Clinical Study Protocol

DRUG SUBSTANCE(S)	VLA2001
VERSION NO.	7.0
STUDY CODE	VLA2001-201
DATE	31 August 2021

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 amended to include booster vaccination with VLA2001

Phase I/II study

PROTOCOL NUMBER: **VLA2001-201**

Sponsor **Valneva Austria GmbH**

[redacted]

Campus Vienna Biocenter 3
A-1030 Vienna, Austria

1. PROTOCOL SIGNATURE PAGE

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 Number: **VLA2001-201**

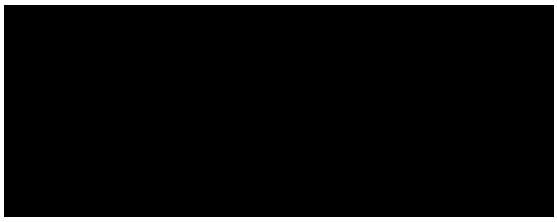
With their signature, Investigators and the Sponsor agree to conduct this study in accordance with the Protocol, International Conference on Harmonization (ICH), Good Clinical Practice (GCP) guidelines and with the applicable local regulatory requirements. Moreover, the site will keep all information obtained from the participation in this study confidential unless otherwise agreed in writing.

Principal Investigator

Print Name	Signature	Date
[redacted]	Signature	Date
[redacted]	Signature	Date
[redacted]	Signature	Date
[redacted]	Signature	Date

2. STUDY PERSONNEL

Clinical Operations



Sponsor's Medical / Safety Officer

Study Medical Monitor

2.1 Study Organization

The contact details of the organisation/individuals involved in the study (e.g.; Investigator(s), Sponsor's representative(s), laboratories, oversight committees [including ethics committees {ECs}, as applicable]) will be maintained by the Sponsor and provided to the Investigator.

3. SERIOUS ADVERSE EVENT REPORTING

The Investigator will comply with applicable laws/requirements for reporting serious adverse events (SAEs). For information on the definition and assessment of adverse events (AEs), refer to Section 15.1 and 15.2, respectively.

All Adverse Events of Special Interest (AESIs) will be treated as important medical event and will therefore be treated as SAEs. For information on the definition of adverse events of special interest (AESIs), refer to Section 15.10.

All SAEs should be reported on the SAE Report Form in the eCRF <u>within 24 hours</u> of the Investigator becoming aware of the event. Under certain circumstances the initial notification could be done by phone, but nevertheless a written SAE Report Form has to be submitted within 24 hours to:

<u>Pharm-Olam International</u>

Fax: [redacted]

Email:

Safety Hotline:

4. PREGNANCY REPORTING

The Investigator will comply with applicable laws/requirements for reporting pregnancies. For information on the definition and assessment of pregnancies, refer to Section 15.11.2.

All Pregnancies* should be reported on the Pregnancy Report Form to Pharm-Olam International by fax or email within 24 hours of the Investigator becoming aware of the event.

Safety Desk

Fax: [redacted]

Email:

Safety Hotline:

* A pregnancy is not considered an SAE. If a seriousness criterion applies in addition to the pregnancy (e.g. hospitalisation, congenital anomaly/birth defect) the pregnancy qualifies as an SAE. In such case a Pregnancy Report Form **and** an SAE Report Form have to be filled out.

5. CLINICAL STUDY SYNOPSIS

INVESTIGATIONAL PRODUCT, DOSAGE AND MODE OF ADMINISTRATION	
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**
Name of Investigational Medicinal Product (IMP)	Inactivated, adjuvanted SARS-CoV-2 vaccine VLA2001
Name(s) of Active Ingredient(s)	Inactivated, adjuvanted SARS-CoV-2 vaccine based on strain hCoV-19/Italy/INMI1-isl/2020 (VLA2001) Adjuvant: a combination of aluminium hydroxide and CpG 1018

VLA2001 is a highly-purified, whole virus, SARS-CoV-2 vaccine produced on Vero cells and inactivated with β-propiolactone. Vaccine is adjuvanted with the licensed adjuvant cytosine phospho-guanine (CpG) 1018 (produced by Dynavax, contained in HEPLISAV-B®) in combination with aluminium hydroxide.

VLA2001 has been developed using the same manufacturing platform as that used for the commercial vaccine IXIARO®, a purified, inactivated, whole virus, aluminium hydroxide-adjuvanted Japanese encephalitis vaccine that has been approved by regulatory authorities worldwide (including the Food and Drug Administration [FDA], European Medicines Agency [EMA] and Therapeutic Goods Administration).

An acceptable safety profile was demonstrated for IXIARO in seven randomised, controlled studies with a total safety database of 3,945 healthy adults. The most common adverse reactions in adults across all studies were headache, myalgia, injection site pain, and injection site tenderness. No specific safety signals (including hypersensitivity reactions and neurologic disorders) were identified for IXIARO through clinical studies and post-marketing pharmacovigilance (IXIARO clinical review memorandum, 2018).

This is a first-in-human phase I/II study that will evaluate three dose levels of VLA2001 (Low dose, medium dose, high dose) for safety, tolerability and immunogenicity in a two-dose primary schedule (Day 1; Day 22) in a healthy young adult population aged 18 to 55 years.

Booster Phase:
Study participants who have completed the primary immunization schedule (two vaccinations), will be invited to participate in a Booster Phase to investigate the immunogenicity and safety of a booster dose with VLA2001 administered at approximately 8-9 months after completing the primary immunization schedule.

CLINICAL CONDITION(S)/INDICATION(S)	
Active immunisation for the prevention of COVID-19 (disease caused by SARS-CoV-2)	
STUDY PHASE	Phase I/II
PLANNED STUDY PERIOD	
Initiation	Q4 / 2020
Duration	The overall study duration (First Subject In–Last Subject Out [LSO]) is estimated to be approximately 16 months. Individual participation is approximately 15 months from enrolment to study completion unless the study is prematurely discontinued.
Completion	Part A (Visit 4, Day 36): LSO Feb 2021 Part B (Visit 6, Day 208 (Month 7)): LSO planned Aug 2021 <u>Booster Phase:</u> Part C (Visit 7-10, Month 9-15: LSO planned Mar 2022) Individual study parts will be analysed sequentially.

STUDY OBJECTIVES

Primary:

1) The primary objective of this study is to evaluate the tolerability, safety 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.

Secondary:

1) To determine the optimal dose level of the inactivated, adjuvanted SARS-CoV-2 vaccine candidate VLA2001 in healthy adults aged 18 to 55 years.
2) 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.
3) To evaluate tolerability, safety and immunogenicity of a booster dose with vaccine candidate VLA2001 in healthy adults aged 18 to 55 years.

Exploratory:

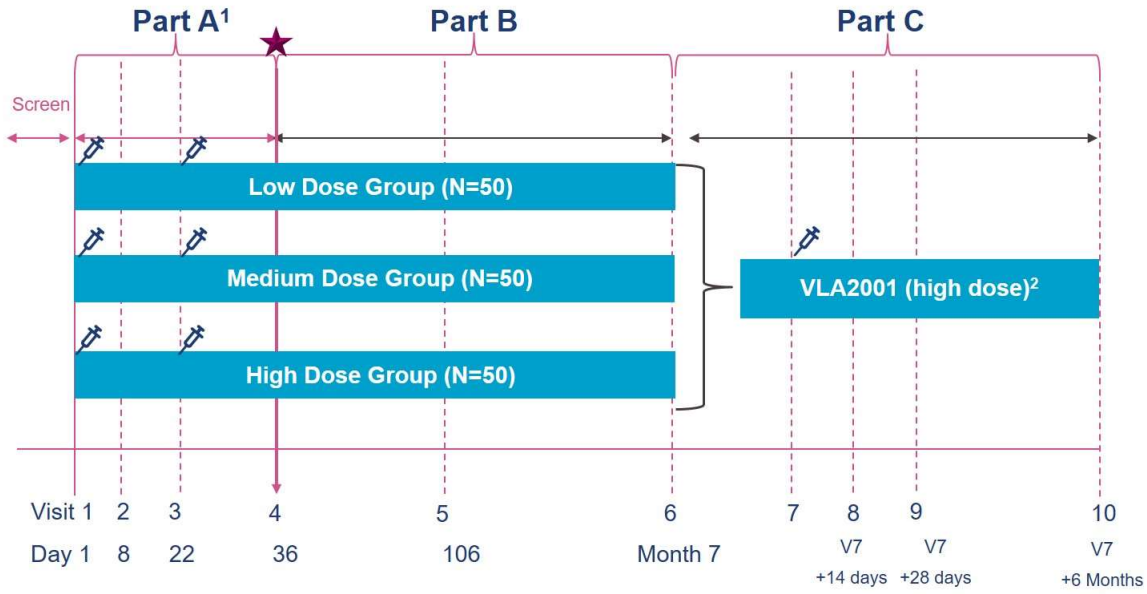
- To evaluate cellular immune response after vaccination with the inactivated, adjuvanted SARS-CoV-2 vaccine candidate VLA2001 after completion of a two-dose primary immunization schedule and after a booster vaccination.

STUDY DESIGN

The study is a randomised, dose-escalation, multicentre study with three dose groups (low, medium and high dose groups); 50 Participants have been recruited to each dose group. The study will be conducted in three parts: Part A (Day 1 to Day 36) and Part B (Day 37 to Day 208). Following an evaluation of initial data (i.e. data up to Day 36) from the study, a Booster Phase (Part C) has been added to the study.

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.

Figure: 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.

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 of 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 e-Diary. The study site will contact the Participant per phone approximately 24 hours after vaccination to assess the safety status of the Participant. The provided information must be compared with the entries in the Participant´s e-Diary. The minimum time before the next Participants are vaccinated is therefore 24 hours. 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 any acute reaction. Before discharge, vital signs will be measured and Participants will be instructed to use their e-Diaries. Safety telephone calls will be performed by the study site approximately 48 hours after vaccination. After confirmation by the investigator that no stopping criteria (see Section 10.6) has been met, 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 Safety and 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. An unscheduled safety telephone call will be performed in case a Grade 3 AE or SAE will be reported by the Participant via e-Diary. All participants will be followed by e-Diary for 7 days post vaccination, starting on the day of vaccination. Participants will return to the study site on Day 8 (Visit 2). After (approximately) 20 participants per dose group have been randomised and followed up 7 days post first vaccination, and periodically up to Day 36 for all randomised Participants, the DSMB will review the accrued safety data. 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. The DSMB will review safety data up to Day 36.

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. DSMB safety data review will occur ad-hoc in line with the DSMB Charter.

Booster Phase:

At Visit 6 (Month 7), all participants who previously had received two study vaccinations will be asked for their consent 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. Visit 7 is expected to be performed in September 2021. This timing will translate to the booster dose being given to the participants at approximately 8 to 9 Months after completion of the primary immunization schedule.

Participants will be asked to return to the study site for two follow-up visits, 2 weeks after the booster vaccination (visit 8) and one month 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.

Additional safety data review by the DSMB will occur when necessary (ad-hoc) as defined in the DSMB Charter. A final review of the generated safety data will be performed by the DSMB once all participants have completed the clinical study.

STUDY ENDPOINTS

Safety endpoints

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

Secondary

- 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

Immunogenicity

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

Secondary

- 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 antibodies against SARS-CoV-2, determined by ELISA, at Day 1, Day 8, Day 22, Day 36, Day 106 and Day 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 SARS-CoV-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.

Exploratory

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

CRITERIA FOR INCLUSION / EXCLUSION

Approximately 150 male and female adults who satisfy the inclusion and exclusion criteria listed below will be invited to participate in the study.

Inclusion criteria

Participants who meet **ALL** of the following criteria are eligible for the study:

1. Participant is 18 to 55 years[i] of age on the Day of screening (Visit 0).
2. Participant who has a smart phone and is willing and able to install and use the e-Diary.
3. Participant has an understanding of the study and its procedures, agrees to its provisions, and voluntarily gives written informed consent prior to any study-related procedures.
4. Participant is **generally healthy**[ii] as determined by the Investigator's clinical judgement based on medical history, physical examination and screening laboratory tests.
5. Participant has a Body Mass Index (BMI) of 18.0-30.0 kg/m^2, inclusive, at screening (Visit 0).
6. If Participant is of childbearing potential:
    a) Participant has practiced an adequate method of contraception (see below) during the 30 days before screening (Visit 0).
    b) Participant has a negative serum or urine pregnancy test at screening (Visit 0) or Visit 1, respectively.
    c) Participant agrees to employ adequate birth control measures up to Day 106 (Visit 5). This includes one of the following measures:
        - Hormonal contraceptives (e.g. implants, birth control pills, patches).
        - Intrauterine hormone-release systems and intrauterine device.
        - Barrier type of birth control measure (e.g. diaphragms, cervical caps).
        - Vasectomy in the male sex partner ≥ 3 months prior to first vaccination.
        - Same sex relationships.

Exclusion criteria

Participants who meet **ANY** of the following criteria are **NOT** eligible for this study:

1. Clinically significant infection or other acute illness, including fever ≥ 38°C within 48 hours prior to the planned study vaccination.
2. History of laboratory-confirmed SARS-CoV-2 infection.

[i] From the day a person turns 18 years until the last day before the person turns 56 years of age.
[ii] Participants are considered generally healthy if they have (1) no active disease (acute illness, exacerbation of a chronic condition or a chronic – progressive illness) which requires treatment and/or follow-up, and (2) no disease that is identified as an exclusion criterion or (3) if they are healthy and have a preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before screening.

3. Participant had close contact to persons with confirmed SARS-CoV-2 infection within 30 days prior to screening (Visit 0).
4. Participant has participated in a clinical study involving an investigational SARS-CoV-2 vaccine or has received or plans to receive a licensed SARS-CoV-2 vaccine during the duration of the study.
5. Participant has an acute or recent infection not due to SARS-CoV-2 (and who is not symptom-free in the week prior to the Screening Visit (Visit 0).
6. Participant has a history of SARS-CoV-1 or MERS infection (self-reported)
7. Participant tests positive for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV).
8. Participant has received any vaccine within 30 days prior Visit 1 other than the study intervention, with the exception of the seasonal influenza vaccination. Participants will be encouraged to receive this vaccination at least 7 days after their study vaccine.
9. Participant has abnormal findings in any required study investigations (including medical history, physical examination, and clinical laboratory) considered clinically relevant by the Investigator.
10. Participants with either medical history of or present acute or progressive, unstable or uncontrolled clinical conditions (e.g. cardiovascular, respiratory, neurologic, psychiatric, or rheumatologic conditions) that pose a risk for participation or completion of the study, based on Investigator's clinical judgement. Examples include Participants with poorly controlled or unstable underlying disease, ongoing suspected or active inflammation, poor compliance with pharmacologic treatment, or presence of high-risk comorbidities (e.g. significant cardiopulmonary disease).
11. Participants with underlying diseases with a high risk of developing severe COVID-19 symptoms if infected, including those with any of the following risk factors:
    - Hypertension.
    - Diabetes mellitus.
    - Chronic liver disease.
    - Chronic pulmonary disease.
    - Asthma.
    - Current vaping or smoking.
    - History of chronic smoking within the prior year.
12. Participant has a history of malignancy in the past 5 years other than squamous cell or basal cell skin cancer. If there has been surgical excision or treatment more than 5 years ago that is considered to have achieved a cure, the Participant may be enrolled. A history of hematologic malignancy is a permanent exclusion. Participants with a history of skin cancer must not be vaccinated at the previous tumour site.

13. Participant has a known or suspected defect of the immune system, such as Participants with congenital or acquired immune deficiency, including infection with HIV, status post organ transplantation or other autoimmune diseases.
14. Participant received immuno-suppressive therapy within 4 weeks prior to Visit 1 or receipt of immunosuppressive therapy is expected during the study. Immuno-suppressive therapy is defined as administration of chronic (longer than 2 weeks) prednisone or equivalent ≥ 0.05 mg/kg/day within 4 weeks prior to Visit 1 (topical and inhaled steroids are allowed), radiation therapy or immunosuppressive cytotoxic drugs/ monoclonal antibodies in the previous 3 years.
15. Participant has a history of any vaccine related contraindicating event (e.g., anaphylaxis, allergy to components of the candidate vaccine, other known contraindications).
16. Participant presents with clinical conditions representing a contraindication to intramuscular vaccination and blood draws.
17. Participant is pregnant (positive serum or urine pregnancy test at screening or Visit 1, respectively), has plans to become pregnant up to Day 106 of the study or lactating at the time of enrolment.
18. Participant has donated blood, blood fractions or plasma within 4 weeks prior to Visit 1 or received blood-derived products (e.g. plasma) within 12 weeks prior to Visit 1 in this study or plans to donate blood or use blood products during the study.
19. Participant with clinically significant bleeding disorder (e.g. factor deficiency, coagulopathy or platelet disorder) or prior history of significant bleeding or bruising following IM injections or venipuncture.
20. Participant has a rash, dermatological condition or tattoos that would, in the opinion of the Investigator, interfere with injection site reaction rating.
21. Participant has a known or suspected problem with alcohol or drug abuse as determined by the Investigator.
22. Participant has any condition that, in the opinion of the Investigator, may compromise the Participant's well-being, might interfere with evaluation of study endpoints, or would limit the Participant's ability to complete the study.
23. Participant is committed to an institution (by virtue of an order issued either by the judicial or the administrative authorities).
24. Participant has participated in another clinical study involving an investigational medicinal product (IMP) or device within 4 weeks prior to Visit 0 (screening) or is scheduled to participate in another clinical study involving an IMP, or device during the course of this study.
25. Participant is a member of the team conducting the study or in a dependent relationship with one of the study team members. Dependent relationships include close relatives (i.e., children, partner/spouse, siblings, parents) as well as employees of the Investigator or site personnel conducting the study.

Additional criteria to be re-confirmed before enrolment into the Booster Phase:

Inclusion criteria

Participants who meet **ALL** of the following criteria are eligible for the Booster phase:

B1. Participant has received complete VLA2001 primary immunization (two vaccinations according to the protocol)

B2. Participant has a smart phone and is willing and able to install and use the e-Diary.

B3. Participant has an understanding of the study and its procedures, agrees to its provisions, and voluntarily gives written informed consent prior to any study-related procedures.

B4. Participant is **generally healthy**[iii] as determined by the Investigator's clinical judgement

B5. If a participant is of childbearing potential:

a. Participant has a negative urine pregnancy test at visit 7 prior to booster vaccination.

b. Participant agrees to employ adequate birth control measures up to 3 months after the Booster vaccination. This includes one of the following measures:

i. Hormonal contraceptives (e.g. implants, birth control pills, patches).
ii. Intrauterine hormone-release systems and intrauterine device.
iii. Barrier type of birth control measure (e.g. diaphragms, cervical caps).
iv. Vasectomy in the male sex partner ≥ 3 months prior to first vaccination.
v. Same sex relationships.

Exclusion criteria

Participant who meet **ANY** of the following criteria are **NOT** eligible for the Booster Phase:

B1. Clinically significant infection or other acute illness, including fever ≥ 38°C within 48 hours prior to the planned Booster vaccination.

B2. Participant has an acute or recent infection not due to SARS-CoV-2 and is not symptom-free in the week prior to the Booster vaccination (Visit 7).

B3. Participant has received any vaccine within 30 days prior Visit 7, with the exception of the seasonal influenza vaccination. Participants will be encouraged to receive this vaccination at least 7 days after their Booster vaccine.

B4. Participant has abnormal findings in any required study investigations (including medical history, physical examination, and clinical laboratory) that is considered clinically relevant by the Investigator.

[iii] Participants are considered generally healthy if they have (1) no active disease (acute illness, exacerbation of a chronic condition or a chronic – progressive illness) which requires treatment and/or follow-up, and (2) no disease that is identified as an exclusion criterion or (3) if they are healthy and have a preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before screening/ before Day 208.

B5. Participant has received immuno-suppressive therapy within 4 weeks prior to Visit 7 or is expected to receive immunosuppressive therapy during the study. Immuno-suppressive therapy is defined as administration of chronic (longer than 2 weeks) prednisone or equivalent ≥ 0.05 mg/kg/day within 4 weeks prior to Visit 7 (topical and inhaled steroids are allowed), radiation therapy or immunosuppressive cytotoxic drugs or monoclonal antibodies in the previous 3 years.

B6. Participant has clinical conditions representing a contraindication to intramuscular vaccination and blood draws.

B7. Participant is pregnant (positive urine pregnancy test at Visit 7, respectively), has plans to become pregnant at time of the enrolment to the Booster Phase (Visit 7).

B8. Participant has a rash, dermatological condition that would, in the opinion of the Investigator, interfere with injection site reaction rating.

B9. Participant has a known or suspected problem with alcohol or drug abuse as determined by the Investigator.

B10. Participant has any condition that, in the opinion of the Investigator, may compromise the Participant's well-being, might interfere with evaluation of study endpoints, or would limit the Participant's ability to complete the study.

B11. Participant is committed to an institution (by virtue of an order issued either by the judicial or the administrative authorities).

B12. Participant has participated in another clinical study involving an investigational medicinal product (IMP) or device within 4 weeks prior to Visit 7 or is scheduled to participate in another clinical study involving an IMP, or device during the course of this study.

Delaying Administration of Study vaccination

Vaccination will be delayed if:

1. Participant has current febrile illness (body temperature equal or greater 38.0°C) or other acute illness within 48 hours prior vaccination.
2. An illness which in the judgement of the investigator may interfere with tolerability (7 days post booster) and safety assessment
3. Participant has received antipyretics within 6 hours prior to the scheduled time of vaccination.
4. Receipt of any vaccine within 30 days prior to study intervention, with the exception of the seasonal influenza vaccine. Participants will be encouraged to receive this vaccination at least 7 days before or after their study vaccine.

In addition, for a rescheduled vaccination all inclusion and none of the exclusion criteria must be met; in case not all of these criteria are met, the Participant will be excluded from further vaccination.

The rescheduled visit should be within the specified time window for the vaccination visit. In case the time window for a rescheduled first vaccination cannot be met, the Participant might be invited for a re-screening.

STATISTICAL ANALYSIS

Sample size justification

No formal sample size calculation has been performed. 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.

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.

Statistical methods

Primary safety analysis: The number and percentage of Participants with solicited local and systemic AEs within 7 days after each and after any vaccination of the primary vaccination series (Day 1; Day 22) will be presented. Differences between treatment groups will be assessed for significance using Fisher's exact test.

Primary immunogenicity analysis: This will be a comparison of GMTs for SARS-CoV-2 neutralizing antibodies at 14 days after the second dose (i.e. Day 36). Geometric mean titres (GMTs) and GMT ratios will be estimated by applying an analysis of variance (ANOVA) including the factor treatment group and study site. Tukey's HSD test will be applied for pair wise comparisons.

Secondary safety analysis: The number and percentage of participants with unsolicited AEs, related AEs, AESIs and SAEs will be presented for each study arm, overall, by system organ class/preferred term and by severity. Differences between study groups will be assessed for significance using Fisher's exact (Fisher-Freeman-Halton) test, whereby a significant overall test will be amended by pair-wise tests, and 95% confidence interval (CI) will be presented for all AE rates.

Secondary immunogenicity analysis: This will include the comparison of the GMTs as well as comparison of geometric mean fold increase (GMFI) between study groups on other study days. ANOVA models will be applied as described for the primary immunogenicity endpoint. Seroconversion rates for various study days as well as rates of Participants reaching certain fold-increase will be compared between the study groups using Fisher's exact (Fisher-Freeman-Halton) test, whereby a significant overall test will be amended by pair-wise tests, and 95% CIs will be calculated.

Data Analysis

The following data analyses will be performed:

- Part A includes safety and immunogenicity data after all participants have completed Visit 4 (Day 36).
- Part B includes safety and immunogenicity data after all Participants have completed Visit 6 (Day 208).
- An additional data analysis will be performed during part B after all Participants have completed Visit 5 (Day 106)
- Part C includes Visits 7 to 10. An analysis of Part C will be done when all participants have completed visit 9.
- Final analysis will be done when all participants have completed the last visit (Visit 10)

Interim/Final Report

An interim report will be compiled based on the Visit 5 data (Day 106) and a second interim report will be compiled based on the full Part B and partial Part C (Visit 7, Visit 8 and Visit 9) data. A final study report will be published after completion of Part C (including Visit 10).

SAFETY ASSESSMENTS

1. Unsolicited adverse events

Unsolicited events, which include clinically relevant laboratory parameter changes and symptoms noted during symptom-driven physical examinations, need to be documented in the respective AE section of the electronic Case Report Form (eCRF) during the applicable study visit (Visits 1 to 9 or unscheduled visit(s) before Visit 9, if applicable), regardless of their source. Serious adverse events and Adverse Events of Special interest (AESIs) will continue to be documented until the end of the study. The Investigator will follow-up each AE until it is resolved or until the medical condition of the Participant is stable. Serious adverse events ongoing at the time of Visit 9 will be followed until resolution, achievement of stable clinical conditions, or until the overall end of the study at the latest. Serious adverse events that are fatal, life-threatening or suspected to be related to study treatment will continue to be reported until 6 months after the last vaccination of the respective Participant (i.e. Visit 9). The following information will be documented for each AE: severity, causality, outcome, seriousness, medically-attended, action taken to treat AE, start and stop dates.

2. Solicited adverse events

Solicited AEs will be reported in the e-Diary by the Participant for 7 consecutive days after each vaccination including booster dose, starting on the day of vaccination. They 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.

a) Injection site reactions

Solicited injection site reactions include injection site pain, itching, tenderness, redness and swelling/induration. Participants will be provided with a measuring tool to measure the size of any measurable injection site reaction.

b) Systemic reactions

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

c) Fever and body temperature

Participants will be provided with a digital thermometer to individually measure their body temperature orally once every evening from vaccination until Day 7 after each vaccination. In case fever (oral body temperature ≥ 38.0°C) occurs, participants should measure their body temperature every 4 to 8 hours until fever resolves (oral body temperature < 38.0°C). The time at which the first body temperature of < 38.0°C is recorded is considered to be the end of the fever episode. All fever measurements should be recorded by the participant in the Participant's diary including the first value that shows a return to normal body temperature.

3. Adverse events of special interest

Participants will be carefully monitored for development of adverse events of special interest (AESI). All AESIs will be treated as medically significant and will therefore be treated as SAEs and an SAE report form will be completed for AESIs, in particular, and the information will be provided to the DSMB. The DSMB will do the following: perform a thorough review of each case, advise whether additional clinical work-up is required, conduct a final adjudication of all AESI and assess whether cases were new in onset and whether there is any relationship to administration of the study vaccine.

Electronic diary

Participants will be instructed and trained to use the electronic diary (e-Diary) to collect solicited AEs within 7 days after each vaccination including the Booster dose. The following information will be collected:

- Oral body temperature.
- Solicited injection site reactions.
- Solicited systemic reactions.
- Symptoms Relating to SARS-CoV-2.
- Other AEs.
- Any new medication or changes in medication taken after vaccination.

Study staff will be prompted to perform a phone call visit if a) no diary data are being reported by the Participant, b) a grade 3 solicited event has been reported, c) indication for serious adverse

event is observed. Study participants will be prompted to contact the study site in case of symptoms relating to COVID-19 (see section 15.2.5).

CASE DEFINITIONS

A case of **COVID-19** is defined as follows:

Virologically (SARS-CoV-2 positive) confirmed SARS-CoV-2 infection with one or more of the following symptoms listed below:

- Fever or chills
- Persistence of Cough as defined by NHS, as a lot of coughing for more than 1 hour, or three or more coughing episodes in 24 hours. If the participant usually has a cough, it may be worse than usual.
- Shortness of breath or difficulty breathing
- Fatigue
- Muscle or body aches
- Headache
- A loss or change of smell and taste
- Sore throat
- Congestion
- Nausea or vomiting (more than one episode and/or persisting)
- Diarrhoea

With the exception of fever, shortness of breath, or difficulty breathing, the symptom must be present for 2 or more consecutive days.

Cases are defined by laboratory confirmation of SARS-CoV-2 and signs/symptoms/examinations that occur within 14 calendar days of the initial symptom(s).

Procedures in the Event of COVID-19 like Signs and Symptoms

As a risk mitigation strategy, all enrolled participants will be intensively monitored during the conduct of the study to rapidly diagnose COVID-19 and referred for treatment according to local site procedures, if applicable.

Participant who report at least one of the above-mentioned symptoms during the study, must contact the study team. In case of confirmed COVID-19 symptoms Participants will be tested on site by a validated test.

In case of a negative test result, Participants will be invited for a second confirmatory test on site after 2 days. In the event the result is still negative, the Participant will continue with scheduled visits.

If either or both tests are positive, the participant will be performing a COVID-19 illness visit at site. Where supported, home or mobile visits may be substituted for this site visit. As part of these visits, samples (a saliva sample and blood samples) will be taken for antigen and antibody assessment as well as recording of COVID-19-related clinical and laboratory information. During the Booster Phase, saliva samples will not be collected in line with the schedule of assessment (section 22.3)

Participant should continue for 14 days after symptoms onset or until resolution of the COVID-19 episode, whichever comes last, with the home-collection self-swab kit every 2 days. Resolution of COVID-19 is defined as having 2 consecutive SARS-CoV-2 negative swabs and 2 consecutive days with no COVID-19 related signs and symptoms.

All confirmed COVID-19 episodes will be communicated to the respective participant and to other authorities according to local regulations. In addition, participants will be educated about current applicable public health guidance for confirmed COVID-19 cases.

6. TABLE OF CONTENTS

7. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ANOVA	Analysis of variance
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BMI	Body mass index
CFR	Case fatality ratio
CI	Confidence interval
CpG	Cytosine phospho-guanine
COVID-19	Coronavirus-induced disease 2019
CRA	Clinical research associate
CRO	Contract research organisation
CRP	C-reactive protein
CSR	Clinical study report
DSMB	Data and safety monitoring board
EC	Ethics committee
eCRF	Electronic case report form
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ET	Early termination (visit)
ESR	Erythrocyte sedimentation rate
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMFI	Geometric mean fold increase
GMT	Geometric mean titre
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator’s Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IMP	Investigational medicinal product

Abbreviation	Definition
ITT	Intent-to-treat (population)
IXRS	Interactive Voice/Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
NHS	National Health Service
NHP	Non Human Primate
PP	Per-protocol population
PBMC	Peripheral blood Mononuclear Cell
PPAS	Per-Protocol Analysis Set
PRNT	Plaque reduction neutralization test
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SOP	Standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
Th	T helper cell
UK	United Kingdom
WBC	White blood cell

8. INTRODUCTION

8.1 Clinical Condition/Indication

8.1.1 Transmission, Disease and Diagnosis

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 was initially isolated and the genome was published internationally by Chinese scientists on January 10, 2019. SARS-CoV-2 is the seventh member of the family of coronaviruses to infect humans. Novel coronaviruses from Wuhan, together with two bat-derived SARS-like strains, form a distinct clade in lineage B of the subgenus *Sarbecovirus*. 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 (Yang and Leibowitz, 2015). SARS-CoV-2 is an enveloped, non-segmented, positive sense RNA virus. Structurally, SARS-CoV-2 has four main structural proteins, which are conserved across coronaviruses; namely the spike glycoprotein, small envelope glycoprotein, membrane glycoprotein, and nucleocapsid protein, along with several accessory proteins. The spike protein facilitates binding of envelope viruses to host cells by attraction with angiotensin-converting enzyme 2 (ACE2) expressed in lower respiratory tract cells. (Astuti and Ysrafil, 2020).

Human infection is characterized by an incubation period of 2 to 7 days (typically 5 days across many studies), up to a maximum of 14 days. Symptoms of COVID-19 are non-specific and the disease presentation can range from no symptoms (asymptomatic) to severe pneumonia and death. Common symptoms include fever, cough, dyspnoea, myalgia, fatigue, sputum, haemoptysis and diarrhoea. Lymphocytopenia and pneumonia are also common (Chaolin et al, 2020; Guan et al, 2020). In a study of 41 patients, complications included acute respiratory distress syndrome (29%), acute heart injury (12%), and secondary infections (10%); 32% of patients required treatment in the intensive care unit (Chaolin et al, 2020). In an analysis of 1099 confirmed cases, 25.2% of patients had at least one underlying disease (such as hypertension, chronic obstructive pulmonary disease). On admission, 50% of the patients presented ground-glass shadow on a chest computed tomography scan (Guan et al, 2020). Recent studies indicate that patients ≥ 60 years of age are at higher risk than children (Li et al, 2020a; Wang et al, 2020). Up to 5% of patients with COVID-19 developed acute respiratory distress syndrome (Wang et al, 2019) (Li et al, 2020a) (Guan et al, 2019). According to the World Health Organisation (WHO), 10% to 15% of patients aged ≤ 50 years' experience moderate to severe infection. Recovery time is about 2 weeks for persons with mild disease and 3 to 6 weeks for persons with severe or critical disease, based on Chinese Centers of Disease Control and Protection data and the current U.S. experience in California and Washington.

Analysis of the first 55,924 laboratory confirmed COVID-19 cases in China showed that mortality increases with age, with the highest mortality among people over 80 years of age (case fatality ratio [CFR] 21.9%). The CFR was higher among males than females (4.7% vs. 2.8%). The CFR was much higher in patients with comorbidities (CFR 7.6% to 13.2%) than those without (CFR 1.4%). (WHO, 2020) Similar results were found in a study analysing 17,425,445 adults in the UK between 01 February and 25 April 2020. In total 5683 deaths were attributed to COVID-19 (Williamson et al, 2020).

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.

No antiviral treatment is currently available for human and animal coronavirus. General strategies for clinical management include bed rest and supportive treatment, including antiviral therapy (Arabi et al, 2018), antibiotic application, immunomodulating therapy (Arabi et al, 2020), organ function support, respiratory support, bronchoalveolar lavage, blood purification and extracorporeal membrane oxygenation (ECMO; Wang et al, 2020; Zumla et al, 2020).

For detailed information on the disease and epidemiology please refer to the Investigator's Brochure.

8.1.2 Prospects for Vaccine Development

More than 140 SARS-CoV-2 vaccine candidates are currently under preclinical development; an additional 24 are in clinical development. Vaccine candidates include inactivated whole virus vaccine compositions, protein subunit, viral vector, virus-like-particle approaches to RNA and DNA vaccine candidates (WHO, 2020).

Two Chinese companies, Sinovac and Sinopharm, launched phase III studies of their inactivated virus vaccine candidates in Brazil and the United Arab Emirates. Sinovac's vaccine candidate, a whole virus grown in Vero cells which is inactivated by ß-propiolactone and adjuvanted with aluminium hydroxide, was tested in phase I/II studies in 743 healthy volunteers. The incidence rate of adverse reactions (15.0% among all participants) was lower compared with results of other candidate vaccines using other platforms (other platforms mostly >60%, some even 100%). No vaccine-related serious adverse events had been observed (Xia et al. 2020).

The epidemic nature of SARS-CoV-19 has to date resulted in more than 46 million infected people and over 1,2 million deaths and is a serious threat to global health (https://coronavirus.jhu.edu, accessed on 2 November 2020). Research is focused on the urgent demand to identify an effective treatment and to develop effective prophylaxis. The goal is to reduce the overall vaccine development process from an average of 10–15 years to 1-2 years. To enable this rapid development, several vaccine approaches need to be tested in parallel in clinical studies, using standardized protocols for vaccine evaluation. Furthermore, development of manufacturing processes to enable rapid production of large quantities of high-quality clinical grade and GMP materials is of great importance. (WHO, 2020). Taken together, this provides strong justification for the development of a vaccine.

8.2 Valneva's Candidate Vaccine

VLA2001 is a highly-purified, whole virus, SARS-CoV-2 vaccine produced on Vero cells and inactivated with β-propiolactone.

VLA2001 viral strain is derived from a Chinese tourist from Hubei diagnosed in a hospital in Rome (Stefanelli et al, 2020).

VLA2001 is adjuvanted with the licensed adjuvant cytosine phospho-guanine (CpG) 1018 (produced by Dynavax, contained in HEPLISAV-B®) in combination with aluminium hydroxide.

VLA2001 has been developed using the same manufacturing platform as that used for the commercial vaccine IXIARO®, a purified, inactivated, whole virus, aluminium hydroxide-adjuvanted Japanese encephalitis vaccine that has been approved by regulatory authorities worldwide (including the Food and Drug Administration [FDA], European Medicines Agency [EMA] and Therapeutic Goods Administration). It is similar in composition to VLA2001, with a good safety profile consistent with findings from pre-licensure clinical studies. As of April 2017, 2,532,480 Participants worldwide have been vaccinated with IXIARO (IXIARO clinical review memorandum, 2018).

VLA2001 has demonstrated excellent purity and overall a biological, chemical and physical profile comparable to that of IXIARO®.

A detailed description of the vaccine and the mechanism of action can be found in the Investigator's Brochure.

8.3 Findings from Nonclinical and Clinical Studies

8.3.1 Non-clinical Summary

VLA2001 was immunogenic in mice and non-human primates. In mice, an increase in immunogenicity (dose sparing effect) was observed when CpG 1018 was used together with Aluminium Hydroxide in preclinical studies with VLA2001. A strong Th1 response may be important to minimize potential risks for vaccine mediated enhanced respiratory disease (VAED) or antibody disease enhancement (ADE) upon infection. A strong Th2 response has been implicated with VAED or ADE for other viruses. The presence of CpG 1018 skewed the immune response in mice after immunization with VLA2001 towards a pronounced Th1 response which mitigates this at the moment theoretical concern.

Cynomolgus macaques immunized with VLA2001 were protected from a combined intranasal and tracheal challenge with SARS-CoV-2. SARS-CoV-2 genomic RNA could transiently be detected in immunized macaques on day 2 post infection at a very low level in nasoparyngeal and tracheal swabs, but not at all in BAL. Subgenomic SARS-CoV-2 RNA was not detectable at all, neither in nasopharyngeal and tracheal swabs, nor in BAL. For further details please refer to the Investigator's Brochure.

8.3.2 Clinical Summary

VLA2001-201 is the first clinical study that is currently ongoing.

For further information on the expected clinical profile of VLA2001, please refer to the Investigator's Brochure.

8.4 Study Rationale

This phase I/II clinical study will be 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. The whole virus is produced on Vero cells and then the antigen undergoes inactivation with β-propiolactone to ensure that surface protein conformation remains intact. Therefore, Valneva anticipates that its candidate vaccine will induce protective antibody responses with specificity to a variety of antigenic virus targets. The vaccine is adjuvanted with CpG 1018 plus aluminium hydroxide. This combination has shown encouraging results from another vaccine candidate (in combination with S-Trimer antigen from SARS-CoV-2, Liang et al. 2020). In non-human primates challenged with SARS-CoV-2, there was an absence of measurable viral load in lung tissue as well as other clinical measures, and in rodents a Th1-polarized T cell response was observed. For both adjuvants an extensive safety databases exists as they are contained in already licensed vaccines.

VLA2001 was immunogenic in mice and an increase in immunogenicity (dose sparing effect) was observed when CpG 1018 was used together with alum. The presence of CpG 1018 skewed the immune response towards a pronounced Th1 response. A strong Th1 response is important to minimize potential risks for enhanced respiratory disease (ERD) or antibody disease enhancement (ADE) upon infection. One potential cause for ERD or ADE is a strong Th2 response. In addition, neutralizing antibodies could be measured at the highest immunization dose (3.0 AU) in the presence of CpG 1018, the measured neutralizing titre was in a similar range as the neutralizing titre determined for the plasma pool derived from convalescent donors.

Due to extensive experience with other inactivated whole-virus vaccine candidates, the established production process and the use of adjuvants already included in other licensed vaccine Valneva considers the risk for safety concerns to be limited.

8.5 Rationale and Justification for the Booster Phase.

Following the successful completion of the Part A primary analysis (Day 36), the high dose was found to be the optimal dose as defined in the primary objective of the study. Based on the assessed comparable safety and superior immunogenicity results at Day 36, the high dose has been selected for further clinical development. Valneva has decided to extend the VAL2001-201 study, by investigating the effects of a Booster dose at 8-9 months after completion of the primary immunization schedule with VLA2001. The booster dose will be offered to all participants who do not meet an exclusion criteria regardless of their initial response to the primary immunization schedule in the different dose groups. Hence, the effect of a booster dose will be studied in a population with different levels of pre-existing antibody levels against SARS-CoV-2.

8.5.1 Possible Benefits for Participant

This is a first-in-human study, therefore the clinical benefits of VLA2001 have not yet be established. The overall benefit and risk balance for individual participants in the study cannot be ascertained.

An initial analysis of the data up to Day 36 from this study has shown that VLA2001 is generally safe and well tolerated across all dose groups tested, with no safety concerns identified by an independent Data Safety Monitoring Board. There were no statistically significant differences between dose groups and no differences between first and second vaccinations in terms of reactogenicity. The majority of Adverse Events (AEs) were mild or moderate and only two subjects reported severe solicited AEs (headache and fatigue). The majority of solicited AEs resolved quickly. VLA2001 was fund to be highly immunogenic with more than 90% of all study participants developing significant levels of antibodies to the

SARS-CoV-2 virus spike protein across all dose groups tested. In the high dose group which is the selected as the optimum dose, the GMT of neutralizing antibodies antibody titers measured 2 weeks after completion of the 2-dose schedule was at or above levels for a panel of convalescent sera.

8.5.2 Possible Benefits for Society

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. The pandemic has had a huge economic impact globally, forcing many businesses to close and people to isolate or shield indoors to prevent the spread of the virus. Many people have lost their jobs as a result. Businesses have been burdened by the extra cost of disinfectant, plastic shields, social distancing (fewer customers) and personal protective equipment. An effective vaccine will help ameliorate these global impacts.

8.5.3 Possible Risks/Inconveniences for the Participant

In general, risks associated with vaccination with an inactivated virus vaccine are considered low and several inactivated whole virus vaccines, such as Japanese encephalitis vaccine IXIARO, have been shown to have an excellent safety profile (Ishikawa et al, 2014; Amicizia et al, 2013).

VLA2001 has been developed using the same Vero cell platform as that used for IXIARO. An acceptable safety profile was demonstrated for IXIARO in seven randomised, controlled studies with a total safety database of 3,945 healthy adults. The most common adverse reactions in adults across all studies were headache, myalgia, injection site pain, and injection site tenderness. No specific safety signals (including hypersensitivity reactions and neurologic disorders) were identified for IXIARO through clinical studies and post-marketing pharmacovigilance (IXIARO clinical review memorandum, 2018).

Five clinical studies have been performed using hepatitis B virus vaccine HEPLISAV-B with CpG 1018 as the adjuvant; 9597 individuals aged 18–70 years received at least one dose of treatment. Reported AEs included injection site pain, injection site redness, injection site swelling, fatigue, headache, malaise and fever. No causal relationship was found between myocardial infarctions/deaths and HEPLISAV-B/CpG 1018. Five Participants had potentially immune-mediated AEs; granulomatosis, polyangiitis, lichen planus, Guillain-Barré Syndrome and Graves' disease. No causal relationship was found between autoimmune AEs and HEPLISAV-B/CpG 1018 (HEPLISAV-B SmPC).

The possibility of Participants experiencing headache, myalgia, injection site pain, and injection site tenderness and potentially immune-mediated AEs cannot be ruled out.

The likelihood of a Participant to experience a vaccine-associated enhanced disease (VAED) following administration of VLA2001 is considered low but cannot be excluded.

Vaccine-induced enhancement of disease has also been described for SARS-CoV and MERS-CoV in animal models, but proof of human SARS-CoV or MERS-CoV vaccine associated enhanced disease does not exist as these candidate vaccines were never tested for efficacy nor used in outbreak situations. For SARS and MERS, the mechanism of enhanced disease observed in mice has been associated with a Th2-mediated eosinophilic infiltration in the lung, which is reminiscent of ERD effects observed after RSV infection of mice immunized with RSV. While vaccine-associated enhanced disease was observed in nonclinical studies with experimental SARS and MERS vaccines, it is not a given that the same risk applies to COVID-19 vaccines. To the sponsor's knowledge, antibody-related COVID-19 disease enhancement has not been observed in nonclinical models yet. In addition, vaccine mediated disease enhancement was not observed in phase I/II studies of other whole virus inactivated SARS-CoV-2 vaccine candidates (Xia et al 2020).

Participants in the present study will be informed of the theoretical risk of disease enhancement in the informed consent form (ICF) and as a risk mitigation strategy, all enrolled Participants will intensively monitored during the conduct of the study to rapidly diagnose COVID-19 and refer for treatment, if applicable.

The blood draws performed during the study carry the possible risks of pain, hematoma, and in very rare cases an infection at the venepuncture site.

After vaccination Participants will remain at the study site for close observation by study team to monitor development of any acute reactions. The first 5 Participants of the three dosing groups (sentinel testing group) will remain under observation for at least 60 minutes after vaccination to monitor development of acute reactions. If at Day 4 safety review (DSMB) of these initial Participants no acute reactions have been observed, the observation time at the study site for the remaining 135 Participants in the study may be reduced to at least 30 minutes.

Necessary emergency equipment and medications must be available at the study site to treat severe allergic reactions.

9. STUDY PURPOSE AND OBJECTIVES

9.1 Study Purpose

The purpose of this study is to evaluate the tolerability, safety and immunogenicity of VLA2001 and to optimise the dose for phase II and III studies. Immunogenicity will be investigated in a larger study sample after safety has been demonstrated in this combined phase I/II study.

This study is being extended to investigate the tolerability, safety and immunogenicity of a booster vaccination with VLA2001.

9.2 Primary Objective

- The primary objective of this study is to evaluate the tolerability, safety 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.

9.3 Secondary Objectives

1) To determine the optimal dose level of inactivated, adjuvanted SARS-CoV-2 vaccine candidate VLA2001 in healthy adults aged 18 to 55 years.
2) 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.
3) To evaluate tolerability, safety and immunogenicity of a booster dose with vaccine candidates VLA2001 in healthy adults aged 18 to 55 years.

9.4 Exploratory Objective

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

10. STUDY DESIGN

10.1 Overall Study Design

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 randomised, double-blind, dose-escalation, multicentre study with three dose groups and 50 Participants recruited to each dose group. The study is conducted in three parts. Part A (Day 1 to Day 36), Part B (Day 37 to Day 208) followed by the Booster Phase: Part C (Visits 7 to 10).
Following an evaluation of Part A data (i.e. data up to Day 36) from the present study, further clinical studies will be initiated.

The study design for Study VLA2001-201 is illustrated in Section 22.1.

Assessments, including immunogenicity and solicited and unsolicited AEs, SAEs or AESIs will be performed at the time points specified in sections 22.2 and 22.3 (specific for Booster Phase) up to Visit 10 (6 months post booster). In addition, samples will be taken for later investigation of cellular immune responses and mucosal immune responses.

10.1.1 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 e-Diary. The study site will contact the Participant per phone approximately 24 hours after vaccination to assess the safety status of the Participant. The provided information must be compared with the entries in the Participant´s e-Diary. The minimum time before the next Participants are vaccinated is therefore 24 hours. 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 e-Diaries. Safety telephone calls will be performed by the study site after approximately 48 hours after vaccination. After confirmation by the investigator that no stopping criteria (see Section 10.6) has been met, 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 Safety and 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 in a 1:1:1 fashion to the three dose groups in the blinded part of the study. Participants will be observed for 30 minutes post vaccination on Day 1. An unscheduled safety telephone call will be performed in case a Grade 3 AE or SAE will be reported by the Participant via e-Diary. All Participants will be followed by e-Diary for 7 days post vaccination, starting on the day of vaccination. Participants will return to the study site on Day 8 (Visit 2). After (approximately) 20 Participants per dose group have been randomised and followed up 7 days post first vaccination, and periodically up to Day 36 for all randomised Participants, the DSMB will review the accrued safety data. 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. The DSMB will review safety and immunogenicity data up to Day 36.

10.1.2 Part B

All Participants will be further followed up on Day 106 (Visit 5) and Day 208 (Visit 6), 6 months after the second vaccination.

10.1.3 Part C (Booster Phase)

During their Day 208/ Month 7 (Visit 6) study visit, all eligible participants will be invited to take part in the Booster Phase (Part C) to investigate tolerability, safety and immunogenicity of a booster dose of VLA2001 (high dose).

Due to planning considerations, all consenting participants will receive the Booster vaccination between mid to end September 2021 (Visit 7), this corresponds to about 8-9 months after completing the primary vaccination series.
Participants will be asked to return to the study site for a follow-up visit approximately two weeks after the booster vaccination then 1 month after the booster vaccination. Participants will be followed-up for safety during a phone call approximately 6 months after the booster vaccination.

A scheduled DSMB review will be performed once all vaccinated Participants have completed their Visit 7. Additional safety data review will occur when necessary (ad-hoc) as defined in the DSMB Charter. A final review of generated safety data will be performed by the DSMB once all participants have completed this clinical study.

10.2 Study Duration

The overall study duration (First Participant In [FSI] –Last Participant Out [LSO]) is estimated to be approximately 16 months. Individual Participant participation is approximately 15

months from enrolment (i.e. Informed Consent signed) to study completion unless the study is prematurely discontinued.

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 follow-up call 6 months (Visit 10) after the Booster vaccination.

10.3 Study Endpoints

10.3.1 Safety Endpoint

10.3.1.1 Primary Endpoint

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

10.3.1.2 Secondary Endpoints

The following secondary tolerability and safety endpoints will be determined:

- 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

10.3.2 Immunogenicity Endpoints

10.3.2.1 Primary Endpoint

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

10.3.2.2 Secondary Endpoints

The following secondary immunogenicity endpoints will be evaluated:

- 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 on Day 8, Day 22, Day 36, Day 106 and Day 208, in Participants negative for SARS-CoV-2 at Screening
- 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 SARS-CoV-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.

10.3.2.3 Exploratory Endpoint

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

10.4 Justification for Study Design and Dosage

This phase I/II study is designed as a blinded, randomised, multicentre study to evaluate the safety, tolerability and immunogenicity of three dose levels of VLA2001. This study is being extended to investigate the safety, tolerability and immunogenicity of a booster vaccination with VLA2001.

VLA2001 is expected to have a safety profile comparable with that of other inactivated vaccines such as IXIARO. However, since this is a first-in-human study with VLA2001 the study will, as a safety precaution, begin with enrolment of 15 sentinel Participants (5 Participants per dosing group). This open-label 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. If no safety concern is detected, four further Participants are vaccinated after 24 hours within the same treatment group. At least a one-hour interval must be followed between vaccinations of Participants. If no safety concern is identified within 48 hours after vaccination, vaccinations in the medium dose level are initiated. Again only one Participant will receive the first medium-dose vaccination, if no safety concerns are identified, another four Participants will be enrolled after 24 hours in the same treatment group. The same process will be followed for the high-dose treatment group. Each of the 15 sentinel Participants will be observed on-site for at least 60 minutes following vaccination.

A Data Safety and Monitoring Board (DSMB) will review the accrued safety data after the sentinel Participants of the high dose group have passed their 3-days post vaccination time

point before randomization of further Participants across all sites will be initiated. The part of the study will be conducted double-blind in order to limit the introduction of a safety bias by the Participants and/or Investigator's staff performing medical safety assessments.

10.4.1 Selection of Study Population

The study will randomize approximately 150 healthy adult Participants aged 18 to 55 years. The proposed study population has been selected to conduct this first-in-human study in adults of good health. A maximum age limit of 55 years has been chosen in this first-in-human study in order to reduce the chance of observed adverse safety outcomes that might be due to medical conditions that are more likely to occur in older adults and were not identified prior to study entry.

10.5 Randomisation and Blinding

The first 15 Participants will be enrolled in the study in an open-label, not randomized dose-escalating manner. The remaining 135 Participants will be randomised in a blinded manner in a 1:1:1 fashion to the three dose groups on Day 1 as described in Section 10.1.

All participants who do not meet any exclusion criteria for a booster dose will be invited to receive a booster dose with VLA2001.

Each Participant will have a unique Participant screening number obtained from the interactive voice response system/interactive web response system (IXRS) assigned at the screening visit. The Investigator will keep a record (i.e. the Participant screening log) of Participants who entered screening.

The IMP will be prepared by study staff in accordance with the treatment allocation provided in the IXRS. An overview of persons who will be (un)blinded is provided below:

<u>Unblinded:</u>

- Fifteen sentinel Participants.
- Members of the DSMB.
- Unblinded statistician(s) at CRO (Pharm-Olam) who will be responsible for following tasks:
    - Generation of the randomization code list
    - Attendance of unblinded sessions of DSMB meetings
    - Generating safety data tables/listings/figures for the DSMB meetings

<u>Blinded:</u>

- The 135 Participants in the randomised part of the study.
- Investigators and other site staff
- Biostatisticians writing the Statistical Analysis Plan and developing the statistical analysis.
- Clinical research associates (CRAs) responsible for monitoring study data.
- All laboratory personnel at central laboratories for safety and immunogenicity laboratory assessments.
- All other Sponsor and contract research organisation (CRO) staff not otherwise specified above will be unblinded as part of the Part A statistical analysis. Laboratory personnel at the Sponsor's testing labs remain blinded throughout the study for additional testing procedures.

10.5.1 Blinding Process

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.

Booster phase:
VAL2001 vaccine will be administered as open label.

Further details are presented in the IMP Manual.

10.5.2 Unblinding

The randomisation assignment is not to be revealed except in emergency cases where unblinding is necessary for the clinical management of an AE/SAE. In such events, the Investigator must either inform the Sponsor before breaking the blind or immediately after unblinding.

In case of emergency, the vaccine administered to the Participants can be revealed through the web-response system (IXRS).

10.6 Study stopping criteria

The DSMB can issue a recommendation to stop the study during ad-hoc DSMB meetings, or to discontinue a treatment group, e.g. in response to an excess rate of AEs with the same suspected underlying pathological mechanism.

Study vaccinations will be suspended, pending DSMB review and assessment, should any of the following criteria be met during the course of the study:

10.6.1 During staggered dose escalation period:

- **One or more Participants** experience an SAE or AESI with no likelier alternative cause than the study vaccine (i.e. related).

- **One or more Participants** experience a severe systemic allergic reaction, e.g. generalized urticaria or anaphylaxis within 24 hours following vaccine administration, with no likelier alternative cause than the study vaccine.

- **One or more Participants** experience Grade 4 local reaction at the vaccination site, characterized by ulceration, necrosis or any Grade 4 local reaction that requires emergency medical care within seven days after study vaccine administration.

- **One or more Participants** in the same treatment group experience the same Grade 3 solicited local AE 48 hours following vaccination.

- **One or more Participants** in the same treatment group experience the same severe (Grade 3 or Grade 4) solicited systemic AE within 48 hours following vaccination, with no likelier alternative cause than the study vaccine.

10.6.2 During entire study period (including the Booster phase):

- **One** or more Participants experience an SAE or AESI with no likelier alternative cause than the study vaccine (i.e. possibly or probably related).

- **Two** or more Participants experience a Grade 3 systemic allergic reaction, e.g. generalized urticaria within 10 days after vaccine administration, or anaphylaxis within 24 hours following vaccine administration, with no likelier alternative cause than the study vaccine.

- **Three** or more Participants in the same dose group experience the same Grade 3[iv] solicited injection site reaction that (1) occurs within 7 days following vaccination and (2) lasts longer than 3 days.

[iv] **Note**: for the purpose of this study, AEs graded as potentially life threatening (Grade 4) will be reported as SAEs (see Section 16.1.2) and will thus fall under the first criterion in Section 11.6.

- **Three** or more Participants in the same dose group experience the same Grade 3 solicited systemic reaction that (1) occurs within 7 days following vaccination, (2) lasts longer than 3 days, and (3) has no likelier alternative cause than the study vaccine.

- **Three** or more Participants in the same dose group experience the same Grade 3 unsolicited AE, including Grade 3 laboratory abnormalities that are assessed to be clinically relevant by the Investigator, that (1) occurs within 36 days following first vaccination, and (2) has no likelier alternative cause than the study vaccine.

Grade 3 and Grade 4 solicited and unsolicited AEs will be confirmed with the site prior to stopping the study due to a pre-defined stopping rule. If any of the above-mentioned criteria is met or the DSMB recommends halting the study or discontinue a dose group for other reasons (e.g. in response to an excess rate of AEs with the same suspected underlying pathological mechanism), the Sponsor will notify the appropriate regulatory authorities and EC according to local requirements.

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of the study intervention under clinical intervention are met. The sponsor has a legal responsibility to notify both the local regulatory authority and other agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating safety reporting to the regulatory authority, IRBs/ECs, and investigators. Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary. An investigator who receives SUSARs or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

If a study stopping rule is met, the DSMB will review all pertinent safety data to provide a recommendation for the study to continue/discontinue based on cumulative safety data evaluation and any other relevant data available at the time of review. Vaccination of Participants already enrolled in the study and restart of recruitment may only proceed after positive DSMB recommendation, and relevant regulatory authorities and EC will be informed.

The Sponsor or Investigator may also stop the study for any medical reason at any time.

If the Sponsor or Investigator decides to terminate the study before it is completed, they will notify each other in writing, stating the medical reason(s) for early termination. In terminating the study, the Sponsor and the Investigator will ensure that adequate consideration is given

to the protection of the Participants' interests. The Sponsor or Investigator will notify the relevant regulatory authorities or EC in writing in accordance with local requirements. Documentation will be submitted for filing in the Central and Investigator File and the Trial Master File.

11. PARTICIPANT SELECTION, WITHDRAWAL AND DISCONTINUATION

Approximately 150 male and female adults who satisfy the inclusion and exclusion criteria listed below will be invited to participate in the study.

11.1 Inclusion Criteria

Participants who meet **ALL** of the following criteria are eligible for the study:

1. Participant is 18 to 55 years[v] of age on the Day of screening (Visit 0).
2. Participant who has a smart phone and is willing and able to install and use the e-Diary.
3. Participant has an understanding of the study and its procedures, agrees to its provisions, and voluntarily gives written informed consent prior to any study-related procedures.
4. Participant is **generally healthy**[vi] as determined by the Investigator's clinical judgement based on medical history, physical examination and screening laboratory tests.
5. Participant has a Body Mass Index (BMI) of 18.0-30.0 kg/m^2, inclusive, at screening (Visit 0).
6. If Participant is of childbearing potential:
    a) Participant has practiced an adequate method of contraception (see below) during the 30 days before screening (Visit 0).

    b) Participant has a negative serum or urine pregnancy test at screening (Visit 0) or Visit 1, respectively.

    c) Participant agrees to employ adequate birth control measures up to Day 106 (Visit 5). This includes one of the following measures:

        - Hormonal contraceptives (e.g. implants, birth control pills, patches).
        - Intrauterine hormone-release systems and intrauterine device.
        - Barrier type of birth control measure (e.g. diaphragms, cervical caps).

[v] From the day a person turns 18 years until the last day before the person turns 56 years of age.
[vi] Participants are considered generally healthy if they have (1) no active disease (acute illness, exacerbation of a chronic condition or a chronic – progressive illness) which requires treatment and/or follow-up, and (2) no disease that is identified as an exclusion criterion or (3) if they are healthy and have a preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment..

- Vasectomy in the male sex partner ≥ 3 months prior to first vaccination.
- Same sex relationships.

11.2 Exclusion Criteria

Participants who meet **ANY** of the following criteria are **NOT** eligible for this study:

1. Clinically significant infection or other acute illness, including fever ≥ 38 °C within 48 hours prior to the planned study vaccination
2. History of laboratory-confirmed SARS-CoV infection
3. Participant had close contact to persons with confirmed SARS-CoV-2 infection within 30 days prior to screening (Visit 0).
4. Participant has participated in a clinical study involving an investigational SARS-CoV-2 vaccine or has received or plans to receive a licensed SARS-CoV-2 vaccine during the duration of the study.
5. Participant has an acute or recent infection not due to SARS-CoV-2 (and who is not symptom-free in the week prior to the Screening Visit (Visit 0).
6. Participant has a history of SARS-CoV1, MERS infection (self-reported)
7. Participant tests positive for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV).
8. Participant has received any vaccine within 30 days prior Visit 1 other than the study intervention, with the exception of the seasonal influenza vaccination. Participants will be encouraged to receive this vaccination at least 7 days after their study vaccine.
9. Participant has abnormal findings in any required study investigations (including medical history, physical examination, and clinical laboratory) considered clinically relevant by the Investigator.
10. Participants with either medical history of or present acute or progressive, unstable or uncontrolled clinical conditions (e.g. cardiovascular, respiratory, neurologic, psychiatric, or rheumatologic conditions) that pose a risk for participation or completion of the study, based on Investigator's clinical judgement. Examples include individuals with poorly controlled or unstable underlying disease, ongoing suspected or active inflammation, poor compliance with pharmacologic treatment, or presence of high-risk comorbidities (e.g. significant cardiopulmonary disease).
11. Participants with an underlying disease with a high risk of developing severe COVID-19 symptoms including those with any of the following risk factors:
    - Hypertension.
    - Diabetes mellitus
    - Chronic liver disease
    - Chronic pulmonary disease.
    - Asthma.
    - Current vaping or smoking.
    - History of chronic smoking within the prior year.

12. Participant has a history of malignancy in the past 5 years other than squamous cell or basal cell skin cancer. If there has been surgical excision or treatment more than 5 years ago that is considered to have achieved a cure, the Participant may be enrolled. A history of hematologic malignancy is a permanent exclusion. Participants with a history of skin cancer must not be vaccinated at the previous tumour site.
13. Participant has a known or suspected defect of the immune system, such as Participants with congenital or acquired immune deficiency, including infection with HIV, status post organ transplantation or other autoimmune diseases
14. Participant received immuno-suppressive therapy within 4 weeks prior to Visit 1 or receipt of immunosuppressive therapy is expected during the study. Immuno-suppressive therapy is defined as administration of chronic (longer than 2 weeks) prednisone or equivalent ≥ 0.05 mg/kg/day within 4 weeks prior to study entry (topical and inhaled steroids are allowed), radiation therapy or immunosuppressive cytotoxic drugs/ monoclonal antibodies in the previous 3 years.
15. Participant has a history of any vaccine related contraindicating event (e.g., anaphylaxis, allergy to components of the candidate vaccine, other known contraindications).
16. Participant presents with clinical conditions representing a contraindication to intramuscular vaccination and blood draws.
17. Participant is pregnant (positive serum or urine pregnancy test at screening or Visit 1, respectively), has plans to become pregnant up to Day 106 of the study or lactating at the time of enrolment.
18. Participant has donated blood, blood fractions or plasma within 4 weeks or received blood-derived products (e.g. plasma) within 12 weeks prior to vaccination in this study or plans to donate blood or use blood products during the study.
19. Participant has a history of coagulation dysfunction (e.g. coagulation factor deficiency, coagulation disease)
20. Participant has a rash, dermatological condition or tattoos that would, in the opinion of the Investigator, interfere with injection site reaction rating.
21. Participant has a known or suspected problem with alcohol or drug abuse as determined by the Investigator.
22. Participant has any condition that, in the opinion of the Investigator, may compromise the Participant's well-being, might interfere with evaluation of study endpoints, or would limit the Participant's ability to complete the study.
23. Participant is committed to an institution (by virtue of an order issued either by the judicial or the administrative authorities).
24. Participant has participated in another clinical study involving an investigational medicinal product (IMP) or device within 4 weeks prior to study enrolment or is scheduled to participate in another clinical study involving an IMP, or device during the course of this study.
25. Receipt or planning receipt of investigational products indicated for the treatment or prevention of SARS-CoV-02 or COVID-19. NOTE: For Participants who get COVID-

19, receipt of licensed treatment options and/or participation in investigational studies is permitted.

26. Participant is a member of the team conducting the study or in a dependent relationship with one of the study team members. Dependent relationships include close relatives (i.e., children, partner/spouse, siblings, parents) as well as employees of the Investigator or site personnel conducting the study.

11.3 Booster Phase

11.3.1 Inclusion Criteria for Booster Phase:

Participants who meet **ALL** of the following criteria are eligible for the Booster phase:

B1. Participant has received complete VLA2001 primary immunization (two vaccinations according to the protocol)

B2. Participant who has a smart phone and is willing and able to install and use the e-Diary.

B3. Participant has an understanding of the study and its procedures, agrees to its provisions, and voluntarily gives written informed consent prior to any study-related procedures.

B4. Participant is **generally healthy**[vii] as determined by the Investigator's clinical judgement

B5. If a participant is of childbearing potential:

a. Participant has a negative urine pregnancy test at Visit 7 prior to booster vaccination.

b. Participant agrees to employ adequate birth control measures up to 3 months after the Booster vaccination.
This includes one of the following measures:

i. Hormonal contraceptives (e.g. implants, birth control pills, patches).
ii. Intrauterine hormone-release systems and intrauterine device.
iii. Barrier type of birth control measure (e.g. diaphragms, cervical caps).
iv. Vasectomy in the male sex partner ≥ 3 months prior to first vaccination.
v. Same sex relationships.

[vii] Participants are considered generally healthy if they have (1) no active disease (acute illness, exacerbation of a chronic condition or a chronic – progressive illness) which requires treatment and/or follow-up, and (2) no disease that is identified as an exclusion criterion or (3) if they are healthy and have a preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before screening/ before Day 208.

11.3.2 **Exclusion Criteria for Booster Phase:**

Participant who meet **ANY** of the following criteria are **NOT** eligible for the Booster phase:

B1. Clinically significant infection or other acute illness, including fever ≥ 38°C within 48 hours prior to the planned Booster vaccination.

B2. Participant has an acute or recent infection not due to SARS-CoV-2 and is not symptom-free in the week prior to the Booster vaccination (Visit 7).

B3. Participant has received any vaccine within 30 days prior Visit 7, with the exception of the seasonal influenza vaccination. Participants will be encouraged to receive this vaccination at least 7 days after their Booster vaccine.

B4. Participant has abnormal findings in any required study investigations (including medical history, physical examination, and clinical laboratory) that is considered clinically relevant by the Investigator.

B5. Participant has received immuno-suppressive therapy within 4 weeks prior to Visit 7 or is expected to receive immunosuppressive therapy during the study. Immuno-suppressive therapy is defined as administration of chronic (longer than 2 weeks) prednisone or equivalent ≥ 0.05 mg/kg/day within 4 weeks prior to Visit 7 (topical and inhaled steroids are allowed), radiation therapy or immunosuppressive cytotoxic drugs or monoclonal antibodies in the previous 3 years.

B6. Participant has clinical conditions representing a contraindication to intramuscular vaccination and blood draws.

B7. Participant is pregnant (positive urine pregnancy test at Visit 7, respectively), has plans to become pregnant up to 3 months after the Booster vaccination.

B8. Participant has a rash, dermatological condition that would, in the opinion of the Investigator, interfere with injection site reaction rating.

B9. Participant has a known or suspected problem with alcohol or drug abuse as determined by the Investigator.

B10. Participant has any condition that, in the opinion of the Investigator, may compromise the Participant's well-being, might interfere with evaluation of study endpoints, or would limit the Participant's ability to complete the study.

B11. Participant is committed to an institution (by virtue of an order issued either by the judicial or the administrative authorities).

B12. Participant has participated in another clinical study involving an investigational medicinal product (IMP) or device within 4 weeks prior to Visit 7 or is scheduled to participate in another clinical study involving an IMP, or device during the course of this study.

11.4 Delay Criteria

Vaccination will be delayed if:

1. Participant has current febrile illness (body temperature equal or greater 38.0°C) or other acute illness within 48 hours prior vaccination.
2. An illness which in the judgement of the investigator may interfere with tolerability/ Day1-8 safety assessment
3. Participant has received antipyretics within 6 hours prior to the scheduled time of vaccination.
4. Receipt of any vaccine within 30 days prior to study intervention, with the exception of the seasonal influenza vaccine. Participants will be encouraged to receive this vaccination at least 7 days before or after their study vaccine.

In addition, for a rescheduled first vaccination all inclusion and none of the exclusion criteria must be met; in case not all of these criteria are met, the Participant will be excluded from further vaccination.

The rescheduled visit should be within the specified time window for the vaccination visit. In case the time window for a rescheduled first vaccination cannot be met, the Participant might be invited for a re-screening. Only a single re-screening is allowed in the study. Re-screened Participants are required to sign a new Informed Consent Form and will be assigned a new participant number.

11.5 Pregnancy Testing and Birth Control

Women of childbearing potential presenting with a negative pregnancy test and practicing the use of adequate birth control before conduct and during the first 3 months of the study are eligible for inclusion into the study.

A woman is considered of childbearing potential if fertile, following menarche and until becoming post-menopausal unless permanently sterile.

Women of childbearing potential must have practiced an adequate contraceptive method during the 30 days before Visit 0 (Screening Visit) and the first 3 months until Visit 5 (Day 106) and present with a negative **serum** pregnancy test at Visit 0 (Screening Visit), a negative **urine** pregnancy test prior to any vaccination. In addition, a **urine** pregnancy test will need to be performed at the Early Termination Visit (if applicable).

Women of childbearing potential are required to practice an acceptable method of birth control for the first 3 months post-vaccination. An acceptable method of birth control is defined as those, which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly.

This includes one of the following measures:

- Hormonal contraceptives (e.g. implants, birth control pills, patches).
- Intrauterine hormone-releasing system or intrauterine device.
- Barrier type of birth control measure (e.g. diaphragms, cervical caps).

- Vasectomy in the male sex partner ≥ 3 months prior to first vaccination.
- Same-sex relationships.

Women without childbearing potential are not required to perform any birth control measure. A woman is considered of non-childbearing potential, if she is:

- Surgically sterilized for ≥ 3 months prior to Visit 1 (permanent sterilization methods include hysterectomy, bilateral salpingectomy or bilateral oophorectomy, or transcervical sterilization [Essure and Adiana procedures], or tubal ligation).
- Postmenopausal for ≥ 1 year prior to Screening as historically confirmed by a gynaecologist.

If a Participant becomes pregnant during the study, she must immediately inform the Investigator and the Participant is asked to attend all remaining visits according to schedule.

11.6 Participant Withdrawal or Discontinuation

Any participant has the right to withdraw from the study at any time for any reason, without the need to justify. A Participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (e.g telephone contact, a contact with a relative or treating physician or information from medical records). The Investigator and Sponsor also have the right to prematurely terminate a Participant's further participation in the study, e. g. in the case of non-compliance or if – in the judgment of the Investigator and/or Sponsor – continued participation would pose an unacceptable risk for the Participant. Additionally, a participant will be **withdrawn from further vaccination** (either second vaccination or booster vaccination) if any of the following criteria are met:

- If participant has ongoing symptoms of COVID-19 disease as defined per protocol (see 15.2.4. Assessment of Symptoms Relating to SARS-CoV-2) and a positive SARS-CoV-2 test.

  Please Note: Participants with a positive test should visit the study site and a COVID-19 illness Visit should be performed.

- If a Participant becomes pregnant prior to study completion study vaccine exposure will be discontinued. Attempts will be made to follow her through completion of the pregnancy and the first 3 months of life of the newborn. The Investigator will record a narrative description of the course of the pregnancy and infant. For further information on pregnancy reporting procedures see Section 16.11.3.

- If a Participant has symptoms, or abnormal laboratory values, which are considered unacceptable by the Participant or the Investigator.

- If a Participant experiences an SAE or AESI with no likelier alternative cause than the study vaccine (i.e. possibly or probably related). In such cases, study vaccinations and further enrolment will be suspended for all Participants pending DSMB review and assessment (see Section 11.6).

- If a Participant experiences a severe systemic allergic reaction, e.g. generalized urticaria within 10 days after vaccine administration or anaphylaxis within 24 hours following vaccine administration, with no likelier alternative cause than the study vaccine.

- If a Participant experiences a Grade 3[viii] solicited injection site reaction that (1) occurs within 7 days following vaccination and (2) lasts longer than 3 days.

- If a Participant experiences a Grade 3 solicited systemic reaction that (1) occurs within 7 days following vaccination and (2) lasts longer than 3 days. However, the Participant may receive further vaccination if there is a more plausible alternative cause for the reaction.

- If a Participant experiences a Grade 3 unsolicited AE, including Grade 3 laboratory abnormality that is assessed to be clinically relevant by the Investigator, that (1) occurs within 36 days after vaccination, and (2) has no likelier alternative cause than the study vaccine or has not resolved prior to the next scheduled study vaccination.

The primary reason for withdrawal/discontinuation of a Participant from treatment and/or from the study should be documented in the electronic Case Report Form (eCRF) (e.g. withdrawal of consent, withdrawal due to AE, Investigator/Sponsor recommended withdrawal, lost to follow up, death).

Participants withdrawn from further vaccination (i.e. did not receive their second vaccination) should perform their remaining regular study visits as scheduled if there are no other reasons for premature withdrawal from the study.

In case of premature withdrawal from the study, all attempts should be made to have the Participant perform an Early Termination (ET) visit (see Section 14.4.2 for procedures/assessments to be performed at an ET visit). Data collected on withdrawn Participants will be used in the analysis and included in the Clinical Study Report (CSR).

[viii] **Note**: for the purpose of this study, AEs graded as potentially life threatening (Grade 4) will be reported as SAEs (see Section 16.1.2) and will thus fall under the first criterion in Section 11.6.

Participants who have not received study interventions regardless of reason, will not be followed.

Participants who do not complete the entire study due to withdrawal or discontinuation for any reason will not be replaced.

11.7 Lost to Follow-up

A Participant will be considered lost to follow-up if she or he repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions should be taken if a Participant fails to return to the study site (clinic) for a required visit:

- The study site must attempt to contact the Participant and reschedule the missed visit as soon as possible and counsel the Participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the Participant wishes to and/or should continue in the study.

- Before the Participant is deemed lost to follow-up, the investigator or designee must take every effort to regain contact with the Participant (e.g. telephone call). These contact attempts should be documented in the medical record.

- Should the Participant continue to be unreachable, she/he will be considered to have withdrawn from the study.

11.8 Re-screening of Participants

A Participant is eligible for re-screening if (s)he completed the screening visit and met in- and exclusion criteria but cannot be randomized or vaccinated for administrative reasons within the given time window (e.g. having served as back-up Participant in the staggered recruitment phase).

12. INVESTIGATIONAL MEDICINAL PRODUCT

12.1 Description of the IMPs

VLA2001 is a highly purified, inactivated, whole virus SARS-Cov-2 vaccines grown on Vero cells. The vaccine production platform, developed by Valneva, uses an inactivated whole-virus approach where live wild-type virus is grown in cell culture and then inactivated (i.e. making it unable to replicate and infect cells) via chemical treatment. Valneva uses β-propiolactone inactivation in order to preserve the native surface structure of the S protein. VLA2001 has similar biological, physical and chemical properties as the approved vaccine IXIARO, produced using the same platform.

The final administered dose of VLA2001 is 0.5 mL.

12.1.1 Primary Immunization – composition of VLA2001

Table 1 Composition of VLA2001 (primary immunization)

Active substance	
SARS-CoV-2 inactivated with β-propiolactone	**Target Antigen Units**
	Low dose: 3 AU/dose **Medium dose: 7 AU/dose** **High dose: 35 AU/dose**
Excipients and buffer components	
Aluminium hydroxide	0.5 mg/dose
Dulbecco's Phosphate Buffered Saline (DPBS)	
HSA	25 ug/dose

Concentrations per final administered dose of 0.5ml (i.e. post bed-side mixing)

Bed side mixed with

CpG 1018	1 mg/dose
Tris buffered saline	

Concentrations per final administered dose of 0.5ml (i.e. post bed-side mixing)

VLA2001 will be administered in combination with CpG 1018 enriched oligodeoxynucleotide phosphorothioate immunostimulatory adjuvant (CpG 1018 adjuvant; licensed by FDA, marketing authorisation by EMA pending). The CpG 1018 adjuvant used is a 22-mer

oligodeoxynucleotide in a Tris buffered saline (20 mM Tris, 100 mM Sodium Chloride, pH 7.5 (HEPLISAV-B SmPC). For this clinical study, one part of the vaccine (labelled VLA2001) will be presented as a liquid formulation containing aluminium hydroxide in glass vials at three dose levels and has to be mixed bedside with CpG 1018 prior to vaccination (volume for administration is 0,5ml).

The bed-side mixing procedure is described in detail in section 13.3.2.

12.1.2 Booster Phase - composition of VLA2001:

For the Booster Phase, there will be no bed-side mixing necessary. For the Booster Phase, VLA2001 will be provided in multi-dose glass vials as a liquid formulation containing aluminium hydroxide and CpG 1018.

Table 2 Composition of VLA2001 (booster vaccination)

Active substance	
SARS-CoV-2 inactivated:	Antigen Units/dose, antigen dose level equivalent to high dose
Excipients and buffer components	
Aluminium Hydroxide	0.5 mg Al^{3+}/dose
CpG 1018	1 mg/dose
Dulbecco's Phosphate Buffered Saline (DPBS) [3)]	
rHA	≤25 µg/dose

12.2 IMP Labelling and Packaging

Packaging and labelling of IMP is performed by Almac. Labels will be written in accordance to local law. Valneva will provide one kit containing one vial of VLA2001 and one vial of CpG.

Booster Phase:

Packaging and labelling of IMP is performed by a central manufacturing organization located in the UK (Almac). Labels will be written in accordance to local law. Valneva will provide one kit containing one multi-dose vial of VLA2001.

12.3 IMP Storage, Dispensing and Accountability

12.3.1 IMP Storage

The IMP should be stored in a refrigerator at +2 to +8°C in a room with access limited to study personnel. Temperature monitoring systems will be used.

PLEASE DO NOT FREEZE THE VACCINE!

12.3.2 Dispensing and Accountability of Investigational Medicinal Product

A drug shipment log will be kept current by the site, detailing the date and quantity of IMP received from and returned to the Sponsor. In addition, a current drug dispensing log has to be maintained, detailing the dates and quantities of IMP administered to each Participant. This documentation will be available to the designated CRA to verify drug accountability during the study and to perform overall drug accountability.

Any unused IMP and empty vials will be accounted for and returned to the Sponsor.

Details of IMP handling, including the procedure for Booster Phase are described in the updated study-specific IMP manual.

13. STUDY PROCEDURES

13.1 Informed Consent and Enrolment

Any healthy volunteer who provides informed consent (i.e., signs and dates the informed consent form) is considered enrolled in the study.

The Investigator will inform the Participant about the procedures, risks and benefits of the study. Fully informed, written consent must be obtained from each Participant prior to any assessment being performed. It is important that the Participant is allowed sufficient time to decide on his/her participation in the study.

13.2 Participant Identification Code

At Visit 0, a 10-digit Participant identification code will be assigned to each Participant. The first four digits are the product identifier (e.g. 2001 for this product) provided by the Sponsor. The fifth digit is the study identifier (i.e. 2001-1 for this phase I/II study); the sixth and seventh digit is the site identification number (i.e. 2001-1-01). The last three digits are assigned in ascending order as the Participants are enrolled (i.e., signing the informed consent form, e.g. 2001-1-01-001).

13.3 Investigational Treatment

13.3.1 Description of Treatment

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].

Booster Phase:

The booster vaccination will be administered IM in the deltoid region of the non-dominant arm; please refer to the updated study-specific IMP manual.

13.3.2 Vaccine Preparation and Administration

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).

Preparation of IMP will be done according to the following procedure:

1. CAUTION: Preservatives, antiseptics, detergents, and other anti-viral substances may inactivate the vaccine. Use only sterile syringes that are free of preservatives, antiseptics, detergents or other anti-viral substances for injection of VLA2001.
2. The VLA2001 glass vial and CpG vials should be removed from the fridge (2-8°) and allowed to reach room temperature before administration
3. The VLA2001 and CpG vials should be gently swirled (5 to 10 seconds) to obtain a homogeneous suspension (no vortex or shaking);
4. The VLA2001 and CpG vials should be inspected visually for any foreign particulate matter and/or variation in physical appearance (e.g. discoloration) prior to withdrawal of the appropriate volume into a syringe. Vials found to contain foreign particulate matter, to be discolored or to leak must be discarded and may not be used; the Sponsor must be informed immediately of such events.
5. Withdraw 0.2ml CpG 1018 with a syringe (the prefilled volume in the CpG vials is approximately 0.7ml). Transfer the 0.2ml CpG 1018 into the VLA2001 vial, the resulting volume is 0.6ml.
6. The mixed vaccine vial should be gently swirled (5 to 10 seconds) to obtain a homogeneous suspension (no vortex or shaking).
7. Take a new needle and withdraw the injection volume of 0.5 mL. The injection site should be prepared according to standard clinical procedures.
8. Injection of 0.5ml mixed vaccine intramuscularly into deltoid region of non-dominant arm by study staff as soon as possible.
9. The used vials and syringes should be kept within the empty kits for drug accountability purposes. Used needles should be disposed in accordance with local requirements.

Under no circumstances should the VLA2001 vaccine be administered intravascularly, as this could lead to hypersensitivity reactions such as shock.

Booster Phase:

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. In addition, the site will receive unlabelled syringes together with an aspiration and an administration needle and specific syringe labels. Once the pharmacist gets the treatment for a participant, they will retrieve 0.5 mL from the respective multi-dose vial with a syringe. Immediately afterwards this syringe will be labelled with a syringe label (participant identifiers will be added manually on the label). With this process the identification of and allocation of the syringe to a specific multi-dose vial and participant is ensured.

The details of the procedure for Booster Phase are described in the updated IMP manual.

Anaphylaxis or other possible severe acute, post-vaccination adverse reactions to vaccines, including VLA2001 vaccine, are very rare, but can occur. Therefore, appropriate emergency equipment and medication as well as adequately trained personnel must be on site whenever a vaccination is performed.

13.3.3 Post- Vaccination Observation

The first Participant of a sentinel dosing group will be observed for 3 hours at the study site following vaccination; all remaining 4 Participants of the sentinel dosing group will be observed for 60 minutes (see Section 10.1) at the study site. All remaining 135 Participant in the randomized and blinded part of the study will be observed at the study site for 30 minutes after each vaccination. This is in order to provide appropriate emergency treatment should this be necessary. In addition, vital signs including pulse rate and blood pressure while seated and at rest will be measured prior to discharge. Any injection site and systemic reactions will be recorded.

Booster Phase:

For the Booster vaccination, participants should be observed in the clinic for 30 minutes after administration.

Prior to leaving the study site, the Participant will be instructed how to complete the respective electronic diary for documentation of AEs (for further information see Section 15.3), will be given a digital thermometer for measuring oral body temperature and a measuring device for assessing injection site reactions (at the vaccination visit only).

13.4 Screening and Study Visits

The overall study design is illustrated in Section 22.1. Please refer to the Schedule of Study Procedures and Assessments in section 22.2 and section 22.3 (specific to the Booster Phase), for the timings of all procedures to be carried out during the study.

Please note:

Study Changes in Response to the COVID-19 Pandemic Situation

Authorities worldwide have issued guidance for Industry, Investigators, and Institutional Review Boards on conducting clinical studies during the COVID-19 pandemic.

Competent health authorities and agencies, including the FDA, the MHRA* and the HRA**, support the implementation of remote activities to ensure continuation of study activities should the COVID 19 situation limit/forbid access to clinical sites.

Valneva will continuously monitor and evaluate the development of the COVID-19 pandemic in the area of study sites to determine if any measures should be implemented to mitigate undue risks to the Participants or in response to local governmental recommendations.

Such measures can include (but not limited to):

- remote monitoring,
- switching in-person visits to telephone call and/or home visits (including appropriate documentation of the phone call/home visit),
- sending of 'Dear Investigator' Letters to inform investigator sites of changes to trial conduct
- self-isolation of trial Participants as a precaution or as a result of confirmed infection, limiting or inhibiting the required clinical trial activities.

Explicit instructions from Valneva and CRO as to what can be accessed where, will be available and communicated in a timely manner to ensure fulfilment of protocol activities during the trial.

Trial participants will be consented to any identifiers leaving the site and be assured that their confidentiality will be protected.

Furthermore, care will be taken that no extra burdens are placed on investigators and site staff around scanning and uploading many documents.

The safety of the Participants participating in the trial remains our priority.

*MHRA Guidance. (see literature)

13.4.1 Unscheduled Visit

An unscheduled visit can be held at any time during the study if deemed necessary by the Investigator (e.g. follow-up on unexpected AEs or SAEs) or the DSMB. Assessments performed at an unscheduled visit will be at the Investigator's or DSMB's discretion. Unscheduled visits and any procedures/assessments performed during such a visit (e.g. physical examination, laboratory test) should be documented in the source data and the eCRF.

In any case a phone call will only take place if a) data are not being entered; b) grade 3 events are reported, c) if a serious AE is reported via the diary, d) if Participants indicate symptoms towards potential COVID-19 infection.

13.4.2 Early Termination Visit

Participants who terminate participation or who are withdrawn from the study prematurely will undergo investigations during an ET visit, if possible. Every effort should be made to have discontinued Participants complete the study ET Visit (see Table 3).

Table 3 Study VLA2001-201 Study Visit Schedule – Early Termination

TIME	ACTION
unscheduled	1. Review/Collect Participant diary (Section 15.3) 2. AE/AESI/SAE documentation (Section 15.2) 3. Concomitant medication (Section 15.4) 4. Symptom-driven physical examination and Vital Signs (Section 15.6 and 15.5) 5. Blood draw [a]: a. Immunogenicity evaluation (Section 14) b. Clinical chemistry, haematology, coagulation assessments (Section 15.7) 6. Urine samples: a. Urine pregnancy test (if applicable) [b] b. Urinalysis (Section 15.7) 7. Documentation of reason for early termination

AE=adverse event; AESI=adverse event of special interest; SAE=serious adverse event

[a] The following amounts of blood will be drawn: HIV/HBsAg/HCV screening – 3 mL; serum pregnancy test – 3.5 mL; immunogenicity – 15 mL; clinical chemistry – 7.5 mL; haematology – 5 mL; coagulation – 3 mL.

[b] A pregnancy test will be performed on all female Participants of child bearing potential at screening (serum pregnancy test), and prior to each vaccination and upon study completion (urine pregnancy test).

If an ET Visit is not possible, a follow-up safety phone call should be made as soon as possible after termination to capture at least concomitant medications and solicited and unsolicited AEs since the last study visit.

The reason for early termination should be clarified in as much detail as possible. If an AE was the reason for early study termination, details of the specific AE(s) should be captured (see Section 11.6). The reason for discontinuation will be recorded on the eCRF, and data collected up to the time of discontinuation will be used in the analysis and included in the clinical study report.

In the event of Participant discontinuation due to an AE, clinical and/or laboratory investigations that are beyond the scope of the required study observations/assessments may be performed as part of the evaluation of the event. These investigations will take place under the direction of the Investigator in consultation with the Sponsor, and the details of the outcome may be reported to the appropriate regulatory authorities by the Sponsor.

13.5 Procedures for Monitoring Participant Compliance

In general, study procedures are to be performed under the supervision of the Investigator or designee at the study site. Participant compliance will be monitored by reviewing the Participant's entries in the e-Diary.

14. ASSESSMENT OF IMMUNOGENICITY

All serum samples obtained for the determination of neutralizing antibodies and IgG antibodies against SARS-CoV-2 will be handled according to the procedures supplied to each investigative site for the preparation, storage and shipment of samples (refer to Laboratory Manual). Immunogenicity samples will be collected from all Participants at the time points indicated in section 22.2 and 22.3. Each clinical study site will be responsible for the separation of serum from whole blood samples and the safe and controlled storage of serum samples prior to shipment to the central laboratory.

Immunogenicity sample (10ml) will be drawn for SARS-CoV-2-specific neutralizing antibody titre evaluation and ELISA antibody titre evaluation.

Serum samples to measure SARS-CoV-2 neutralizing antibody levels will be collected from Participants on Day 1 (prior vaccination), Day 8, Day 22 (prior vaccination), Day 36, Day 106 and Day 208. An authorized laboratory will measure neutralizing antibodies to SARS-CoV-2 using wild-type virus neutralizing assay. In addition to the functional assays, samples will be analysed for IgG against SARS-CoV-2 by ELISA.

The cell-mediated immune response (T-cell response) will be assessed on Day 1, Day 36 and Day 208 by characterizing PBMCs; methods may include T-cell ELISpot assays to SARS-CoV-2 antigens.

Booster Phase:

During the Booster Phase, a blood sample (10 ml) will be collected at Visit 7 (before vaccination), Visit 8 and Visit 9, to measure SARS-CoV-2-specific neutralizing antibody titre and ELISA antibody titre.
Similarly, cell-mediated immune response (T-cell response) will be assessed by characterizing PBMCs at Visit 7 and Visit 8.
More details about the Booster Phase assessments can be found in section 22.3.

At the end of the study, results of immunogenicity assessments will be provided to the Investigator.

14.1 Additional Testing Procedures

Instructions for obtaining and processing saliva sampling are provided in the Laboratory Manual.

Self-swabbing samples will be assessed by validated assays for the detection of SARS-CoV-2.

Samples obtained in this study may, in addition to its use for assessment of SARS-CoV-2 specific antibody and cellular immune responses, also be used for further development of the vaccine, including but not limited to the following assays:

- Development of additional neutralization assays (e.g. pseudovirion neutralization assay)
- Detection of antibodies by enzyme linked immunosorbent assay (ELISA) against different SARS-CoV-2 antigens
- Detection of cellular immune responses using different test methods (e.g. ELISpot, intracellular cytokine staining)
- Clinical diagnostic work-up.

Such development may occur at laboratories other than the central analytical laboratory used for this study.

A blood sample for use in passive transfer studies will be collected to support the establishment of a robust clinical endpoint for identification of neutralizing antibody levels associated with protection from COVID-19. These samples may also be used for the preparation of assay controls.

15. ASSESSMENT OF SAFETY

15.1 Definitions

15.1.1 Adverse Events

An AE is defined as any untoward medical occurrence in a Participant administered an investigational product that does not necessarily have a causal relationship with the treatment. All new abnormalities or any exacerbation in intensity or frequency (worsening) of a pre-existing condition during or after vaccination must be documented as AEs.

15.1.2 Serious Adverse Event

A SAE is defined as any untoward medical occurrence that at any dose meets one or more of the following criteria:

- Outcome is fatal/results in death (including foetal death).
- Is life-threatening – defined as an event in which the Participant was, in the judgment of the Investigator, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death had it been more severe.
- Requires inpatient hospitalisation or results in prolongation of an existing hospitalisation.
- Results in persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions).
- Results in congenital anomaly/birth defect.
- Is a medically important condition – a medical event that may not be immediately life-threatening or result in death or require hospitalisation but may jeopardize the Participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above. This definition also applies to progression of disease leading to a serious outcome.

In case of hospitalisation or prolonged hospitalisation for diagnostic or elective medical procedures that were planned prior to vaccination to treat a pre-existing condition that did not change in severity, neither the condition leading to the hospitalisation or prolonged hospitalisation, nor the actual medical procedure need to be reported as an SAE. In this case, the underlying diagnosis or condition should be reported in the medical history section of the eCRF and the corresponding medical procedure should be documented as a comment to the underlying diagnosis or condition in the medical history section of the eCRF.

The Sponsor will classify the SAEs as either expected or unexpected:

Expected:	An AE that is listed in the current Investigator's Brochure (IB)
Unexpected:	An AE that is not listed in the current IB, or it differs because of greater severity or greater specificity

For the purpose of this study, AEs graded as potentially life-threatening (Grade 4) (see Section 15.2.3 for solicited AEs) will be reported as SAEs.

15.1.3 Adverse Events of Special Interest

An AESI (serious or non-serious) is an event of scientific and medical concern specific to the Sponsor's product. Please refer to Sections 15.10 and 22.5, where symptoms/illnesses considered as an AESI for this study are described.

15.1.4 Medically-Attended Adverse Event

All AEs where Participants are seeking medical care (i.e. doctor’s office, emergency service, hospital, but not including use of self-medication).

15.1.5 Pre-existing Diseases

Pre-existing diseases that are present before entry into the study, that are described in the medical history, and that manifest with the same severity, frequency, or duration after vaccine exposure, will not be recorded as AEs. Furthermore, routine health checks required due to pre-existing diseases will not be recorded. However, when there is an increase in the severity of a pre-existing disease, the event must be described on the AE CRF page.

15.1.6 Untoward Medical Occurrences Not Considered Adverse Events

Each untoward medical occurrence experienced before vaccine exposure (for example, from the time of signed informed consent up to but not including vaccine exposure) will be described in the medical history.

15.2 Collection, Documentation and Assessment of Adverse Events

15.2.1 Unsolicited Adverse Events

Participants will be provided and trained to use an electronic diary to make notes on unsolicited AEs up to D36 (Visit 4, see Section 15.3). Additionally, the Investigator will enquire about AEs during study visits. Clinically relevant laboratory parameter changes constitute unsolicited AEs, too, unless they are considered a symptom of an underlying AE or part of a syndrome that is reported as AE (e.g. presence of blood cells in urine in a person diagnosed

with urinary tract infection). In addition, symptoms noted during the symptom-driven physical exams (unless already covered by an AE) constitute AEs.

All unsolicited AEs need to be documented in the respective AE section of the eCRF during the applicable study visit (Visits 1 to 6 or unscheduled visit(s), if applicable), regardless of their source (AEs noted in the Participant diary [see Section 15.3], open question to Participant, laboratory parameters, symptom-driven physical examination). Serious adverse events will continue to be documented until the end of the study.

Any symptom is regarded as a separate AE. However, if the Investigator considers several symptoms to be in the context of one underlying diagnosis, the Investigator may merge these symptoms into one single appropriate AE. The AE term entered into the eCRF should contain all symptoms summarized to one event (e.g. 'Influenza with flu-like-symptoms, fever and headache').

The Investigator will follow-up each AE until it is resolved or until the medical condition of the Participant is stable. All relevant follow-up information will be reported to the Sponsor until the end of the study for each Participant. Serious adverse events ongoing at the time of Visit 8 will be followed until resolution or achievement of stable clinical conditions, latest until the overall end of the study.

Beyond study end, SAEs that are fatal, life-threatening or suspected to be related to study treatment will be followed up to be reported until 6 months after the last study visit of the respective Participant.

The following information will be documented for each AE: severity, causality, outcome, and seriousness, medically-attended, action taken to treat AE, action taken on IMP, start and stop dates.

Booster Phase:
Participants taking part in the Booster Phase will use the electronic diary to collect solicited AEs and make notes on unsolicited AEs occurring until Visit 10.

15.2.1.1 Severity

The Investigator will assess the severity of AEs using his/her clinical expertise and judgment based on the most appropriate description below:

Mild (Grade 1): Awareness of signs or symptoms, but easily tolerated, does not interfere with daily activities.

Moderate (Grade 2): Discomfort enough to interfere with usual activity and with or without requiring medical intervention.

Severe (Grade 3): Incapable of work or usual activity and requiring medical intervention.

15.2.1.2 Causality

Causality is a determination of whether there is a reasonable possibility that the vaccine administration is aetiologically related to/associated with the AE.

Solicited adverse events of vaccination site reactions will be considered causally related to study treatment.

For all other adverse events, the Investigator will determine a **causal relationship** to the study vaccine. Several factors will be considered in making this assessment, including: 1) the temporal relationship of the event to the administration of the study vaccine 2) whether an alternative etiology has been identified and 3) biological plausibility.

Causality of all adverse events should be assessed by the Investigator using the following question:

"Is there a reasonable possibility that the adverse event may have been caused by the study vaccine?"

- YES (related): There is a reasonable possibility that the study vaccine contributed to the adverse event

- NO (not related): There is no reasonable possibility that the adverse event is causally related to the administration of the study vaccine. There are other, more likely causes and administration of the study vaccine is not suspected to have contributed to the adverse event

Probable: Reaction that follows a reasonable temporal sequence from administration of the IMP, or that follows a known or expected response pattern to the suspected treatment; and that could not reasonably be explained by known characteristics of the Participant's clinical state.

Possible: Reaction that follows a reasonable temporal sequence from administration of the IMP, or that follows a known or expected response pattern to the suspected treatment; but that could readily have been produced by a number of other factors.

Unlikely: Reports not following a reasonable temporal sequence from administration of the IMP; an event, which may have been produced by the Participant's clinical state or by other environmental factors. A more likely alternative aetiology exists.

Not related (unrelated): Events for which sufficient information exists to conclude that the aetiology is unrelated to the IMP.

Adverse events with a causality reported as probable or possible will be considered related to the IMP. Adverse events with missing causality assessment will be regarded as related unless further specified. All other AEs will be considered as not related to IMP.

15.2.2 Assessment and Outcome of Adverse Events

Each AE that occurs from first vaccination to study completion/termination will be described in the eCRF (i.e. one AE per form) using the medical diagnosis (preferred), symptom, or sign, in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial expressions. Adverse events will be evaluated by the Investigator for:

- Seriousness as defined in Section 15.1.2.
- Severity as defined in Section 15.2.1.1.
- Causal relationship to vaccine exposure as defined in Section 15.2.1.2.

For each AE, the outcome will also be documented as either:

- Recovered/Resolved
- Recovered/Resolved with sequelae
- Recovering/Resolving
- Not recovered/not resolved
- Fatal
- Unknown

If the severity rating for an ongoing AE changes before the event resolves, the AE will not be reported a second time. Instead the original AE report will be revised. For purposes of data capture the highest severity rating during the course of a single AE will be the severity rating entered on the AE CRF.

NOTE: *A Participant's death per se is not an event, but an outcome. The event that resulted in the Participant's death must be fully documented and reported, regardless of being considered related to treatment or not.*

15.2.3 Solicited Adverse Events

Solicited AEs will be collected in the e-Diary by the Participant for 7 consecutive days after each vaccination, starting on the day of vaccination. They will be graded by the investigator

or the designee according to the FDA's Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, see Table 4, Table 5 and Table 6.

For solicited AEs which are serious and/or medically attended, the investigator carries out more detailed assessments are performed for unsolicited AEs (causality, outcome, action taken) and documents them in the eCRF. For solicited local and systemic AEs persisting beyond 6 days after vaccination, stop date is also documented in the eCRF (AE section).

15.2.3.1 Injection Site Reaction – Measurement and Evaluation

Solicited injection site reactions include injection site pain, itching, tenderness, redness and swelling/induration. Participants will be provided with a measuring tool to measure the size of any measurable injection site reaction (longest diameter).

Table 4 Grading of Injection Site Reactions

Vaccine-specific Criteria	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)[c]
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalisation
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Emergency room visit or hospitalisation
Erythema / Redness [a]	2.5–5.0 cm 0.98–1.96 inch	5.1–10.0 cm 1.97–3.94 inch	> 10.0 cm > 3.94 inch	Necrosis or exfoliative dermatitis
Induration / Swelling [b]	2.5–5.0 cm (0.98–1.96 inch) and does not interfere with activity	5.1–10.0 cm (1.97–3.94 inch) or interferes with activity	> 10.0 cm (> 3.94 inch) or prevents daily activity	Necrosis

[a] In addition to grading the measured local reactions at the greatest single diameter.
[b] Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement.
[c] Any Grade 4 injection site reaction will be reported as SAE, Grade 3 severity should be documented.

15.2.3.2 Systemic Reactions – Measurement and Evaluation

Solicited systemic reactions include fever/body temperature (Section 15.2.3.3), fatigue, headache, nausea/vomiting, muscle pain.

Table 5 Grading of Systemic Reactions

Vaccine-specific Criteria	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)[d]
Nausea/vomiting	No interference with activity or one to two episodes/ 24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	Emergency room visit or hospitalisation for hypotensive shock
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalisation
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	Emergency room visit or hospitalisation
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	Emergency room visit or hospitalisation

[a] Any Grade 4 systemic reaction will be reported as SAE, Grade 3 severity should be documented.

15.2.3.3 Fever and Body Temperature

Participants will be provided with a digital thermometer to individually measure their body temperature orally once every evening from vaccination until Day 7 after each vaccination.

In case fever (oral body temperature ≥ 38.0°C occurs, Participants should measure their body temperature every 4 to 8 hours until fever resolves (oral body temperature < 38.0°C . The time at which the first body temperature of < 38.0°C is recorded is considered to be the end of the fever episode. 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. 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.

Table 6 Grading of Fever

Mild	38.0°C – 38.4°C
Moderate	38.5°C – 38.9°C
Severe	39.0°C – 40.0°C
Potentially Life-Threatening	>40.0°C

15.2.4 Assessment of Symptoms Relating to SARS-CoV-2

Participants who present at least one of the below mentioned symptoms during the study must contact their study team:

- Fever or chills
- Persistent cough (as defined by NHS, as a lot of coughing for more than 1 hour, or three or more coughing episodes in 24 hours. If the participant usually has a cough, it may be worse than usual.
- Shortness of breath, difficulty breathing
- Fatigue
- Muscle or body aches
- A loss of smell and taste
- Headache
- Sore throat
- Congestion
- Nausea or vomiting (more than one episode and/or persisting)
- Diarrhoea

With the exception of fever, shortness of breath, or difficulty breathing, the symptom must be present for 2 or more consecutive days.

15.2.5 Procedures in the Event of COVID-19 like Signs and Symptoms

As a risk mitigation strategy, all enrolled participants will be intensively monitored during the conduct of the study to rapidly diagnose COVID-19 and referred for treatment according to local site procedures, if applicable.

Participant who presents with at least one of the above-mentioned symptoms during the study, must contact the study team. In case of confirmed COVID-19 symptoms Participants will be tested on site by a validated test.

In case of a negative test result, Participants will be invited for a second confirmatory test on site. In the event the result is still negative, the Participant will continue with scheduled visits.

If either or both tests are positive, the participant will be performing a COVID-19 illness visit at site. Where supported, home or mobile visits may be substituted for this site visit As part of these visits, samples (a saliva sample and blood samples) will be taken for antigen and antibody assessment as well as recording of COVID-19-related clinical and laboratory

information. During the Booster Phase, saliva samples will not be collected in line with the schedule of assessment (section 22.3)

Participant should continue for 14 days after symptoms onset or until resolution of the COVID-19 episode, whichever comes last, with the home-collection self-swab kit every 2 days. Resolution of COVID-19 is defined as having 2 consecutive SARS-CoV-2 negative swabs and 2 consecutive days with no COVID-19 related signs and symptoms.

All confirmed COVID-19 episodes will be communicated to the respective participant and to other authorities according to local regulations. In addition, participants will be educated about current applicable public health guidances for confirmed COVID-19 cases.

15.3 Electronic Diary

Electronic diaries (e-Diary) will be used to record solicited AEs within 7 days after each vaccination and to make notes on unsolicited AEs until D36 and until V10 in the Booster Phase. Assessments by the Participant should occur at the same time each day, starting approximately 8 hours after vaccination. The Participant will be properly instructed on the reporting requirements and how to complete and use the Participant diaries, thermometer and measuring ruler (for assessment of measurable injection site reactions).

The following information will be collected:

- Oral body temperature.
- Solicited injection site reactions.
- Solicited systemic reactions.
- Symptoms Relating to SARS-CoV-2 infection.
- Other AEs.
- Any new medication or changes in medication taken after vaccination.

Study staff will be prompted to perform a phone call visit if a) no diary data are being reported by the Participant, b) a grade three solicited event has been reported, c) criteria for serious adverse event have been met and/ or d) symptoms relating to SARS-CoV-2 have been reported.

<u>Access to ePRO:</u>

Participants need to download “Patient Cloud” app from their APP Store

- Site need to register the patient in the EDC (Patient Cloud module) to generate the ´Activation code´ and provide the same to Participant. Once Participant enters the activation code in the Patient Cloud App, the access is granted. This is just one time activity (no need to repeat it if ePRO has multiple visits).

- Note that the Site personnel (CRC/PI) should also be granted access to Patient Cloud in EDC so they can generate the activation codes for the Participants.
- During investigator meeting and site initiation visit the CRO will provide training on how to use ePRO App. So the Site personnel can train the Participants as need be. As well, an ePRO manual will be created that clearly explain how to use the App.

The electronic diary will serve as source documentation. Entries in the diaries will be transcribed onto the appropriate eCRFs. Any entry on the eCRF that does not correspond with an entry in the diary will be explained by the Investigator on the relevant diary page.

15.4 Medical, Medication, and Non-Drug Therapy History

15.4.1 Medical history

At screening, the Participant's medical history will be described for the following body systems including severity (mild, moderate, or severe as defined in Section 15.2.1.1) or surgery and start and end dates, if known: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; metabolic; hematopoietic/lymphatic; dermatological; and genitourinary.

In addition, the medical history prior to screening will include the following:

- Previous SARS-CoV-2 infection.
- Information on planned hospitalisations (including elective surgery) during the study for medical conditions existing prior to or at study entry. Such planned hospitalisations do not need to be reported as SAEs.

Booster Phase:
During the Booster Phase, the Medical history will be reviewed in line with the Inclusion and Exclusion criteria and according to the schedule of assessments (section 22.3)

15.4.2 Concomitant Medications and Non-Drug Therapies

All medications or vaccines (including over-the-counter or prescription medicines) received from 2 weeks prior to study enrolment until completion/termination must be recorded in the eCRF along with the information listed below. Vitamins and/or herbal supplements are not to be recorded.

- Product name

- Reason for use
- Dates and routes of administration including start and end date
- Dosage information including dose frequency

The Study Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

In addition, medications to treat SAEs will be reported to the Sponsor on SAE Report Forms as described in Section 3. In the context of this study, information on non-drug therapies will only be collected in relation to SAEs.

The following medications are **not permitted** if administered within the specified study periods (unless such treatment has to be administered in an emergency situation):

- NOTE: for Participants who become hospitalized with COVID-19, receipt of licensed treatment options and/or participation in investigational treatment studies is permitted
- Receipt of any vaccine (licensed or investigational) other than licensed influenza vaccines within 30 days prior to and after administration of study intervention (except in medical emergencies such as tetanus or rabies exposure).
- Investigational products indicated for the treatment or prevention of SARS-CoV-2 or COVID-19
- Another IMP.
- Immunosuppressive treatment[ix] during the course of the study (unless such treatment has to be administered in an emergency situation).
    - Glucocorticoids at a dose ≥20 mg/day of prednisone or equivalent given daily or on alternate days for ≥14 consecutive days between randomization and the Participant´s schedule
    - Other systemically administered drugs with significant immunosuppressive activity, such as azathioprine, tacrolimus, cyclosporine, methotrexate, or cytotoxic chemotherapy between randomization and the Participant´s schedule
- Any blood products or immunoglobulins.

[ix] Treatment that can be expected to influence immune response. Such treatment includes, but is not limited to, systemic or high dose inhaled (> 800 µg/day of beclomethasone dipropionate or equivalent) corticosteroids, radiation treatment or other immunosuppressive or cytotoxic drugs. Use of inhaled (low dose), intranasal or topical steroids is permitted.

For documentary purposes, any of the treatments listed above (including emergency treatment) given within these time periods requires special documentation and is to be documented as a protocol deviation.

The following medications and procedures will **delay** vaccination:

- Participant has current febrile illness (body temperature equal or greater 38.0°C) or other acute illness within 48 hours prior vaccination.
- Receipt of any vaccine within 30 days prior to study intervention, with the exception of the seasonal influenza vaccine. Participants will be encouraged to receive this vaccination at least 7 days before or after their study vaccine.
- Antipyretics received within 6 hours prior to vaccination.

Use of any other medications or non-drug therapies is not restricted.

Additionally, medications that are not permitted prior to study enrolment, resulting in exclusion from the study, are reflected in the exclusion criteria in Section 11.2.

Booster Phase:
During the Booster Phase prior and concomitant medications will be reviewed throughout the study according to the schedule of assessment (section 22.3).

15.5 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), on Day 8, Day 36, Day 106 and Day 208. At both vaccinations visits (Day 1 and Day 22) these data should be recorded prior to vaccination and in addition, pulse rate and blood pressure should 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 should be recorded shortly before discharge from study site (3 hours or respectively, 60 min minutes after vaccination).

Vital sign values are to be recorded on the appropriate eCRF. For each vital sign value, the Investigator will determine whether the value is considered an AE (see definition in Section 15.1.1). If assessed as an AE, the medical diagnosis (preferably), symptom, or sign, will be recorded on the AE CRF. Additional tests and other evaluations required to establish the significance or etiology of an abnormal result, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the Investigator.

Booster Phase:
During the Booster Phase, vital signs will be measured according to the schedule of assessment (section 22.3).

15.6 Physical Examinations

At screening (Visit 0), a physical examination will include, but will not be limited to assessment of height and weight, general appearance, head and neck, eyes and ears, nose and throat, chest, lungs, heart, abdomen, extremities and joints, lymph nodes, skin, and neurological. They will be described as normal or abnormal in the e-CRF

A symptom-driven physical examination will be performed at all study visits except the Screening Visit (Visit 0), i.e. only if the Participant reports a symptom. In this case, a system-based assessment will be performed for a detailed check of the affected body system(s). A symptom-driven examination should also be performed in case the Participant has complaints within the observation time after vaccination (See Section 22.2 and 22.3 for Booster Phase).

Abnormal conditions detected at screening or prior to vaccination at Visit 1 will be recorded as medical history. At all other study visits, if a new abnormal or worsened abnormal pre-existing condition is detected, the condition will be recorded as an AE.

Booster Phase:
During the Booster Phase, a symptom-driven physical examination will be performed according to the schedule of assessment (section 22.3)

15.7 Clinical Laboratory Parameters

Blood and urine samples will be obtained for assessment of clinical laboratory parameters as outlined in the Schedule of Study Procedures and Assessments (see Section 22.2 and 22.3 for Booster Phase). Parameters will be analysed by central laboratories according to the applicable laboratory standard operating procedure (SOP).

For women of childbearing potential, a urine sample and a serum test for pregnancy tests for beta-HCG should be performed at the site using a licensed test (dipstick).

A baseline safety laboratory blood [30.0 mL] and urine sample will be obtained at Visit 0 (screening visit) from all Participants for standard clinical chemistry, haematology, coagulation panel and urinalysis as well as for HIV/HBsAg/HCV testing.

Clinical chemistry (approx. 8.0 mL)	Creatinine, sodium, potassium, calcium, aspartate transaminase (AST), alanine aminotransferase (ALT), alkaline phosphatase, bilirubin and C-reactive protein (CRP).
Haematology panel (approx. 9.0 mL)	Haemoglobin, haematocrit, erythrocyte count, white blood cell (WBC) count, differential WBC count (basophils, eosinophils, lymphocytes, monocytes, neutrophils), platelets, erythrocyte sedimentation rate (ESR).
Coagulation panel (approx. 5 mL)	Small blood coagulation (prothrombin time, activated partial thromboplastin time and fibrinogen).
Urinalysis	Standard urine dipstick for determining pH-value, specific gravity, leucocytes, nitrite, protein, glucose, ketones, urobilinogen, bilirubin, erythrocytes.
HBsAg/ HCV / HIV test (approx. 8.0 mL)	A positive HIV test obtained by enzyme-linked immunosorbent assay (ELISA) will have to be confirmed by a second method [e.g. Western blotting or PCR], at Visit 0 only. No HIV/HBsAg/HCV test needs to be performed if negativity has been established within the last 30 days prior to Visit 0.
Pregnancy test approx. 2.0 mL	A serum pregnancy test will be performed for all female Participants of childbearing potential at the screening visit only and a beta-human chorionic gonadotropin urine pregnancy test will be done prior to vaccination at Visit 1 and Visit 3

Baseline serology will be drawn for detection of antibodies against SARS-CoV-2, HIV, HBV and HCV at the local lab. The results of SARS-CoV-2 tests that were performed up to 7 days before Visit 0 are acceptable. The results of negative HIV tests that were performed up to 30 days before Visit 0 are acceptable. A positive HIV test obtained by ELISA will have to be confirmed by a second method (e.g. Western blot or PCR) [blood (for all tests): 5 mL]. In addition, an HLA typing test will be done at Screening (20 mL)

Laboratory values will be evaluated according to the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (FDA). For the individual toxicity criteria refer to section 22.4.

Laboratory assessments for which no severity grading is described in section 22.4 are graded as described in Section 15.2.1.1 upon the Investigator's judgement.

The Investigator's assessment of each abnormal laboratory value, including its clinical significance, is to be recorded in the eCRF:

- Abnormal laboratory assessments that are considered clinically relevant, in the opinion of the Investigator, need to be documented as unsolicited AEs and assessed further for severity according to the toxicity grading scale provided in Section 22.4, causality and other assessments done for unsolicited AE (see Section 15.2.1).

- Abnormal laboratory assessments that are considered a symptom of an underlying AE or part of a syndrome that is reported as AE (e.g. presence of blood cells in urine in a person diagnosed with urinary tract infection) do NOT additionally need to be documented as unsolicited AE, but a respective comment should be added to the underlying AE.

Additional tests and other evaluations required to establish the significance or aetiology of an abnormal laboratory result or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the Investigator.

Booster Phase:
During the Booster Phase, clinical laboratory parameters will be assessed according to the schedule of assessment (section 22.3).

15.8 Saliva Samples

Saliva samples will be taken from ALL Participants at the time points indicated in the Schedule of Procedures (section 22.3) for future investigation of mucosal immune responses to VLA2001.

Booster Phase:
During the Booster Phase, saliva samples will not be collected in line with the schedule of assessment (section 22.3).

15.9 Case Definitions

A COVID-19 case is defined as follows:

Virologically (SARS-CoV-2 positive) confirmed SARS-CoV-2 infection with one or more of the following symptoms listed below:

- Fever or chills
- Persistent of cough, as defined by NHS, as a lot of coughing for more than 1 hour, or three or more coughing episodes in 24 hours. If the participant usually has a cough, it may be worse than usual.
- Shortness of breath or difficulty breathing

- Fatigue
- Muscle or body aches
- Headache
- New loss of taste or smell
- Sore throat
- Congestion
- Nausea or vomiting (more than one episode and/or persisting)
- Diarrhoea

With the exception of fever, shortness of breath, or difficulty breathing, the symptom must be present for 2 or more consecutive days.

Cases are defined by laboratory confirmation of SARS-CoV-2 and signs/symptoms/examinations that occur within 14 calendar days of the initial symptom(s).

A case of **severe COVID-19** is defined as follows:

Virologically confirmed SARS-CoV-2 infection with any of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, $SpO2^{x}$ ≤ 93% on room air at sea level or PaO2/FiO2 < 300 mm Hg).
- Respiratory failure (defined as needing high-flow oxygen, non-invasive ventilation, mechanical ventilation or extra corporal membrane oxygenation).
- Evidence of shock (systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, or requiring vasopressors).
- Significant acute renal, hepatic, or neurologic dysfunction.
- Admission to an intensive care unit.
- Death.

[x] Oximetry parameters: SpO2=oxygen saturation; PaO2=partial pressure of oxygen; FiO2=fraction of inspired oxygen

15.10 Adverse Events of Special Interest

Enhanced respiratory disease has been reported in animal models for SARS-CoV-1 vaccines. Although several NHP studies for SARS-CoV-2 vaccines including inactivated vaccines showed no evidence of enhanced disease, disease enhancement remains a theoretical safety concern. Therefore, COVID-19 manifestations and complications associated with COVID-19 (such as but not limited to pneumonia, neurological or vascular complications, severe pneumonia, severe neurological or vascular events, acute respiratory distress syndrome, renal complications, sepsis, septic shock, death) will be closely monitored as AESIs. In addition, because the vaccine contains a relatively novel adjuvant (CpG 1018) for which immune-mediated disorders are considered AESI (Munoz et al, 2020), those will also receive particular attention. **All AESIs will be treated as medically significant and will therefore be treated as SAEs.** A list of AESIs can be found in Annex 22.5.

15.11 Adverse Event Reporting Procedures

All AEs will be reported from the time a signed and dated informed consent form (ICF) is obtained until the end of the study/early withdrawal. Clinically relevant medical events not meeting the above criteria and occurring between ICF signature and the first vaccination will be collected on the medical history electronic case report form (eCRF) page as pre-existing conditions. The sponsor will evaluate any safety information that is spontaneously reported by an Investigator beyond the time frame specified in the protocol. All AEs will be followed until resolution or until clinically stable.

15.11.1 Serious Adverse Event

Any SAE should be reported via the Safety Gateway within EDC-system within 24 hours after the Investigator has become aware of the event.

Under certain circumstances the initial notification could be done by phone, but nevertheless a written SAE Report Form must be submitted to the Safety Officer within 24 hours (see Section 2).

The study centre will be provided with specific reporting procedures. SAEs will be entered into the SAE *eCRF* page using a recognized medical term or diagnosis that accurately reflects the event. All identified patient's documents supporting the SAE should be sent to the CRO as soon as they are requested by the Medical Monitor/Drug Safety Officer by e-mail (preferable) or by fax using the contact information on Page 3. Fatal or life-threatening SAEs that the Investigator suspects are related to the study vaccine should be telephoned to the local Medical Monitor immediately upon the Investigator's awareness of the event.

All SAEs are reported to the Sponsor for the entire study period and for 30 days after the last visit for each participant.

SAE term should represent diagnosis. Only in case no diagnosis can be identified, each symptom should be reported separately.

Medical or diagnostic procedures due to an underlying disease or symptom are not considered an AE but a consequent measure following an AE. A correct SAE report will therefore have to specify the disease or symptom as the reportable AE and the medical or diagnostic procedure as action taken.

In addition, expedited and periodic reporting to Competent Authorities and ECs will be performed in accordance with local requirements. Further reporting details can be found in the study-specific SAE procedure which is in accordance with respective EU requirements, ICH GCP, national laws and site-specific requirements. Serious adverse events that are considered as probably or possibly related and additionally are unexpected need to be reported according to the requirements for suspected unexpected serious adverse reactions (SUSARs).

Serious adverse event reports will be reviewed by the study site's physician, the Safety Officer, the study medical monitor, the Sponsor and the independent DSMB.

All AESIs will be treated as medically significant and will therefore be treated as SAEs. Thus, SAE reporting procedures are also to be applied for AESIs.

Beyond study end, SAEs that are fatal events, life-threatening or suspected to be related to study treatment will be followed up until 6 months after the last vaccination of the respective Participant.

15.11.2 Pregnancy

The risk of maternal to foetal transmission of SARS-CoV-2 during pregnancy cannot be excluded. Thus, women must not become pregnant during the first 3 months post-vaccination until Visit 5 (Day 106) as well as the first 3 months after the Booster vaccination.

Reporting requirements start with administration of the vaccination until study completion (or ET Visit). All pregnancies that occur during the clinical study period will be followed-up for 3 months after delivery or termination of the pregnancy. Any effect on either mother or foetus should be determined. A pregnancy which led to a congenital anomaly/birth defect must be followed-up by the Investigator longer or until resolution or stabilization. Duration of prolonged follow-up will be decided on an individual basis and in accordance with the Sponsor. The Investigator will prepare a narrative on the course of the pregnancy and the outcome.

The Investigator should report pregnancies within 24 hours of being notified using the Pregnancy Report Form. Reporting procedures are similar to SAE reporting procedures (contacts and processing), although a pregnancy is not considered an SAE.

If a seriousness criterion applies in addition to the pregnancy (e.g. hospitalisation, congenital anomaly/birth defect) the pregnancy qualifies as an SAE. In such case a Pregnancy Report Form **and** an SAE Report Form must be filled out.

15.11.3 Data Safety Monitoring Board

An independent DSMB, consisting of experts that will be selected based upon their expertise in infectious diseases (preferably clinical experience with COVID-19) vaccines clinical research and/or clinical medicine, will be utilised in this study to provide independent monitoring of safety data/issues during the course of the study and make recommendations to the Sponsor regarding further conduct of the study, further vaccinations in the study and/or protocol modifications to be installed for safety reasons. A DSMB charter including a detailed description will be prepared.

Responsibilities of the DSMB

- Review of accrued safety data of the 15 sentinel Participants including safety data at least 3 days post vaccination of the high dose group to decide whether it is safe to proceed with recruitment.
- Review of accrued safety data of the first 60 randomised Participants (overall 20 Participants per dose group) including safety data at least 7 days post vaccination.
- Review of any case reports of SAEs/AESIs on an ad-hoc basis.
- Periodically review unblinded listings and summary tabulations of SAEs, deaths, solicited AEs, unsolicited AEs and AEs leading to withdrawal from further vaccinations.
- All cases of COVID-19 and severe COVID-19 will be assessed by the Sponsor and presented to the DSMB for adjudication against the case definitions.
- Participate in ad-hoc DSMB reviews initiated if enrolment is interrupted by the principal Investigator, the Sponsor or the medical monitor at the CRO for any safety reasons, or if a pre-specified study stopping rule applies.

The DSMB can issue a recommendation to stop the study during ad-hoc DSMB meetings, or to discontinue a treatment group, e.g. in response to an excess rate of AEs with the same suspected underlying pathological mechanism.

Booster phase:
During the Booster Phase, a scheduled DSMB review will be performed once all vaccinated Participants have completed their Visit 7.

15.11.4 Sponsor

Listings of available blinded safety data will be closely reviewed by the Sponsor to identify any potential safety concerns until the last Participant reaches Day 36 and during the Booster Phase.

15.11.5 Investigator

To ensure information exchange on safety across sites, Investigators will be provided with safety information pertaining to all severe (Grade 3) AEs and all SAEs reported in the eCRF.

16. STATISTICS

16.1 Sample Size and Power Calculations

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.

Booster Phase:
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 Participants.

16.2 Datasets and Analysis Cohorts

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, (S)AEs and AESIs. All analyses based on the SAS will be carried out using the actual treatment received.

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 allocated to, rather than by the actual treatment they received.

Per-Protocol Analysis Set (PPAS)

The Per-Protocol Analysis Set (PPAS) will consist of the FAS population excluding Participants that meet one of the following criteria, which possibly have an impact on the immunogenicity read-out:

- Participants with less than two vaccinations.
- Participants who received the wrong study medication.
- Participants who fulfilled exclusion criteria

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.

16.3 Handling of Missing, Unused, and Spurious Data

All immunogenicity analysis will be based on observed values. Missing values will neither be replaced nor estimated. For missing data in AE evaluation (e.g. severity information) a worst case approach will be applied.

16.4 Methods of Analysis

A Statistical Analysis Plan (SAP) will be provided describing in more detail, how the study results will be evaluated. The SAP will be finalized prior to the Blind Data Review Meeting for Part A analysis

Data will be summarized by treatment group and, where appropriate, by visit and SARS-CoV-2 baseline serostatus. Descriptive statistics (number of observations, mean, standard deviation, minimum, median, and maximum) will be provided for continuous variables (e.g. age and weight). Frequency counts and percentages will be presented for categorical variables (e.g. gender).

All data exclusions, including premature terminations, will be detailed and tabulated. Data listings will include enrolled Participants.

Baseline characteristics including demographic variables, medical and vaccination history and concomitant medications will be subject to descriptive analyses.

AEs and medical history will be coded using the MedDRA coding dictionary. Concomitant medications (including vaccinations) will be coded using the WHO Drug Dictionary.

More detailed criteria to identify Participants in each analysis set, other research questions of interest not covered in this protocol, the definition of endpoints and details of their calculation, as well as further details on how to deal with missing, unused and spurious data will be covered in the SAP. If a change of the planned analyses is considered necessary after protocol finalization, this will be described and justified in the SAP. If a change is made after the statistical analysis has been performed, this will be described and justified in the CSR.

16.4.1 Primary Safety Endpoint

The number and percentage of Participants with solicited local and systemic AEs within 7 days after each and after any vaccination will be presented. Differences between the treatment groups will be assessed for significance using Fisher's exact test, a significant overall test will be amended by pair-wise tests.

This analysis will be repeated stratified by baseline SARS-CoV-2 serostatus.

16.4.2 Primary Immunogenicity Endpoint

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

Therefore, GMTs and GMT ratios will be estimated by applying an analysis of variance (ANOVA) including the factor treatment group and study site. This will be done using log10 transformed data and taking the anti-log of the resulting point estimates for the least squares means, least squares means differences and the corresponding 95% CIs. Tukey's HSD test will be applied for pair wise comparisons.

16.4.3 Secondary Endpoints

16.4.3.1 Secondary Safety Endpoints

The number and percentage of Participants with unsolicited AEs (including those with clinically relevant laboratory parameter changes), related AEs, AESIs and SAEs will be presented for each study arm, overall, by system organ class/preferred term and by severity. Differences between study groups will be assessed for significance using Fisher's exact (Fisher-Freeman-Halton) test, whereby a significant overall test will be amended by pair-wise tests, and 95% confidence interval (CI) will be presented for all AE rates.

The number and percentage of Participants with abnormal laboratory parameters will be presented for each study arm, overall and by parameter.

Further details will be provided in the Statistical Analysis Plan (SAP).

All analyses of safety data will be based on the SAS.

16.4.3.2 Secondary Immunogenicity Endpoints

Secondary immunogenicity analysis will include the comparison of the GMTs as well as comparison of geometric mean fold increase (GMFI) between study groups on other study days. ANOVA models as described for the primary immunogenicity endpoint will be applied.

Seroconversion rates for various study days as well as rates of Participants reaching certain fold-increase will be compared between the study groups using Fisher's exact (Fisher-Freeman-Halton) test, whereby a significant overall test will be amended by pair-wise tests, and 95% confidence intervals will be calculated. Immunogenicity analysis will be repeated stratified by serostatus for SARS-CoV-2 at screening.

Immunogenicity analysis will generally be based on the PPAS. Immunogenicity analysis conducted on the FAS will be defined in the SAP.

16.4.4 Exploratory Endpoints

Results of the cellular immune response will be analysed descriptively by treatment group.

16.5 Planned Data Analysis of the Study

The following data analyses will be performed:

- Part A includes safety and immunogenicity data after all Participants have completed Visit 4 (Day 36).
- Part B includes safety and immunogenicity data after all Participants have completed Visit 6 (Day 208).
- An additional data analysis will be performed during part B after all Participants have completed Visit 5 (Day 106)
- Part C includes Visits 7 to 10. An analysis of Part C will be done when all participants have completed visit 9.
- Final analysis will be done when all participants have completed the last visit (visit 10)

Individual study parts will be analysed sequentially.

Part A analysis will be performed once the last Participant has completed Day 36 (Visit 4) and will comprise the primary immunogenicity and safety endpoints; the study will be unblinded at this time. Part B analysis will be performed once the last Participant has completed Day 208 (Visit 6).

16.6 Clinical Study Report

Interim Clinical Study reports will be published after part B and part C. A final Clinical Study Report will be published upon availability of all data.

17. ETHICS AND REGULATORY ASPECTS

17.1 Compliance Statement

This study will be conducted in accordance with this protocol, current ICH GCP guidelines, Declaration of Helsinki, and with the applicable national and local regulatory requirements.

17.2 Ethics Committee and Regulatory Authorities

Before enrolment of healthy volunteers into this study, the protocol, informed consent form, any promotional material/advertisements, and any other requested information will be reviewed and approved/given favourable opinion by the EC and applicable regulatory authorities in accordance with local requirements. The study will commence only upon the Sponsor's receipt of approval/favourable opinion from the EC.

If the protocol and/or any other information given to the Participant is/are amended, the revised document(s) will be reviewed and approved/given favourable opinion by the EC and applicable regulatory authorities in accordance with local requirements, where applicable. The protocol amendment will only be implemented upon the Sponsor's receipt of approval. Amendments that are intended to eliminate an apparent immediate hazard to Participants may be implemented prior to receiving EC and authority approval. However, in this case, approval must be obtained as soon as possible after implementation.

17.3 Participant Information and Informed Consent

It is the Investigator's responsibility to obtain freely given, written, informed consent from the Participant before the Participant is exposed to any study-related procedures, including screening tests for eligibility.

The informed consent form will include a comprehensive explanation of the proposed treatment without any exculpatory statements, in accordance with the elements required by ICH GCP and applicable regulatory requirements. Volunteers will be allowed sufficient time to consider participation in the study after having the nature and risks of the study explained to them. By signing the informed consent form, volunteers agree that all evaluations required by the study will be completed, unless they withdraw voluntarily or are terminated from the study for any reason.

The Investigator will explain that the Participants are completely free to refuse to enter the study or to withdraw from it at any time, without any prejudice and need for justification. The Participants will be informed that representatives of the Sponsor and health authority inspector may review their source records, and that these persons are bound by confidentiality obligations.

The Participant will be given a copy or a second original of the ICF. An original of the signed

and dated ICF must be retained in the site's records and is subject to inspection by representatives of the Sponsor or representatives from regulatory agencies.

The Sponsor will provide to the Investigator in written form any new information that significantly bears on the Participants' risks associated with study vaccine exposure. The informed consent form will be updated, if necessary. This new information and/or revised informed consent form, which has been approved by the applicable EC and regulatory authorities, will be provided by the Investigator to the Participants who consented to participate in the study.

18. QUALITY CONTROL AND QUALITY ASSURANCE

18.1 Source Data and Records

Source data are defined as all information related to clinical findings, observations or other activities in the study, captured in original records or certified copies of original records. The Investigator will permit study-related monitoring, audits, EC review and regulatory inspections, by providing direct access to source data/records. Source records should be preserved for the maximum period of time required by local regulations.

Source data entries must be made in accordance with local requirements. Signed and dated copies of the laboratory result reports must be kept within the Participant's source data file.

For data collected via the electronic Participant diary (e-Diary), the e-Diary is regarded as source document.

18.2 Investigator's Responsibility

The Investigator will comply with the protocol (which has been approved/given favourable opinion by the EC), ICH GCP, and applicable regulatory requirements. The Investigator is ultimately responsible for the conduct of all aspects of the study at the study site and verifies by signature the integrity of all data transmitted to the Sponsor. The term 'Investigator', as used in this protocol and in study documents, refers to the Investigator or authorized study personnel whom the Investigator has designated to perform certain duties. Sub-Investigators or other authorized study personnel are eligible to sign for the Investigator, except where the Investigator's signature is specifically required.

18.3 Training

The study monitor will ensure that the Investigator and study site personnel understand all requirements of the protocol, the investigational status of the vaccine, and his/her regulatory responsibilities as an Investigator. Training may be provided at an Investigator's meeting, at the study site, web-based, and/or by instruction manuals. In addition, the study monitor will

be available for consultation with the Investigator and will serve as the liaison between the study site and the Sponsor.

18.4 Monitoring

A designated monitor will check electronic system data and source data at regular intervals throughout the study to verify completeness, accuracy and consistency of the data, protocol adherence, and adherence to GCP guidelines. The monitor will work and perform Source Data Verification according to the Monitoring Plan. The Investigator will cooperate with the monitor to ensure that any discrepancies identified are resolved.

18.5 Audit and Inspection

Upon request, the Investigator will make all study-related source data and records available to a qualified quality assurance auditor mandated by the Sponsor or to regulatory inspectors. The main purposes of an audit or inspection are to confirm that the rights and welfare of the Participants have been adequately protected, and that all data relevant for the assessment of safety and efficiency of the investigational product have appropriately been reported to the Sponsor.

18.6 Non-Compliance with the Protocol/Deviations from the Protocol

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

18.7 Confidentiality of Participant's Data

The Investigator will exercise all reasonable precautions within the constraints of the applicable regulatory requirements to maintain the confidentiality of Participants' identities. On exported electronic source data or any other documents submitted to the Sponsor, Participants will only be identified by Participant number. Documents not for submission to the Sponsor, e.g. Participant identification log and original ICF, will be maintained by the Investigator in strict confidence.

19. DATA HANDLING AND RECORD KEEPING

19.1 Information of Investigators

An Investigator Brochure (IB) containing all important data relating to the safe use of the IMP will be supplied to the Investigator prior to study start.

The Investigator will be kept informed on new relevant safety data as the study proceeds.

19.2 Electronic Case Report Forms

19.2.1 Data Recorded Directly on Case Report Forms

An eCRF will be used for this study. Data will be recorded directly onto source documents before documentation in the eCRF.

19.2.2 Electronic Case Report Form Entries

Electronic case report form entries and corrections will only be performed by study site staff authorized by the Investigator. Each user is informed of the clinical study's web-site internet address and is allocated to a user account with personal password to access the confidential website. The personal password must be kept confidential and must only be used by the person to whom it was assigned. For additional authorized users at the site, a new user account must be requested to ensure that each entry/change can be allocated to the person who performed the entry/change.

All visit data need to be recorded in the eCRF database as soon as possible after each study visit, no later than 1 business day after data have been collected.

19.2.3 Changes to Electronic Case Report Form Data

Corrections may be requested as follows:

- Investigators' responses are checked as they are entered and are rejected if they do not fulfil quality criteria. A message will specify the type of error or syntax error and assist in its correction.
- If required, the CRA can ask for information to be corrected during monitoring.
- Computerized data-check programs and manual checks will identify clinical data discrepancies for resolution. Corresponding queries will be created within the data capturing system and the site will be informed about new issues to be resolved on-line.

All discrepancies will be solved on-line directly by the Investigator or by authorized staff.

Corrections of eCRF data may be performed by authorized staff only. The person performing the changes in the eCRF is required to confirm electronically the changes made.

19.2.4 Electronic Case Report Form Entry Validation

The Investigator will thoroughly review the data on the eCRF and will finally certify the contents of the eCRF by electronic signature after completion of each Participant. If a correction is made to the eCRF data after the Investigator's final approval, the certification must be repeated after the changes have been performed.

19.2.5 Data Collection

All visits and assessments are entered into an interactive form. Electronic case report forms will be source document verified following guidelines established before study onset and detailed in the Monitoring Plan. The study database will be maintained. Details of eCRF handling are provided in a study specific eCRF manual.

19.3 Coding of Adverse Events, Drugs and Diseases

After data entry, AEs and medical history will be coded according to the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). The same version will be applied to all study parts. Previous and concomitant medication and vaccines will be coded according to the latest version of the WHO Drug Reference List and Anatomical Therapeutic Chemical Classification System.

19.4 Investigator File

19.4.1 Maintenance

The Investigator will maintain complete and accurate study documentation in a separate file (i.e. Investigator File) provided during the initiation visit. The Investigator is responsible for maintaining complete, up to date and accurate study records to enable the conduct of the study to be fully documented. The records should include the clinical protocol as well as any amendments, study approval letters, all original ICFs, drug dispensing and accountability logs and all relevant correspondence pertaining to the study.

19.4.2 Archiving and destruction

All study-related documents should be kept by the Investigator for the maximum period of time required by local regulations. No study document should be destroyed without prior written agreement between the Investigator and the Sponsor. Should the Investigator elect to assign the study documents to another party, or move them to another location, the Sponsor must be notified.

19.4.3 Provision of Additional Information

On request, the Investigator will supply the Sponsor with additional data relating to the study or copies of relevant source records, duly anonymized. In case of particular issues or

governmental queries, it is also necessary to have access to the complete study records, provided that the Participant's confidentiality is protected in accordance with applicable regulations.

20. PUBLICATION POLICY

All results generated in this study will be considered to be strictly confidential. The Investigator may not submit the results for publication or presentation without prior written permission of the Sponsor. Authorship for any publication will be determined in mutual agreement. Within the scope of publication, co-authorship may be offered, at the sole discretion of the Sponsor, on a case-by-case basis taking scientific contribution into consideration. This is according to uniform requirements for manuscripts submitted to biomedical journals proposed by the International Committee of Medical Journal Editors.

21. LIABILITIES AND INSURANCE

In case of any damage or injury occurring to a Participant in association with the participation in the study, insurance has been contracted.

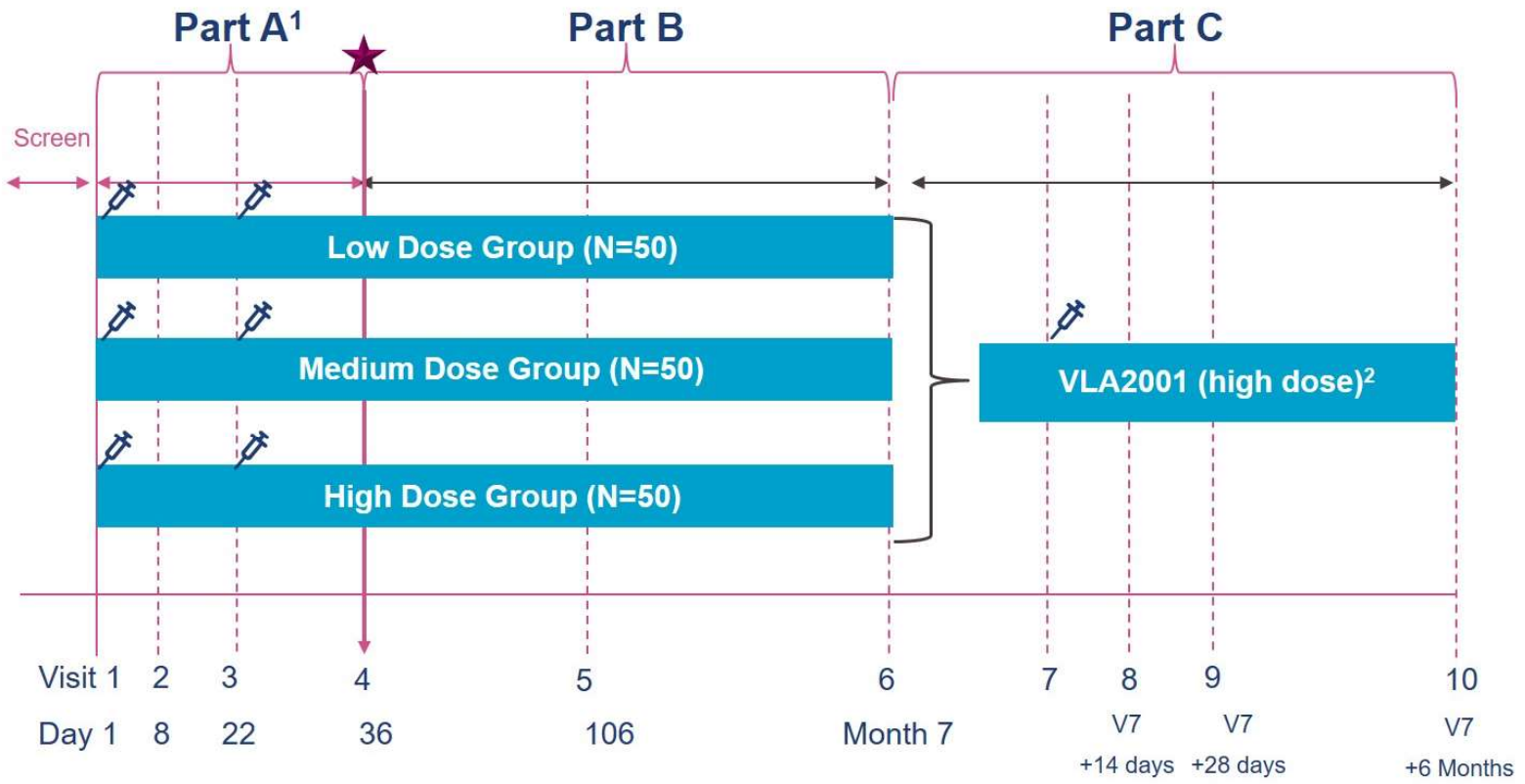
The name, address and the insurance policy number will be given to both the Investigator prior to enrolment. Moreover a copy of the insurance conditions will be filed on site.

The Investigator is responsible for dispensing the investigational product according to this protocol, and for its secure storage and safe handling throughout the study.

22. SUPPLEMENTS

22.1 Study Flow Chart

Figure 1 Study Design for First-in-Human Clinical Study VLA2001-201



[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.

22.2 Schedule of Study Procedures and Assessments

The investigator may schedule visits (unplanned visits in addition to those listed in the table, in order to conduct evaluations or assessments required to protect the well-being of the participant

Procedures/Assessments	**Visit 0 Scree-ning** (Day -7 to Day 0)	**Visit 1** [l] Day 1	**Safety phone calls for sentinel group***	**Visit 2** Day 8 (+/- 1d)	**Visit 3** Day 22 (+/- 2d)	**Visit 4** Day 36 (+/- 2d)	**Visit 5** Day 106 (+/- 7d)	**Visit 6** Day 208 M7 (+/- 14d)	**Unplanned COVID-19 Illness Visit**	**Ad hoc Safety Call** in case of e-Diary entry (Grade 3 AE or SAE)	**Visit ET**
Informed consent [a]	X										
Inclusion/Exclusion criteria check	X	X (Review)									
Delay criteria check		X			X						
Demographics [b]	X										
Medical history [c] (including vaccination history)	X	X (Update)									
Physical/Symptom-driven examination [d]	X	X		X	X	X	X	X	X		X
Prior/Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Vital signs [e]	X	X			X		X	X			X
Baseline serology [f] 30 mL]	X										
Serum/Urine Pregnancy test [g] [2 mL]	X	X			X						
Safety labs [h] [10 mL]	X			X	X	X		X	X		X [m]
Randomisation		X									
Immunogenicity sample [i] [10 mL]		X		X	X	X	X	X	X		X
Blood for PBMC Isolation [j] [50 mL]		X				X		X			
Saliva Sample [k]	X	X		X	**X**	X	X	X	X		X
Blood for passive transfer studies [n] [50 mL]						X					
VACCINATION		**X**			**X**						
Electronic Participant Diary		E	R	R	R/E	R				R	R
AE/AESI/SAE Assessment		X	X	X	X	X	X	X	X	X	X

(S)AE=(serious) adverse event; AESI=adverse event of special interest; PBMC=peripheral blood mononuclear cells; R=review

*Safety call sentinel group: first Participant per dosing group approx. 24 hours, Participants 2 to 5 approx. 48 hours after vaccination

[a] Occurs at enrolment before Screening.
[b] Demographics include year of birth, height, weight, BMI, gender, race and ethnicity.
[c] Symptoms noted at Visit 1 (prior to first vaccination) are not considered AEs but will be recorded as medical history.
[d] At the screening visit, 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 symptom is reported by the Participant, an assessment of the affected body system(s) will be performed.
[e] **Vital signs** will include systolic and diastolic blood pressure and pulse rate while seated and at rest, and body temperature measured orally before vaccination. In addition, after an observation period of 30 minutes (60 minutes for the 15 sentinel Participants) following vaccination pulse rate as well as blood pressure while seated and at rest will again be assessed.
[f] A **baseline serology** will be drawn for detection of antibodies against SARS-CoV-2, HIV, HBV and HCV at the local lab. The results of SARS-CoV-2 tests that were performed up to 7 days before Visit 0 are acceptable. The results of negative HIV tests that were performed up to 30 days before Visit 0 are acceptable. A positive HIV test obtained by ELISA will have to be confirmed by a second method (e.g. Western blot or PCR) [blood (for all tests): 5 mL].
[g] A serum **pregnancy test** will be performed for all female Participants of childbearing potential at the screening visit only and a **urine** pregnancy test will be done prior to vaccination at Visit 1 and Visit 3 [blood: 2 mL].
[h] Baseline **safety labs** for standard **clinical chemistry** (i.e. creatinine, sodium, potassium, calcium, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin, CRP), **haematology** (i.e. haemoglobin, haematocrit, erythrocyte count, white blood count, differential white blood cell count, platelets, erythrocyte sedimentation rate , **coagulation panel** (i.e. prothrombin time, aPTT, fibrinogen) [EDTA blood: 30 mL] and **urinalysis** (i.e. pH, specific gravity, leucocytes, nitrite, protein, glucose, ketones, urobilinogen, bilirubin, erythrocytes.
[i] An **immunogenicity sample** will be drawn [10mL] for SARS-CoV-2-specific neutralizing antibody titre evaluation and ELISA testing, development or performance of further assays related to development of this vaccine candidate and/or retrospective safety analysis if deemed necessary by the Data Safety Monitoring Board upon clinical indication or on demand if requested later by regulatory authorities.
[j] 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. PBMCs may also be used for further research activities considered relevant to SARS-CoV-2, e.g., HLA typing.
[k] Saliva samples will be obtained from all Participants for future investigation of mucosal immune responses to VLA2001.
[l] All procedures/assessments (apart from e-Diary explanation and AE assessment) occur prior to vaccination (unless stated otherwise).
[m] A safety lab sample will be obtained if early termination occurs before Day 36 (Visit 4).
[n] A blood sample [approx. 50mL] will be collected to isolate serum from all Participants consenting to the additional blood volume for studies to support the establishment of a robust clinical endpoint for identification of neutralizing antibody levels associated with protection from COVID-19.

Please note:
- *Due to local requirements, medical history should be checked with Participants' medical records (GP / hospital) prior Day 1*

22.3 Schedule of Study Procedures and Assessments for the Booster Phase

The investigator may schedule visits (unplanned visits in addition to those listed in the table, in order to conduct evaluations or assessments required to protect the well-being of the participant

Procedures/Assessments	**Visit 6** Day 208 M7 (+/- 14d)	**Visit 7** [i] Planned for mid-end September 2021 for all participants (+/- 14d)	**Visit 8** 14 days after booster vaccination (Visit7) (+/- 2d)	**Visit 9** 28 days after booster vaccination (Visit7) (+/- 7d)	**Visit 10** Safety follow-up call 6 months after booster vaccination (Visit 7) (+/- 14d)	**Unplanned COVID-19 Illness Visit**	**Ad hoc Safety Call** in case of e-Diary entry (Grade 3 AE or SAE)	**Visit ET**
Informed consent	X							
Inclusion/Exclusion criteria check	X	X						
Delay criteria check		X						
Symptom-driven physical examination [a]	X	X	X	X		X		X
Prior/Concomitant medications	X	X	X	X	X	X	X	X
Vital signs [b]	X	X						
Urine Pregnancy test [c]		X						
Safety labs [d] [10 mL]	X	X	X	X		X		X
Immunogenicity sample [e] [10 mL]	X	X	X	X		X		X
Blood for PBMC Isolation [f] [50 mL]	X	X	X					
Saliva Sample [k]	X							
VACCINATION		X						
Electronic Participant Diary		E	R	R			R	R
AE/AESI/SAE Assessment	X	X	X	X	X	X	X	X

(S)AE=(serious) adverse event; AESI=adverse event of special interest; PBMC=peripheral blood mononuclear cells; R=review

[a] **A symptom-driven physical examination** will be performed, i.e. only in case symptom is reported by the Participant, an assessment of the affected body system(s) will be performed.

[b] **Vital signs** will include systolic and diastolic blood pressure and pulse rate while seated and at rest, and body temperature measured orally before vaccination. In addition, after an observation period of 30 minutes following vaccination pulse rate as well as blood pressure while seated and at rest will again be assessed.

[c] A **urine** pregnancy test will be done prior to vaccination at Visit 7.

[d] **Safety labs** for standard **clinical chemistry** (i.e. creatinine, sodium, potassium, calcium, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin, CRP), **haematology** (i.e. haemoglobin, haematocrit, erythrocyte count, white blood count, differential white blood cell count, platelets, erythrocyte sedimentation rate , **coagulation panel** (i.e. prothrombin time, aPTT, fibrinogen) [EDTA blood: 30 mL] and **urinalysis** (i.e. pH, specific gravity, leucocytes, nitrite, protein, glucose, ketones, urobilinogen, bilirubin, erythrocytes.

[e] An **immunogenicity sample** will be drawn [10mL] for SARS-CoV-2-specific neutralizing antibody titre evaluation and ELISA testing, development or performance of further assays related to development of this vaccine candidate and/or retrospective safety analysis if deemed necessary by the Data Safety Monitoring Board upon clinical indication or on demand if requested later by regulatory authorities.

[f] A blood sample [approx. 50mL] will be collected to isolate PBMCs from all Participants for future investigation of cellular immune responses to VLA2001. PBMCs may also be used for further research activities considered relevant to SARS-CoV-2, e.g., HLA typing.

[k] Saliva samples will be obtained from all Participants for future investigation of mucosal immune responses to VLA2001.

[i] All procedures/assessments (apart from e-Diary explanation and AE assessment) occur prior to vaccination.

22.4 Toxicity Grading Scale for Abnormal Laboratory Assessments

	Mild (Grade 1) [a]	Moderate (Grade 2)	Severe (Grade 3)	Potentially life threatening (Grade 4) [b,e]
Haematology Parameters				
Haemoglobin (Female) – gm/dL	11.0–12.0	9.5–10.9	8.0–9.4	< 8.0
Haemoglobin (Male) – gm/dL	12.5–13.5	10.5–12.4	8.5–10.4	< 8.5
Haematocrit	Outside normal range [c]			
Erythrocyte count	Outside normal range [c]			
WBC Increase – cell/mm^3	10,800–15,000	15,001–20,000	20,001–25,000	> 25,000
WBC Decrease – cell/mm^3	2,500–3,500 [d]	1,500–2,499	1,000–1,499	< 1,000
Neutrophils Decrease – cell/mm^3	1,500–2,000	1,000–1,499	500–999	< 500
Lymphocytes Decrease – cell/mm^3	750–1,000	500–749	250–499	< 250
Monocytes	Outside normal range [c]			
Eosinophils – cell/mm^3	650–1500[4]	1501–5000	> 5000	Hyper-eosinophilic
Basophils	Outside normal range [c]			
Platelets Decreased – cell/mm^3	125,000 – 140,000 [d]	100,000 – 124,000	25,000–99,000	< 25,000
ESR	Outside normal range [c]			
Clinical Chemistry Parameters				
Creatinine – mg/dL	1.5–1.7 [d]	1.8–2.0	2.1–2.5	> 2.5 or requires dialysis
Sodium – Hyponatremia mEq/L	132–134	130–131	125–129	< 125
Sodium – Hypernatremia mEq/L	144–145 [d]	146–147	148–150	> 150
Potassium – Hyperkalaemia mEq/L	5.1–5.2 [d]	5.3–5.4	5.5–5.6	> 5.6
Potassium – Hypokalaemia mEq/L	3.5–3.6 [d]	3.3–3.4	3.1–3.2	< 3.1
Calcium – Hypocalcaemia mg/dL	8.0–8.4 [d]	7.5–7.9	7.0–7.4	< 7.0
Calcium – Hypercalcaemia mg/dL	10.5–11.0	11.1–11.5	11.6–12.0	> 12.0
AST – increase by factor	1.1–2.5 x ULN	2.6–5.0 x ULN	5.1–10 x ULN	> 10 x ULN
ALT – increase by factor	1.1–2.5 x ULN	2.6–5.0 x ULN	5.1–10 x ULN	> 10 x ULN

	Mild (Grade 1) [a]	Moderate (Grade 2)	Severe (Grade 3)	Potentially life threatening (Grade 4) [b,e]
Alkaline phosphatase – increase by factor	1.1–2.0 x ULN	2.1–3.0 x ULN	3.1– 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1–1.25 x ULN	1.26–1.5 x ULN	1.51–1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1–1.5 x ULN	1.6–2.0 x ULN	2.0–3.0 x ULN	> 3.0 x ULN
CRP	Outside normal range [c]			
Coagulation Factors				
PT – increase by factor	1.0–1.10 x ULN	1.11–1.20 x ULN	1.21–1.25 x ULN	> 1.25 ULN
PTT (aPTT) – increase by factor	1.0–1.2 x ULN	1.21–1.4 x ULN	1.41–1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400–500 [d]	501–600	> 600	–
Fibrinogen decrease - mg/dL	150–200 [d]	125–149	100–124	< 100 or associated with gross bleeding or disseminated intravascular coagulation

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; aPTT=activated partial thromboplastin time; CRP=C reactive protein; ESR=erythrocyte sedimentation rate; FDA=Food and Drug Administration; PT=prothrombin time; SAE=serious adverse event; ULN=upper limit of normal; WBC=white blood cell

[a] In case the laboratory's normal ranges and absolute Grade 1 limits overlap, Grade 1 limits will prevail, i.e. the value will be classified as Grade 1 abnormality even if it is within central laboratory normal ranges. Values between the central laboratory normal ranges and absolute Grade 1 limits will be reported as no abnormality (Grade 0).

[b] The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as potentially life threatening (Grade 4). For example, a low sodium value that falls within a grade 3 parameter (125–129 mE/L) should be recorded as a grade 4 hyponatremia unsolicited AE if the Participant had a new seizure associated with the low sodium value.

[c] As neither the FDA Scale nor the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (December 2004) provide any grading for haematocrit, erythrocyte count, monocytes, Basophils, ESR and CRP, these will only be analysed as 'outside normal range', as determined by central laboratory standards and graded as described in Section 15.2.1.1 upon Investigator's judgement.

[d] Central laboratory values should be adjusted to FDA toxicity grading scale. Specifically, if central laboratory reference range is more stringent than FDA toxicity grading scale the central laboratory values should be reported as no abnormality (Grade 0). Similarly, if laboratory values are within the central laboratory normal reference range, but fall into FDA toxicity grading scale, the values should be reported as indicated by the FDA toxicity grading scale.

[e] Any Grade 4 abnormal laboratory value should be reported as an SAE (see Section 16.1.2).

22.5 Adverse Events of Special Interest

Neuroinflammatory Disorders:	Acute disseminated encephalomyelitis (including site specific variants: eg, non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculomyelitis), anosmia, ageusia, cranial nerve disorders including paralyses/paresis (eg, Bell's palsy), generalized convulsion, Guillain-Barre syndrome (including Miller Fisher syndrome and other variants), immune-mediated peripheral neuropathies and plexopathies (including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy), meningoencephalitis, myasthenia gravis, multiple sclerosis, narcolepsy, optic neuritis, transverse myelitis, uveitis
Musculoskeletal and Connective Tissue Disorders	Antisynthetase syndrome, dermatomyositis, juvenile chronic arthritis (including Still's disease), mixed connective tissue disorder, polymyalgia rheumatic, polymyositis, psoriatic arthropathy, relapsing polychondritis, rheumatoid arthritis, scleroderma (including diffuse systemic form and CREST syndrome), spondyloarthritis (including ankylosing spondylitis, reactive arthritis [Reiter's Syndrome] and undifferentiated spondyloarthritis), systemic lupus erythematosus, systemic sclerosis, Sjogren's syndrome
Vasculitides	Large vessels vasculitis (including giant cell arteritis such as Takayasu's arteritis and temporal arteritis), medium sized and/or small vessels vasculitis (including polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome [allergic granulomatous angiitis], Buerger's disease [thromboangiitis obliterans], necrotizing vasculitis and anti-neutrophil cytoplasmic antibody [ANCA] positive vasculitis [type unspecified], Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis)
Gastrointestinal Disorders	Crohn's disease, celiac disease, liver injury, ulcerative colitis, ulcerative proctitis
Hepatic Disorders	Autoimmune hepatitis, autoimmune cholangitis, primary sclerosing cholangitis, primary biliary cirrhosis
Renal Disorders	Acute kidney injury, autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis,

Cardiac Disorders	Autoimmune myocarditis/cardiomyopathy Acute cardiac injury including: • Microangiopathy • Heart failure and cardiogenic shock • Stress cardiomyopathy • Coronary artery disease • Arrhythmia • Myocarditis, pericarditis
Skin Disorders	Alopecia areata, psoriasis, vitiligo, Raynaud's phenomenon, erythema nodosum, autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis), cutaneous lupus erythematosus, morphoea, lichen planus, Stevens-Johnson syndrome, Sweet's syndrome
Haematologic Disorders	Autoimmune haemolytic anaemia, autoimmune thrombocytopenia, antiphospholipid syndrome, thrombocytopenia Coagulation disorder • Deep vein thrombosis • Pulmonary embolus • Cerebrovascular stroke • Limb ischemia • Haemorrhagic disease
Metabolic Disorders	Autoimmune thyroiditis, Grave's or Basedow's disease, Hashimoto´s thyroiditis, diabetes mellitus type 1, Addison's disease
Other Disorders	Goodpasture syndrome, idiopathic pulmonary fibrosis, pernicious anaemia, sarcoidosis
Immunologic	Enhanced disease following immunization, cytokine release syndrome related to COVID-19 disease
Respiratory	Acute respiratory distress syndrome (ARDS)
Dermatologic	Chilblain-like lesions, single organ cutaneous vasculitis, erythema multiforme
Infection	severe COVID-19 (see Section 15.9)

23. REFERENCES

Arabi YM, Alothman A, Balkhy HH et al. Treatment of Middle East Respiratory Syndrome with a combination of lopinavir-ritonavir and interferon-beta1b (MIRACLE trial): study protocol for a randomized controlled trial. Trials 2018;19:81

Arabi YM, Mandourah Y, Al-Hameed F et al. Corticosteroid therapy for critically Ill patients with Middle East respiratory syndrome. Am J Respir Crit Care Med. 2020;197:757–767

Astuti I, Ysrafil. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): An overview of viral structure and host response. Diabetes Metab Syndr 2020;14(4):407-412

Chaolin H, Yeming W, Xingwang L. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lance. 2020;(395):497–506

Gao Q, Bao L, Mao H et al. Development of an inactivated vaccine candidate for SARS-CoV-2. Science 369(6499):77–81

Guan W, Ni Z, Hu Y et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Eng J Med 2020;382:1708–1720

HEPLISAV-B Summary of product characteristics https://rsc.niaid.nih.gov/sites/default/files/1-14-2-2-package-insert-heplisav-b.pdf (Accessed 28 Aug 2020)

IXIARO Clinical Review Memorandum, 2018 https://www.fda.gov/files/vaccines,%20blood%20&%20biologics/published/Clinical-Review--IXIARO.pdf (accessed 29 Aug 2020)

John Hopkins Resource Center https://coronavirus.jhu.edu/ (accessed 28 Aug 2020)

Li Q, Guan X, Wu P et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med 2020;382(13): 1199–1207

Joshua G. Liang, Danmei Su, Tian-Zhang Song et al. S-Trimer, a COVID-19 subunit vaccine candidate, induces protective immunity in nonhuman primates https://doi.org/10.1101/2020.09.24.311027

Munoz FM, Cramer JP, Dekker CL et al. Vaccine-associated Enhanced Disease: Case Definition and Guidelines for Data Collection, Analysis, and Presentation of Immunization Safety Data. Submitted.

Sinovac Press Release from 13.06.2020; Sinovac Announces Positive Preliminary Results of Phase I/II Clinical Trials for Inactivated Vaccine Candidate Against COVID-19; http://www.sinovac.com/?optionid=754&auto_id=904 (accessed 28 Aug 2020)

Wang D., Hu B., Hu C. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323(11): 1061-1069

Williamson E, Walker AJ, Bhaskaran KJ et al. OpenSAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients.medRxiv2020.05.06.20092999;doi: https://doi.org/10.1101/2020.05.06.20092999

World Health Organisation. Report of the WHO: China Joint Mission on Coronavirus Disease 2019 (COVID-19); 16–24 February 2020. https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf (accessed 28 Aug 2020)

World Health Organization. Draft landscape of COVID-19 candidate vaccines. July 20, 2020 https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines (accessed 28 Aug 2020)

World Health Organisation. A Coordinated Global Research Roadmap: 2019 Novel Coronavirus. 2020 https://www.who.int/blueprint/priority-diseases/key-action/Coronavirus_Roadmap_V9.pdf (accessed 28 Aug 2020)

Xia et al. Effect of an Inactivated Vaccine Against SARS-CoV-2 on Safety and Immunogenicity Outcomes Interim Analysis of 2 Randomized Clinical Trials JAMA 2020; doi:10.1001/jama.2020.15543

Xia et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial Lancet 2020; DOI:https://doi.org/10.1016/S1473-3099(20)30831-8

Yang D, Leibowitz JL. The structure and functions of coronavirus genomic 3' and 5' ends. Virus Res. 2015;206:120–133

Zumla A, Hui DS, Azhar EI, Memish ZA, Maeurer M. Reducing mortality from 2019-nCoV: host-directed therapies should be an option. Lancet. 2020;395:e35–e36

Agrawal AS, Tao X, Algaissi a, et al Immunization with inactivated Middle East Respiratory Syndrome coronavirus vaccine leads to lung immunopathology on challenge with live virus. Hum Vaccin Immunother. 2016;12(9):2351-2356

Hondo-okubo Y, Barnard D, Ong CH, Peng BH; Tseng CT Severe acute respiratory syndrome associated vaccines formulated with delta inulin adjuvants provide enhances protection while ameliorating lung eosinophilic immunopathology. J. Virol. 2015;89(6):2995-3007.

*MHRA Guidance:

https://www.gov.uk/guidance/managing-clinical-trials-during-coronavirus-covid-19#remote-monitoring-for-trials

MHRA Blog:
https://mhrainspectorate.blog.gov.uk/2020/03/12/advice-for-management-of-clinical-trials-in-relation-to-coronavirus/

**HRA Guidance:
https://www.hra.nhs.uk/covid-19-research/covid-19-guidance-sponsors-sites-and-researchers/

Curran J, Dol J, Boulos L, et al. Transmission characteristics of SARS-CoV-2 variants of concern Rapid Scoping Review. medRxiv. Published online January 1, 2021:2021.04.23.21255515. doi:10.1101/2021.04.23.21255515

Tegally H, Wilkinson E, Giovanetti M, et al. Emergence of a SARS-CoV-2 variant of concern with mutations in spike glycoprotein. Nature. Published online 2021. https://doi.org/10.1038/s41586-021-03402-9

Cherian S, Potdar V, Jadhav S, et al. Convergent evolution of SARS-CoV-2 spike mutations, L452R, E484Q and P681R, in the second wave of COVID-19 in Maharashtra, India. bioRxiv. Published online January 1, 2021:2021.04.22.440932. doi:10.1101/2021.04.22.440932

Public Health England. SARS-CoV-2 Variants of Concern and Variants under Investigation in England. Technical Briefing 10. Public Health England; 2021. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/984274/Variants_of_Concern_VOC_Technical_Briefing_10_England.pdf

Bager P, Wohlfahrt J, Fonager J, Albertsen. Increased Risk of Hospitalisation Associated with Infection with SARS-CoV-2 Lineage B.1.1.7 in Denmark. doi:Bager, Peter and Wohlfahrt, Jan and Fonager, Jannik and Albertsen, Mads and Yssing Michaelsen, Thomas and Holten Møller, Camilla and Ethelberg, Steen and Legarth, Rebecca and Fischer Button, Mia Sara and Gubbels, Sophie Madeleine and Voldstedlund, Marianne and Mølbak, Kåre and Skov, Robert Leo and Fomsgaard, Anders and Grove Krause, Tyra, Increased Risk of Hospitalisation Associated with Infection with SARS-CoV-2 Lineage B.1.1.7 in Denmark. Available at SSRN: https://ssrn.com/abstract=3792894 or http://dx.doi.org/10.2139/ssrn.3792894

NERVTAG paper on COVID-19 variant of concern B.1.1.7. GOVUK. Published online 2021. https://www.gov.uk/government/publications/nervtag-paper-on-covid-19-variant-of-concern-b117, http://files/64/nervtag-paper-on-covid-19-variant-of-concern-b117.html %[2021/02/08/18:37:19

Pearson CA, Eggo. Estimates of severity and transmissibility of novel South Africa SARS-CoV-2 variant 501Y.V2. https://cmmid.github.io/topics/covid19/reports/sa-novelvariant/2021_01_11_Transmissibility_and_severity_of_501Y_V2_in_SA.pdf

Jassat W MC. Increased Mortality among Individuals Hospitalised with COVID-19 during the Second Wave in South Africa.; 2021. https://www.medrxiv.org/content/10.1101/2021.03.09.21253184v1

Funk T, Pharris A, Spiteri G, et al. Characteristics of SARS-CoV-2 variants of concern B.1.1.7, B.1.351 or P.1: data from seven EU/EEA countries, weeks 38/2020 to 10/2021. Eurosurveillance.2021;26(16).doi:https://doi.org/10.2807/1560-7917.ES.2021.26.16.2100348

Muik A, Wallisch A-K, Sänger B, et al. Neutralization of SARS-CoV-2 lineage B.1.1.7 pseudovirus by BNT162b2 vaccine–elicited human sera. Science. Published online 2021:eabg6105. https://science.sciencemag.org/content/sci/early/2021/01/28/science.abg6105.full.pdf

Gallais F, Gantner P, Bruel T, et al. Anti-SARS-CoV-2 Antibodies Persist for up to 13 Months and Reduce Risk of Reinfection. medRxiv. Published online January 1, 2021:2021.05.07.21256823. doi:10.1101/2021.05.07.21256823

Graham MS, Sudre CH, May A, et al. Changes in symptomatology, reinfection, and transmissibility associated with the SARS-CoV-2 variant B.1.1.7: an ecological study. Lancet Public Health. 2021;6(5):e335-e345. doi:10.1016/S2468-2667(21)00055-4

Wibmer CK, Ayres F, Hermanus T, et al. SARS-CoV-2 501Y.V2 escapes neutralization by South African COVID-19 donor plasma. Nat Med. Published online March 2021. https://www.ncbi.nlm.nih.gov/pubmed/33654292

Li R, Ma X, Deng J, et al. Differential efficiencies to neutralize the novel mutants B.1.1.7 and 501Y.V2 by collected sera from convalescent COVID -19 patients and RBD nanoparticle-vaccinated rhesus macaques. Cell Mol Immunol. Published online February 2021. https://www.ncbi.nlm.nih.gov/pubmed/33580167

Cele S, Gazy I, Jackson L, et al. Escape of SARS-CoV-2 501Y.V2 variants from neutralization by convalescent plasma. :19. https://www.medrxiv.org/content/10.1101/2021.01.26.21250224v1

Sabino EC, Buss LF, Carvalho MPS, et al. Resurgence of COVID-19 in Manaus, Brazil, despite high seroprevalence. The Lancet. 2021;397(10273):452-455. https://linkinghub.elsevier.com/retrieve/pii/S0140673621001835

Naveca F, Nasciment V, Souza V, et al. Phylogenetic relationship of SARS-CoV-2 sequences from Amazonas with emerging Brazilian variants harboring mutations E484K and N501Y in the Spike protein. Virological. Published online 2021. https://virological.org/t/phylogenetic-relationship-of-sars-cov-2-sequences-from-amazonas-with-emergingbrazilian-variants-harboring-mutations-e484k-and-n501y-in-the-spike-protein/585

SARS-CoV-2 lateral flow antigen tests: evaluation of VUI-202012/01. GOVUK. https://www.gov.uk/government/publications/sars-cov-2-lateral-flow-antigen-testsevaluation-of-vui-20201201/sars-cov-2-lateral-flow-antigen-tests-evaluation-of-vui-20201201, http://files/62/sars-cov-2-lateral-flow-antigen-tests-evaluation-of-vui20201201.html %[2021/02/08/16:54:26

Weekly epidemiological update on COVID-19 - 25 May 2021 Edition 41, published 25 May 2021. https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---25-may-2021.

Harvey, W.T., Carabelli, A.M., Jackson, B. et al. SARS-CoV-2 variants, spike mutations and immune escape. Nat Rev Microbiol (2021). https://doi.org/10.1038/s41579-021-00573-0

Collier, D. A. et al. Sensitivity of SARS-CoV-2 B.1.1.7 to mRNA vaccine-elicited antibodies. Nature https://doi.org/10.1038/s41586-021-03412-7 (2021).

Gupta, R.K. Will SARS-CoV-2 variants of concern affect the promise of vaccines? Nat Rev Immunol 21, 340–341 (2021). https://doi.org/10.1038/s41577-021-00556-5