GlaxoSmithKline Biologicals SA

217741 (CV2 SARS-COV2-002 BST)

A Phase 1, Open-Label, Safety, Reactogenicity, and Immunogenicity Trial of the CV2CoV mRNA Vaccine Against SARS-CoV-2 in Seropositive Adult Participants

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Statistical Analysis Plan

Version 4.0

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VERSION HISTORY

Version	Date	Details
IND Submission Version	30NOV2021	Prepared for IND submission
SAP v2.0	07APR2022	Alignment with Protocol v2.0
SAP v3.0	20JUNE2022	Alignment with Protocol Amendment 2
SAP v4.0	17Apr2023	Updated based on changes to ANCOVA model and prior Covid-19 infection incorporated into immunogenicity and Demography summaries.

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List of Abbreviations

Abbreviation	Definition
Ab	antibody
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
BMI	body mass index
CI	confidence interval
CMI	cell mediated immune
COVID-19	coronavirus disease
CSR	clinical study report
CV2CoV	SARS-CoV-2 improved vaccine (monovalent; targets Wuhan strain [D614])
eCRF	electronic case report form
eDiary	electronic diary
EOS	end of study
FSH	follicle-stimulating hormone
GM	Geometric Mean
GMI	geometric mean increase
GMT	geometric mean titer
ICF	informed consent form
ICS	intracellular staining assay
IgG	immunoglobulin g
IP	investigational product
IRT	interactive response technology
LLOQ	lower limit of quantification
LNP	Lipid nanoparticle
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
NA	not applicable
NAb	Neutralizing antibody
N protein	nucleocapsid protein
NT50	50% neutralization titer
PBMC	peripheral blood mononuclear cell
PP	Per protocol

Abbreviation	Definition
PT	Preferred Term
RBD	receptor-binding domain
RT-PCR	reverse transcription polymerase chain reaction
S protein	spike protein
SAP	statistical analysis plan
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOC	system organ class
SOE	schedule of events
SRT	Safety Review Team
Th	T helper
ULOQ	Upper limit of quantification
WHO	World Health Organization
WHODRUG	World Health Organization Drug Dictionary
WOCBP	Women of Childbearing Potential
WT	wild type

1. Introduction

The COVID-19 pandemic caused by the SARS-CoV-2 virus was declared by the WHO on 11 March 2020 (WHO 2020). As of 11 November 2021, more than 250 million cases have been reported worldwide, leading to more than 5.0 million deaths (WHO 2021). To date, there are several vaccines available, licensed, under emergency use authorizations or conditional approvals using different technologies. All available vaccines utilize antigens from the ancestral Wuhan strain (D614; wild-type, hereafter referred to as "WT").

This is a Phase 1 first-time-in-human study designed to evaluate the safety, reactogenicity, and immunogenicity of the GSK-CureVac second-generation CV2CoV vaccine to prevent COVID-19 disease caused by existing and new emerging strains of the SARS-CoV-2 virus. This study will evaluate the CV2CoV vaccine in a booster vaccination setting.

CureVac developed a first-generation mRNA vaccine (CVnCoV) using WT, for which vaccine safety and efficacy are being evaluated (NCT04652102). To continue addressing current vaccine needs for further protection against SARS-CoV-2, GSK and CureVac are collaborating to develop CV2CoV mRNA second-generation vaccine based on CureVac's mRNA vaccine platform. The CV2CoV vaccine is based on a new mRNA backbone that features targeted optimizations designed to improve intracellular mRNA stability and translation for increased and extended protein expression. These optimizations potentially allow for strong immune responses at low doses, which are intended to support the development of future multivalent vaccines to target rapidly spreading COVID-19 variants (CureVac 2021).

This statistical analysis plan (SAP) was developed to provide the details of the planned statistical methodology for the final analysis and the 2 interim analyses (Section 12).

This SAP is based upon the following study documents:

- Study Protocol 217741 (CV2 SARS-COV2-002 BST) Protocol Amendment 2 (27 May 2022)
- Participant Case Report Form Version 5.0 (20 Oct 2022)

This SAP is to be finalized prior to first participant first visit. Major changes in the analysis that are made after database lock will be documented in the CSR along with the rationale and other details regarding the changes.

2. Objectives

2.1. Primary Objective and Endpoints

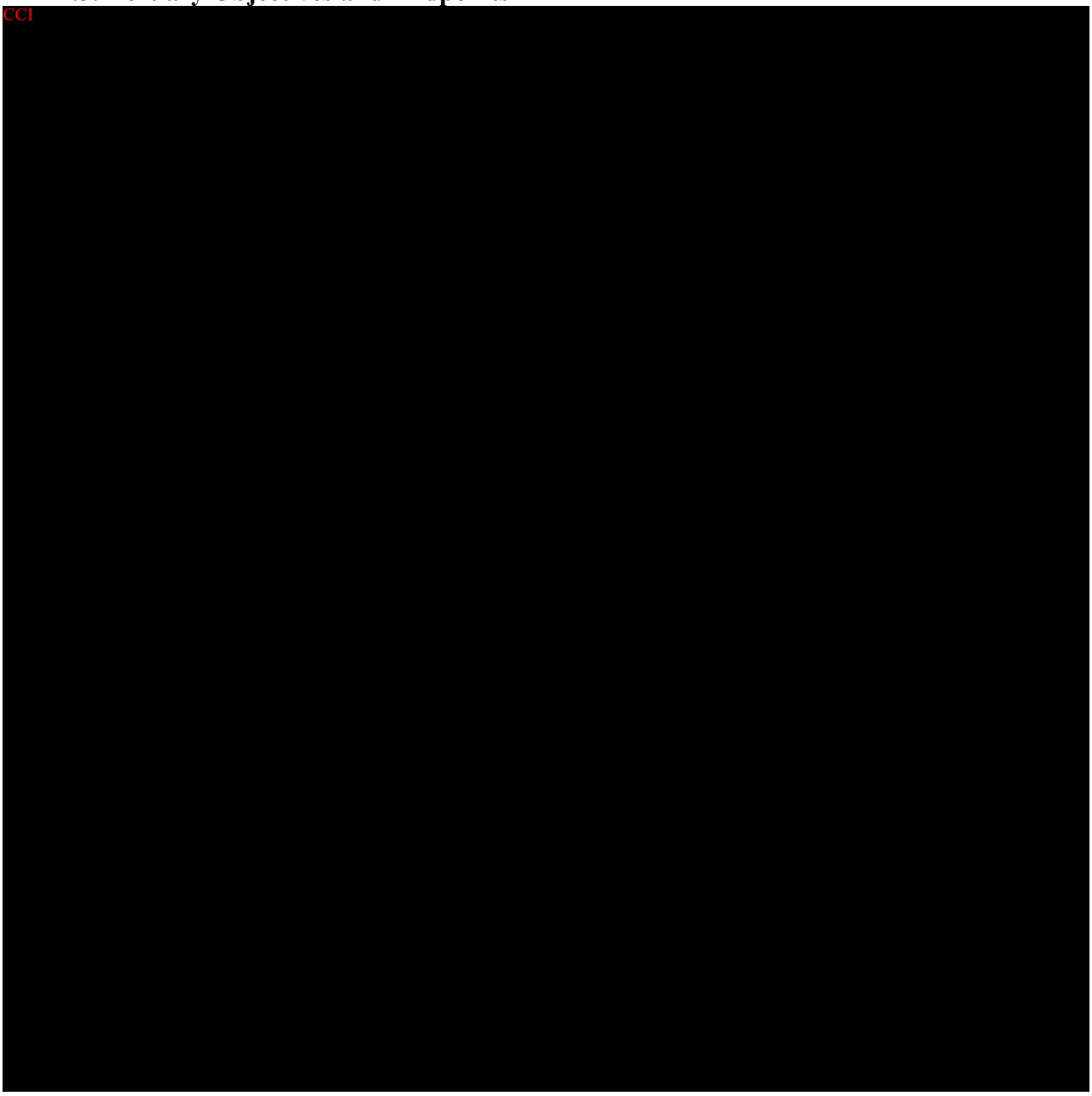
Objectives	Endpoints
Primary – Safety	
To evaluate the safety and reactogenicity of CV2CoV at each dose level in SARS-CoV-2 seropositive healthy adult participants after booster vaccination	• Percentage of participants with MAAEs, SAEs, and AESIs from study vaccination through the end of the study (approximately 180 days after the study vaccine administration, Day 1 through 180), each summarized separately • Percentage of participants with each solicited local and systemic AE within the 7-day postvaccination period (Days 1 to 7) • Percentage of participants with unsolicited AEs up to 28 days after study vaccination, including clinically relevant abnormal laboratory findings (Day 1 through Day 28)

2.2. Secondary Objectives and Endpoints

Objectives	Endpoints
Secondary – Immunogenicity	
To explore the dose response and effect of CV2CoV at each dose level on neutralizing Ab titers against pseudovirus bearing spike protein from SARS-CoV-2 WT in SARS-CoV-2 seropositive healthy adult participants after booster vaccination	• GMTs of neutralizing Ab titers against pseudovirus bearing spike protein from either SARS-CoV-2 WT at each collection time point (Days 1, 8, 15, 29, 85, and 180) • Percentage of participants with seroresponse (≥4-fold rise from baseline) at Day 29 after the booster dose. • GMI from baseline of neutralizing Ab titers against pseudovirus bearing spike protein from SARS-CoV-2 WT at each collection time point (Days 8, 15, 29, 85, and 180)
To describe serum binding Ab (IgG) levels specific for vaccine antigens in SARS-CoV-2 seropositive healthy adult participants after booster vaccination	• GMTs of binding IgG against SARS-CoV-2 S protein and RBD at each collection time point (Days 8, 15, 29, 85, and 180) • GMI from baseline of binding IgG against SARS-CoV-2 S protein and RBD at each collection time point (Days 8, 15, 29, 85, and 180)

2.3. Tertiary Objectives and Endpoints

CCI



3. Investigational Plan

3.1. Overall Study Design and Plan

This Phase 1 study will evaluate the safety, reactogenicity, and immunogenicity of the CV2CoV vaccine in SARS-CoV-2 seropositive healthy adult participants. The study will be conducted in 5 sequential cohorts with dose escalation from 2 µg to 20 µg. Each cohort will include the dose and age groups as indicated in Table 3-1. A study design schematic is provided in Figure 3-1.

A total of up to approximately 180 healthy adult participants will be enrolled, 30 per dose group. The 30 participants will be distributed between the younger (≥18 to <65 years old) and older (≥65 years old) age groups, with a minimum of 10 and a maximum of 20 participants in each age group. There will be 3 sentinel participants in each age group within each dose group. (Table 3-1).

The screening period will be up to 14 days, study vaccine administration will occur on Day 1, and participants will have approximately 180 days (6 months) of follow-up after study vaccine administration. The study will be open label.

Participants in all cohorts will be screened for eligibility up to 14 days before enrollment. Participants will receive study vaccine according to their cohort (Table 3.1-1), dose group, and age group; and study visits will proceed according to the schedule of events (SOE) provided in Appendix 15.1. Participants will be sequentially enrolled to the dose level assigned to their cohort.

Enrollment in each dose cohort and the progression from vaccination in younger to older adult participants will be staggered based on SRT data review will progress as described in protocol Section 7.8. Holding rules for dosing are described in protocol Section 5.9.

Three sentinel participants in the younger age group (Cohort 1) will be enrolled before opening enrollment to the older age group (Cohort 1).

Escalation to the next higher dose cohorts will be based on the SRT review of safety data from the same age group.

Enrollment into Cohorts 2 and 3 (8 and 12 µg, respectively) will begin after the SRT has reviewed Days 1 to 8 safety data (including Day 8 laboratory data) from 3 sentinel participants from the previous dose cohort.

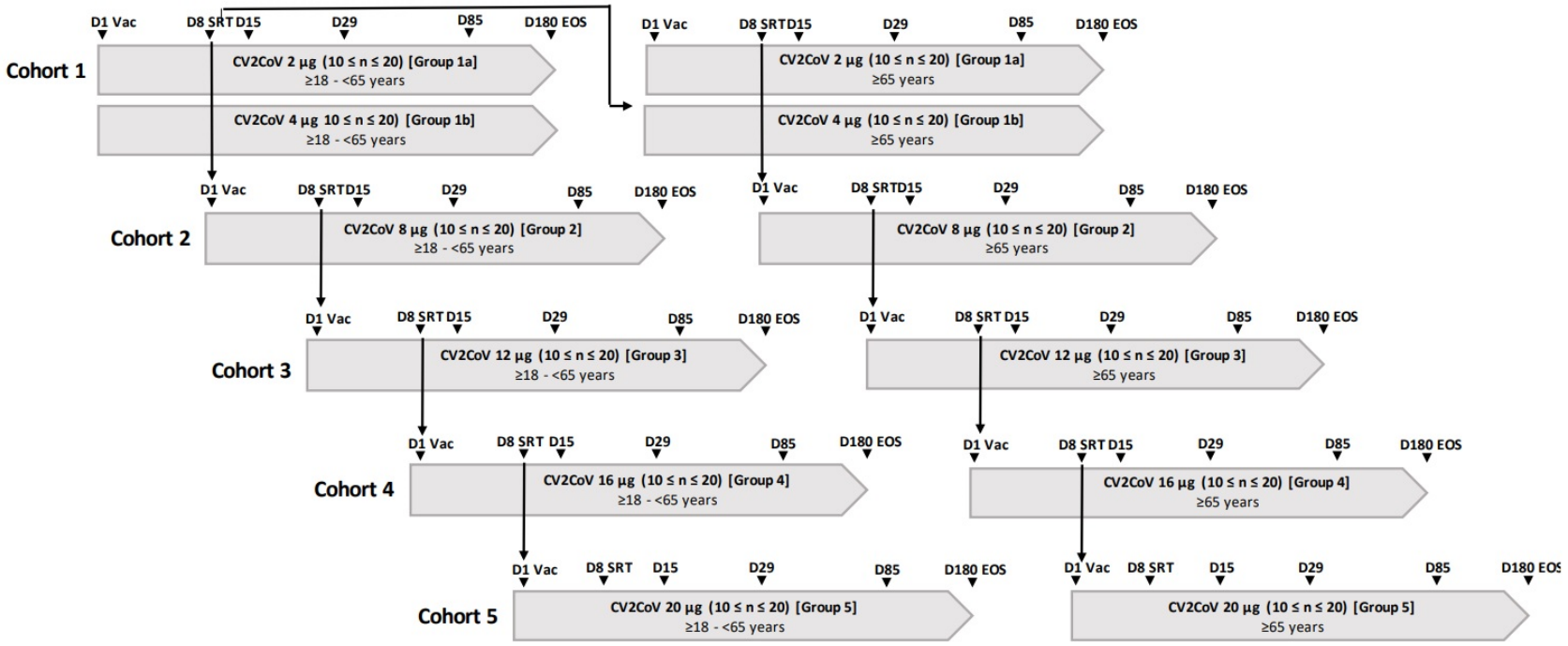
Enrollment into Cohorts 4, and 5 (16 µg, and 20 µg, respectively), will begin after the SRT has reviewed Day 1 to 8 safety data (including Day 8 laboratory data) from all participants in the previous dose cohorts.

A first interim analysis of safety and immunogenicity data up to 14 days after study vaccine administration in participants enrolled in Cohorts 1, 2, and 3 will be performed. A second interim analysis of safety and immunogenicity data will be performed 14 days after participants in Cohorts 4 and 5 have received study vaccine.

Table 3.1-1: Study Cohorts, Groups, and Study Vaccine Administration

Cohort	Dose Group	Dose Level	Younger Adults ≥18 to <65 Years of Age	Older Adults ≥65 Years of Age	Total Dose Group Sample Size
1	1a	2 µg	$10 \leq n \leq 20$	$10 \leq n \leq 20$	30
	1b	4 µg	$10 \leq n \leq 20$	$10 \leq n \leq 20$	30
2	2	8 µg	$10 \leq n \leq 20$	$10 \leq n \leq 20$	30
3	3	12 µg	$10 \leq n \leq 20$	$10 \leq n \leq 20$	30
4	4	16 µg	$10 \leq n \leq 20$	$10 \leq n \leq 20$	30
5	5	20 µg	$10 \leq n \leq 20$	$10 \leq n \leq 20$	30

Figure 3.1-1 Study Design Figure



3.2. Study Endpoints

Please refer to Section 2 of this SAP.

3.3. Treatments

Investigational product (IP) refers to the CV2CoV vaccine that will be administered during the study. CCI [redacted] The LNPs are composed of a CCI [redacted]. The diluent composition for CV2CoV is 0.9% sodium chloride.

The following IP will be used in the study:

Description	Investigational Product CV2CoV[a]
CCI [redacted]	CCI [redacted]
CCI [redacted]	WT CCI [redacted]
CCI [redacted]	CCI [redacted]

a. Product reference: CV07050201.
b. CCI [redacted]

3.4. Overdose Management

An overdose is any dose of study vaccine given to a participant that exceeds the planned dose for an individual within a given dose group.

There is no specific treatment recommended for an overdose. Overdose itself is not to be reported as an AE, however, any AEs associated with the overdose will be analyzed as relevant AEs/SAEs. Overdose participants will be included in the Safety Set and excluded from Per Protocol (PP) Set.

4. General Statistical Considerations

Participants will be identified in the listings by the participant identification number concatenated with the site number. Data will be displayed in all listings sorted by age group, dose group and participant number.

Continuous data will be described using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). **Categorical data** will be described using the participant count and percentage for each category.

For the **summary statistics** of all numerical variables unless otherwise specified, mean, confidence interval, median, standard deviation, minimum and maximum will be displayed.

A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values.

There is no formal hypothesis testing in this study where statistical methods are applied; the emphasis will be on estimation with 2-sided 95% CIs.

The denominator for all percentages will be the number of participants with non-missing values of corresponding parameter in that treatment within the analysis population of interest, unless otherwise specified.

A table, figure, or listing is to be generated for any required item even where no data is available or reported. In such cases, the outputs will state: "**No Data Reported**". This will confirm to the health authorities that all data for the tables, figures, listings, and narratives are accounted for.

If a participant has no data they will be excluded from the specific output.

Baseline will be defined as the last non-missing evaluation prior to study vaccine administration, unless otherwise specified.

Study day will be calculated as follows:

a) study day prior to the injection will be calculated as: date of assessment – date of the injection

b) study day on or after the date of the injection will be calculated as: date of assessment – date of the injection + 1

For Safety assessment of AEs, the intervals will be calculated as follow

- solicited AEs: the day of vaccination and 6 subsequent days (Day 1 through 7)
- unsolicited AEs: the day of vaccination and 28 subsequent days (Day 1 through 28)
- Medically attended adverse events (MAAEs), adverse events of special interest (AESI) and serious adverse events (SAEs): the day of vaccination and 180 subsequent days (Day 1 through 180)

For calculations regarding antibody levels/titers, antibody values reported as below the lower limit of quantification (LLOQ) will be replaced by 0.5 × LLOQ. Values that are greater than the

upper limit of quantification (ULOQ) will be converted to the ULOQ. Missing results will not be imputed.

The LLOQ and ULOQ for NAb are the following:
LLOQ = To be defined by lab when assay calibrated.
ULOQ = To be defined by lab when assay calibrated.
calibrating conversion factor to WHO standard is 1/1.872.
NAb Result (IU/mL) = Result (NT50 titer) x 1/1.872.

Details on LLOQs and ULOQs for IgG and conversion factors are described in Appendix 15.2.

All safety data will be summarized by dose group.

All statistical analyses will be performed using SAS® software Version 9.4 or later.

4.1. Sample Size

The sample size is based on clinical considerations to inform dose regimen decisions for continued clinical development. Approximately 180 participants will be enrolled in this Phase 1 study, with 6 dose-level cohorts each comprising 2 age groups. With 30 participants in each cohort, there is a 78.5% probability to observe at least 1 AE if the incidence rate is 5% and a 95.8% probability to observe at least 1 AE if the incidence rate is 10%. With 30 participants in each cohort, a 10% unevaluable rate for immunogenicity results, and a standard deviation of 0.45 for log10-transformed increase from Day 1, the ratio of the upper limit of a 2-sided 95% CI and the point estimate of Geometric Mean Increase (GMI) is 1.5.

4.2. Randomization, Stratification, and Blinding

Participants in Cohort 1 will be randomized to receive either the 2 µg or 4 µg dose levels; participants in the other cohorts will be sequentially enrolled to the dose level assigned to their cohort.

Three sentinel participants in the younger age group (Cohort 1) will be enrolled before opening enrollment in the older age group (Cohort 1).

The study will be open label.

4.3. Analysis Set

The following analysis sets have been defined: Enrolled Set, Per Protocol (PP) Set, and Safety Set.

4.3.1. Enrolled Set

The Enrolled Set will include all participants who have a signed informed consent form (ICF) and were assigned to a group, vaccinated, or had an immunogenicity blood draw. The Enrolled Set will be used for participant disposition, protocol deviation and enrollment by public disclosure required age category summaries.

4.3.2. Per Protocol Set

The Per Protocol (PP) Set will include all eligible participants who received a dose of study intervention IP as per protocol and who have values for predose and Day 29 neutralizing Ab titers against pseudovirus bearing S protein from [redacted] Results from a blood sample deviating from the dosing or blood sampling schedule (Appendix 15.1) and results from a blood sample after intercurrent conditions that may interfere with immunogenicity (eg, virologically confirmed SARS-CoV-2 infections or immunodeficient conditions) or from participants who received COVID-19 vaccination within 29 days postvaccination will be excluded from the PP Set. The analysis will be done according to the dose that participants received at Day 1.

The PP Set will be used for the analysis of immunogenicity, demography and the analysis of PBMC subset.

Significant protocol deviations will be reviewed and may lead to exclusion from the PP Set.

4.3.3. Safety Set

The Safety Set will include all participants who received any IP. All analyses using the Safety Set will group participants according to the study vaccine actually received.

The Safety Set will be used for safety and demography analyses.

5. Participant Disposition

5.1. Disposition

Participant disposition will be summarized by dose group for all participants. A disposition of participants includes the number and percentage of participants for the following categories: participants who were enrolled, who were vaccinated, participants who discontinued from the study (i.e., did not complete the Day 180 visit), and participants who were in the Enrolled Set, PP Set and Safety Set.

A participant may withdraw or be withdrawn from the study for any of the following reasons:

- The participant does not meet the protocol inclusion or exclusion criteria

- The participant is noncompliant with the protocol
- The participant has a serious or intolerable AE(s) that in the investigator's opinion requires withdrawal from the study
- The participant has safety laboratory results that reveal clinically significant hematological or biochemical changes from the baseline values, per investigator judgment
- The participant has symptoms or an intercurrent illness not consistent with the protocol requirements or that justify withdrawal
- The participant is lost to follow-up
- Other reasons (e.g., pregnancy, development of contraindications of use of the IP)
- The participant withdraws consent, or the investigator or sponsor decides to discontinue their participation in the study withdrawal of consent by participant or the investigator or sponsor decides to discontinue their participation in the study.

Participant status summaries will also be provided that include participants who completed each visit, participants vaccinated with study vaccine, participants who had immunogenicity results at an applicable visit, and participants who completed the study. Participant status summary will be also presented by dose and age group.

Participant disposition and discontinuation data will be presented in a listing sorted by age, dose group and participant number.

The number of participants included in each analysis set will be summarized. A listing of participants in each analysis set will also be provided by age, dose group and participant number. Participants excluded from the analysis sets will be listed with reason for exclusion(s) and sorted by age, dose group and participant number.

The primary reasons for study discontinuation include:

- AE,
- Death,
- Lost To Follow-up,
- Physician Decision,
- Pregnancy,
- Protocol Deviation,
- Site Terminated by Sponsor,
- Study Terminated by Sponsor,
- Withdrawal of Consent by Participant,

- Vaccine Not Administered,
- Other.

5.2. Protocol Deviations

Major protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, or reliability of the study data or that may significantly affect a participant's rights, safety, or well-being. Major protocol deviations rules will be developed and finalized before database lock.

Major protocol deviations include, but are not limited to, the following:

- Study vaccine not administered at all
- Invalid/missing informed consent
- Fraudulent data
- Administration of concomitant vaccine(s) forbidden in the protocol
- Participants got vaccinated but not as per protocol
- Vaccine storage temperature deviation which is not accepted by quality
- Expired vaccine administered
- Ineligible participant
- Administration of any medication forbidden by the protocol
- Participants did not comply with blood sample schedule
- Serological results not available pre- or post-vaccination for at least neutralizing Abs against pseudovirus bearing S protein from [redacted]
- Serological results available but results unreliable (e.g. wrong blood sample management)

The number of participants with major protocol deviations will be summarized by dose group. Major protocol deviations will be listed with date of occurrence, deviation description, and analysis set from which participant is excluded. The major protocol deviation summary will be based on the Safety Set.

The major protocol deviations will be listed by age group, dose group, participant number and will be reported in the CSR.

6. Demographics and Baseline Characteristics

6.1. Demographics

A summary of demographics and baseline information will be presented by dose group. The demographic characteristics consist of age (years), gender at birth, ethnicity, and race. The

baseline characteristics consist of height (cm), weight (kg), BMI (kg/m^2), N protein, and prior Covid-19 infection, defined as either self-reported Covid-19 infection or a positive N protein result from the last result/test prior to vaccination.

Descriptive statistics (mean, standard deviation, median, minimum and maximum) for age, height, weight and BMI will be provided by dose group in each age group and overall.

The number and percentage of participants will be provided for gender at birth, ethnicity, race, baseline RT PCR, prior Covid-19 infection and baseline N protein status by dose group in each age group and overall.

Percentages will be based on the total number of participants in the analysis set defined in the output.

Participant demographic and baseline characteristics will be sorted by age group, dose group and participant number, including child-bearing potential (applicable only for women).

6.2. Baseline Disease Characteristics

Not applicable

6.3. Medical History

6.3.1. General Medical History

Medical history will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of participants with any medical history, medical history that ended before Visit 1, and medical history that is still ongoing at Visit 1(at the time of first vaccination) will be summarized overall and for each system organ class (SOC) and preferred term (PT) by dose group. Percentages will be calculated based on safety set.

Participant medical history data including specific details will be presented in a listing sorted by age group, dose group and participant number.

6.4. Inclusion and Exclusion Criteria

Enrolled participants who failed any inclusion/met any exclusion criteria will be classed as major protocol deviations.

7. Treatments and Medications

7.1. Prior and Concomitant Medications

All medications/vaccination will be coded according to the World Health Organization (WHO) drug dictionary (WHODrug), which will be updated whenever available throughout the study.

7.1.1. Prior Medications

Any medications (including vaccines) that were administered to the participant within 6 months of Screening (within 18 months for prior vaccines) will be considered as prior medication for this study.

Prior medication will be listed sorted by age group, dose group, participant number and summarized by dose groups using the Safety Set. They will be summarized by the generic preferred name and anatomical therapeutic chemical (ATC) class level 4. More than one ATC class per medication is possible and the medication will be reported under all applicable classes. A participant with multiple occurrences within an ATC is counted only once for that ATC class. Similarly, a participant with multiple occurrences within a generic preferred name is counted only once.

7.1.2. Concomitant Medications

Concomitant medications are defined as any medications and vaccine (other than study vaccines) taken after the first dose of the study vaccine that were taken:

- Within 6 months of Screening or
- First prior to the dosing and on-going after first dose up to 6 months or
- Within 2 weeks of study vaccination for herbal products, vitamins, minerals, and over-the-counter medications.

Concomitant medications will be listed and summarized in a similar manner to that of prior medications.

For the purpose of inclusion in prior and concomitant medications tables, incomplete start and stop dates will be imputed according to the below rules (where UK, UKN, and UNKN indicate unknown or missing day, month, and year, respectively):

<u>Missing Start Dates</u>

<u>If day is missing and month and year are available:</u>

- UK-MMM-YYYY: Assume 01-MMM-YYYY (first day of the month), but if month and year are the same as the first study vaccination month and year, then assume the date of first vaccination.

<u>If day and month are missing and year is available:</u>

- UK-UKN-YYYY: Assume 01-JAN-YYYY (first day of the year), but if year is the same as the first study vaccination year, then assume the date of first study vaccination.

If day, month and year (date) are missing:

- UK-UKN-UNKN: Assume date of first study vaccination.

Missing Stop Dates

If day missing and month and year are available:

- UK-MMM-YYYY: Assume the last day of the month

If day and month are missing and year is available:

- UK-UKN-YYYY: Assume 31-DEC-YYYY

if day, month and year (date) are missing:

- UK-UKN-UNKN: Do not impute and assume ongoing

(Note - In case of single dose vaccine or treatment, start date may be same as that of end date.)

7.2. Study Treatments

7.2.1. Extent of Exposure and Compliance

A listing of vaccine exposure will be provided. The listing will include assigned study vaccine, actual vaccine received, date and time of the vaccination and sorted by age group, dose group and participant number.

8. Analysis of Safety and Immunogenicity Study Objectives

8.1. Analysis of Primary Safety Objective

8.1.1. Analysis of Medically attended Adverse Events (MAAEs), Serious Adverse Events (SAEs), and Adverse Events of Special Interest (AESIs) from study vaccination through the end of the study (Day 1 – 180)

Participants' MAAEs and SAEs from study vaccination through the end of the study (approximately 180 days after the study vaccine administration, day 1-180) will be presented as the percentage of participants with such events throughout the study duration by dose and age group. Participant's AESIs from study vaccination through the end of the study (day 1-180) will be presented by dose group.

8.1.2. Analysis of solicited local and systemic adverse events up to 7 days after study vaccination (day 1-7), unsolicited adverse events, abnormal laboratory findings up to 28 days after study vaccination (day 1- 28) and non-serious Covid-19 adverse events (Day 1 – study end)

The percentage of participants with at least one solicited local or systemic AE for 7 days following vaccination (day 1-7), participants with unsolicited AEs up to 28 days after study vaccination (day 1-28), participants with abnormal laboratory findings up to 28 days after study

vaccination (day 1-28) and non-serious Covid-19 adverse events (day 1 – study end) will be computed by dose group.

8.2. Analysis of Secondary Immunogenicity Endpoints

8.2.1. GMTs of neutralizing Ab titers and GMI from baseline of neutralizing Ab titers against SARS CoV-2 WT and GMTs of serum binding IgG Ab titers and GMI from baseline of IgG titers against SARS CoV-2 S protein and RBD at each collection time point

For continuous variables, summary statistics, Geometric Mean Titer (GMT) and associated 95% CIs, and interquartile ranges will be provided. Listings will also be provided by age group and dose group with a symbol used to indicate participants with prior Covid-19 Infection status. Graphical presentations will be considered as needed.

Immunogenicity of the study vaccine will be assessed through GMTs at each collection time point (day 1) before the booster dose and after the booster dose (Days 8, 15, 29, 85, and 180). GMTs and GMIs from baseline will be summarized with descriptive statistics including a bar chart (on log scale) for each age group and prior Covid-19 infection status versus time.

The GMT will be calculated using the following formula:

$$10^{\left\{\frac{\sum_{i=1}^{n}\log_{10}(t_i)}{n}\right\}}$$

Where $t_1, t_2, \ldots, t_n$ are n observed immunogenicity titers.

The GMI measures the changes in immunogenicity titers or levels within participants (change from baseline in log titers). The GMI will be calculated using the following formula:

$$10^{\left\{\frac{\sum_{i=1}^{n}\log_{10}\left(v_{ij}/v_{ik}\right)}{n}\right\}} = 10^{\left\{\frac{\sum_{i=1}^{n}\log_{10}(v_{ij})-\log_{10}(v_{ik})}{n}\right\}}$$

where, for n participants, v_{ij} and v_{jk} are observed immunogenicity titers for participant I at time points j and k, k=*baseline*.

Antibody titers will be summarized at baseline and each postvaccination visit (the number of participants with nonmissing data, median, minimum, maximum, GMT, and 95% CI). Geometric

mean increase and the corresponding 95% CI for the GMI as well as the minimum and maximum fold-rise value will be presented by age group or prior Covid-19 infection, dose group and visit. The 95% CI will be calculated based on the t-distribution of the log-transformed fold-rise values for GMTs and GMIs, then back-transformed to the original scale for presentation.

Supporting data listings will be provided for the All Enrolled Set by age group, dose group and participant number.

Bar charts (including 95% CIs) of GMT for serum IgG and Nab antibody levels by dose, age group, prior Covid-19 infection and visit will be provided in addition to summary tables. Neutralizing antibody titers above 37.44 and above 187.2 for antibodies related to the Wuhan strain will also be summarized.

The GMT at each postvaccination time point, the GMI from baseline, and the 95% CIs in all cohorts will be analyzed using an ANCOVA model on log10 transformed titers with dose group and age group as fixed in the model and prior Covid-19 infection and prevaccination baseline value as covariables.

8.2.2. Percentage of participants with seroresponse (≥4-fold rise from baseline) at Day 29 after the booster dose

The proportion of participants with neutralizing seroresponse of serum CCI [redacted] Omicron BA.1, BA.2, Beta and Delta variants specific Ab from baseline at Day 29 by dose group and prior Covid-19 infection will be tabulated with 2-sided 95% Clopper Pearson CIs. The same summaries will be generated for seroresponse rate 14 days after booster dose (Day 15) as supportive analyses.

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

8.4. Analysis of COVID -19 Incidence-Adverse Event of Special Interest

Proportion of participants with the following will be summarized by dose group:

1. Laboratory-confirmed (RT PCR) symptomatic SARS-CoV-2 infection
2. Laboratory-confirmed asymptomatic or symptomatic (RT-PCR or N protein seroconversion) SARS-CoV-2 infection
3. Laboratory-confirmed severe SARS CoV-2 infection
4. Medically attended visits due to laboratory-confirmed SARS-CoV-2 infection
5. Hospitalizations or death due to laboratory-confirmed SARS-CoV-2 infection

Frequencies and estimates of the proportion of participants with the above events from study vaccination through the end of the study will be computed by dose group.

9. Safety Analysis

Safety, tolerability, and reactogenicity will be assessed by clinical review of all relevant parameters including solicited and unsolicited AEs, SAEs, AESIs, MAAEs, AEs leading to withdrawal from study participation, safety laboratory test results, vital signs, and physical examination findings.

All safety analyses will be based on Safety Set. All safety analyses will be provided by dose group and age group unless otherwise specified.

9.1. Adverse Events

An AE is defined as any untoward medical occurrence in a participant enrolled into this study regardless of its causal relationship to the IP. This definition includes exacerbations of pre-existing conditions. Stable pre-existing conditions which do not change in nature or severity during the study are not considered AEs; however, these should be reported as part of the medical history at screening.

SOC will be displayed in alphabetical order. PT will also be displayed alphabetically within SOC. Percentages will be based upon the number of participants in the Safety Set within each dose group.

Incomplete AE onset date/time and end date will be imputed following the rules below.

Missing Start Dates

If day is missing and month and year are available:

- UK-MMM-YYYY: Assume 01-MMM-YYYY (first day of the month), but if month and year are the same as the first study vaccination month and year, then assume the date of first vaccination.

If day and month are missing and year is available:

- UK-UKN-YYYY: Assume 01-JAN-YYYY (first day of the year), but if year is the same as the first study vaccination year, then assume the date of first study vaccination.

If day, month and year (date) are missing:

- UK-UKN-UNKN: Assume date of first study vaccination.

Missing Stop Dates

If day missing and month and year are available:

- UK-MMM-YYYY: Assume the last day of the month

If day and month are missing and year is available:

- UK-UKN-YYYY: Assume 31-DEC-YYYY

if day, month and year (date) are missing:

- UK-UKN-UNKN: Do not impute and assume ongoing

All AEs will be classified by SOC and PT according to the latest version of the MedDRA.

Unless otherwise specified, AEs will be summarized by dose group based on the Safety Set. A listing of AEs will be provided by age group, dose group and participant number.
All events from screening until vaccination will be considered as medical history.

9.1.1. Relationship of Adverse Events to Study Drug

Investigators will not be required to assess the causality of solicited AEs if the onset is during the solicitation period.

The investigator will determine the causal relationship between the study vaccine and the AE for all unsolicited AEs, SAE, MAAE and AESIs. The relationship of unsolicited AEs to the study vaccine (Yes, No) will be captured on the eCRF.

The number and percentage of participants along with the frequency of AEs (unsolicited AEs and SAEs) by SOC, PT, and relationship will be produced.

A participant with 2 or more AEs within the same SOC or PT level but different relationship will be counted only once in the level using the related incident. If the causality is missing, then a "missing" category will be included in the summary.

9.1.2. Severity of Adverse Event

The severity of AEs (mild, moderate, severe) will be captured on the eCRF. Adverse events (unsolicited AEs, solicited AEs, and SAEs) will be summarized including the number of

participants and percentages by dose group, as well as by SOC, PT, and severity. If the severity is missing, then a "missing" severity category will be included in the summary. A participant with 2 or more AEs within the same SOC or PT level but different severity will be counted only once at the most severe level.

9.1.3. Outcome of Adverse Event

The outcome of an AE will be assessed as at the time of last observation per the following categories:

- Fatal
- Not Recovered/ Not Resolved
- Recovered/Resolved
- Recovered/Resolved with sequelae
- Recovering/Resolving
- Unknown

The number and percentage of participants along with the frequency of adverse events (unsolicited, AESIs, MAAEs and SAEs) will be summarized by SOC, PT, and outcome.

A participant with 2 or more AEs within the same SOC or PT level but different outcome will be counted only once with higher outcome grading.

9.1.4. Solicited Adverse Event

Solicited AEs are prespecified local and systemic. Solicited AEs will be collected through 7 days following the vaccination (Day 1-7) using eDiary. Solicited AEs with onset during the 7-day solicitation period that continue beyond the 7-day period will be reported as unsolicited AEs.

The following specific solicited adverse events will be used to assess reactogenicity.

Local reactions at injection site:

- Injection Site Pain
- Redness
- Swelling
- Lymphadenopathy (localized axillary, cervical or supraclavicular swelling or tenderness ipsilateral to the vaccination arm)

Systemic reactions:

- Fever
- Headache

- Fatigue
- Myalgia
- Arthralgia
- Chills

The number and percentage of participants with any local solicited AEs, and systemic solicited AEs will be presented for each age group and dose group among participants with eDiary information available.

All solicited AEs local and systemic will be listed by age and participant number. Solicited adverse events reported until 7 days (Day 1 through Day 7) postvaccination will be summarized by maximum severity and by dose group.

Prolonged Solicited AEs that continue beyond day 7 will be reported on the eCRF as Unsolicited AEs and will be listed as such. The number and percentage of participants with prolonged solicited AEs will be presented for each age group (any, any local, any systemic, each solicited AE).

In addition, the duration (in days) of solicited AEs which started within day 1-7 will be summarized by dose group for each age group. The duration for any severity will be calculated as Stop date – Start date + 1, where start date is the first day with AE while stop is the last day with the AE in or beyond the solicited period. The duration of solicited AE with specific severities (mild/moderate/severe, moderate/severe, severe) will be the number of days with the severity.

Currently on the eCRF the investigator can document discrepancy in the severity of AEs on the eDiary, if:

- The participant does not report the severity of the event in the eDiary or
- The investigator judges that the participant over- or underestimated the severity of the event

When available the severity provided by the investigator will be used instead of the eDiary grading to generate the summaries of solicited events.

The percentage of eDiary days completed will be summarized by dose and age group. A day is considered completed in the eDiary if it was entered by the participant or the investigator. The percentage of completed days will be calculated as follows:

(SumSymp/(7*NumSymp*ExpSubj))*100

SumSymp is the sum of the total number of days completed for a specific symptom across all symptoms and exposed subjects. NumSymp is the number of symptoms and ExpSubj is the number of exposed subjects.

9.1.5. Unsolicited Adverse Event

Unsolicited AEs are defined as any AEs reported spontaneously by the participant, observed by the study staff during study visits or those identified during review of medical records or source documents. Solicited AEs with an onset after the 7-day solicitation period (Day 1-7) will be considered unsolicited AEs. An unsolicited AE is defined as any AE that is volunteered from the participant and occurs within 28 days after vaccination (Day 1-28).

The percentage of participants with unsolicited AEs onset date within day 1-28 will be provided by age group, dose group, by grade, outcome and causality (any, fatal, causally related, fatal/causally related).

The number and percentage of participants with unsolicited AEs onset date within day 1-28 will be provided by SOC and PT for each dose group (any grade, grade 3, related).

Unsolicited AEs will be summarized and listed up to day 28 after study vaccination (Day 1-28).

A data listing for all Unsolicited AEs will be provided by age group, dose group and participant number.

9.1.6. Adverse Events of Special Interest

An AESI (serious or nonserious) is defined as an AE or SAE of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor could be appropriate (ICH E2F; CIOMS VI).

Adverse events of special interest will include the following events:

- Virologically-confirmed SARS-CoV-2 infections (see protocol Section 6.6 for disease definitions)
- Potential immune-mediated disorders (see protocol Section 13.4 for definitions)
- Anaphylaxis or severe hypersensitivity within 24 hours after study vaccine administration
- Pericarditis or myocarditis

AESIs will be identified using MedDRA queries and Investigator identification as per eCRF. Refer to appendix 15.3 for details on these queries.

The percentage of participants with AESIs with onset date within day 1-28 and within day 1-180, identified by either the investigator or by MedDRA queries will be provided by SOC and PT for each dose group.

Similarly, AESIs that are related to COVID-19 will be presented in a separate listing by age group, dose group and participant number.

AESIs will be reported until exit from study (up to day 180 after the study vaccine administration, Day 1-180).

9.1.7. Serious Adverse Events

An SAE is defined as any event that:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event that may not result in death, be life-threatening, or require hospitalization but, based upon appropriate medical judgment, jeopardizes the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

The percentage of participants with SAEs onset date within day 1-180 will be provided by dose group, by grade, outcome and causality.

The number and percentage of participants with SAE onset date within day 1-28 and within day 1-180 will be summarized by SOC, PT and causality for each dose group (any, fatal, causally related, fatal/causally related).

SAEs will be summarized and listed from the time participant signs the ICF until exit from study (up to day 180 after the study vaccine administration, day 1-180).

A data listing for all SAEs will be provided by age group, dose group and participant number.

9.1.8. Medically Attended Adverse Events

Medically attended adverse events (MAAEs) is defined as an AE that results in a visit to a medical professional. Medically attended visits are defined as telemedicine visit, physician's office visit, urgent care visit, emergency room visit, hospitalization, or death. Scheduled study visits will not be considered medically attended visits. Medically attended adverse events related

to study vaccination are to be reported from the time of first study vaccination until completion of the participant's last study-related procedure, which may include contact for safety follow-up.

The percentage of participants with MAAE onset date within day 1-180 will be provided by dose group and by grade.

All MAAEs and treatment-related MAAEs with onset date within day 1-28 and within day 1-180 will be presented in separate summary tables for each dose and age group and total by SOC and PT. All MAAEs will be presented in a data listing by age group, dose group and participant number.

MAAEs will be reported in both listings and summaries from the time participant signs the ICF until exit from study (up to day 180 after the study vaccine administration, day 1-180).

9.1.9. Adverse Events Leading to Treatment Discontinuation

Not applicable.

9.1.10. Adverse Events Leading to Study Discontinuation

Adverse events leading to study discontinuation are identified on the study disposition page of the eCRF by the AE number.

The number and percentage of participants with AE leading to discontinuation with onset date within day 1-28 will be summarized by SOC and PT for each dose group.

AEs leading to study discontinuation will be presented and a data listing will be provided by age group, dose group and participant number.

9.1.11. Death

The summary of AEs with an outcome of "Fatal" with onset date within day 1-180 will also be presented by SOC. The SOCs will presented alphabetically. Within each SOC, the PTs will be presented in alphabetical order.

All participants who have an AE with an outcome of "Death" will be presented in a listing by age group, dose group and participant number.

Deaths will be reported for both summaries and listings from the time participant signs the ICF until exit from study (up to day 180 after the study vaccine administration, day -180).

9.2. Clinical Laboratory Evaluations

The following laboratory assessments will be performed:

Hematology:	Basophils, eosinophils, erythrocytes (red blood cells), hemoglobin, leukocytes (white blood cells), lymphocytes, monocytes, neutrophils, and platelets
Chemistry:	Bilirubin (total and direct), alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, and uric acid
SARS-CoV-2:	• SARS-CoV-2 serology (Ab), which will include S and N protein for prevaccination timepoints and N protein for postvaccination timepoints to monitor for undetected SARS-CoV-2 infections • SARS-CoV-2 RT-PCR (nasal swab)
HIV/HBV/HCV	• Hepatitis B surface antigen test • HIV 4th generation antigen/Ab test • Anti-HCV test
Other analyses:	Female participants of childbearing potential: β-human chorionic gonadotropin (serum test at Screening; urine test at additional time points) Serum FSH, to confirm postmenopausal status (see protocol Section 13.2)

Individual safety laboratory measurements for hematology, chemistry and coagulation laboratory panel will be provided. All listings will include the age group, dose group, participant number, laboratory test name result, date and time of measurements, reference range, and flag for measurements that are outside the reference range and sorted by age group, dose group and participant number.

Laboratory abnormalities will be graded for severity using the FDA toxicity grading table (DHHS 2007). Clinically relevant laboratory abnormalities will be reported as AEs using the AE grading

A by-participant listing will be provided for pregnancy test by age group, dose group and participant number.

9.3. Vital Sign Measurements

Vital sign measurements will include systolic and diastolic blood pressure, oxygen saturation, pulse rate, respiratory rate, and body temperature. Observed values and changes from baseline will be summarized for each vital sign parameter by time point, and dose group.

A supporting by-participant listing of vital sign parameters along with the investigator assessment will be provided by age group, dose group and participant number.

9.4. Physical Examination

A complete physical examination including height and weight will be performed at Screening. Symptom-directed physical examinations will be performed as clinically indicated at subsequent visits. The results of the physical examination findings will be listed by participants and dose group, and sorted by age group, dose group and participant number.

9.5. Electrocardiogram

Not applicable.

10. Pharmacokinetics

Not applicable.

11. Pharmacodynamics

Not applicable.

12. Interim Analysis

A first interim analysis of safety and immunogenicity data covering at least neutralizing Ab titers against pseudovirus bearing S protein from CCI [redacted] up to 14 days after study vaccine administration in participants enrolled in Cohorts 1, 2, and 3 will be performed including at least day 1 and day 15 data. A second interim analysis of safety and immunogenicity data covering at least neutralizing Ab titers against pseudovirus bearing S protein from CCI [redacted] was planned, however this was cancelled as the study was closed early.

13. Changes in the Planned Analysis

Not applicable.

14. References

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Biologics Evaluation and Research (US). Guidance for industry. Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventative vaccine clinical trials.

September 2007 [cited 2021 Jul 09]. Available from: https://www.fda.gov/media/73679/download

World Health Organization (WHO). WHO coronavirus (COVID-19) dashboard [Internet]. 2021 [cited 2021 Jul 07]. Available from: https://covid19.who.int/

15. Appendices

15.1. Schedule of Events

	Screening	D1	D2[a]	D8	D15	D29	D85	D180 (EOS)	Early Termination Visit	Unscheduled Visit for Suspected COVID-19[b]	Unscheduled COVID-19 Convalescent Visit[c]
Window	**D–14 to –1**	**0**	**NA**	**±1**	**±3**	**±3**	**±5**	**±7**	**±7**	**NA**	**NA**
Visit	**1**	**2**	**NA**	**3**	**4**	**5**	**6**	**7**	**7**	**NA**	**NA**
Informed consent	X										
Inclusion/exclusion	X										
Reassess study vaccine eligibility[d]		X									
Demographics	X										
Medical history (including vaccination history)	X								X	X	X
Treatment assignment		X									
Pregnancy test[e]	X	X									
Clinical SARS-CoV-2 serology[f]	X	X					X	X	X		
SARS-CoV-2 RT-PCR (nasal swab)[g]	X	X								X	
Physical examination[h]	X	X		X	X	X	X	X	X	X	X
Vital sign measurements[i]	X	X		X	X	X	X	X	X	X	X
Clinical safety laboratory tests[j]	X	X		X							
Blood sample for binding IgG[f, k]		X		X	X	X[i]	X	X	X		
Blood sample for neutralization[f, k]		X		X	X	X[i]	X	X	X		
Blood for PBMC preparation for ICS (subset of participants)		X			X						
Vaccine administration		X									
COVID-19 evaluation[e]											X[l]
Initiate eDiary for solicited AEs		X									
Site staff review of eDiary			X	X							
Adverse events[m]	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication/vaccination	X	X	X	X	X	X	X	X	X	X	X

Note: Due to the ongoing pandemic, safety follow-up visits may be completed via televisits, as permitted by country regulations. In-person visits should be maintained in the study unless there is a public health emergency limiting access to study sites. During such an emergency, televisits can be employed to keep personal access to subjects and ascertain their safety at a high level.

a. A safety follow-up telephone call to each sentinel participant will be performed on Day 2 prior to the vaccination of the next participant.
b. Required for participants with suspected COVID-19.
c. Required for participants with confirmed COVID-19.

d. Prior to study vaccine administration, participants will be reassessed for development of any new condition that would be considered exclusionary including acute illness, pregnancy, or development of new risk factors for severe COVID-19 illness. Assessment will be based on pregnancy test results, participant-reported symptomology, vital sign measurements, and physical examination findings. (Note: Sentinel participants will be required to remain at the study site for approximately 4 hours after study vaccination for observation. All other participants will be required to remain at the study site for approximately 60 minutes after study vaccination for observation.)

e. WOCBP only: A serum pregnancy test will be performed at Screening. A urine pregnancy test by dipstick will be performed prior to study vaccination. Negative confirmation is required prior to study vaccine administration.

f. Clinical SARS-CoV-2 serology testing will be performed at Screening and on D1 to confirm the serostatus of the participant and on D85 and D180 for detection of SARS-CoV-2 infection during the study. On D1, the serology sample should be collected *before* study vaccine administration. At baseline, D85, and D180 the serology analysis will include N protein to monitor for undetected SARS-CoV-2 infections. Binding IgG and neutralization will only be obtained at Day 85 and D180 in participants who did not receive a licensed or authorized COVID-19 vaccine after Day 29.

g. SARS-CoV-2 nasopharyngeal or mid-turbinate swab for RT-PCR diagnostic testing will be performed at Screening for eligibility and Day 1 for analysis (result not required for eligibility). The screening sample for RT-PCR testing must be obtained and tested within the 7 days before Day1. Additional swabs may be taken at any visit (or between visits) as clinically indicated according to institutional practice.

h. A complete physical examination including height and weight will be performed at Screening. Symptom-directed physical examinations will be performed as clinically indicated at subsequent visits.

i. Vital sign measurements (temperature, pulse, respiration rate, and blood pressure) should be collected before and after study vaccination on D1. Vital sign measurements should also be performed before any scheduled blood collection. Participants who are febrile (temperature ≥38.0°C or ≥100.4°F) before study vaccination on D1 should be rescheduled for study vaccination within the relevant window period of Screening.

j. Clinical safety laboratory testing will include hematology, serum chemistry, and coagulation. Screening laboratory tests may be repeated once for enrollment requirements. HIV 1/2, HB surface antigen, and anti-HCV testing will be performed at Screening only. Unscheduled visit may occur for the evaluation and follow-up of any AE. At unscheduled visits, clinical safety laboratory testing will be done as per investigator decision.

k. Blood draws for immunogenicity assessments (binding IgG and neutralization) after D29 will only be obtained from participants who have not yet received a COVID-19 booster vaccination with an authorized or licensed product.

l. Participants will be instructed to inform the investigator in the event of a positive SARS-CoV-2 diagnostic test. In this case, he/she will be invited to perform an unscheduled visit on site for COVID-19 evaluation according to the definitions provided in protocol Section 6.6. All effort should be made by the investigator to ensure the disease assessment is performed in a timely manner versus the test results.

m. Solicited local and systemic AEs will be collected during 7 days after study vaccination (Day 1 to 7) via eDiaries. Unsolicited AEs will be recorded for 28 days after study vaccination. SAEs, MAAEs, and AESIs will be collected for the duration of the study.

15.3. MedDRA queries for identifying AESIs

The tables below are MedDRA version specific and may be revised with a new MedDRA version:

Table 15.3 1: Preferred terms for AESIs which are not pIMDs

Myocarditis	Autoimmune myocarditis
	Eosinophilic myocarditis
	Giant cell myocarditis;
	Hypersensitivity myocarditis
	Immune-mediated myocarditis
	Myocarditis
Pericarditis	Autoimmune pericarditis
	Pericarditis
	Pericarditis adhesive
	Pericarditis constrictive
	Pleuropericarditis
Severe Hypersensitivity	Grade 3 unsolicited AEs under MedDRA SMQ hypersensitivity, narrow search (includes anaphylaxis), with an onset within 24 hours after vaccination

COVID 19 infection will be based on PCR test (there is no MEDRA query)

Table 15.3 2: Preferred terms for AESIs which are pIMDs

Event Category	Immune-Mediated Disorder	MedDRA PT	PT Code
Neuroinflammatory disorders	Cranial nerve disorders and inflammations	Anosmia	10002653
		IIIrd nerve paralysis	10021283
		IIIrd nerve paresis	10054202
		IVth nerve paralysis	10023110
		IVth nerve paresis	10054201
		Trigeminal palsy	10049788
		Trigeminal nerve paresis	10068008
		VIth nerve paralysis	10047641
		VIth nerve paresis	10071044
		Facial paralysis	10016062
		Facial paresis	10051267
		Acoustic neuritis	10063162
		Glossopharyngeal nerve paralysis	10051270
		Tongue paralysis	10043972
		Vagus nerve paralysis	10064661
		Vocal cord paralysis	10047674
		Vocal cord paresis	10049234
		XIth nerve paralysis	10048842
		Hypoglossal nerve paralysis	10069450
		Hypoglossal nerve paresis	10067129
		Bulbar palsy	10006542
		Oculofacial paralysis	10030069
		Neuritis cranial	10029244
		Cranial nerve disorder	10061093
		Paresis cranial nerve	10061911
		Cranial nerve paralysis	10061908
		Cranial nerve palsies multiple	10011314
		Optic neuritis	10030942
	Multiple sclerosis	Multiple sclerosis	10028245
		Radiologically isolated syndrome	10079292
		Primary progressive multiple sclerosis	10063401
		Progressive multiple sclerosis	10053395
		Marburg's variant multiple sclerosis	10067067
		Secondary progressive multiple sclerosis	10063400
		Multiple sclerosis relapse	10048393
		Relapsing multiple sclerosis	10080700
		Multiple sclerosis relapse prophylaxis	10070495
		Progressive relapsing multiple sclerosis	10067063
		Relapsing-remitting multiple sclerosis	10063399
		Tumefactive multiple sclerosis	10078556
		Expanded disability status scale score decreased	10071385
		Expanded disability status scale score increased	10071384
	Myelitis / Transverse myelitis	Myelitis transverse	10028527
		Myelitis	10028524
		Acute flaccid myelitis	10082097
		Noninfectious myelitis	10071764
	Guillain-Barré syndrome	Guillain-Barré syndrome	10018767
		Miller Fisher syndrome	10049567
	Acute disseminated encephalomyelitis and demyelination (including site specific variants)	Demyelination	10012305
		Intramyelinic oedema	10083038
		Autoimmune demyelinating disease	10075688
		Clinically isolated syndrome	10071068
		Leukoencephalomyelitis	10048999
		Leukoencephalopathy	10024382
		Acute disseminated encephalomyelitis	10000709
		Acute haemorrhagic leukoencephalitis	10058994

		Concentric sclerosis	10010252
		Encephalitis periaxialis diffusa	10049020
		Limbic encephalitis	10078012
		Neuromyelitis optica spectrum disorder	10077875
		Neuromyelitis optica pseudo relapse	10080353
		Autoimmune encephalopathy	10075691
		Bickerstaff's encephalitis	10076985
		Noninfective encephalitis	10074712
		Encephalitis autoimmune	10072378
		Immune-mediated encephalitis	10083074
		Rasmussen encephalitis	10071141
		Encephalitis allergic	10056387
		Encephalitis brain stem	10048997
		Encephalitis haemorrhagic	10014589
		Encephalomyelitis	10014619
		Noninfective encephalomyelitis	10074713
		Encephalitis post immunisation	10014602
		Panencephalitis	10056332
		Encephalitis toxic	10014607
		Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids	10075197
	Myasthenia gravis	Myasthenia gravis	10028417
		Myasthenia gravis crisis	10062758
		Ocular myasthenia	10049168
		Myasthenic Syndrome	10028424
	Autoimmune / Immune-mediated peripheral neuropathies and plexopathies	Autoimmune neuropathy	10070439
		Immune-mediated neuropathy	10078963
		Neuritis	10029240
		Anti-myelin-associated glycoprotein associated polyneuropathy	10078324
		Subacute inflammatory demyelinating polyneuropathy	10081726
		Chronic inflammatory demyelinating polyradiculoneuropathy	10057645
		Lewis-Sumner syndrome	10065580
		Demyelinating polyneuropathy	10061811
		Polyneuropathy idiopathic progressive	10036111
		Multifocal motor neuropathy	10065579
		Acute motor-sensory axonal neuropathy	10076657
		Acute motor axonal neuropathy	10076658
		Cervical neuritis	10008293
		Mononeuritis	10027910
		Mononeuropathy multiplex	10027918
		Brachial plexopathy	10065417
		Radiculitis brachial	10037778
		Neuralgic amyotrophy	10029229
	Narcolepsy	Narcolepsy	10028713
Musculoskeletal disorders	Systemic lupus erythematosus	Systemic lupus erythematosus	10042945
		SLE arthritis	10040968
		Cutaneous lupus erythematosus	10056509
		Acute cutaneous lupus erythematosus	10057928
		Chronic cutaneous lupus erythematosus	10057929
		Subacute cutaneous lupus erythematosus	10057903
		Lupus cystitis	10074714
		Lupus encephalitis	10025130
		Lupus endocarditis	10058225
		Lupus enteritis	10067738
		Lupus hepatitis	10067737
		Lupus myocarditis	10066391
		Lupus myositis	10079642
		Lupus nephritis	10025140

		Lupus pancreatitis	10067750
		Lupus pleurisy	10073694
		Lupus pneumonitis	10057481
		Lupus-like syndrome	10050551
		Neuropsychiatric lupus	10063663
		Central nervous system lupus	10076328
		Pericarditis lupus	10058149
		Peritonitis lupus	10062898
		Systemic lupus erythematosus rash	10042946
		Systemic lupus erythematosus disease activity index abnormal	10067659
		Systemic lupus erythematosus disease activity index decreased	10067658
		Systemic lupus erythematosus disease activity index increased	10067657
	Systemic Scleroderma (Systemic sclerosis)	Scleroderma	10039710
		Scleroderma renal crisis	10062553
		Scleroderma associated digital ulcer	10073229
		Reynold's syndrome	10070953
		Systemic sclerosis pulmonary	10042954
		Systemic scleroderma	10078638
		Anti-RNA polymerase III antibody increased	10082280
		Anti-RNA polymerase III antibody positive	10082283
		CREST syndrome	10011380
	Muscular Autoimmune / Immune-mediated disorders	Polymyalgia rheumatica	10036099
		Dermatomyositis	10012503
		Polymyositis	10036102
		Autoimmune myositis	10082418
		Immune-mediated myositis	10083073
		Juvenile polymyositis	10076673
		Antisynthetase syndrome	10068801
	Rheumatoid arthritis and associated conditions	Rheumatoid arthritis	10039073
		Autoimmune arthritis	10071155
		Immune-mediated arthritis	10083155
		Laryngeal rheumatoid arthritis	10059669
		Rheumatoid lung	10039081
		Rheumatoid scleritis	10067427
		Rheumatic brain disease	10079411
		Rheumatoid neutrophilic dermatosis	10072362
		Rheumatoid nodule	10048694
		Juvenile idiopathic arthritis	10059176
		Cogan's syndrome	10056667
		Palindromic rheumatism	10033534
		Still's disease	10042061
	Spondyloarthropathies	Arthritis reactive	10003267
		Reiter's syndrome	10038294
		Ankylosing spondylitis	10002556
		Spondylitis	10061371
		Spondyloarthropathy	10051265
		Juvenile spondyloarthritis	10076675
		Enteropathic spondylitis	10076549
		Psoriatic arthropathy	10037162
		Juvenile psoriatic arthritis	10076674
	Relapsing polychondritis	Polychondritis	10065159
	Mixed connective tissue disease	Overlap syndrome	10068786
		Mixed connective tissue disease	10027754
	Gout	Gout	10018627
		Gouty arthritis	10018634
		Gouty tophus	10018641

Gastrointestinal disorders	Inflammatory Bowel disease	Crohn's disease	10011401
		Colitis ulcerative	10009900
		Colitis microscopic	10056979
		Autoimmune colitis	10075761
		Immune-mediated enterocolitis	10078961
		Inflammatory bowel disease	10021972
		Arthritis enteropathic	10003253
		Proctitis ulcerative	10036783
		Autoimmune enteropathy	10081456
	Autoimmune / Immune-mediated pancreatitis	Autoimmune pancreatitis	10069002
		Immune-mediated pancreatitis	10083072
	Celiac disease	Coeliac disease	10009839
Liver disorders	Autoimmune / Immune-mediated hepatobiliary diseases	Autoimmune hepatitis	10003827
		Immune-mediated hepatitis	10078962
		Biliary cirrhosis primary	10004661
		Primary biliary cholangitis	10080429
		Cholangitis sclerosing	10008609
Endocrine and Metabolic disorders	Autoimmune / immune-mediated thyroid diseases	Autoimmune hypothyroidism	10076644
		Immune-mediated hypothyroidism	10083075
		Atrophic thyroiditis	10077172
		Autoimmune thyroiditis	10049046
		Immune-mediated thyroiditis	10083071
		Silent thyroiditis	10079012
		Hashimoto's encephalopathy	10069432
		Hashitoxicosis	10067873
		Basedow's disease	10004161
		Marine Lenhart syndrome	10068828
		Autoimmune thyroid disorder	10079165
	Autoimmune / Immune-mediated endocrinopathy (NOS)	Autoimmune endocrine disorder	10078953
		Immune-mediated endocrinopathy	10078964
	Diabetes mellitus type I	Type 1 diabetes mellitus	10067584
		Fulminant type 1 diabetes mellitus	10072628
	Polyglandular autoimmune syndrome	Polyglandular autoimmune syndrome type I	10036072
		Polyglandular autoimmune syndrome type II	10036073
		Polyglandular autoimmune syndrome type III	10064115
	Autoimmune hypophysitis	Lymphocytic hypophysitis	10063685
	Addison's disease	Addison's disease	10001130
Skin disorders	Psoriasis	Psoriasis	10037153
	Vitiligo	Vitiligo	10047642
	Erythema nodosum	Erythema nodosum	10015226
	Alopecia areata	Alopecia areata	10001761
	Lichen planus	Lichen planopilaris	10081142
		Lichen planus	10024429
	Sweet’s syndrome	Acute febrile neutrophilic dermatosis	10000748
	Autoimmune / Immune-mediated bullous skin diseases	Pemphigus	10034280
		Pemphigoid	10034277
		Dermatitis herpetiformis	10012468
		Autoimmune dermatitis	10075689
		Immune-mediated dermatitis	10083156
	Localised Scleroderma	Morphoea	10027982

Vasculitides	Vasculitis and vasculitides	Acute haemorrhagic oedema of infancy	10070599
		Administration site vasculitis	10075969
		Anti-neutrophil cytoplasmic antibody positive vasculitis	10050894
		Aortitis	10002921
		Application site vasculitis	10076027
		Arteritis	10003230
		Arteritis coronary	10003232
		Behcet's syndrome	10004213
		Capillaritis	10068406
		Central nervous system vasculitis	10081778
		Cerebral arteritis	10008087
		Chronic pigmented purpura	10072726
		Cutaneous vasculitis	10011686
		Diffuse vasculitis	10012978
		Eosinophilic granulomatosis with polyangiitis	10078117
		Erythema induratum	10015213
		Granulomatosis with polyangiitis	10072579
		Haemorrhagic vasculitis	10071252
		Henoch-Schonlein purpura	10019617
		Henoch-Schonlein purpura nephritis	10069440
		Hypersensitivity vasculitis	10020764
		Injection site vasculitis	10067995
		Kawasaki's disease	10023320
		Langerhans' cell histiocytosis	10069698
		Lupus vasculitis	10058143
		MAGIC syndrome	10078132
		Microscopic polyangiitis	10063344
		Nodular vasculitis	10029491
		Ocular vasculitis	10066926
		Optic ischaemic neuropathy	10030924
		Optic neuropathy	10061323
		Polyarteritis nodosa	10036024
		Pulmonary vasculitis	10037457
		Renal arteritis	10038373
		Renal vasculitis	10038546
		Retinal vasculitis	10038905
		Rheumatoid vasculitis	10048628
		Segmented hyalinising vasculitis	10067527
		Takayasu's arteritis	10043097
		Temporal arteritis	10043207
		Thromboangiitis obliterans	10043540
		Urticarial vasculitis	10048820
		Vaccination site vasculitis	10076191
		Vascular purpura	10047097
		Vasculitic rash	10047111
		Vasculitic ulcer	10075714
		Vasculitis	10047115
		Vasculitis gastrointestinal	10048319
		Vasculitis necrotising	10047124
Other	Stevens-Johnson syndrome	Stevens-Johnson syndrome	10042033
		Erythema multiforme	10015218
		Toxic epidermal necrolysis	10044223
		SJS-TEN overlap	10083164
	Blood autoimmune / immune-mediated disoders	Autoimmune anaemia	10080243
		Autoimmune haemolytic anaemia	10073785
		Warm type haemolytic anaemia	10047822
		Cold type haemolytic anaemia	10009868
		Coombs positive haemolytic anaemia	10010941
		Evans syndrome	10053873

		Immune thrombocytopenic purpura	10074667
		Thrombocytopenic purpura	10043561
		Thrombotic thrombocytopenic purpura	10043648
		Autoimmune aplastic anaemia	10071576
		Autoimmune neutropenia	10055128
		Autoimmune pancytopenia	10069509
		Immune-mediated pancytopenia	10083004
		Antiphospholipid syndrome	10002817
		Pernicious anaemia	10034695
	Autoimmune / immune-mediated glomerulonephritis	Glomerulonephritis rapidly progressive	10018378
		IgA nephropathy	10021263
		IgM nephropathy	10077209
		C1q nephropathy	10081461
		Glomerulonephritis membranous	10018372
		Glomerulonephritis membranoproliferative	10018370
		Membranous-like glomerulopathy with masked IgG-kappa deposits	10083098
		Mesangioproliferative glomerulonephritis	10066453
		Anti-glomerular basement membrane disease	10081981
		Autoimmune nephritis	10077087
		Immune-mediated nephritis	10083070
		Chronic autoimmune glomerulonephritis	10073016
		Tubulointerstitial nephritis and uveitis syndrome	10069034
	Ocular autoimmune / immune-mediated diseases	Uveitis	10046851
		Vogt-Koyanagi-Harada disease	10082001
		Ocular pemphigoid	10067776
		Autoimmune retinopathy	10071578
		Acute macular outer retinopathy	10079367
		Autoimmune uveitis	10075690
		Immune-mediated uveitis	10083069
		Autoimmune eye disorder	10081123
	Autoimmune / immune-mediated heart disease	Autoimmune myocarditis	10064539
		Immune-mediated myocarditis	10082606
		Autoimmune pericarditis	10079058
	Sarcoidosis	Sarcoidosis	10039486
		Pulmonary sarcoidosis	10037430
		Neurosarcoidosis	10078011
		Cutaneous sarcoidosis	10011674
		Liver sarcoidosis	10068664
		Muscular sarcoidosis	10028365
		Ocular sarcoidosis	10065700
	Sjögren’s syndrome	Sjogren's syndrome	10040767
	Autoimmune lung disease	Idiopathic pulmonary fibrosis	10021240
		Idiopathic interstitial pneumonia	10078268
		Interstitial lung disease	10022611
		Pulmonary fibrosis	10037383
		Autoimmune lung disease	10080701
		Immune-mediated pneumonitis	10082452
	Goodpasture’s syndrome	Goodpasture’s syndrome	10018620
	Raynaud's phenomenon	Raynaud's phenomenon	10037912

Note: This list is reviewed for each new MedDRA version and the list applicable at database lock will be documented within the ADAM package.