Title Page

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WHO UTN:	U1111-1254-4840
Trial Title:	A Multi-site, Phase I/II, 2-Part, Dose-Escalation Trial Investigating the Safety and Immunogenicity of a Prophylactic SARS-CoV-2 RNA Vaccine (BNT162b3) Against COVID-19 Using Different Dosing Regimens in Healthy Adults
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Version History

Table 1 SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	02DEC2020	Not Applicable	Original version
2	12MAY2021	Adapted to protocol version 8.0	New protocol version
		Analyses based on completer sets were deleted	This analysis was planned for snapshot analyses and is not relevant for the final analysis
		Deleted 'Major protocol deviations are those that are considered to have a significant effect on the treatment efficacy'	Updated to broader definition of major protocol deviations
		Minor changes/clarifications of tables, listings and figures	Analysis is more adequate.
		Only local and systemic reactions assessed by subject will be analysed as primary endpoint. As additional analyses, the local and systemic reactions assessed by the investigator will also be included in tables displaying "worst possible grade" for data completeness.	Reactions assessed by the investigator should also be included in the analysis.
		-TEAEs occurring in the time intervals including 7 days after each immunization will not be analyzed separately - TEAEs after 28 days after last dose are included one of the analyzed time intervals -TEAEs with DLT and deaths will be analyzed - Removal of solicited reacto TEAEs that came from diary from the unsolicited TEAEs was changed	Updated AE analysis
		Table of laboratory data by grades will only be done for lymphocytes	The table will be most useful for lymphocytes.

3	26APR2022	Adapted to protocol version 10.	New protocol version
		Data assessed after the vaccination with a non-trial vaccine will be excluded from all statistical analyses.	Adaption to ongoing COVID-19 pandemic
		Update of reactogenicity analysis: Analysis of grade >=3 was replaced by an analysis of worst grade.	Analysis is more adequate.

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1. Introduction

This document presents the statistical analysis plan (SAP) for BNT162-04, a dose-escalation phase I/II study in healthy 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 12 MAY 2021 (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 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
Primary	
To describe the safety and tolerability profiles of BNT162b3 in healthy adults after prime/boost (P/B) immunization.	• Solicited local reactions at the injection site (pain, tenderness, erythema/redness, induration/swelling) recorded up to 7 d after each immunization. • 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. • The proportion of subjects with at least 1 unsolicited TEAE occurring after prime immunization up to boost immunization or 28 d after the prime immunization (whichever comes first) and up to 28 d after the boost immunization.
Secondary	
To describe the immune response in healthy adults after P/B immunization measured by a functional	As compared to baseline at 7 d and 21 d after prime immunization and at 7 d , 14 d, 21 d, 28 d, 63 d, 162 d and 365 d after the boost immunization: • Functional antibody responses.

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
Exploratory	
[redacted]	[redacted]

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 a prophylactic SARS-CoV-2 RNA vaccine (BNT162b3) against COVID-19 using different dosing regimens in healthy adults.
Study Population	**Part A:** Healthy 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:** Mannheim and Berlin, Germany
Investigational Medical Products	**Name**: BNT162b3 vaccine - Anti-viral RNA vaccine for active immunization against COVID-19 **Part A:** **Type**: RNA-LNP vaccine utilizing the BioNTech modRNA format: product code BNT162b3 The vaccine BNT162b3 will be administered using a P/B regimen. **Dose**: The doses are detailed in the protocol Table 1 and 2. **Dose frequency:** 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	**Part A:** **Subject level**: Each trial subject will be in the trial for maximally 417 days (i.e. from Day -30 to Day 387) **Study level**: Approximately 16 months
Planned Number of Subjects	12 subjects for each cohort are required in Part A.

Randomization and Blinding	**Part A:** 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 3.

2. Statistical Hypotheses

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

3. Interim Analyses

The final analysis will be performed once all subjects have completed Visit 7 'end of treatment'. An analysis update will be performed once all subjects will have completed Visit 10.

In Part A, no formal interim statistical analysis will be performed. However, the 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. Snapshot analyses may be performed for younger and older dose cohorts.

A snapshot analysis is a preliminary analysis of an ongoing study based on all data collected until a pre-defined data cut-off date.

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 Part A, the inclusion of 12 subjects per group is considered to be adequate for a safety assessment of vaccine per cohort. The probability to observe a particular treatment emergent adverse event (TEAE) with incidence of 15% at least once in 12 subjects per group is 85.8%.

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).

Safety Boost Set (SAFB)

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

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 dose cohort according to the actual dose 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 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 dose (i.e. actual dose taken differs from the scheduled)

(3) Non-Compliance (e.g., only one vaccine was administered or no vaccine was administered)

(4) Intake of prohibited concomitant medication

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

Major and all protocol deviations will be presented in a listing. The number and percentage of subjects with major protocol deviations will be summarized in total and by protocol deviation type and by cohort.

5.3. Subgroups

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

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.

Data assessed after the vaccination with a non-trial vaccine will be excluded from all statistical analyses.

6.1.1. Tables and Listings

Tables

In general, data will be summarized by cohort and all cohorts combined (cohort-total). Furthermore, selected cohorts may be combined (e.g. young and older cohorts). The cohorts and cohort-total will be presented in columns.

Descriptive summary tables as well as figures will be based on scheduled visits.

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. 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 Adverse Event (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 using the SAFB if the SAF and the SAFB sets differ. The IMM will be used for the analysis of immunogenicity data. The analyses may be repeated using the IMMPP if the two analysis sets differ significantly. This will be decided at the DRM.

If subjects by accident receive two different doses, they will switch the dose cohort and will be displayed for each immunization with the corresponding dose cohort. 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 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.

6.2. Subject Dispositions

For the SCR, a listing of subjects having failed screening will be presented.

Subject disposition will be listed with date of informed consent, date of screening, date of immunization and date of study completion/discontinuation.
The number and percentage of subjects in the analysis sets will be summarized by group (i.e. by cohort) and cohort-total for the subjects in the SAF.

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), of subjects who completed the end of treatment phase (merged from End of Trial variable and End of Treatment variable (each subject has only one data entry)) and who completed the follow-up phase will be presented by group (i.e. by cohort) and cohort-total.

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

Subjects in the SCR but excluded from SAF, subjects in SAF but excluded from 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. Age (calculated as Age[years] + age_month [months]/12), weight [kg], height [cm], and body mass index (BMI) (kg/m^2) will be summarized as continuous data by cohort and cohort-total.

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 cohort and cohort-total.

A listing of demography will be provided.

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 up 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 first vaccination up to 28 days after the last 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) September 1, 2020 B3 standard drug codes resulting in Anatomical-Therapeutic-Chemical (ATC) codes indicating therapeutic classification.

Listings of prior and concomitant medications will be provided.

6.3.3. Medical History

Medical history data will be coded using the Version Medical Dictionary for Regulatory Activities (MedDRA®) coding system 23.1 including specific terms for COVID-19.

A listing of medical history data will be provided.

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).

Clarification: Only local and systemic reactions assessed by subject will be analysed as primary endpoint. As additional analyses, the local and systemic reactions assessed by the investigator will also be included in tables displaying "worst possible grade" for data completeness.

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 cohort) and all cohorts combined (cohort-total).

6.4.1. Solicited local reactions

Definition
Solicited local reactions at the injection site consist of pain, tenderness, erythema/redness or induration/swelling. They are assessed by the subject in a diary and by the investigator at specific time points stated in the protocol.

Local reactions will be graded using criteria based on the guidance 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 prime 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 prime immunization' includes study day 1 to study day 8. This applies to the other intervals accordingly.

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 following analyses will be done for local reactions assessed by the subject, for local reactions assessed by the investigator and for both combined:

Differing from protocol section 9.4.2, the number and percentage of subjects reporting at least one local reaction in each 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.

The following analyses will be done for local reactions assessed by subjects:

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).

Moreover, the frequency of subjects with solicited local reactions and any 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.

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

Local reactions assessed by subject will be presented graphically using a bar plot.

6.4.2. Solicited systemic reactions

Definition

Solicited systemic reactions consist of nausea, vomiting, diarrhea, headache, fatigue, myalgia, arthralgia, chills, loss of appetite, malaise, or fever. They are assessed by the subject in a diary and by the investigator at specific time points stated in the protocol.

Solicited systemic reactions will be graded based on the guidance 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 prime 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 prime immunization' includes study day 1 to study day 8. This applies to the other intervals accordingly.

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.

AEs will be coded using the Version MedDRA® 23.1 including specific terms for COVID-19 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 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 boost immunization or day 28 (inclusive) after initial immunization (whatever comes first)
- Boost immunization up to day 28 (inclusive) after boost immunization
- All TEAEs (regardless of relationship assessment) occurring from
  - Prime immunization up to day 28 after boost immunization (inclusive).
  - If no boost immunization, up to 28 days (inclusive) after prime immunization

  All TEAEs assessed as related through visit 10.

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 be 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
- TEAEs with dose limiting toxicity (DLT)
- Any treatment emergent serious adverse event (TESAE)
- Related TESAE
- Deaths

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.

The same analysis will be done for treatment emergent AESIs (TEAESIs) by time intervals.

The same analysis will be done excluding TEAEs which fulfil the following criteria:

• Are based on solicited reporting via subjects' diaries (all preferred terms included in 'BNT162-01_AEs_based_on_solicited_reporting_via_subjects_diaries_v3.0') and

• For prime or boost immunization, respectively, has a start and end date in the time period between dosing and

1) the day of last diary entry (inclusive) or
2) day 7 after dosing (inclusive)

whatever comes first.

TEAEs with missing start or end date will remain included.

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 following AE types:

Any TEAE, Related TEAE, Grade >=3 TEAE, Related grade >=3 TEAE, Any TESAE, Related TESAE, TEAEs with unresolved, fatal or unknown outcome, and any TEAE but excluding TEAEs which are based on solicited reporting via diaries as defined for the overall summary. 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. 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.

AE listings

All AEs, AEs with DLT, AEs of subjects who discontinued early due to an AE and SAEs will be listed.

TEAE figures

The most frequent TEAEs excluding TEAEs which are based on solicited reporting via diaries will be presented graphically using a bar plot by time interval.

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 cohort) and all cohorts combined (cohort-total).

The functional antibody response will be assessed at the following time points:

P/B at day 1 (day of primary immunization, pre-dose), 7±1 days and 21±2 days after primary immunization and at 7±3 days, 14±3 days, 21±4 days, 28±4 days, 63±7 days, 162±9, and 365±14 days after the boost immunization.

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.

The functional antibody response will be listed.

Figure: 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, GMFR with 95% CI will be presented.

Functional antibody titers fold increase will be listed.

Figure: The fold increase of functional antibody titers will be presented graphically displaying GMFR with 95% CI at all time points.

6.5.3. Seroconversion

Definition

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

Analysis

The number of subjects with seroconversion will be summarized by number and percentage with 95% CI for all post-baseline time points. The denominator of the percentages will be the number of subjects with data available at the respective visit.

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.

Further safety data that will be presented 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 cohort) and cohort-total.

Drug exposure will be listed.

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 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: Only in women who are not of childbearing potential.

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 lymphocytes data will be categorized as defined in table 9 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) will be summarized using descriptive summary statistics for each parameter by group and cohort-total.

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. 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 (not CS), normal and missing values will be summarized for each parameter by group and cohort-total.

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.

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.

6.7.3. 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 3 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 3. If a value is out of range, it is categorized as CS or not clinically significant (NCS) in the CRF.

Table 3 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.

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 (not CS), normal and missing values will be summarized for each parameter by group and cohort-total.

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 3 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

- .
- TEAEs after 28 days after last dose are included in the overall time interval ('All TEAEs assessed as related through visit 10')
- In protocol section 9.4.2 it is stated "For each injection, the number and percentage of subjects reporting at least one local reaction or systemic reaction (i.e., solicited data collected using subject diaries) will be summarized for each of the following types using the Safety Set:
  • Any local reactions or systemic reactions
  • Grade ≥3 local reactions or systemic reactions".
  However, for each injection, the number and percentage of subjects reporting at least one local reaction or systemic reaction (i.e., solicited data collected using subject diaries) will be summarized for any local or systemic reactions as well as worst type of local or systemic reaction. No summary of grade ≥3 local reactions or systemic reactions will be presented.

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
DLT	Dose limiting toxicity

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
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

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
VNT	Virus Neutralization Test
WHO DD	World Health Organisation Drug Dictionary
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] [redacted]

[2] [redacted]