of two parts, Part A and B. All analyses of Part A except for exploratory endpoints are described in this SAP including the analysis of CRF and laboratory data. The exploratory endpoint analyses will be described in a separate biomarker SAP developed by BioNTech. Due to changes in the overall clinical development plan, Part B will no longer be conducted.

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[a]
Primary	
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after single dose (SD; prime only) or prime/boost (P/B) immunization.	• Solicited local reactions at the injection site (pain, tenderness, erythema/redness, induration/swelling) recorded up to 7 days (d) after each immunization (trial days 8 and 29). • Solicited systemic reactions (nausea, vomiting, diarrhea, headache, fatigue, myalgia, arthralgia, chills, loss of appetite, malaise, and fever) recorded up to 7 d after each immunization (trial days 8 and 29). • The proportion of subjects with at least 1 unsolicited treatment emergent adverse event (TEAE): o For BNT162a1, BNT162b1, BNT162b2 and BNT162c2 (P/B): Occurring up to 21 d after the prime immunization (trial day 22) and 28 d after the boost immunization (trial day 50). o For BNT162c2 (SD): The proportion of subjects with at least 1 unsolicited TEAE occurring up to 28 d after the immunization (trial day 29).
Secondary	
To describe the immune response in healthy adults after SD or P/B immunization measured by a functional	For BNT162a1, BNT162b1, BNT162b2 and BNT162c2 (P/B): As compared to baseline at 7 and 21 d after primary immunization and at 7, 14[b], 21, 28, 63, and 162 d after the boost immunization: • Functional antibody responses (titers).

antibody titer, e.g., virus neutralization assay or an equivalent assay available by the time of trial conduct.	• Fold increase in functional antibody titers. • Number of subjects with seroconversion defined as a minimum of 4-fold increase of functional antibody titers as compared to baseline For BNT162c2 (SD): As compared to baseline at 7, 21, 28, 42, 84, and 183 d after the primary immunization (trial days 8 to 184): • Functional antibody responses (titers). • Fold increase in functional antibody titers. • Number of subjects with seroconversion defined as a minimum of 4-fold increase of functional antibody titers as compared to baseline.
Exploratory	
The exploratory endpoints are described in the protocol, section 1.1.	

a) The given days are approximate; the respective schedule of activities defines assessment windows.

b) Only cohorts starting prime dosing after approval of amendment 09.

Table 3 Primary and secondary endpoints

Objective Clinical Category	Statistical Category	Variable/ Endpoint	SD or P/B	Time point [a]	Analysis Set
Primary Objective: To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after SD or P/B immunization.					
Safety	Primary	Solicited local reactions at the injection site	SD and P/B	recorded up to 7 d after each immunization	SAF/ completers sets
	Primary	Solicited systemic reactions	SD and P/B	recorded up to 7 d after each immunization.	SAF/ completers sets
	Primary	The proportion of subjects with at least 1 unsolicited TEAE	P/B	occurring up to 21 d after the prime immunization and 28 d after the boost immunization.	SAF/SAFB/ completers sets
			SD	occurring up to 28 d after the immunization.	SAF/SAFB/ completers sets
Secondary Objective: To describe the immune response in healthy adults after SD or P/B immunization measured by a functional antibody titer, e.g., virus neutralization assay or an equivalent assay available by the time of trial conduct.					
Immuno-genicity	Secondary	Functional antibody responses	P/B: at 7 and 21 d after primary immunization and at 7, 14[b], 21, 28, 63, and 162 d after the boost immunization. SD: at 7, 21, 28, 42, 84, and 183 d after the primary immunization.		IMM/ IMMPP
	Secondary	Fold increase in functional antibody titers			IMM/ IMMPP
	Secondary	Seroconversion			IMM/ IMMPP

SAF = Safety Set, SAFB = Safety boost set, IMM = Immunogenicity set, IMMPP = Immunogenicity per-protocol set, TEAE = Treatment Emergent Adverse Event

a) The given days are approximate; the respective schedule of activities defines assessment windows.
b) Only cohorts starting prime dosing after approval of amendment 09.

The completers sets comprise Prime + 7 Days Completer Set, Prime to Boost or Prime + 28 Days Completer Set, Boost + 7 Days Completer Set, Boost + 28 Days Completer Set and Prime or Boost + 28 Days Completer Set.

1.2. Study Design

Study Design	The present study is a multi-site, phase I/II, dose-escalation trial investigating the safety and immunogenicity of four prophylactic SARS-CoV-2 RNA vaccines against COVID-19 using different dosing regimens in healthy and immunocompromised adults. The dose-finding part (Part A) includes several dose cohorts (treatment groups) for each vaccine.
Study Population	**Part A:** Healthy and immunocompromised adults aged 18 to 85 years. A detailed description of the inclusion and exclusion criteria can be found in section 5.1 and 5.2 of the protocol.
Geographic Regions	**Part A:** Multiple sites in Germany
Investigational Medical Products	**Name**: BNT162 vaccines - Anti-viral RNA vaccines for active immunization against COVID-19 **Part A:** **Type**: RNA-LNP vaccines utilizing different BioNTech RNA formats, i.e., uRNA (product code BNT162a1), modRNA (two variants, product codes BNT162b1 and BNT162b2) and saRNA (product code BNT162c2). The vaccines BNT162a1, BNT162b1, BNT162b2 and BNT162c2 will be administered using a P/B regimen. The vaccine BNT162c2 will additionally be administered using an SD regimen. **Dose**: The doses are detailed in the protocol Table 1, 2 and 3. **Dose frequency:** One injection or two injections 21 days apart. Injection volumes will be up to 1.5 mL. **Administration route:** Intramuscular Trial subjects with the first-in-human immunization will be immunized using a sentinel dosing/subject staggering.
Treatment and Study Duration	In total, the planned trial duration for subjects is expected to be approximately 214 d for Cohorts 1 to 10 and 760 d for Cohorts 11 to 13.

Planned Number of Subjects	For each vaccine, 12 subjects for each cohort are required in Part A for non – expansion cohorts. For the expansion cohorts, 30 subjects will be included in cohort 11, 90 subjects in cohort 12 and 30 subjects in cohort 13.
Randomization and Blinding	No randomization, open-label

1.1. Schedule of Visits and Procedures

The schedule of visits and procedures can be found in the protocol in Table 5, 6 and 7.

2. Statistical Hypotheses

In Part A, there is no formal statistical hypothesis under test.

3. Interim Analyses

In Part A, no formal interim statistical analysis will be performed. However, preliminary analyses based on all data collected until a pre-defined data cut-off date (snapshot analyses) may be performed for each cohort once subjects within a cohort will have been followed up for at least 7 days following the dose.

Furthermore, an analysis update will be performed once all subjects will have completed Visit 10.

3.1. Data Monitoring Committee (DMC)

In Part A, 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 have been performed.

For further details regarding the sample size calculations see protocol section 9.2.

5. Analysis Sets and Subgroups

5.1. 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).

Prime + 7 Days Completer Set

All subjects who are included in the SAF and received the prime immunization and who were in the trial at least up to day 7 (inclusive) after prime immunization.

Prime to Boost or Prime + 28 Days Completer Set

All subjects who are included in the SAF and received the prime immunization and who either received also the boost immunization or who were in the trial at least up to day 28 (inclusive) after prime immunization.

Boost + 7 Days Completer Set

All subjects who are included in the SAF and received the boost immunization and who were in the trial at least up to day 7 (inclusive) after boost immunization.

Boost + 28 Days Completer Set

All subjects who are included in the SAF and received the boost immunization and who were in the trial at least up to day 28 (inclusive) after boost immunization.

Prime or Boost + 28 Days Completer Set

All subjects who are included in the SAF and received the prime immunization and

- who either received also the boost immunization and were in the trial at least up to day 28 (inclusive) after boost immunization

or

- who didn't receive the boost immunization and were in the trial at least up to day 28 (inclusive) after prime immunization.

Note to completers sets:

Subjects were not in the trial up to a certain day if, for example, they dropped out before or didn't complete the time interval due to the cut-off of a snapshot analysis.

Safety Boost Set (SAFB)

The safety boost set is defined as all subjects who received two doses of IMP (prime and boost immunization).

Note: Subjects receiving BNT162c2 as SD will be excluded from the SAFB as they receive only a prime immunization 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 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.

Note: In all analysis sets, subjects will be assigned to the groups (i.e. vaccine type and cohort) according to the actual treatment they received ("as treated").

5.2. Protocol Deviations

Protocol deviations are failures to adhere to the inclusion/exclusion criteria and protocol requirements and will be classified into major protocol deviations and minor protocol deviations. Major protocol deviations are those that are considered to have a significant effect on the treatment efficacy.

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

The following criteria might 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 (only one vaccine was administered of P/B vaccines or no vaccine was administered)

(4) Intake of prohibited concomitant medication

Protocol deviations will be reported as related to COVID-19 or not.

Major protocol deviations will be presented in a listing. [Mock Listing 16.2.1-2.X] For each vaccine, the number and percentage of subjects with major protocol deviations will be summarized in total and by protocol deviation type and by cohort and cohort-total.

5.3. Subgroups

In Part A, no subgroup analysis is planned. But unless otherwise specified, additional totals for younger (18 to 55 years) and older (56 to 85 years) subjects will be given.

6. Statistical Analyses

6.1. General Considerations

The following described statistical analyses only refer to Part A of the study.

No formal statistical testing will be done.

Unless otherwise specified, analyses will be based on data pooled across all study sites.

6.1.1. Tables and Listings

Tables

In general, data will be summarized by groups (i.e., by vaccine type [BNT162a1, BNT162b1, BNT162b2, BNT162c2 SD and BNT162c2 P/B] and cohort) and all cohorts combined for each type (cohort-total). Furthermore, selected cohorts may be combined. The cohorts and cohort-total will be presented in columns and the different vaccine types in different tables.

There will be additional total columns for younger (18 to 55 years) and older (56 to 85 years) subjects.

Continuous variables will be summarized by group 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 increase 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 by group 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 as well as CIs will only be calculated if values of at least 3 subjects are available.

Listings

Important Case Report Form (CRF) data as well as all relevant generated and transformed variables together with the original data items will be listed. Separate listings will be provided for each vaccine type. Unless otherwise specified, cohort will always be included in listings, and listings will be sorted first by cohort, then by subject number and finally, if applicable, by visit number and/or a relevant date (e.g. date of onset of AE).

Mock tables, figures and listings

The referenced mock tables, figures and listings are given in the following documents:

- BNT162-01_TFLshells_14.1_Disposition_and_Baseline Characteristics_final_v1.0
- BNT162-01_TFLshells_14.2_Primary_Endpoints_(Safety)_final_v1.0
- BNT162-01_TFLshells_14.3_Secondary_Endpoints_(Immunogenicity)_final_v1.0
- BNT162-01_TFLshells_14.4_Further_Safety_Endpoints_final_v1.0

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 using the SAFB if the SAF and the SAFB sets differ regarding subjects with a planned boost immunization (for example due to a snapshot analysis during study conduct or drop-outs). The completers sets will be used for analysis of local and systemic reactions as well as adverse events. The IMM will be used for the analysis of immunogenicity data. The analyses of all vaccines will be repeated using the IMMPP if the two analysis sets differ significantly (≥10% difference in subjects belonging to the sets).

If subjects by accident receive two different doses or vaccines, they will switch the group and will be displayed for each immunization with the corresponding group. For combined analyses, subjects who received two different doses will be assigned to the lower dose.

Data of subjects who failed to complete all visits of the study (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

Baseline is defined as last value prior to first dose of IMP.

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 immunization to first reaction will be calculated as follows:
Time from first immunization to first reaction [days] = first reaction date – prime immunization date + 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 immunization will be calculated as follows:
Days since last immunization = onset date of AE– date of last immunization+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 Treatment Day are defined as follows:

- Study day:
  - 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

Fold increase will be calculated as follows:

- Fold increase = post-dose value / baseline value

6.1.3. Missing data

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

Clinical laboratory variables below the lower limit of quantification (LLOQ) will be evaluated as 0.5 * LLOQ in the summary tables. In the listings they will be displayed as "<LLOQ" or similar.

6.2. Subject Dispositions

For the SCR, the number and percentage of subjects having failed screening will be presented along with a summary of the primary reason for screening failure. [Mock Table 14.1-1]

Subject disposition will be listed with date of informed consent, date of screening, date of immunization and date of study completion/discontinuation. [Mock Listing 16.2.1-1.X]
The number and percentage of subjects in the analysis sets will be summarized by group (i.e. by vaccine type and cohort) and cohort-total for the subjects in the SAF. [Mock Table 14.1-2.X]

For the SAF, number and percentage of subjects having prematurely discontinued the study with a summary of the primary reason (e.g., adverse events, death, withdrawal by subject, lost to follow-up) will be presented by group (i.e. by vaccine type and cohort) and cohort-total. [Mock Table 14.1-3.1 and 3.2.X]

Subjects having prematurely discontinued will be listed with date and reason for premature discontinuation. [Mock Listing 16.2.1-3.X]

Subjects in the SCR but excluded from SAF, subjects in SAF but excluded from SAFB/ IMM/ IMMPP will be listed with reason for exclusion. [Mock Listing 16.2.1-4.1.X] Subjects inclusion in the completers sets will be listed.

6.3. Baseline Characteristics

6.3.1. Demographics

Demographic and baseline variables will be summarized for subjects in the SAF analysis set. Age [years], weight [kg], height [cm], and body mass index (BMI) (kg/m^2) will be summarized as continuous data by group and cohort-total. [Mock Table 14.1-4.1.X]

Sex (male vs female), ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown) and race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Not reported, Unknown, Other) will be summarized as categorical data by group and cohort-total. [Mock Table 14.1-4.2.X]

A listing of demography will be provided. [Mock Listing 16.2.1-5.X]

6.3.2. Concomitant Medication

Prior and concomitant medications will be defined using start and stop dates recorded, relative to the first and last dose of study medication. Any medication taken before 28 days prior to the start date of IMP will not be classified as prior or concomitant medication. A prior medication will be defined as any therapy taken 28 days prior up to (but not including) the start date of IMP. A concomitant medication will be defined as any medication either

- taken prior to (but not including) the start date of IMP 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 vaccination up to 28 days after the second vaccination.

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 2020 B3 standard drug codes resulting in Anatomical-Therapeutic-Chemical (ATC) codes indicating therapeutic classification.

Listings of prior and concomitant medications will be provided. [Mock Listing 16.2.1-6.1.X and 6.2.X]

6.3.3. Medical History

Medical history data will be coded using the Updated Version Medical Dictionary for Regulatory Activities (MedDRA®) coding system 23.0 including specific terms for COVID-19.

A listing of medical history data will be provided. [Mock Listing 16.2.1-7.X]

6.4. Primary Analyses

Hereinafter, the primary analyses for Part A are described.

The primary endpoints are solicited local reactions at the injection site, solicited systemic reactions and the proportion of subjects with at least 1 unsolicited treatment emergent adverse event (TEAE). All primary analyses will be performed using the SAF and analyses of adverse events will possibly be repeated using the SAFB.

All primary analysis endpoints will be summarized by group (i.e. by vaccine type and cohort) and all cohorts combined for each type (cohort-total).

6.4.1. Solicited local reactions

Definition

Solicited local reactions at the injection site are assessed and reported by the study subject in a diary and consist of pain, tenderness, erythema/redness or induration/swelling. The local reactions assessed by the investigator will not be analyzed.

Local reactions will be graded based on the criteria given in 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 8.2.9 of the protocol. The grades are Grade 0 (Absent), Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe) and Grade 4 (Potentially life threatening).

The solicited local reactions will be evaluated for the following time intervals:

- Prime immunization up to day 7 (inclusive) after initial immunization
- Boost immunization up to day 7 (inclusive) after boost immunization
- Both intervals combined

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

Clarification: The interval 'prime immunization up to day 7 after initial immunization' includes study day 1 to study day 8. This applies to the other intervals accordingly.

All local reactions qualifying as AE will additionally be included in the adverse events tables.

Analysis

Local reactions with missing time and occurring on the day of prime immunization will be assigned to all intervals starting with the prime immunization. Local reactions with missing time and occurring on the day of the boost immunization will be assigned to all intervals including the boost immunization. Local reactions 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.

The number and percentage of subjects reporting at least one local reaction in each time interval will be summarized for each of the following types:

- Any local reactions
- Grade ≥3 local reactions. [Mock Table 14.2.1-1.X]

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.

Furthermore, this table will be repeated showing only completers: 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 and which are included in the respective completers set.

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. [Mock Table 14.2.1-2.X] 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.

Furthermore, this table will also be repeated showing only completers as described above.

Time after prime and after boost from

- first dose to first local reaction,
- first dose to first local reaction with grade >=3,
- first local reaction to last local reaction and
- first local reaction with grade >=3 to last local reaction with grade >= 3

will be summarized descriptively overall and by local reaction term.

The same variables will be described for any reaction (local or systemic).

The compliance with the diary from each immunization up to 7 days after each immunization will be presented. Therefore, 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 study will be listed. [Mock Table 16.2.2-1.X] Additionally, all days with information on local reactions in the diary will be listed.

For each vaccine type, local reactions will be presented graphically using a bar plot [Mock Figure 14.2.1-3.X].

6.4.2. Solicited systemic reactions

Definition

Solicited systemic reactions are assessed and reported by the study subject in a diary and consist of nausea, vomiting, diarrhea, headache, fatigue, myalgia, arthralgia, chills, loss of appetite, malaise, or fever. The systemic reactions assessed by the investigator will not be analyzed.

Solicited systemic reactions will be graded based on the criteria given in US Food and Drug Administration (FDA) Guidance for Industry 'Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials'. The grades are Grade 0 (Absent), Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe) and Grade 4 (Potentially life threatening). Fever is graded as Mild (38.0-38.4°C), Moderate (38.5-38.9°C), Severe (39.0-40.0°C and Potentially life threatening (>40.0°C).

The solicited systemic reactions will be evaluated for the following time intervals:

- Prime immunization up to day 7 (inclusive) after initial immunization
- Boost immunization up to day 7 (inclusive) after boost immunization
- Both intervals combined

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

Clarification: The interval 'prime immunization up to day 7 after initial immunization' includes study day 1 to study day 8. This applies to the other intervals accordingly.

All systemic reactions qualifying as AE will additionally be included in the adverse events tables.

Analysis

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

6.4.3. Adverse events

Definition

For detailed information on adverse events see section 10.3 of the protocol.

Adverse events (AEs) will be coded using the Updated Version MedDRA® 23.0 including specific terms for COVID-19 to get a system organ class (SOC) and preferred term (PT) for each AE.

A treatment emergent adverse event (TEAE) 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). AEs with an onset date more than 28 days after the last immunization 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.

Clarification: AEs with an onset date at the date of the first immunization will only be considered as treatment emergent, if the AE occurred after the first immunization.

The TEAEs will be evaluated for the following time intervals, clarifying and harmonizing the intervals defined in the protocol:

- Prime immunization up to day 7 (inclusive) after initial immunization
- Prime immunization up to boost immunization or day 28 (inclusive) after initial immunization (whatever comes first)
- Boost immunization up to day 7 (inclusive) after boost immunization
- Boost immunization up to day 28 (inclusive) after boost immunization
- Prime immunization up to day 28 (inclusive) after boost immunization or after prime immunization (if no boost was given)

The intervals starting or ending with an immunization, will start or end with the date and time of the immunization. TEAEs are assigned to the time intervals according to their start date and time.

Adverse events of special interest (AESI)

Enhanced respiratory disease or flu-like symptomatology not resolved after 7 days or with symptom kinetics that are inconsistent with a relationship to RNA immunization will considered AESIs. AESIs are marked in the CRF.

Analysis

TEAEs with missing time and occurring on the day of prime immunization will be assigned to all intervals starting with the prime immunization. TEAEs with missing time and occurring on the day of the boost immunization will be assigned to all intervals including the boost immunization. TEAEs with missing date will be assigned to all the respective intervals if it cannot be ruled out, that it belongs to a time interval.

The following TEAE types will be analyzed:

- Any TEAE
- Related TEAE
- Grade >=3 TEAE
- Related grade >=3 TEAE
- Any treatment emergent serious adverse event (TESAE)
- Related TESAE

Overall summary of TEAEs

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 for each defined time interval [Mock Table 14.2.3-1.1.X]

The same analysis will be repeated using the respective completers set for each time interval.

The same analysis will be done excluding TEAEs which were based on solicited reporting via subjects diaries and had a duration of <= 7 days (end date – start date + 1). Subjects with missing start or end date will be included.

The same analysis will be done for treatment emergent AESIs (TEAESIs) by time intervals. [Mock Table 14.2.3-1.2.X]

For each defined time interval, the number and percentage of subjects reporting at least one TEAE will be summarized by PT nested within SOC for each of the defined AE types. [Mock Tables 14.2.3-2.1.X to 2.6.X]

The same analysis will be repeated using the respective completers set for each time interval.

The same analysis will be done excluding TEAEs which were based on solicited reporting via subjects diaries and had a duration of <= 7 days (end date – start date + 1). Subjects with missing start or end date will be included.

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

TEAE by grade

The number and percentage of subjects with TEAEs will be summarized by worst grade by PT nested within SOC by time interval. [Mock Table 14.2.3-3.X] The worst grade will be counted if a TEAE is reported more than once by the same subject for this SOC / PT in one time interval. As described in section 10.3.1.7 of the protocol version 8, the grading changed during the study from a 3-point scale to a 4-point scale. The assessment of AE and/or SAE intensity should be done consistently for all subjects treated with the same treatment and dose.

AE listings

All AEs and SAEs will be listed. [Mock Listing 14.2.3-4.X and 16.2.2-3.X]

TEAE figures

For each vaccine type, the most frequent TEAEs (preferred term ≥ 5% in the vaccine) will be presented graphically using a bar plot. [Mock Figure 14.2.3-4.X]

6.5. Secondary Analyses

Hereinafter, the secondary analyses for Part A are described.

Secondary endpoints are functional antibody responses, fold increase in functional antibody titers and the number of subjects with seroconversion. All secondary analyses will be performed using the IMM and possibly additionally the IMMPP population, see section 5.1.

All secondary analysis endpoints will be summarized by group (i.e. by vaccine type and cohort) and all cohorts combined for each type (cohort-total).

The functional antibody response will be assessed at the time points indicated in the tables 5, 6 and 7 of the protocol.

6.5.1. Functional antibody response

Definition

For data from VisMederi Srl, the functional antibody response is based on the virus neutralization test (VNT). For each subject and each time point two functional antibody titers will be determined, as each sample will be measured in replicate. The functional antibody response per subject and timepoint is defined as the geometric mean of the two functional antibody titers.

Other data on functional antibody response will be presented as included in the SDTM data.

Analysis

Functional antibody titers will be summarized using descriptive statistics for all time points. Additionally, GMT with 95% CI will be presented. [Mock Table 14.3.1-1.X]

The functional antibody response will be listed.

Figure: For each vaccine type, functional antibody titers will be presented graphically displaying GMT with 95% CI at all time points.

6.5.2. Functional antibody titers fold increase

Definition

The fold increase of the functional antibody response will be calculated for all post-baseline time points as post-dose value / baseline value.

Analysis

The fold increase in functional antibody titers will be summarized using descriptive statistics for all post-baseline time points. Additionally, GMT with 95% CI will be presented. [Mock Table 14.3.2-1.X]

Functional antibody titers fold increase will be listed.

6.5.3. Seroconversion

Definition

Seroconversion is defined as a minimum of 4-fold increase of functional antibody reponse as compared to baseline.

Analysis

The number of subjects with seroconversion will be summarized by number and percentage with 95% confidence interval for all post-baseline time points. The denominator of the percentages will be the number of subjects with data available at the respective visit. [Mock Table 14.3.3-1.X]

Seroconversion data of the functional antibody titer will be listed.

6.6. Exploratory Analyses

Exploratory analyses will be described in a separate biomarker SAP provided by BioNTech.

6.7. Further Safety Analyses

Hereinafter, the further safety analyses for Part A are described. All analyses will be performed in the SAF.

Safety data that will be summarized includes IMP compliance, clinical laboratory assessments, vital signs, and Electrocardiograms (ECGs).

6.7.1. Compliance

IMP compliance will be summarized by group (i.e. by vaccine type and cohort) and cohort-total. [Table 14.4.1-1.X]

Drug exposure will be listed. [Mock Listing 16.2.4-1.X]

6.7.2. 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 Table 5, 6 and 7 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 (NCS).

Abnormal clinical laboratory data will be graded. The abnormal clinical laboratory data is categorized in 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) will be summarized using descriptive summary statistics for each parameter by group and cohort-total. [Mock Table 14.4.2-1.1.X.X and 1.2.X.X]

Number and percentage of subjects with low, normal and high clinical laboratory values at each time-point will be summarized for each parameter by group and cohort-total. [Mock Table

14.4.2-2.1.X.X] The same table will be provided for the grading scheme (grades mild, moderate, severe and life threatening). [Mock Table 14.4.2-3.X.X]

The number and percentage of subjects with CS abnormal, abnormal (not CS), normal and missing values will be summarized for each parameter by group and cohort-total. [Mock Table 14.3.4-2.2.X.X]

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) by group. 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. [Mock Table 14.2.4-2.3.X.X]

All clinical laboratory data will be presented in the data listings along with normal ranges [Mock Listing 16.2.4-2.X.X]. Abnormal clinical laboratory values will be flagged in the listing.

6.7.3. 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 Table 5, 6 and 7 of the protocol . Only body temperature assessed at the vital signs assessments will be shown (no body temperature assessed in the diary). Normal ranges of the vital sign parameters are given in Table 4. If a value is out of range, it is categorized as CS or not clinically significant (NCS) in the CRF.

Table 4 Normal Ranges for Vital Signs

Parameter	Range
Systolic blood pressure	90-140 mmHg
Diastolic blood pressure	<= 90 mmHg
Pulse rate	50-100 bpm
Respiration rate	8-20 breaths per minute
Temperature (where applicable)	35.5-37.5 °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 by group and cohort-total. [Mock Table 14.4.3-1.X and 2.X]

Vital sign values for each parameter will be assigned an normal/abnormal classification according to whether the value is within or outside of the reference range for that parameter (see Table 4). The number and percentage of subjects with CS abnormal, abnormal (not CS), normal and missing values will be summarized for each parameter by group and cohort-total. [Mock Table 14.4.3-3.X]

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.

6.7.4. ECG

Definition

Standard 12-lead ECGs will be recorded at the times given in Table 5, 6 and 7 of the protocol using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and corrected QT intervals. ECGs will be judged by the investigator as CS/NCS; only the investigator assessment and heart rate will be recorded in the CRF.

Analysis

ECG investigator assessments as well as heart rate will be listed.

6.7.5. Further Safety data

Physical examination, drugs of abuse, alcohol use, viral screening and the SARS-CoV-2 testing will be listed.

7. Supporting Documentation

7.1. Appendix 1: Changes to Protocol-Planned Analyses

No changes from the protocol.

7.2. Appendix 2: List of Abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomical-Therapeutic-Chemical
BMI	Body Mass Index
bpm	beats per minute
C	Celsius
CI	Confidence Interval
cm	centimeter
CMI	Cell-mediated immune testing
CRF	Case Report Form
COVID-19	Corona Virus Disease 2019
CS	Clinically Significant
D	day
d	day
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ELISA	Enzyme-Linked Immunosorbent Assay
ELISpot	Enzyme-Linked Immuno-Spot
EoT	End-of-trial (visit);
FDA	Food and Drug Administration
FU	Follow-up (visit)
geoMean	Geometric Mean
GMFR	Geometric Mean Fold Rise
GMT	Geometric Mean Titer
h	hour
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product

kg	kilogram
LLN	Lower Limit of Normal
LLOD	Lower Limit of Detection
m	meter
max	maximum
MedDRA™	Medical Dictionary for Regulatory Activities
min	minimum
min	minute
mL	millilitre
mmHg	millimeter of mercury
N	Number of Subjects
n	Number of Observations
NCS	Not clinically significant
P/B	Prime/boost
PT	Preferred Term
SAF	Safety Set
SAP	Statistical Analysis Plan
SARS-CoV-2	The virus leading to COVID-19
SAS	Statistical Analysis Software
SCR	Screened Set
SD	Standard Deviation
SD	Single Dose
SOC	System Organ Class
SOP	Standard Operating Procedures
SRC	Safety Review Committee
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
TLF	Tables, Listings, and Figures
ULN	Upper Limit of Normal
ULOD	Upper Limit of Detection
VNT	Virus Neutralization Test
WHO DD	World Health Organisation Drug Dictionary

WOCBP	Women of Childbearing Potential
µg	Microgram

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.

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

8. References

[1] Staburo GmbH, STABURO/SOP001, "Standard Operating Procedure for Statistical Programming", Version 05

[2] Staburo GmbH, STABURO/SOP002, "Standard Operating Procedure for Quality Control of Programs", Version 05