STATISTICAL ANALYSIS PLAN

PROTOCOL TITLE:	A Phase I/II Randomized, Two Parts, Dose- Finding Study To Evaluate The Safety, Tolerability And Immunogenicity Of an Inactivated, Adjuvanted SARS-COV-2 Virus Vaccine Candidate (VLA2001), Against COVID-19 In Healthy Subjects
PROTOCOL (Short Name, Version, and Date):	VLA2001-201, Version 7.0, 31Aug2021
STUDY DRUG:	VLA2001
STUDY PHASE:	PHASE I/II
SPONSOR:	Valneva Austria GmbH, Campus Vienna Biocenter 3 A-1030 Vienna, Austria
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SAP DATE:	26Oct2021
STATUS:	Final version 4.0

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I confirm that I have reviewed this document and agree with the content.

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LIST OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
AESI	Adverse Event of Special Interest
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
COVID-19	Coronavirus-induced disease 2019
DSMB	Data and Safety and Monitoring Board
eCRF	Electronic Case Report Form
ELISA	enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immune absorbent spot
ELU	Elisa Laboratory Units per milliliter
FAS	Full Analysis Set
FDA	Food and Drug Administration
GMT	Geometric mean titre
HBsAg	Hepatitis B surface antigen
HCV	hepatitis C virus
HIV	Human immunodeficiency virus
ICS	Intracellular Cytokine Staining
IM	Intramuscular
ITT	Intent-to-Treat
LS	Least Squares
MedDRA	Medical Dictionary for Regulatory Affairs
MNA	Microneutralization Assay
PBMC	Peripheral blood Mononuclear Cell
PHA	Phytohemagglutinin
PPAS	Per-Protocol Analysis Set
PT	Preferred Term

Abbreviation	Description
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SD	Standard Deviation
SOC	System Organ Class
TLF	Tables, Listings and Figures
WHO	World Health Organization

1 PURPOSE

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Valneva Austria GmbH and is based on protocol VLA2001-201, Version 7.0, 31Aug2021.

The purpose of this SAP is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

In the event of future amendments to the protocol, this SAP may need to be modified as necessary to account for changes relevant to the statistical analysis.

1.1 RESPONSIBLITIES

[redacted] will perform the statistical analyses and is responsible for the production and quality control of all derived datasets and tables, figures and listings.

2 INTRODUCTION

Since December 2019, coronavirus-induced disease 2019 (COVID-19) has spread around the world, with over 24 million confirmed cases as of the 27 Aug 2020 (https://coronavirus.jhu.edu/, accessed 28 Aug 2020). SARS-CoV-2 is the seventh member of the family of coronaviruses to infect humans. SARS-CoV-2 is a group 2b coronavirus (as are MERS-CoV and SARS-CoV), with a whole genome similarity of up to 80% to SARS-CoV. SARS-CoV-2 is an enveloped, non-segmented, positive sense RNA virus. It is not known if SARS-CoV-2 will remain as worldwide pandemic. It is also not known if immunity is acquired after symptomatic or asymptomatic SARS-CoV-2 infection and how long it might last.

SARS-CoV-2 has a high infection rate and has the potential to cause serious illness, especially in older populations and those people who are immunocompromised. A vaccine for SARS-CoV-2 will help reduce the severe and unprecedented disruption the pandemic has caused to people's lives worldwide. It will reduce the burden of healthcare services that had to find extra resources to care for critically ill COVID-19 patients and will also reduce the risk to frontline workers of contracting the virus.

This phase I/II clinical study is the first study using the SARS-CoV-2 vaccine candidate VLA2001 in humans. Valneva´s vaccine virus is produced using an established antigen production process. VLA2001 is a highly-purified, whole virus, SARS-CoV-2 vaccine produced on Vero cells and inactivated with β-propiolactone. The viral strain is derived from a Chinese tourist from Hubei diagnosed in a hospital in Rome (Stefanelli et al, 2020). VLA2001 will be adjuvanted with the licensed adjuvant cytosine phospho-guanine (CpG 1018, produced by Dynavax, contained in HEPLISAV-B®), in combination with aluminium hydroxide.

2.1 STUDY OBJECTIVES

2.1.1 Primary Objective(s)

The primary objective of this study is to evaluate the safety, tolerability and immunogenicity of the inactivated, adjuvanted SARS-CoV-2 vaccine candidate VLA2001 up to 14 days after completion of a two-dose primary immunization schedule in healthy adults aged 18 to 55 years.

2.1.2 Secondary Objective(s)

- To determine the optimal dose level of inactivated, adjuvanted SARS-CoV-2 vaccine candidate VLA2001 in healthy adults aged 18 to 55 years.

- To evaluate tolerability, safety and immunogenicity of the inactivated, adjuvanted SARS-CoV-2 vaccine candidate VLA2001 up to 6 months after the last vaccination in healthy adults aged 18 to 55 years.

- To evaluate tolerability, safety and immunogenicity of a booster dose with vaccine candidate VLA2001 in healthy adults aged 18 to 55 years.

2.1.3 Exploratory Objective(s)

To evaluate cellular immune response after vaccination with inactivated, adjuvanted SARS-CoV-2 vaccine candidate VLA2001 after completion of a two-dose primary immunization schedule and after a booster vaccination.

2.2 STATISTICIAL HYPOTHESES

There are no formal statistical hypotheses in this study.

2.3 STUDY POPULATION

This study will include healthy young adult population (male and female) aged 18 to 55 years. A complete list of inclusion and exclusion criteria for the participants in the study population can be found in the study protocol. Individuals who meet all the inclusion criteria and none of the exclusion criteria at screening are eligible to participate in the trial.

2.4 TRIAL DESCRIPTION

This is a first-in-human phase I/II study that will evaluate three dose levels of VLA2001 (low, medium, high) for safety, tolerability and immunogenicity in a two-dose schedule in a healthy young adult population aged 18 to 55 years.
The study will be a combined open-label followed by a randomised, double-blind, dose-escalation, multicentre study with three dose groups (low, medium and high dose groups); 50 participants will be recruited to each dose group. The study is conducted in three parts: Part A (Day 1 to Day 36) and Part B (Day 37 to Day 208) followed by the Booster Phase: Part C (Visit 7 to Visit 10). Following an evaluation of Part A data (i.e. data up to Day 36) further clinical studies will be initiated. An additional data analysis will be performed during part B after all Participants have completed Visit 5 (Day 106).

The study will start with an open-label, staggered recruitment for the first 15 participants and subsequently in the blinded part of the study for all remaining 135 participants. Randomization will be done in 1:1:1 fashion for the 3 dose levels.

PART A:

For safety reasons, the first 15 participants will be included into the study in an open-label, not randomized manner following a staggered dose escalation of VLA2001. Dose escalation will be done at a single site to ensure permanent oversight on safety data by one principal investigator during the recruitment of the 15 sentinel participants.

Dose escalation starts with the first vaccination of the first sentinel participant in the low dose treatment group. After vaccination, the first participant of a dosing group will be observed for the development of any acute reaction at the study site for 3 hours after the vaccination procedure. Prior to discharge from the study site, vital signs will be measured and the participant will be instructed to use the eDiary. The next 4 participants of the same dosing group will be vaccinated at least with a one-hour interval between each participant. These 4 participants will be observed for 60 minutes at the study site to monitor for the development of acute reaction. Before discharge, vital signs will be measured and participants will be instructed to use their eDiaries. After confirmation by the investigator, the procedure will be repeated with the first participant of the next dose level. The minimum time before vaccination of a new dose level will be 48 hours.

A Data and Safety Monitoring Board (DSMB) will review the accrued safety data at Day 4 of all 15 sentinel participants. After favourable DSMB review randomization of the remaining 135 participants across all sites will be initiated.

The remaining 135 participants will be enrolled, screened and randomised to the three dose groups in the blinded part of the study. Participants will be observed for 30 minutes post vaccination on Day 1. All participants will be followed by e-Diary for 7 days post vaccination, starting on the day of vaccination. All participants will receive their second vaccination on Day 22 (Visit 3) and will be followed up on Day 36 (Visit 4), 14 days after the second vaccination.

PART B:

In Part B, participants will be followed up on Day 106 (Visit 5) and Day 208/Month 7 (Visit 6), 6 months after the second vaccination.

PART C (BOOSTER PHASE):

At Day 208/Month 7 (Visit 6), all participants who previously had received two study vaccinations will be invited to take part in the Booster Phase (Part C). Independently of the dose received during the primary immunization, participants will receive a booster dose (high dose) of VLA2001.

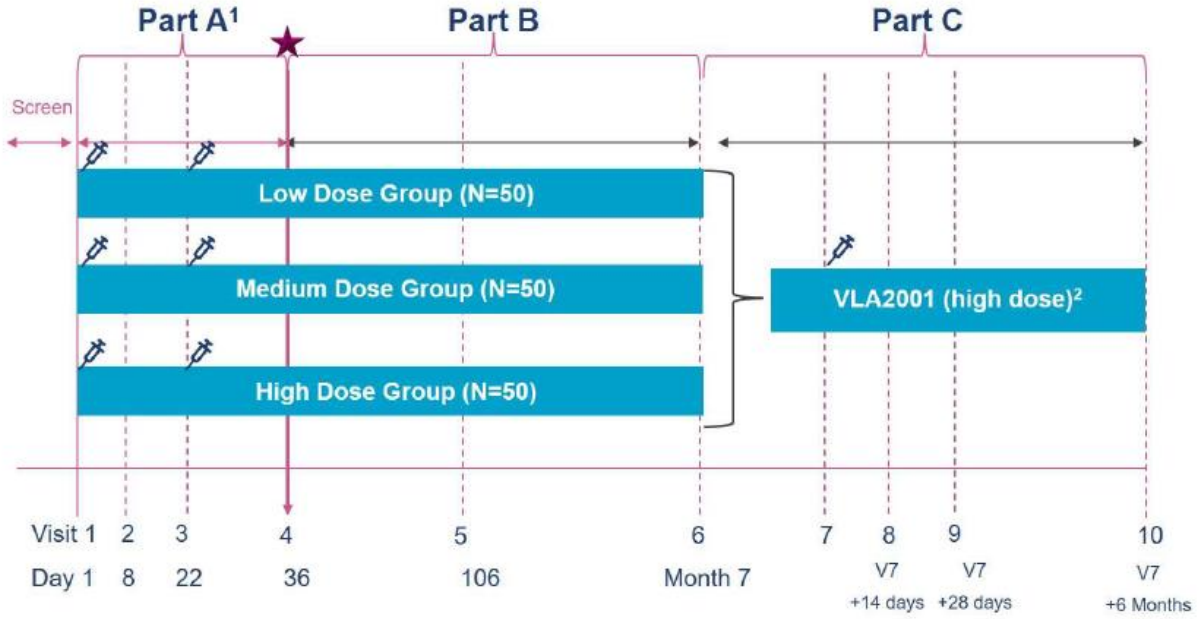
The Booster vaccination will also be offered to participants who have either had a confirmed COVID-19 disease or who have received a national COVID-19 vaccination.

The Booster vaccination will be administered at Visit 7. Participants will be asked to return to the study site for two follow-up visits, 14 days after the booster vaccination (visit 8) and 28 days after the booster vaccination (Visit 9).

6 months after the Booster vaccination, participants will be followed-up through a safety phone call. This telephone call is also the end of the study for the participants that consented to the booster part of the study.

Part A of the study will be completed when the last participant has completed Day 36 (14 days after the second vaccination). Part B of the study will be completed when the last participant has completed Day 208 (6 months after the second vaccination). The Booster Phase (Part C) will be completed when the last participant has completed the safety followup call 6 months (Visit 10) after the Booster vaccination.

The overall study duration (First Participant In – Last Participant Out [LSO]) is estimated to be approximately 16 months. Individual participation is approximately 15 months from enrolment (i.e. Informed Consent signed) to study completion unless the study is prematurely discontinued.
Below is a schematic of the study design:



[1] The first five subjects in each dose group (sentinel subjects) will be dosed in an open-label, dose-escalating manner. The 3-day safety data from all subjects will be reviewed by the Data and Safety Monitoring Board before full recruitment (the blinded part of the study) commences.
[2] Dose selected for use in further development based on VLA2001-201 Day 36 analysis.

2.5 STUDY SAMPLE SIZE DETERMINATION

A total of 150 participants is considered sufficient to obtain initial safety data for VLA2001, especially since inactivated vaccines are a well-established, safe vaccine technology. Fifty participants per group will allow for 95% confidence that an AE with a true underlying incidence of about 2% would be observed in the present study.
In addition, assuming 10% of participants with protocol deviations, about 45 participants per dose group will be evaluable for immunogenicity. This sample size is in a range generally expected to allow selection of an appropriate dose level.

For the Booster Phase of this study, no formal sample size calculation has been performed and no minimal or maximal number of participants is defined. Based on operational considerations the total number of participants is expected to be up to approximately 80.

2.6 TREATMENT ASSIGNMENT AND BLINDING

For the blinded part, IMP will be provided to the study sites in a blinded manner, i.e. no visual differentiation will be possible, same volumes will have to be administered for all dose groups. Identification of and allocation of the syringe to a specific participant is ensured by placing a tear-off label containing a kit number, Participant number, date of injection and operator onto the label.
For the booster phase, VLA2001 vaccine will be administered as open label.

2.7 ADMINISTRATION OF TRIAL MEDICATION

The vaccination schedule consists of two doses of VLA2001 for each study participant, administered by intramuscular (IM) injection in the deltoid region of non-dominant arm preferably 21 days apart, on Day 1 and Day 22 [Low dose, Medium dose, High dose].
The booster vaccination will be administered IM in the deltoid region of the non-dominant arm.

For primary immunization, one part of the vaccine (labelled VLA2001) will be presented as a liquid formulation containing aluminium hydroxide in glass vials at three dose levels (each vial is pre-filled with 0.4ml) and has to be mixed bedside with CpG 1018 (0,2ml) prior to vaccination (volume for administration is 0.5ml).
For the Booster Phase, there will be no bed-side mixing necessary. VLA2001 will be provided in multi-dose vials to the study sites where each multi-dose vial will have a unique kit number.

2.8 SCHEDULE OF ASSESSMENTS AND PROCEDURES

For the schedule of study procedures and assessments refer to protocol section 22.2 and 22.3.

3 ENDPOINTS

3.1 SAFETY ENDPOINTS

3.1.1 Primary Endpoint

Frequency and severity of solicited adverse events (AEs) (local and systemic reactions) within 7 days after any vaccination of the primary vaccination series.

3.1.2 Secondary Endpoints

- Frequency and severity of any unsolicited AE until Day 36.
- Frequency and severity of any vaccine-related AE until Day 36.
- Frequency and severity of any AE until Day 208.
- Frequency and severity of any vaccine-related AE until Day 208.
- Frequency and severity of any SAE until Day 36.
- Frequency and severity of any AESI until Day 36.
- Frequency and severity of any SAE until Day 208.
- Frequency and severity of an AESI until Day 208.

Booster Phase:

- Frequency and severity of solicited AEs (local and systemic reactions) within 7 days after the booster vaccination
- Frequency and severity of any unsolicited AE up to Visit 9
- Frequency and severity of any vaccine-related AE up to Visit 9
- Frequency and severity of any SAE up to Visit 10
- Frequency and severity of any AESI up to Visit 10

3.2 IMMUNOGENICITY ENDPOINTS

3.2.1 Primary Endpoint

Geometric mean titre (GMT) for neutralizing antibodies against SARS-CoV-2 determined by wild-type virus microneutralizing assay at Day 36.

3.2.2 Secondary Endpoints

- Immune response as measured by neutralizing antibody titres against SARS-CoV-2 on Day 8, Day 22, Day 106 and Day 208.
- Proportion of participants with seroconversion in terms of neutralizing antibodies on Day 8, Day 22, Day 36, Day 106 and Day 208.
- Fold increase of SARS-CoV-2 neutralizing antibody titres on Day 8, Day 22, Day 36, Day 106 and Day 208 compared with baseline.
- GMTs for IgG against SARS-CoV-2, determined by ELISA, at Day 1, 8, 22, 36, 106 and 208.
- Proportion of participants with seroconversion in terms of IgG antibodies against SARS-CoV-2 as determined by ELISA on Day 8, Day 22, Day 36, Day 106 and Day 208.

Booster Phase:

- Geometric mean fold rise (GMFR) from pre-booster time point (Visit 7) to 2 weeks after booster dose (Visit 8) with regards to neutralizing antibodies.
- Geometric mean fold rise (GMFR) from pre-booster time point (Visit 7) to 4 weeks after booster dose (Visit 9) with regards to neutralizing antibodies.
- Proportion of Participants with 4-fold increase from pre-booster dose (Visit 7) to 2 weeks after booster dose (Visit 8) with regards to neutralizing antibodies.
- Proportion of Participants with 4-fold increase from pre-booster dose (Visit 7) to 4 weeks after booster dose (Visit 9) with regards to neutralizing antibodies.
- Geometric mean titres (GMT) measured as neutralizing antibody titres against SARSCoV-2 at Visit 7, Visit 8 and Visit 9.
- Geometric mean fold rise (GMFR) from pre-booster dose (Visit 7) to 4 weeks after booster dose (Visit 9) with regards to S-protein binding antibodies (ELISA).
- Geometric mean fold rise (GMFR) from pre-booster dose (Visit 7) to 2 weeks after booster dose (Visit 8) with regards to S-protein binding antibodies (ELISA).
- Proportion of Participants with 4-fold increase from pre-booster dose (Visit 7) to 4 weeks after booster dose (Visit 9) in regards to S-protein binding antibodies (measured by ELISA).

- Proportion of Participants with 4-fold increase from pre-booster dose (Visit 7) to 2 weeks after booster dose (Visit 8) in regards to S-protein binding antibodies (measured by ELISA).
- GMT measured as IgG antibodies against SARS-CoV-2, as determined by ELISA, at Visit 7, Visit 8 and Visit 9.

3.3 EXPLORATORY ENDPOINT

Cellular immune response on Day 1, Day 36, Day 208, Visit 7 and Visit 8.

4 ANALYSIS POPULATIONS

4.1 SAFETY ANALYSIS SET (SAS)

The Safety Analysis Set (SAS) includes all participants who entered into the study and received at least one vaccination. The SAS will be used for all baseline, safety and tolerability analyses including demographic data, local/systemic tolerability, laboratory data, Adverse Events (AEs), Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESIs). All analyses based on the SAS will be carried out using the actual treatment received.

4.2 FULL ANALYSIS SET (FAS)

The Full Analysis Set (FAS) is defined to include all participants enrolled who received at least one vaccination. Participants will be analysed according to the treatment group they had been randomized to i.e. the planned treatment, rather than by the actual treatment they received.

4.3 PER-PROTOCOL ANALYSIS SET (PPAS)

The Per-Protocol Analysis Set (PPAS) will consist of the FAS population including participants who have no major protocol deviations until the respective analysis time point (i.e. PPAS Day 36, PPAS Day 106 and PPAS Day 208). Participants who received an already licensed COVID-19 vaccine outside of the study or participants who received less than 2 vaccinations will be excluded.
These criteria for potential protocol violations are identified at the time of study planning. However, during the course of the trial unforeseen events may occur or new scientific knowledge may become available, therefore final decisions on all protocol violations will be made on a case by case decision in a data review meeting.
Immunogenicity analysis will be primarily carried out on the PPAS.

4.4 MODIFIED PER-PROTOCOL ANALYSIS SET (mPPAS)

Modified PPAS will include all participants from PPAS except those participants who were tested positive for COVID-19 anytime during study until the respective analysis timepoint (i.e. PPAS Day 36, PPAS Day 106 and PPAS Day 208) after first vaccination.

4.5 PROTOCOL DEVIATIONS

Any deviations from the protocol will be tracked, actions defined, as feasible, and reviewed in data review meetings for assessment of their influence on the quality of the study analysis.

All deviations will be evaluated and classified as major or minor before database lock and unblinding (refer to protocol deviation management plan for more details). All deviations will be listed.

Major protocol deviations that lead to exclusion from the PP Population may include the following but are not limited to:

- Participants with less than two vaccinations.
- Participants who received the wrong study medication.
- Participants who fulfilled exclusion criteria (e.g. participant received any nationally deployed Covid vaccine)

4.6 SAFETY ANALYSIS SET (SAS): BOOSTER GROUP

The Safety Analysis Set (SAS) for the booster phase will include all participants who received the booster vaccination. All analyses based on the SAS will be carried out using the actual treatment received.

4.7 ITT ANALYSIS SET: BOOSTER GROUP

The ITT for the booster group will include participants who received the booster dose with VLA2001.

5 GENERAL ASPECTS FOR STATISTICAL ANALYSES

5.1 GENERAL METHODS

- All analyses and summaries will be produced using SAS® version 9.4 (or higher).
- Categorical variables will be summarized using the number of observations (n), frequency and percentage of participants. All percentages will be presented as one-decimal point, unless otherwise specified. Percentages equal to 100 will be presented as 100% and percentages will not be presented for zero frequencies.
- Continuous variables will be summarized using the number of participants with evaluable data, mean, standard deviation (SD), median, minimum and maximum. Geometric means and corresponding statistics will be presented for titre data. The same number of decimal places as in the raw data will be presented when reporting minimum and maximum, 1 more decimal place than in the raw data will be presented when reporting the mean and median, and 2 more decimal places than in the raw data will be presented when reporting the SD. Lower and upper bound values for the confidence interval will be reported to 2 more decimal places than the raw data.
- Any calculated p-values will be presented to 3 decimal places; p-values less than 0.001 will be presented as ‘$p<0.001$’ and p-values greater than 0.999 will be presented as ‘$p>0.999$’.
- Unscheduled or repeat assessments will not be included in summary tables unless specified. All assessments will be included in the participant listings.
- All tables, listings and figures will include footers that identify the name of the program that created the output, together with the date and time on which it was created. Headers will include the total number of pages that the presentation contains and, for each page, the number of the page within the presentation.

5.2 KEY DEFINITIONS

5.2.1 Study Day

Study Day 1 is defined as the randomization day i.e. the day of first study drug administration. Subsequent days are numbered consecutively (Day 2, Day 3, etc.). Before the day of first study drug administration, study days will be numbered sequentially with negative values (i.e., Day -1, Day -2, etc.).

5.2.2 Baseline Values

Baseline values will be taken as the last non-missing assessments before dosing with study drug.

5.3 DATA HANDLING CONVENTIONS

5.3.1 Missing Data

Unless otherwise stated no imputation will be done for the missing data values. For the participants who are discontinued from the trial, all data until the point of discontinuation will be used in the summary and analyses. Reason for discontinuation will be presented in participant data listing and disposition table.

Data that are potentially spurious or erroneous will be examined using standard data management procedures and data queries will be issued prior to database lock and statistical analysis.

The Following rules will be followed for handling partial/missing date information for prior and concomitant medications:

Partial dates for medications will be imputed to decide if a medication is to be considered prior or concomitant (please refer to section 6.4 for definition of prior and concomitant medications).

Partial start dates in prior and concomitant medications will be imputed with a conservative algorithm, to the first day of the month (if missing day) or the first month of the year (if missing month). Partial end dates in prior and concomitant medications will be imputed to the last day of the month (if missing day) or the last month of the year (if missing month).

If end date of medication is missing, then medication will be considered concomitant. If start date of medication is missing and the end date is on or after the first dose of study drug or the medication is ongoing, then medication will be considered concomitant.

5.3.2 Visit Windowing

Data will be analyzed using the nominal visit i.e. study visit and analysis visit will be similar. Unscheduled visits will be listed, but not mapped to a specific analysis visit.

5.3.3 Pooling of Sites

Data from all the sites will be pooled for analysis and summarization.

6 STUDY PARTICIPANTS

6.1 DISPOSITION OF PARTICIPANTS

The following participant data will be summarized for each dose group and overall for all screened participants:

- Participants screened (i.e. all participants who signed informed consent).
- Screen failure participants and reasons for screen failure
- Participants randomized
- Participants in each analysis population
- Participants who received the booster dose
- Participants who are early terminated and reasons for early termination.

All disposition data will also be listed.

6.2 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Descriptive statistics of the demographic and baseline characteristics for each dose group and overall will be presented for safety analysis set. The following demographic and baseline characterics will be summarized:

- Age at the time of informed consent (years)
- Sex
- Childbearing potential and reason for no childbearing potential
- Ethnicity
- Height at screening (cm)
- Weight at screening (kg)
- Body Mass Index (BMI) at screening (kg/m^2)
- COVID-19 Test Result at screening (Positive, Negative)
- HBsAg Test Result at screening (Positive, Negative)
- HCV Test Result at screening (Positive, Negative)
- HIV Test Result at screening (Positive, Negative)

All demographic and baseline data will also be listed.

6.3 MEDICAL HISTORY AND VACCINATION HISTORY

Medical history will be coded with Medical Dictionary for Regulatory Activities (MedDRA) version 23.1.

Medical history (including vaccination history) data will be summarized using counts and percentages by System Organ Class (SOC), Preferred Term (PT) by dose group and overall for the safety analysis set. A participant will only be counted once in an SOC and an SOC/PT combination. All medical history data will also be listed.

6.4 PRIOR AND CONCOMITANT MEDICATIONS

Prior and concomitant medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) B3 September 2020.

Prior medications are defined as medications that started and stopped before the date of first dosing. Any medication that started on the date of dosing will not be considered prior. Any medication that stopped on the date of dosing will be considered prior.

Concomitant medications are defined as all medications (excluding study treatment) that started on or after the date of first dosing. This also includes medications ongoing on the first dosing date. Medications that started before the date of dosing and are ongoing after the date of dosing will be considered as concomitant.

For the rules to be used for handling missing or partial dates refer to Section 5.3.1.

Prior and concomitant medications will be summarized for each dose group and overall with the number and percentage of participants receiving medication by ATC class and preferred term (PT) for the safety analysis set. Medications will be sorted in alphabetical order of ATC Level and then decreasing PT frequency in overall column. A participant will only be counted once within a given ATC level and an ATC/PT combination.

All medications will be listed with ATC class, preferred term and reported medication name.

6.5 CONCOMITANT PROCEDURES

All data related to concomitant procedures a participant received during the study will be presented in a participant data listing.

6.6 TREATMENT EXPOSURE

Number of doses taken will be summarized by dose groups and overall for the safety analysis set. In addition, exposure to study drug will be summarized and will be calculated as:
Exposure duration = (Date of last dose of study drug - Date of first dose of study drug) +1

7 SAFETY ANALYSES

Safety analysis will be carried out using the safety analysis set.

7.1 ANALYSIS OF PRIMARY SAFETY ENDPOINT

7.1.1 Solicited Adverse Events within 7 days after vaccination

Solicited AEs will be collected in the eDiary by the participant for 7 consecutive days after each vaccination, starting on the day of vaccination. Solicited AEs will be graded by the investigator according to the FDA's Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. The following solicited reactions will be assessed:

Solicited injection site reactions: These include injection site pain, itching, tenderness, redness and swelling/induration.

Solicited systemic reactions: These include fever/body temperature, fatigue, headache, nausea/vomiting, muscle pain.

All fever measurements should be recorded by the participant in the participant diary including the first value that shows a return to normal body temperature. Oral body temperature ≥ 38.0°C is defined as fever. If more than one body temperature value is recorded in the participant diary on a given day, the highest daily temperature reading will be recorded in the eCRF.

The number and percentage of participants with solicited injection site and systemic AEs within 7 days after vaccination along with the exact 95% Clopper-Pearson confidence interval (CI) for all AE rates will be presented for each dose group and overall. Differences between the dose groups will be assessed for significance using Fisher-Freeman-Halton exact test and p-values will be presented for this test. If the overall group difference is statistically significant then multiplicity adjusted p-values (using Hochberg method) for pairwise group differences will be calculated for Fisher's exact test.

Solicited AEs will also be summarized by severity grades. If a participant has the same reaction with multiple severity grades then the most severe grade will be counted.

All data for solicited adverse events will also be presented in participant data listings.

Booster Phase:
The number and percentage of participants with solicited injection site and systemic AEs within 7 days after booster vaccination along with the exact 95% Clopper-Pearson confidence interval (CI) for all AE rates will be presented. Solicited AEs will also be summarized by severity grades. If a participant has the same reaction with multiple severity grades then the most severe grade will be counted.

Duration of solicited injection site reactions and solicited systemic reactions after booster dose will also be summarized. In case of missing end date for a reaction after booster dose the last available date of reaction will be considered as the end date in calculation of the duration. Duration for a reaction will be calculated as: (Last occurence date of reaction after booster – start date of occurrence of reaction after booster +1).

All data for solicited adverse events in the booster phase will also be presented in participant data listings.

7.2 ANALYSIS OF SECONDARY SAFETY ENDPOINTS

7.2.1 Unsolicited Adverse Events

All adverse events will be coded with Medical Dictionary for Regulatory Activities (MedDRA) version 23.1.

A participant with the same unsolicited AE with different reported relationships to study treatment will be summarized at the closest relationship. Also, a participant with the same AE at different severity grades will be summarized at the most severe grade.

An overall summary of adverse events will be presented by dose groups and overall and will include:

- Participants with any unsolicited AE until Day 36
- Participants with any unsolicited AE until Day 208
- Participant with any serious unsolicited AE until Day 36
- Participant with any serious unsolicited AE until Day 208
- Participant with any AESI until Day 36
- Participant with any AESI until Day 208
- Participants with any treatment related unsolicited AE until Day 36
- Participants with any treatment related unsolicited AE until Day 208
- Participants with any medically attended unsolicited AE until Day 36
- Participants with any medically attended unsolicited AE until Day 208

The following summaries of adverse events will be added for the additional interim analysis after Day 106. All adverse events collected up to the point of datacut will be presented.

- Participants with any unsolicited AE until day of Data Cut for Day 106 analysis
- Participant with any serious unsolicited AE until day of Data Cut for Day 106 analysis
- Participant with any AESI until day of Data Cut for Day 106 analysis
- Participants with any treatment related unsolicited AE until day of Data Cut for Day 106 analysis
- Participants with any medically attended unsolicited AE until day of Data Cut for Day 106 analysis

The follow-up time for participants until the point of data cut for the Day 106 analysis will be summarized.

The number and percentage of participants with unsolicited AEs along with the exact 95% Clopper-Pearson confidence interval (CI) for all AE rates will be presented for each dose group and overall. Differences between the dose groups will be assessed for significance using Fisher-Freeman-Halton exact test and p-values will be presented for this test. If overall group difference comes out to be significant then multiplicity adjusted p-values (using Hochberg method) for pairwise group difference will be calculated using Fisher's exact test.

In addition, following summaries will be presented by SOC and PT for each dose cohort and overall:

- Summary of unsolicited AEs until Day 36
- Summary of unsolicited AEs until Day 208
- Summary of serious unsolicited AEs until Day 36
- Summary of serious unsolicited AEs until Day 208
- Summary of AESI until Day 36
- Summary of AESI until Day 208
- Summary of treatment related unsolicited AEs until Day 36
- Summary of treatment related unsolicited AEs until Day 208

- Summary of unsolicited AEs by maximum severity
- Summary of unsolicited AEs by closest causality relationship

The following summaries of adverse events presented by SOC and PT will be added for the additional interim analysis after Day 106:

- Participants with any unsolicited AE until day of Data Cut for Day 106 analysis
- Participant with any serious unsolicited AE until day of Data Cut for Day 106 analysis
- Participant with any AESI until day of Data Cut for Day 106 analysis
- Participants with any treatment related unsolicited AE until day of Data Cut for Day 106 analysis
- Summary of unsolicited AEs by maximum severity until day of Data Cut for Day 106 analysis
- Summary of unsolicited AEs by closest causality relationship until day of Data Cut for Day 106 analysis

Participants with multiple adverse events within an SOC or SOC/PT combination are counted only once for that SOC or SOC/PT combination. For the summary table of AEs by maximum severity, if a participant experiences multiple events in the same SOC or SOC/PT combination, the highest recorded severity will contribute counts to the summary table. For the summary table of AEs by closest causality relationship, if a participant experiences multiple events in the same SOC or SOC/PT combination, the closest relationship to study drug will contribute counts to the summary table. All data from the adverse events eCRF will also be listed.

Booster Phase:

An overall summary of adverse events will be presented separately for the booster phase and will include:

- Participants with any unsolicited AE up to Visit 9 in the booster phase
- Participants with any treatment related unsolicited AE up to Visit 9 in the booster phase
- Participant with any serious unsolicited AE up to Visit 9 in the booster phase
- Participant with any AESI up to Visit 9 in the booster phase
- Participants with any unsolicited AE up to Visit 10 in the booster phase
- Participants with any treatment related unsolicited AE up to Visit 10 in the booster phase
- Participant with any serious unsolicited AE up to Visit 10 in the booster phase
- Participant with any AESI up to Visit 10 in the booster phase

In addition, following summaries will be presented by SOC and PT for the booster phase:

- Summary of unsolicited AEs up to Visit 9 in the booster phase
- Summary of treatment related unsolicited AEs up to Visit 9 in the booster phase
- Summary of serious unsolicited AEs up to Visit 9 in the booster phase
- Summary of AESI up to Visit 9 in the booster phase
- Summary of unsolicited AEs up to Visit 10 in the booster phase
- Summary of treatment related unsolicited AEs up to Visit 10 in the booster phase
- Summary of serious unsolicited AEs up to Visit 10 in the booster phase
- Summary of AESI up to Visit 10 in the booster phase
- Summary of unsolicited AEs by maximum severity up to Visit 9 in the booster phase

- Summary of unsolicited AEs by closest causality relationship up to Visit 9 in the booster phase
- Summary of unsolicited AEs by maximum severity up to Visit 10 in the booster phase
- Summary of unsolicited AEs by closest causality relationship up to Visit 10 in the booster phase

Adverse events that started in the booster phase will be presented separately in participant data listings.

7.3 CLINICAL LABORATORY TESTS

Blood and urine samples will be obtained for assessment of clinical laboratory parameters. Clinical laboratory assessments (hematology, chemistry, urinalysis, coagulation) will be performed on the visits as described in the schedule of study assessments and procedures in protocol section 22.2.

Clinical laboratory parameters at all scheduled visits and the change from baseline to post baseline visits will be summarized using appropriate summary statistics by dose groups. Categorical urinalysis parameters will be summarized using count and percentages by dose cohorts for each scheduled visit.

Separate summary tables for each dose cohort and overall will be presented for the laboratory results thar are marked as abnormal clinically significant by the investigator.

All clinical laboratory results will also be listed. Laboratory values that are outside the normal range will be flagged in a participant data listing.

Separate summary table and listing will be presented for the booster phase.

7.4 VITAL SIGNS

Vital signs will include body temperature (°C) measured orally, pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg) while seated and at rest.
Vital signs will be measured at Screening (Visit 0), Visit 5 Day 106 and Visit 6 Day 208. At both vaccinations visits (Visit 1 Day 1 and Visit 3 Day 22) these data will be recorded prior to vaccination and in addition, pulse rate and blood pressure will be assessed after vaccination while seated and at rest after a 30-minute observation period. In addition, for the sentinel dosing group, pulse rate and blood pressure will be recorded shortly before discharge from study site (3 hours or respectively, 60 min minutes after vaccination).

Tables presenting descriptive statistics for the observed data at each scheduled visit and the corresponding change from baseline at the post-baseline visits will be presented for each dose cohort. All vital signs data will also be listed.

Separate Summary table and listing will be presented for the booster phase.

7.5 PHYSICAL EXAMINATION

At the screening (Visit 0), a physical examination will be performed on the following body systems being described as normal or abnormal: general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. At

subsequent visits, and prior to discharge after vaccinations on Visits 1 and 2, a symptom-driven physical examination will be performed, i.e. only in case a symptom is reported by the participant, an assessment of the affected body system(s) will be performed.

Physical examination results (Normal, Not clinically significant, Clinically significant) will be summarized for all body systems examined at all scheduled visits by dose cohorts. Physical examination results will also be listed. Separate summary table and listing will be presented for the booster phase.

7.6 SERUM/URINE PREGNANCY TEST

For women of childbearing potential, a urine sample and a serum test for pregnancy will be performed at screening and before the 1st and 2nd vaccination. In addition, a urine pregnancy test will be done prior to vaccination at Visit 7. All results will be presented in participant data listings.

8 IMMUNOGENICITY ANALYSES

Immunogenicity samples (10ml) will be drawn for SARS-CoV-2-specific neutralizing antibody titre evaluation using wild-type virus microneutralization assay (WT-MNA) and binding IgG antibody titre evaluation by ELISA. In addition, a blood sample [approx. 50mL] will be collected to isolate PBMCs from all participants except sentinel participants for future investigation of cellular immune responses to VLA2001.

Serum samples to measure SARS-CoV-2 neutralizing antibody levels will be collected from participants on Day 1 (prior first vaccination), Day 8, Day 22 (prior second vaccination), Day 36, Day 106 and Day 208. An authorized laboratory will measure virus specific neutralizing antibodies to SARS-CoV-2 using wild-type virus microneutralizing assay (WT-MNA). In brief, infectious virus is incubated with sera. Virus susceptible cell monolayers are exposed to the test sera/virus mixture. Patches of infected cells (microplaques) are detected via an antibody pair specific for the SARS-CoV-2 RBD Spike protein and visualised using colored substrate. Neutralizing titer of test sera is expressed as ND_{50}; serum dilution at where 50% of virus is neutralized. The Part A Day 36 analysis was performed with values below the limit of quantification of the WT-MNA (ND_{50}=58; i.e titre <58) before the WT-MNA was fully validated and LLOQ values were replaced with a value of 29 (i.e LLOQ/2=29). All subsequent analyses are performed with values below the limit of quantification of the fully validated WT-MNA (ND_{50}=62; i.e titre <62) and values lower than LLOQs will be replaced by 31 (LLOQ/2= 31). For results given as e.g. ND_{50}>SDUL reported value will be replaced with the highest sample dilution tested (SDUL) in all analyses..

In addition to the functional assays, samples are analysed for IgG against SARS-CoV-2 by a human anti-SARS-CoV-2 pre-spike IgG antibody ELISA (S-ELISA). In brief, the SARS-CoV-2 pre-spike recombinant antigen is adsorbed onto the 96-well microplate. Dilution series of human sera, standard and controls are added to microtitre plates coated with the SARS-CoV-2 pre-spike recombinant antigen. Presence of binding IgGs is detected with an anti-human IgG antibody conjugated to peroxidase, followed by addition of the peroxidase substrate. The optical density of the colored end product is proportional to the amount anti-SARS-CoV-2 pre-spike IgG antibodies present in the serum sample. Values below the quantitation limit of the ELISA (50.3 ELU/mL) and samples scored

as “negative” will be replaced by 25 ELU/mL. Also values above the quantitation limit (>15798 ELU/mL) will be replaced by 15798 ELU/mL.

Immunogenicity analysis will be presented for the respective PPAS and modified PPAS population. In addition analysis can also be presented for FAS population. Immunogenicity analysis may also be presented for “Unscheduled COVID-19 illness visit” that will be performed if a participant tests positive for COVID-19 during the study.

Immunogenicity analysis may also be presented stratified for MNA positive/negative at Visit 1. MNA result will be considered positive if result (ND50) >=LLOQ, i.e. >=62. Otherwise if the result (ND50) < LLOQ then MNA will be considered negative.

All secondary immunogenicity analysis for booster phase will be presented by primary treatment group (Low Dose/ Medium Dose/ High Dose) of participant and the tables will also be presented stratified by following factors: Received other COVID-19 vaccine any time during study / Not received other COVID-19 vaccine any time during study/ COVID-19 positive any time during study who did not receive other COVID-19 vaccine any time during study.

Immunogenicity analysis will also be presented for participants in PPAS and mPPAS who received a booster dose.

8.1 ANALYSIS OF PRIMARY IMMUNOGENICITY ENDPOINT

The primary immunogenicity analysis will be a comparison of geometric mean titres (GMTs) for SARS-CoV-2 neutralizing antibodies at 14 days after the second dose (i.e. Day 36).

GMTs along with corresponding 95% CI will be estimated by applying analysis of variance (ANOVA) for $\log_{10}$ transformed neutralizing antibody titre including the factors dose group and study site. Estimates (least squares means, least squares means differences and the corresponding 95% CIs) obtained from ANOVA will be back transformed (antilog_{10}) to get the estimates of GMT, and corresponding 95% CI. If ANOVA suggests dose group differences to be statistically significant then Tukey’s HSD test will be applied for pair wise comparisons of dose groups. The table will also include the following descriptive summary statistics: number of non-missing observations (n), median, minimum, maximum.

If $\log_{10}$ transformed data is not normally distributed then GMTs (CI) will be calculated by taking the antilogarithm of the mean (CI) of the $\log_{10}$ transformed titre. Also p-value from Kruskal Wallis test will be calculated to check if the results are significantly different among dose groups at 5% level of significance. If the test suggests significant p-value then pairwise group comparison will be perfomed using Dwass, Steel, Critchlow-Fligner (DSCF) multiple comparisons post-hoc procedure to determine which pair of dose groups differ significantly.

In addition, as an exploratory analysis, data for SARS-CoV-2 neutralizing antibodies for an external convalescent group of participants will be presented. All dose groups will also be compared with this group.

A graph overlaying scatter plot over box plots for SARS-CoV-2 neutralizing antibodies tires will be presented by visits and dose cohorts. Similar scatter plot will be presented for convalescant participants also.

In addition, reverse cumulative distribution functions will be plotted for SARS-CoV-2 neutralizing antibodies tires (ND50) by dose groups for scheduled visits Day 1, 8, 22, 36, 106, 208.

8.2 ANALYSIS OF SECONDARY IMMUNOGENICITY ENDPOINTS

8.2.1 Immune Response as Measured by Neutralizing Antibody Titres Against SARS-CoV-2

The same methodology as described for primary endpoints will be used for analysis of neutralizing antibody titres against SARS-CoV-2 for all timepoints. Descriptive summary statistics including number of non-missing observations (n), median, minimum, maximum GMTs along with 95% CI for neutralizing antibody titres against SARS-CoV-2 will be presented over time for all sample visits.

8.2.2 Proportion of Participants With Seroconversion in Terms of Neutralizing Antibodies

Seroconversion will be defined as ≥ 4-fold increase in SARS-CoV-2-specific neutralizing antibody titre levels between Day 1 and post-vaccination sample collection timepoints. The fold increase is defined as a participant's post-Baseline titre at a visit divided by the baseline (Day 1) titre. The number and proportion of participants with seroconversion in terms of neutralizing antibodies on Day 8, Day 22, Day 36, Day 106 and Day 208, in participants negative for SARS-CoV-2 infection at Screening will be presented along with exact 95% Clopper-Pearson confidence interval (CI) for each dose group and overall. Differences between the dose groups will be assessed for significance using Fisher-Freeman-Halton exact test and p-values will be presented for this test. If overall group difference is statistically significant, i.e. p-value for Fisher-Freeman-Halton exact test is ≤ 0.05, then multiplicity adjusted p-values (using Hochberg method) for pairwise group difference will be calculated for Fisher's exact test.
In addition, the number and proportion of participants with ≥ 2-fold increase, ≥ 10-fold increase and ≥ 20-fold increase will also be presented for each post baseline visit.

8.2.3 Fold Increase of SARS-CoV-2 Neutralizing Antibody Titres

Geometric mean fold increase (GMFI) of SARS-CoV-2 neutralizing antibody titres on Day 8, Day 22, Day 36, Day 106 and Day 208 compared with baseline will be estimated using the same methodology as described for the primary immunogenicity endpoint. In the ANOVA model the dependent variable $\log_{10}$ titre will be replaced with $\log_{10}$ fold increase.

8.2.4 Immune Responses as Measured by IgG anti SARS-CoV-2 IgG S-ELISA

The same methodology as described for primary endpoint will be used for the summary and analysis of IgG antibody titres determined by ELISA. The analysis will be presented for each of the scheduled sampling timepoint i.e. Day 1, 8, 22, 36, 106 and 208.
A graph overlaying scatter plot over box plots for IgG antibody titres will be presented by visits and dose cohorts.

8.2.5 Proportion of Participants With Seroconversion In Terms of IgG Antibodies Against SARS-CoV-2 As Determined By ELISA

The same methodology as described in section 8.2.2 will be used for the summary and analysis of proportion of participants with seroconversion in terms of IgG antibodies. Seroconversion will be defined as ≥ 4-fold increase in SARS-CoV-2-specific IgG antibody levels between Day 1 and post-vaccination sample collection timepoints.

8.2.6 Fold Increase of SARS-CoV-2 IgG measured by anti-SARS-CoV-2 S-ELISA

Geometric mean fold increase (GMFI) of SARS-CoV-2 IgG antibody titres on Day 8, Day 22, Day 36, Day 106 and Day 208 compared with baseline will be estimated using the same methodology as described for the primary immunogenicity endpoint. In the ANOVA model the dependent variable $\log_{10}$ titre will be replaced with $\log_{10}$ fold increase.

8.3 ANALYSIS OF SECONDARY IMMUNOGENICITY ENDPOINTS FOR THE BOOSTER PHASE

Analysis for booster phase will be presented for booster group ITT population.

8.3.1 Geometric mean fold rise (GMFR) for SARS-CoV-2 Neutralizing Antibody Titres

Geometric mean fold rise (GMFR) of SARS-CoV-2 neutralizing antibody titres at Visit 8 and Visit 9 compared with pre-booster time point (Visit 7) and corresponding CI will be calculated using the same methodology as described for the primary immunogenicity endpoint.
The fold increase will be calculated as a participant's titre at a visit divided by the pre-booster time point (Visit 7) titre.

8.3.2 Proportion of Participants With 4-fold increase in Terms of Neutralizing Antibody Titres

The number and proportion of participants with 4-fold increase from pre-booster dose (Visit 7) to Visit 8 and Visit 9 in terms of neutralizing antibodies will be presented. Exact 95% Clopper-Pearson confidence interval (CI) will also be presented for proportions.

8.3.3 Geometric mean titres (GMT) for SARS-CoV-2 Neutralizing Antibody Titres

GMTs along with corresponding 95% CI for neutralizing antibodies will be calculated using the same methodology as described for the primary immunogenicity endpoint. The results will be presented for Visit 7, Visit 8 and Visit 9.

8.3.4 Geometric mean fold rise (GMFR) for S-protein binding antibodies (ELISA)

Geometric mean fold rise (GMFR) of S-protein binding antibodies (IgG antibodody titres) measured by ELISA at Visit 8 and Visit 9 compared with pre-booster time point (Visit 7) and corresponding CI will be calculated using the same methodology as described for the primary immunogenicity endpoint.

8.3.5 Proportion of Participants With 4-fold increase in Terms of S-protein binding antibodies (ELISA)

The number and proportion of participants with 4-fold increase from pre-booster dose (Visit 7) to Visit 8 and Visit 9 in terms of S-protein binding antibodies (IgG antibodody titres) will be presented. Exact 95% Clopper-Pearson confidence interval (CI) will also be presented for proportions.

8.3.6 Geometric mean titres (GMT) for S-protein binding antibodies (ELISA)

GMTs along with corresponding 95% CI for S-protein binding antibodies (IgG antibodies against SARS-CoV-2, as determined by ELISA) will be calculated using the same methodology as described for the primary immunogenicity endpoint. The results will be presented for Visit 7, Visit 8 and Visit 9.

9 EXPLORATORY ANALYSES

9.1 IFN Gamma T-CELL ELISpot (T-SPOT)

The cell-mediated (cellular) immune response (T-cell response) will be assessed on Day 1, Day 36 and Day 208 by IFN gamma T-cell ELISpot assays to SARS-CoV-2 antigens.

For T-cell ELISpot assay, the isolated PBMCs are incubated with SARS-CoV-2 specific peptides to allow stimulation of any SARS-CoV-2 antigen specific T-cells present. Secreted cytokine, e.g. IFN-gamma, is captured by specific antibodies on the membrane which forms the base of the plate well, PBMCs and other unwanted materials are removed by washing. A secondary conjugated antibody directed to a different epitope of the cytokine molecule, is added and binds to the cytokine captured on the membrane. A soluble substrate is added and cleaved by the conjugate to form a spot of insoluble precipitate at the site of reaction. Each spot represents the footprint of the individual cytokine-secreting T-cell and evaluating the number of spots obtained provides a measurement of the abundance of antigen specific effector T-cells in peripheral blood. Results are reported as number of spot forming units (SFU) per 250 000 PBMCs. SFU for each stimulation panel are normalized to the negative control (SFU of Nil control are substracted). The sample is considered reactive against individual stimulation panel if the normalized SFU $\geq$6.

Results of the cellular immune response will be summarized descriptively by dose group and overall and will be presented for both the PPAS and modified PPAS for each visit and stratified for T-spot baseline reactivity (“Reactive on Day 1” and “Non-Reactive on Day 1”). A sample is considered ‘Reactive’ at baseline (Day 1) if the normalized SFU $\geq$ 6 in at least one SARS-CoV-2 specific stimulation panel (i.e. Panel 1, 2, 3, 4, 14) on Day 1. In addition, the p-value from Kruskal Wallis test will be calculated to check if the results are significantly different among dose groups for each stimulation panel. If the test suggests a significant p-value, then a pairwise group comparison will be perfomed using Dwass, Steel, Critchlow-Fligner (DSCF) multiple comparisons post-hoc procedure to determine which pair of dose groups differ significantly. In addition, a Signed Rank Test will be performed within each dose group to test for significant difference between tested days (i.e. Day 1 vs Day 36, Day 1 vs Day 208, Day 36 vs Day 208) for each stimulation panel.

Following parameters will be summarized:

- Panel 1 Spike Protein N terminus
- Panel 2 Spike Protein C terminus
- Panel 3 Nucleocapsid Protein
- Panel 4 Membrane Protein
- Panel 13 A cross reactive pool of coronavirus epitopes
- Panel 14 Spike Protein, full sequence

A graph overlaying scatter plot over box plots presenting the above mentioned parameters of ELISpot (Spot forming units/$2.5x10^5$ PBMC) will be presented by dose groups and assessment days per stimulation panel.

Booster Phase:
The cell-mediated (cellular) immune response (T-cell response) will be assessed on Visit 7 and Visit 8 of the booster phase by IFN gamma T-cell ELISpot assays to SARS-CoV-2 antigens.
Results of the cellular immune response will be summarized descriptively and will be presented for the booster group ITT population for each visit in the booster phase.

9.2 INTRACELLULAR CYTOKINE STAINING (ICS)

The Intracellular cytokine staining assay has been designed to measure cytokine production following stimulation of isolated cryopreserved PBMCs from vaccinated individuals with peptide pools. In brief, cryopreserved cells are thawed, then stimulated overnight with a pool of overlapping peptides derived from the SARS-CoV-2 spike protein (Panel 14), nucleocapsid protein (Panel 3), or control protein phytohemagglutinen (PHA). Following stimulation, the cells are stained for surface markers, fixed and permeabilised and then stained for intracellular cytokines. Following cytokines are assessed: Th1: IFNγ, IL-2, TNFα and Th2: IL-4, IL-5, IL-13. The percentage of positive cells among CD4+ and CD8+ T-cells was assessed for (1) each singular functional marker and stimulating peptide (single positives); (2) all permutations of 2 markers and stimulating peptide (double positives); (3) three cytokines specific for Th1 or Th2 response per stimulating peptide (triple positives).

Descriptive statistics will be presented for each singular cytokine (i.e. TNF+, IFNG+, IL-2+, IL13+, IL5+, IL4+) and stimulation panel (i.e. P3, P14, PHA). This will be presented by dose group and overall and for both the PPAS and modified PPAS. Following visits will be presented: Day 1, Day 36, Day 208.

In addition, graphs presenting percentage of positive cells among CD4+ and CD8+ T-cells for each participant will be presented by each visit and dose group for each singular cytokine ((i.e. TNF+, IFNG+, IL-2+, IL13+, IL5+, IL4+) and stimulation panel (i.e. P3, P14, PHA).

For the second interim analysis (Day 106 Analysis), ICS data will be analyzed and presented in TLFs only for the high dose group.

ICS results for singular cytokines will also be presented in participant data listings.

Booster Phase:

Descriptive statistics will be presented for each singular cytokine (i.e. TNF+, IFNG+, IL-2+, IL13+, IL5+, IL4+) and stimulation panel (i.e. P3, P14, PHA). This will be presented for the booster group ITT population. Following visits will be presented: Visit 7 and Visit 8.
ICS results for singular cytokines will be presented in participant data listings separately for the booster phase.

9.3 CORRELATION BETWEEN NEUTRALIZING ANTIBODY TITRES (MNA) AND IgG ANTIBODY TITRES (ELISA)

Correlation between neutralizing antibody titres (MNA) and IgG antibody titres (ELISA) will be presented as an exploratory analysis. For this, a scatter plot will be presented between neutralizing antibody titres and IgG antibody titres. Scatter plots will be grouped by the assessment visit days.

10 INTERIM ANALYSIS

An interim analysis will be performed once Part A of the study is completed i.e. when the last participant has completed Day 36 (14 days after the second vaccination). A second interim analysis will be performed after all participants have completed Day 106 visit. A third interim analysis will be performed after all participants have completed Visit 9.

11 SOFTWARE AND PROGRAMMING SPECIFICATIONS

All datasets, TLFs, and statistical analyses will be generated using SAS, Release 9.4 or higher (SAS Institute Inc., Cary, NC, USA). Computer-generated datasets, table, listing and figure output will adhere to the following specifications:

11.1 GENERAL PROGRAMMING SPECIFICATIONS

- One SAS program can create several outputs or a separate SAS program can be created for each output at statistical programmer's discretion.
- Each output will be stored in a separate file.
- Dataset files will be delivered in SAS7BDAT format.
- TLF output files will be delivered in Word format / rtf format (or the pdf format if sponsor requests).

11.2 TABLE, LISTING, AND FIGURE FORMAT

11.2.1 General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Courier New font, size 8.
- The data displays for all TLFs will have a 1.5-inch binding margin on top of a landscape- oriented page and a minimum 1-inch margin on the other 3 sides.
- Headers and footers for figures will be in Courier New font, size 8.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.

- TLFs will be in black and white (no color), unless otherwise specified.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

11.2.2 Headers

- All output should have the following header at the top left of each page:

    - For the Part A analysis:

      Valneva Austria GmbH
      Protocol: VLA2001-201
      Part A Analysis

    - For the second interim analysis:

      Valneva Austria GmbH
      Protocol: VLA2001-201
      Second Interim Analysis

    - For the third interim analysis:

      Valneva Austria GmbH
      Protocol: VLA2001-201
      Third Interim Analysis

- All outputs should have Page n of N at the top or bottom right corner of each page. TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date (date output was generated) should appear along with program name and location as the last footer on each page.

11.2.3 Display Titles

- Each TLF should be identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering is strongly recommended but sponsor preferences should be obtained prior to final

determination. A decimal system (x.y and x.y.z) should be used to identify TLFs with related contents. The title is centered. The analysis set should be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title (if needed)
Analysis Set

11.2.4 Column Headers

- Column headings should be displayed immediately below the solid line described above in initial upper-case characters.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of participants in the analysis set.

11.2.5 Body of the Data Display

11.2.5.1 Table Conventions

- Units will be included where available
- Percentage values should be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Values that round down to 0.0 will be displayed as '<0.1'.
- The percentage of participants is normally calculated as a proportion of the number of participants assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of participants exposed. Details of this should be described in footnotes or programming notes.

- For categorical summaries (number and percentage of participants) where a participant can be included in more than one category, describe in a footnote or programming note if the participant should be included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.

- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

11.2.5.2 Listing Conventions

- Missing data should be represented on participant listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.
- Dates should be printed in SAS® YYMMDD10. format ("YYYY-MM-DD": 2000-07-01). Missing portions of dates should be represented on participant listings as UNK (2000-07-UNK).
- All observed time values must be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available

11.2.6 Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left-justified with single line spacing immediately below the solid line underneath the data display.
- Footnotes should begin with "Note:" if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line where possible.
- Footnotes will be present on the page where they are first referenced and thereafter on each page of the table, unless the footnote is specific only to certain pages. Participant specific footnotes should be avoided.
- Footnotes will be used as needed, however, it must add value to the table, listing, or figure. If more than six lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last 2 lines of the footnote section will be a standard source that indicates the name of the program used to produce the data display, date the program was run, and the listing source (or data source for a listing) (i.e., 'Program: myprogram.sas Listing source: 16.x.y.z').

12 QUALITY CONTROL

12.1 SPECIFICATIONS

Once the SAP is finalized, dataset and TLF specifications will be developed and reviewed by the study team. An internal round table review of draft specifications will be conducted by the Lead Programmer, Lead Validator, Lead Statistician and Senior Reviewer (or member of Statistics Management).

The client will have the opportunity to review, comment and approve (via signature) all dataset and TLF specifications.

12.2 OUTPUTS

Validation of analysis datasets and tables are conducted through independent parallel programming of the statistical output according to the agreed upon specifications defined in the protocol, SAP, table shells, and dataset specifications. In this process, two programmers working independently (i.e., without input from one another), program the same output and compare results (via SAS PROC COMPARE). Any discrepancies are discussed and resolved, and the validation cycle is repeated until no further differences are noted between the two outputs.

All programs are submitted in batch mode to document the results of the PROC COMPARE indicating no unequal observations. Additionally, tracking logs are maintained which document all QC and validation findings and their resolution.

For CDISC datasets the Pinnacle 21 report will be used to validate the datasets for CDISC compliance.

Once the validation cycle is complete, the output (dataset or TLF) is subjected to the lead statisticians review as well as an internal round table review including the Lead Programmer, Lead Validator, Lead Statistician.

The client will have the opportunity to review, comment and approve (via signature) all final datasets and TLFs.

13 APPENDICES

13.1 CHANGES TO THE PROTOCOL SPECIFIED ANALYSES

As discussed with the sponsor, the analysis will not be stratified by serostatus for SARS-CoV-2 at screening because the chance that there are seropositive sujects enrolled in the study is negligible due to exclusion criteria #2 as per protocol.

13.2 INDEX OF TABLES

Table	Title	Population	Included in Interim Part A Analysis?	Included in Second Interim Analysis?	Included in Third Interim Analysis?
14.1.1	Participant Enrollment and Disposition Overall and by Sites	All Participants	Yes	Yes	Yes
14.1.2	Demographic and Baseline Characteristics	Safety	Yes	Yes	No
14.1.3	Medical and Vaccination History	Safety	No	No	No
14.1.4.1	Prior Medications	Safety	No	No	No
14.1.4.2	Concomitant Medications	Safety	No	No	No
14.1.5	Treatment Exposure	Safety	Yes	Yes	No
14.2.1.1	Overall Summary of Adverse Events	Safety	Yes	Yes	Yes
14.2.1.2	Solicited Injection Site Reactions Within 7 Days After Vaccination	Safety	Yes	Yes	No
14.2.1.3	Solicited Systemic Reactions Within 7 Days After Vaccination	Safety	Yes	Yes	No
14.2.1.4	Solicited Injection Site Reactions Within 7 Days After Vaccination By Maximum Severity	Safety	Yes	Yes	No
14.2.1.5	Solicited Systemic Reactions Within 7 Days After Vaccination By Maximum Severity	Safety	Yes	Yes	No
14.2.1.6	Overall Summary of Unsolicited Adverse Events	Safety	Yes	Yes	Yes
14.2.1.7	Summary of Unsolicited AEs Until Day 36	Safety	Yes	Yes	No
14.2.1.8	Summary of Unsolicited AEs Until Day 208	Safety	No	No	Yes
14.2.1.9	Summary of Serious Unsolicited AEs Until Day 36	Safety	Yes	Yes	No
14.2.1.10	Summary of Serious Unsolicited AEs Until Day 208	Safety	No	No	Yes

14.2.1.11	Summary of AESI Until Day 36	Safety	Yes	Yes	No
14.2.1.12	Summary of AESI Until Day 208	Safety	No	No	Yes
14.2.1.13	Summary of Treatment Related Unsolicited AEs Until Day 36	Safety	Yes	Yes	No
14.2.1.14	Summary of Treatment Related Unsolicited AEs Until Day 208	Safety	No	No	Yes
14.2.1.15	Summary of Unsolicited AEs by Maximum Severity Until Day 208	Safety	No	No	Yes
14.2.1.16	Summary of Unsolicited AEs by Causality Until Day 208	Safety	No	No	Yes
14.2.1.17	Summary of Follow-Up for participants at time of Data Cut for Day 106 analysis	Safety	No	Yes	No
14.2.1.18	Summary of Unsolicited AEs Until day of Data Cut for Day 106 analysis	Safety	No	Yes	No
14.2.1.19	Summary of Serious Unsolicited AEs Until day of Data Cut for Day 106 analysis	Safety	No	Yes	No
14.2.1.20	Summary of AESI Until day of Data Cut for Day 106 analysis	Safety	No	Yes	No
14.2.1.21	Summary of Treatment Related Unsolicited AEs Until day of Data Cut for Day 106 analysis	Safety	No	Yes	No
14.2.1.22	Summary of Unsolicited AEs by Maximum Severity until day of Data Cut for Day 106 analysis	Safety	No	Yes	No
14.2.1.23	Summary of Unsolicited AEs by Causality until day of Data Cut for Day 106 analysis	Safety	No	Yes	No
14.2.1.24	Solicited Injection Site Reactions Within 7 Days After Booster Vaccination	Safety (Booster)	No	No	Yes
14.2.1.25	Solicited Systemic Reactions Within 7 Days After Booster Vaccination	Safety (Booster)	No	No	Yes
14.2.1.26	Solicited Injection Site Reactions Within 7 Days After Booster Vaccination By Maximum Severity	Safety (Booster)	No	No	Yes
14.2.1.27	Solicited Systemic Reactions Within 7 Days After Booster Vaccination By Maximum Severity	Safety (Booster)	No	No	Yes

14.2.1.28	Duration of Solicited Injection Site Reactions after Booster Dose	Safety (Booster)	No	No	Yes
14.2.1.29	Duration of Solicited Systemic Reactions after Booster dose	Safety (Booster)	No	No	Yes
14.2.1.30	Overall Summary of Unsolicited Adverse Events (Booster Phase)	Safety (Booster)	No	No	Yes
14.2.1.31	Summary of Unsolicited AEs Up to Visit 9 (Booster Phase)	Safety (Booster)	No	No	Yes
14.2.1.32	Summary of Treatment Related Unsolicited AEs Up to Visit 9 (Booster Phase)	Safety (Booster)	No	No	Yes
14.2.1.33	Summary of Serious Unsolicited AEs Up to Visit 9 (Booster Phase)	Safety (Booster)	No	No	Yes
14.2.1.34	Summary of AESI Up to Visit 9 (Booster Phase)	Safety (Booster)	No	No	Yes
14.2.1.35	Summary of Unsolicited AEs Up to Visit 10 (Booster Phase)	Safety (Booster)	No	No	No
14.2.1.36	Summary of Treatment Related Unsolicited AEs Up to Visit 10 (Booster Phase)	Safety (Booster)	No	No	No
14.2.1.37	Summary of Serious Unsolicited AEs Up to Visit 10 (Booster Phase)	Safety (Booster)	No	No	No
14.2.1.38	Summary of AESI Up to Visit 10 (Booster Phase)	Safety (Booster)	No	No	No
14.2.1.39	Summary of Unsolicited AEs by Maximum Severity Up to Visit 9 (Booster Phase)	Safety (Booster)	No	No	Yes
14.2.1.40	Summary of Unsolicited AEs by Closest Causality Relationship Up to Visit 9 (Booster Phase)	Safety (Booster)	No	No	Yes
14.2.1.41	Summary of Unsolicited AEs by Maximum Severity Up to Visit 10 (Booster Phase)	Safety (Booster)	No	No	No
14.2.1.42	Summary of Unsolicited AEs by Closest Causality Relationship Up to Visit 10 (Booster Phase)	Safety (Booster)	No	No	No
14.2.2.1	Hematology: Summary and Change from Baseline	Safety	No	No	No
14.2.2.2	Hematology: Abnormal Clinically Significant Results	Safety	No	No	No
14.2.2.3	Biochemistry: Summary and Change from Baseline	Safety	No	No	No

14.2.2.4	Biochemistry: Abnormal Clinically Significant Results	Safety	No	No	No
14.2.2.5	Urinalysis: Summary and Change from Baseline	Safety	No	No	No
14.2.2.6	Urinalysis: Abnormal Clinically Significant Results	Safety	No	No	No
14.2.2.7	Urinalysis: Summary for Categorical Parameters	Safety	No	No	No
14.2.2.8	Coagulation: Summary and Change from Baseline	Safety	No	No	No
14.2.2.9	Coagulation: Abnormal Clinically Significant Results	Safety	No	No	No
14.2.2.10	Hematology: Summary and Change from Baseline (Booster Phase)	Safety (Booster)	No	No	No
14.2.2.11	Hematology: Abnormal Clinically Significant Results (Booster Phase)	Safety (Booster)	No	No	No
14.2.2.12	Biochemistry: Summary and Change from Baseline (Booster Phase)	Safety (Booster)	No	No	No
14.2.2.13	Biochemistry: Abnormal Clinically Significant Results (Booster Phase)	Safety (Booster)	No	No	No
14.2.2.14	Urinalysis: Summary and Change from Baseline (Booster Phase)	Safety (Booster)	No	No	No
14.2.2.15	Urinalysis: Abnormal Clinically Significant Results (Booster Phase)	Safety (Booster)	No	No	No
14.2.2.16	Urinalysis: Summary for Categorical Parameters (Booster Phase)	Safety (Booster)	No	No	No
14.2.2.17	Coagulation: Summary and Change from Baseline (Booster Phase)	Safety (Booster)	No	No	No
14.2.2.18	Coagulation: Abnormal Clinically Significant Results (Booster Phase)	Safety (Booster)	No	No	No
14.2.3	Vital Signs: Summary and Change from Baseline	Safety	No	No	No
14.2.3.1	Vital Signs: Summary and Change from Baseline (Booster Phase)	Safety (Booster)	No	No	No
14.2.4	Summary of Physical Examination Results	Safety	No	No	No

14.2.4.1	Summary of Physical Examination Results (Booster Phase)	Safety (Booster)	No	No	No
14.3.1.1	SARS-CoV-2 Neutralizing Antibodies (ND50) Over Timepoints	Per-Protocol	Yes	Yes	Yes
14.3.1.2	SARS-CoV-2 Neutralizing Antibodies (ND50) Over Timepoints	Modified Per-Protocol	Yes	Yes	Yes
14.3.1.3	SARS-CoV-2 Neutralizing Antibodies (ND50) Over Timepoints (Booster Participants)	Per-Protocol	No	No	Yes
14.3.1.4	SARS-CoV-2 Neutralizing Antibodies (ND50) Over Timepoints (Booster Participants)	Modified Per-Protocol	No	No	Yes
14.3.2.1	Proportion of Participants With Seroconversion in Terms of Neutralizing Antibodies (ND50): Secondary Immunogenicity Analysis	Per-Protocol	Yes	Yes	Yes
14.3.2.2	Proportion of Participants With Seroconversion in Terms of Neutralizing Antibodies (ND50): Secondary Immunogenicity Analysis	Modified Per-Protocol	Yes	Yes	Yes
14.3.2.3	Proportion of Participants With Seroconversion in Terms of Neutralizing Antibodies (ND50) (Booster Participants)	Per-Protocol	No	No	Yes
14.3.2.4	Proportion of Participants With Seroconversion in Terms of Neutralizing Antibodies (ND50) (Booster Participants)	Modified Per-Protocol	No	No	Yes
14.3.3.1	Fold Increase of SARS-CoV-2 Neutralizing Antibody Titres (ND50): Secondary Immunogenicity Analysis	Per-Protocol	Yes	Yes	Yes
14.3.3.2	Fold Increase of SARS-CoV-2 Neutralizing Antibody Titres (ND50): Secondary Immunogenicity Analysis	Modified Per-Protocol	Yes	Yes	Yes
14.3.3.3	Fold Increase of SARS-CoV-2 Neutralizing Antibody Titres (ND50) (Booster Participants)	Per-Protocol	No	No	Yes
14.3.3.4	Fold Increase of SARS-CoV-2 Neutralizing Antibody Titres (ND50) (Booster Participants)	Modified Per-Protocol	No	No	Yes

14.3.4.1	IgG antibody Titres Against SARS-CoV-2 S-protein, Determined by ELISA: Secondary Immunogenicity Analysis	Per-Protocol	Yes	Yes	Yes
14.3.4.2	IgG antibody Titres Against SARS-CoV-2 S-protein, Determined by ELISA: Secondary Immunogenicity Analysis	Modified Per-Protocol	Yes	Yes	Yes
14.3.4.3	IgG antibody Titres Against SARS-CoV-2 S-protein, Determined by ELISA (Booster Participants)	Per-Protocol	No	No	Yes
14.3.4.4	IgG antibody Titres Against SARS-CoV-2 S-protein, Determined by ELISA (Booster Participants)	Modified Per-Protocol	No	No	Yes
14.3.5.1	Proportion of Participants With Seroconversion in Terms of S-protein specific IgG Antibodies: Secondary Immunogenicity Analysis	Per-Protocol	Yes	Yes	Yes
14.3.5.2	Proportion of Participants With Seroconversion in Terms of S-protein specific IgG Antibodies: Secondary Immunogenicity Analysis	Modified Per-Protocol Day 208	Yes	Yes	Yes
14.3.5.3	Proportion of Participants With Seroconversion in Terms of S-protein specific IgG Antibodies (Booster Participants)	Per-Protocol	No	No	Yes
14.3.5.4	Proportion of Participants With Seroconversion in Terms of S-protein specific IgG Antibodies (Booster Participants)	Modified Per-Protocol	No	No	Yes
14.3.6.1	Fold Increase of SARS-CoV-2 S-protein specific IgG Antibody Titres Determined by ELISA: Secondary Immunogenicity Analysis	Per-Protocol	yes	Yes	Yes
14.3.6.2	Fold Increase of SARS-CoV-2 S-protein specific IgG Antibody Titres Determined by ELISA: Secondary Immunogenicity Analysis	Modified Per-Protocol	yes	Yes	Yes
14.3.6.3	Fold Increase of SARS-CoV-2 S-protein specific IgG Antibody	Per-Protocol	No	No	Yes

	Titres Determined by ELISA (Booster Participants)				
14.3.6.4	Fold Increase of SARS-CoV-2 S-protein specific IgG Antibody Titres Determined by ELISA (Booster Participants)	Modified Per-Protocol	No	No	Yes
14.4.1.1	Cellular Immune Response (T-Cell Response) measured by IFNgamma ELISpot: Exploratory Analysis	Per-Protocol	Yes	Yes	Yes
14.4.1.2	Cellular Immune Response (T-Cell Response) measured by IFNgamma ELISpot: Exploratory Analysis	Modified Per-Protocol	Yes	Yes	Yes
14.4.1.1.1	Cellular Immune Response (T-Cell Response) measured by IFNgamma ELISpot (Booster Participants)	Per-Protocol	No	No	Yes
14.4.1.2.1	Cellular Immune Response (T-Cell Response) measured by IFNgamma ELISpot (Booster Participants)	Modified Per-Protocol	No	No	Yes
14.4.1.3	Cellular Immune Response measured by IFNgamma ELISpot (Reactogenicity against stimulation panel): Exploratory Analysis	Per-Protocol	Yes	Yes	Yes
14.4.1.4	Cellular Immune Response measured by IFNgamma ELISpot (Reactogenicity against stimulation panel): Exploratory Analysis	Modified Per-Protocol	Yes	Yes	Yes
14.5.1.1	SARS-CoV-2 Neutralizing Antibody Titres (ND50) Over Timepoints	Per-Protocol (Plus Convalescent Participants)	Yes	Yes	Yes
14.5.1.2	SARS-CoV-2 Neutralizing Antibody Titres (ND50) Over Timepoints	Modified Per-Protocol (Plus Convalescent Participants)	Yes	Yes	Yes
14.6.1.1	Cellular Immune Response Measured by ICS: %CD4+ T-Cells for Each Singular Cytokine and Stimulation Panel	Per-Protocol	No	Yes	Yes
14.6.1.2	Cellular Immune Response Measured by ICS:%CD4+ T-Cells for Each Singular Cytokine and Stimulation Panel	Modified Per-Protocol	No	Yes	Yes

14.6.1.3	Cellular Immune Response Measured by ICS:%CD8+ T-Cells for Each Singular Cytokine and Stimulation Panel	Per-Protocol	No	Yes	Yes
14.6.1.4	Cellular Immune Response Measured by ICS: %CD8+ T-Cells for Each Singular Cytokine and Stimulation Panel	Modified Per-Protocol	No	Yes	Yes
14.7.1.1	SARS-CoV-2 Neutralizing Antibodies (ND50) Over Timepoints (Booster Phase)	ITT (Booster)	No	No	Yes
14.7.2.1	Fold Increase of SARS-CoV-2 Neutralizing Antibody Titres (ND50) (Booster Phase)	ITT (Booster)	No	No	Yes
14.7.3.1	Proportion of Participants With 4-Fold Increase in Terms of Neutralizing Antibodies (ND50) (Booster Phase)	ITT (Booster)	No	No	Yes
14.7.4.1	IgG antibody Titres Against SARS-CoV-2 S-protein, Determined by ELISA (Booster Phase)	ITT (Booster)	No	No	Yes
14.7.5.1	Fold Increase of SARS-CoV-2 S-protein specific IgG Antibody Titres Determined by ELISA (Booster Phase)	ITT (Booster)	No	No	Yes
14.7.6.1	Proportion of Participants With 4-Fold Increase in Terms of in Terms of S-protein specific IgG Antibodies (Booster Phase)	ITT (Booster)	No	No	Yes
14.8.1.1	Cellular Immune Response (T-Cell Response) measured by IFNgamma ELISpot (Booster Phase)	ITT (Booster)	No	No	Yes
14.9.1.1	Cellular Immune Response Measured by ICS: %CD4+ T-Cells for Each Singular Cytokine and Stimulation Panel (Booster Phase)	ITT (Booster)	No	No	Yes
14.9.1.2	Cellular Immune Response Measured by ICS:%CD8+ T-Cells for Each Singular Cytokine and Stimulation Panel (Booster Phase)	ITT (Booster)	No	No	Yes

13.3 INDEX OF LISTINGS

Listing	Title	Population	Included in Interim Part A Analysis?	Included in Second Interim Analysis?	Included in Third Interim Analysis?
16.1.1	Participant Enrollment and Disposition	All Participants	Yes	Yes	Yes
16.1.2.1	Participant Inclusion and Exclusion Criteria	All Participants	No	No	No
16.1.2.2	Protocol Deviations	All Participants	No	Yes	Yes
16.1.3.1	Demographic Characteristics	All Participants	Yes	Yes	No

16.1.3.2	Baseline Serology and Antibody Testing	All Participants	Yes	Yes	No
16.1.4	Medical and vaccination History	All Participants	No	No	No
16.1.5.1	Prior Medications	All Participants	No	No	No
16.1.5.2	Concomitant Medications	All Participants	No	No	No
16.1.5.3	Concomitant Procedures	All Participants	No	No	No
16.1.6	Study Drug Vaccine Administration	All Participants	Yes	Yes	No
16.1.6.1	Study Drug Vaccine Administration (Booster Phase)	All Participants	No	No	Yes
16.2.1.1	Solicited Adverse Events (AE eCRF)	All Participants	Yes	Yes	Yes
16.2.1.1.1	Solicited Adverse Events (AE eCRF) (Booster Phase)	All Participants	No	No	Yes
16.2.1.2	Unsolicited Adverse Events	All Participants	Yes	Yes	Yes
16.2.1.2.1	Unsolicited Adverse Events (Booster Phase)	All Participants	No	No	Yes
16.2.1.3	Electronic Participant Diary: Body Temperture	All Participants	Yes	Yes	No
16.2.1.3.1	Electronic Participant Diary: Body temperature (Booster Phase)	All Participants	No	No	Yes
16.2.1.4	Electronic Participant Diary: Injection Site and Systemic Reactions	All Participants	Yes	Yes	No
16.2.1.4.1	Electronic Participant Diary: Injection Site and Systemic Reactions (Booster Phase)	All Participants	No	No	Yes
16.2.1.5	Diary Review Data	All Participants	Yes	Yes	No
16.2.1.5.1	Diary Review Data (Booster Phase)	All Participants	No	No	Yes
16.2.1.6	Additional Symptoms List	All Participants	Yes	Yes	Yes
16.3.2.1	Clinical Laboratory: Hematology	All Participants	No	No	No
16.3.2.2	Clinical Laboratory: Chemistry	All Participants	No	No	No
16.3.2.3	Clinical Laboratory: Urinalysis	All Participants	No	No	No
16.3.2.4	Clinical Laboratory: Coagulation	All Participants	No	No	No
16.3.2.5	Clinical Laboratory: Hematology (Booster Phase)	All Participants	No	No	No

16.3.2.6	Clinical Laboratory: Chemistry (Booster Phase)	All Participants	No	No	No
16.3.2.7	Clinical Laboratory: Urinalysis (Booster Phase)	All Participants	No	No	No
16.3.2.8	Clinical Laboratory: Coagulation (Booster Phase)	All Participants	No	No	No
16.3.4	Vital Signs	All Participants	No	No	No
16.3.4.1	Vital Signs (Booster Phase)	All Participants	No	No	No
16.3.5	Physical Examination	All Participants	No	No	No
16.3.5.1	Physical Examination (Booster Phase)	All Participants	No	No	No
16.3.6	Serum/Urine Pregnancy Test	All Participants	No	No	No
16.3.6.1	Serum/Urine Pregnancy Test (Booster Phase)	All Participants	No	No	No
16.4.1.1	SARS-CoV-2 Neutralizing Antibodies (MNA)	All Participants	Yes	Yes	Yes
16.4.1.2	Seroconversion and Fold Increase for SARS-CoV-2 Neutralizing Antibodies ND50 (MNA)	All Participants	Yes	Yes	Yes
16.4.1.3	SARS-CoV-2 Neutralizing Antibodies (MNA) (Booster Phase)	All Participants	No	No	Yes
16.4.1.4	Fold Increase for SARS-CoV-2 Neutralizing Antibodies ND50 (MNA) (Booster Phase)	All Participants	No	No	Yes
16.4.2.1	SARS-CoV-2 IgG Antibodies (ELISA)	All Participants	Yes	Yes	Yes
16.4.2.2	Seroconversion and Fold Increase for SARS-CoV-2 IgG Antibodies (ELISA)	All Participants	Yes	Yes	Yes
16.4.2.3	SARS-CoV-2 IgG Antibodies (ELISA) (Booster Phase)	All Participants	No	No	Yes
16.4.2.4	Fold Increase for SARS-CoV-2 IgG Antibodies (ELISA) (Booster Phase)	All Participants	No	No	Yes
16.4.3	Cellular Immune Response Measured by IFNgamma ELISpot	All Participants	Yes	Yes	Yes
16.4.3.1	Cellular Immune Response Measured by IFNgamma ELISpot (Booster Phase)	All Participants	No	No	Yes
16.4.4.1	Cellular Immune Response Measured by ICS: %CD4+ and %CD8+ T- Cells for Stimulation Panel P3 and Singular Cytokines	All Participants	No	Yes	Yes
16.4.4.2	Cellular Immune Response Measured by ICS: %CD4+ and %CD8+ T- Cells	All Participants	No	Yes	Yes

	for Stimulation Panel P14 and Singular Cytokines				
16.4.4.3	Cellular Immune Response Measured by ICS: %CD4+ and %CD8+ T- Cells for Stimulation Panel PHA and Singular Cytokines	All Participants	No	Yes	Yes
16.4.4.4	Cellular Immune Response Measured by ICS: %CD4+ and %CD8+ T- Cells for Stimulation Panel P3 and Singular Cytokines (Booster Phase)	All Participants	No	No	Yes
16.4.4.5	Cellular Immune Response Measured by ICS: %CD4+ and %CD8+ T- Cells for Stimulation Panel P14 and Singular Cytokines (Booster Phase)	All Participants	No	No	Yes
16.4.4.6	Cellular Immune Response Measured by ICS: %CD4+ and %CD8+ T- Cells for Stimulation Panel PHA and Singular Cytokines (Booster Phase)	All Participants	No	No	Yes

13.4 INDEX OF FIGURES

Figure	Title	Population	Included in Interim Part A Analysis?	Included in Second Interim Analysis?	Included in Third Interim Analysis?
1.1.1	Solicited Adverse Events Within 7 Days After First Vaccination	Safety	Yes	Yes	No
1.1.2	Solicited Adverse Events Within 7 Days After Second Vaccination	Safety	Yes	Yes	No
1.1.3	Solicited Injection Site Reactions Within 7 Days After First Vaccination	Safety	Yes	Yes	No
1.1.4	Solicited Systemic Reactions Within 7 Days After First Vaccination	Safety	Yes	Yes	No
1.1.5	Solicited Injection Site Reactions Within 7 Days After Second Vaccination	Safety	Yes	Yes	No
1.1.6	Solicited Systemic Reactions Within 7 Days After Second Vaccination	Safety	Yes	Yes	No
1.2.1	Plot of SARS-CoV-2 Neutralizing Antibodies (ND50) Over Time by Dose Groups	Per-Protocol	Yes	Yes	Yes
1.2.1.1	Plot of SARS-CoV-2 Neutralizing Antibodies (ND50) Over Time by Dose Groups	Modified Per-Protocol	Yes	Yes	Yes

1.2.2	Plot of SARS-CoV-2 Neutralizing Antibodies (ND50) for Convalescent Sera	All Convalescent Participants	Yes	Yes	No
1.2.3	Plot of SARS-CoV-2 Neutralizing Antibodies (ND50) Over Time by Dose Groups for MNA Positive Participants at Visit 1	Per-Protocol	Yes	Yes	Yes
1.2.3.1	Plot of SARS-CoV-2 Neutralizing Antibodies (ND50) Over Time by Dose Groups for MNA Positive Participants at Visit 1	Modified Per-Protocol	Yes	Yes	Yes
1.2.4	Plot of SARS-CoV-2 Neutralizing Antibodies (ND50) Over Time by Dose Groups for MNA Negative Participants at Visit 1	Per-Protocol	Yes	Yes	Yes
1.2.4.1	Plot of SARS-CoV-2 Neutralizing Antibodies (ND50) Over Time by Dose Groups for MNA Negative Participants at Visit 1	Modified Per-Protocol	Yes	Yes	Yes
1.3	Plot of S-protein specific IgG Antibody Titres (ELISA) Over Time by Dose Groups	Per-Protocol	Yes	Yes	Yes
1.4.1	Plot of IFNgamma Spot Forming Units per $2.5x10^5$ PBMC by Dose Groups and Assessment Days for Panel 1 Spike Protein N Terminus	Per-Protocol	Yes	Yes	Yes
1.4.2	Plot of IFNgamma Spot Forming Units per $2.5x10^5$ PBMC by Dose Groups and Assessment Days for Panel 2 Spike Protein C terminus	Per-Protocol	Yes	Yes	Yes
1.4.3	Plot of IFNgamma Spot Forming Units per $2.5x10^5$ PBMC by Dose Groups and Assessment Days for Panel 3 Nucleocapsid Protein	Per-Protocol	Yes	Yes	Yes
1.4.4	Plot of IFNgamma Spot Forming Units per $2.5x10^5$ PBMC by Dose Groups and Assessment Days for Panel 4 Membrane Protein	Per-Protocol	Yes	Yes	Yes
1.4.5	Plot of IFNgamma Spot Forming Units per $2.5x10^5$ PBMC by Dose Groups and Assessment Days for Panel 13 Cross-Reactive Panel	Per-Protocol	Yes	Yes	Yes
1.4.6	Plot of IFNgamma Spot Forming Units per $2.5x10^5$ PBMC by Dose Groups and Assessment Days for Panel 14 Spike Protein, full sequence	Per-Protocol	Yes	Yes	Yes
1.5	Scatter Plot Between Neutralizing Antibody Titres ND50 (MNA) and IgG Antibody Titres (ELISA)	Per-Protocol	Yes	Yes	Yes

1.5.1	Scatter Plot between Neutralizing Antibody Titres ND50 (MNA) and IgG Antibody Titres (ELISA) for Day 36	Per-Protocol	Yes	Yes	No
1.6.1	Reverse Cumulative Distribution Function for SARS-CoV-2 Neutralizing Antibody Titres (ND50) For Day 1 by Dose Groups	Per-Protocol	Yes	Yes	No
1.6.2	Reverse Cumulative Distribution Function for SARS-CoV-2 Neutralizing Antibody Titres (ND50) For Day 8 by Dose Groups	Per-Protocol	Yes	Yes	No
1.6.3	Reverse Cumulative Distribution Function for SARS-CoV-2 Neutralizing Antibody Titres (ND50) For Day 22 by Dose Groups	Per-Protocol	Yes	Yes	No
1.6.4	Reverse Cumulative Distribution Function for SARS-CoV-2 Neutralizing Antibody Titres (ND50) For Day 36 by Dose Groups	Per-Protocol	Yes	Yes	No
1.6.5	Reverse Cumulative Distribution Function for SARS-CoV-2 Neutralizing Antibody Titres (ND50) For Day 106 by Dose Groups	Per-Protocol	Yes	Yes	No
1.6.6	Reverse Cumulative Distribution Function for SARS-CoV-2 Neutralizing Antibody Titres (ND50) For Day 208 by Dose Groups	Per-Protocol	Yes	No	Yes
1.7.1	Plot of Percentage of TNF+ CD4+ T-Cells (stimulation Panel P3) by Dose Groups and Assessment Days	Per-Protocol	No	Yes	Yes
1.7.2	Plot of Percentage of IFNG+ CD4+ T-Cells (stimulation Panel P3) by Dose Groups and Assessment Days	Per-Protocol	No	Yes	Yes
1.7.3	Plot of Percentage of IL-2+ CD4+ T-Cells (stimulation Panel P3) by Dose Groups and Assessment Days	Per-Protocol	No	Yes	Yes
1.7.4	Plot of Percentage of IL13+ CD4+ T-Cells (stimulation Panel P3) by Dose Groups and Assessment Days	Per-Protocol	No	Yes	Yes
1.7.5	Plot of Percentage of IL-5+ CD4+ T-Cells (stimulation Panel P3) by Dose Groups and Assessment Days	Per-Protocol	No	Yes	Yes
1.7.6	Plot of Percentage of IL4+ CD4+ T-Cells (stimulation Panel P3) by Dose Groups and Assessment Days	Per-Protocol	No	Yes	Yes
1.7.7	Plot of Percentage of TNF+ CD8+ T-Cells (stimulation Panel P3) by Dose Groups and Assessment Days	Per-Protocol	No	Yes	Yes

1.7.8	Plot of Percentage of IFNG+ CD8+ T-Cells (stimulation Panel P3) by Dose Groups and Assessment Days	Per-Protocol	No	Yes	Yes
1.7.9	Plot of Percentage of IL-2+ CD8+ T-Cells (stimulation Panel P3) by Dose Groups and Assessment Days	Per-Protocol	No	Yes	Yes
1.7.10	Plot of Percentage of IL13+ CD8+ T-Cells (stimulation Panel P3) by Dose Groups and Assessment Days	Per-Protocol	No	Yes	Yes
1.7.11	Plot of Percentage of IL-5+ CD8+ T-Cells (stimulation Panel P3) by Dose Groups and Assessment Days	Per-Protocol	No	Yes	Yes
1.7.12	Plot of Percentage of IL4+ CD8+ T-Cells (stimulation Panel P3) by Dose Groups and Assessment Days	Per-Protocol	No	Yes	Yes
1.7.13	Plot of Percentage of TNF+ CD4+ T-Cells (stimulation Panel P14) by Dose Groups and Assessment Days	Per-Protocol	No	Yes	Yes
1.7.14	Plot of Percentage of IFNG+ CD4+ T-Cells (stimulation Panel P14) by Dose Groups and Assessment Days	Per-Protocol	No	Yes	Yes
1.7.15	Plot of Percentage of IL-2+ CD4+ T-Cells (stimulation Panel P14) by Dose Groups and Assessment Days	Per-Protocol	No	Yes	Yes
1.7.16	Plot of Percentage of IL13+ CD4+ T-Cells (stimulation Panel P14) by Dose Groups and Assessment Days	Per-Protocol	No	Yes	Yes
1.7.17	Plot of Percentage of IL-5+ CD4+ T-Cells (stimulation Panel P14) by Dose Groups and Assessment Days	Per-Protocol	No	Yes	Yes
1.7.18	Plot of Percentage of IL4+ CD4+ T-Cells (stimulation Panel P14) by Dose Groups and Assessment Days	Per-Protocol	No	Yes	Yes
1.7.19	Plot of Percentage of TNF+ CD8+ T-Cells (stimulation Panel P14) by Dose Groups and Assessment Days	Per-Protocol	No	Yes	Yes
1.7.20	Plot of Percentage of IFNG+ CD8+ T-Cells (stimulation Panel P14) by Dose Groups and Assessment Days	Per-Protocol	No	Yes	Yes
1.7.21	Plot of Percentage of IL-2+ CD8+ T-Cells (stimulation Panel P14) by Dose Groups and Assessment Days	Per-Protocol	No	Yes	Yes
1.7.22	Plot of Percentage of IL13+ CD8+ T-Cells (stimulation Panel P14) by Dose Groups and Assessment Days	Per-Protocol	No	Yes	Yes
1.7.23	Plot of Percentage of IL-5+ CD8+ T-Cells (stimulation Panel P14) by Dose Groups and Assessment Days	Per-Protocol	No	Yes	Yes

1.7.24	Plot of Percentage of IL4+ CD8+ T-Cells (stimulation Panel P14) by Dose Groups and Assessment Days	Per-Protocol	No	Yes	Yes
1.7.25	Plot of Percentage of TNF+ CD4+ T-Cells (stimulation Panel PHA) by Dose Groups and Assessment Days	Per-Protocol	No	Yes	Yes
1.7.26	Plot of Percentage of IFNG+ CD4+ T-Cells (stimulation Panel PHA) by Dose Groups and Assessment Days	Per-Protocol	No	Yes	Yes
1.7.27	Plot of Percentage of IL-2+ CD4+ T-Cells (stimulation Panel PHA) by Dose Groups and Assessment Days	Per-Protocol	No	Yes	Yes
1.7.28	Plot of Percentage of IL13+ CD4+ T-Cells (stimulation Panel PHA) by Dose Groups and Assessment Days	Per-Protocol	No	Yes	Yes
1.7.29	Plot of Percentage of IL-5+ CD4+ T-Cells (stimulation Panel PHA) by Dose Groups and Assessment Days	Per-Protocol	No	Yes	Yes
1.7.30	Plot of Percentage of IL4+ CD4+ T-Cells (stimulation Panel PHA) by Dose Groups and Assessment Days	Per-Protocol	No	Yes	Yes
1.7.31	Plot of Percentage of TNF+ CD8+ T-Cells (stimulation Panel PHA) by Dose Groups and Assessment Days	Per-Protocol	No	Yes	Yes
1.7.32	Plot of Percentage of IFNG+ CD8+ T-Cells (stimulation Panel PHA) by Dose Groups and Assessment Days	Per-Protocol	No	Yes	Yes
1.7.33	Plot of Percentage of IL-2+ CD8+ T-Cells (stimulation Panel PHA) by Dose Groups and Assessment Days	Per-Protocol	No	Yes	Yes
1.7.34	Plot of Percentage of IL13+ CD8+ T-Cells (stimulation Panel PHA) by Dose Groups and Assessment Days	Per-Protocol	No	Yes	Yes
1.7.35	Plot of Percentage of IL-5+ CD8+ T-Cells (stimulation Panel PHA) by Dose Groups and Assessment Days	Per-Protocol	No	Yes	Yes
1.7.36	Plot of Percentage of IL4+ CD8+ T-Cells (stimulation Panel PHA) by Dose Groups and Assessment Days	Per-Protocol	No	Yes	Yes