GlaxoSmithKline Biologicals SA

218595

A Phase 1, Open-label, Safety and Immunogenicity Study of a Booster Dose of the Investigational CV0501 mRNA COVID-19 Vaccine in Adults at Least 18 Years Old

31Jan2023

Statistical Analysis Plan

Version *3.0*

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VERSION HISTORY

Version	Date	Details
SAP v1.0	12MAY2022	Prepared for IND submission
SAP v2.0	19AUG2022	Updated for protocol amendments 1 (23JUN2022) and 2 (26JUL2022)
SAP v3.0	31JAN2023	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
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
BMI	body mass index
CI	confidence interval
CCI	CCI
COVID-19	coronavirus disease
CSR	clinical study report
CV0501	an investigational, monovalent, nucleoside-modified, mRNA COVID-19 vaccine targeting the Omicron variant of SARS-CoV-2
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic diary
EOS	end of study
FtiH	first-time-in human
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
IMP	investigational medicinal product
LLOQ	lower limit of quantification
LNP	Lipid nanoparticles
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
PBMC	peripheral blood mononuclear cell
PP	Per protocol
PPI	Per protocol Immunogenicity

Abbreviation	Definition
PT	Preferred Term
SAP	statistical analysis plan
RT-PCR	reverse transcription polymerase chain reaction
S protein	spike protein
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOC	system organ class
SRT	Safety Review Team
TLF	Table, Listing and figures
Th	T helper
ULOQ	Upper limit of quantification
WHO	World Health Organization
WT	Wild type

1. Introduction

The COVID-19 pandemic caused by SARS-CoV-2 virus was declared by the WHO on 11 Mar 2020 (WHO 2020). As of 19 Jan 2022, more than 332 million cases have been reported worldwide, leading to more than 5.5 million deaths (WHO 2022). To date, there are multiple licensed or conditionally approved vaccines available that rely on a variety of vaccine technologies. All currently available vaccines are based on antigens from the original Wuhan strain (D614; wild-type, hereafter referred to as "WT").

This is a Phase 1 FTiH study designed to evaluate the safety, reactogenicity, and immunogenicity of the GSK-CureVac CV0501 modified mRNA vaccine encoding the Omicron variant to prevent COVID-19. This study will evaluate the CV0501 vaccine as a booster vaccination in a healthy adult population of participants who have previously received at least 2 doses of an mRNA COVID-19 vaccine.

GSK and CureVac are collaborating to develop CV0501, a modified-nucleotide mRNA vaccine based on the same LNP. platform as the CVnCoV vaccine. The CV0501 mRNA encodes S protein from the Omicron variant and has been optimized to improve intracellular mRNA stability and translation for increased and extended protein expression, relative to unmodified S protein mRNA

This statistical analysis plan (SAP) was developed to provide the details of the planned statistical methodology for the analysis of both interim analyses and the preparation of the final clinical study report (CSR).

This SAP is based upon the following study documents:

- Study Protocol CV2 SARS-CV0501-012 BST (218595) Protocol Amendment 2 (26 Jul 2022)
- Participant Case Report Form (25 Jan 2023)

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 tolerability of CV0501 at each dose level	• Percentage of participants with each solicited local and systemic AEs during 7 days after vaccination (i.e., the day of study vaccination and 6 subsequent days (day 1 through 7) • Percentage of participants with each abnormal clinical safety laboratory finding for 8 days after study vaccination • Percentage of participants with unsolicited AEs for 28 days after study vaccination • Percentage of participants with MAAEs, AESIs and SAEs from study vaccination through the end of the study (for 180 days after the study vaccine administration), each summarized separately

2.2. Secondary Objectives and Endpoints

Objectives	Endpoints
Secondary – Immunogenicity	
To evaluate neutralizing Ab titers against SARS-CoV-2 WT, Omicron, and Delta* variants following CV0501 booster vaccination in adult participants	• GMTs of neutralizing Ab titers against pseudovirus bearing S protein from SARS-CoV-2 WT, Omicron, and Delta variants at each collection timepoint • GMI from baseline of neutralizing Ab titers against pseudovirus bearing S protein from SARS-CoV-2 WT, Omicron, and Delta variants at each collection time point
To describe seroresponse to CV0501 based on neutralizing Ab titers against pseudoviruses bearing S protein from SARS-CoV-2 WT, Omicron, and Delta* variants	• Seroresponse rate 28 days after the booster dose (day 29) based on neutralizing Ab titers against pseudoviruses bearing S protein from SARS-CoV-2 WT, Omicron, and Delta variants at each collection timepoint, with seroresponse defined as postboost titers $\geq 4\times$ preboost titers

3. Investigational Plan

3.1. Overall Study Design and Plan

This open-label, dose escalation first-time-in human (FtiH) Phase 1 study will evaluate the safety (including reactogenicity) and immunogenicity of a single booster dose of CV0501 vaccine in adults who have previously received at least 2 doses of an mRNA COVID-19 vaccine. Approximately 180 participants will be enrolled. The study will comprise two parts (Part A and Part B).

Part A: Participants in Cohorts 1 to 5 will be enrolled in a staggered manner to 1 of 5 cohorts with planned dose escalation of CV0501 from 12 µg up to 200 µg. Each cohort of Part A will evaluate a single dose level of CV0501 vaccine and will include 2 age groups (younger adults, ≥ 18 to < 65 years old, and older adults, ≥ 65 years old), as indicated in Table 3-1. The dose levels for the groups in Cohorts 1-3 are fixed. The dose levels for the Cohorts 4 and 5 will be as recommended by the SRT, based on their review of all available safety data and dosing scenarios.

Part B: Designed to comprise 2 single age group cohorts (≥18 to <65 years old), will start based on the first interim analysis of safety and immunogenicity, provided that the SRT assesses the 12µg dose to be immunogenic and safe. The SRT may recommend dropping Cohorts 6 and 7 (Groups 6a and 7a) based on immunogenicity data from the groups that received the 12µg dose level. If the SRT determines that enrollment in Cohorts 6 and 7 may proceed, enrollment may proceed in parallel according to Table 3-2.

Table 3 1 Study Cohorts, Groups, and Study Vaccine Administration (Part A)

Cohort	Vaccine	Dose Level	Group A Younger Adults ≥18 to <65 Years of Age (n range)	Group B Older Adults ≥65 Years of Age (n range)	Total Cohort Sample Size
1	CV0501	12 µg	1a (min 10; max 20)	1b (min 10; max 20)	30
2		25 µg	2a (min 10; max 20)	2b (min 10; max 20)	30
3		50 µg	3a (min 10; max 20)	3b (min 10; max 20)	30
4		75 or 100* µg	4a (min 10; max 20)	4b (min 10; max 20)	30
5		100,150, or 200* µg	5a (min 10; max 20)	5b (min 10; max 20)	30

*Depending on the reactogenicity/safety findings from groups in Cohorts 1-3, the SRT may recommend 1 of 3 prespecified dosing scenarios comprising these dose levels for groups in Cohorts 4 and 5, as described in Section 3.1.1 of protocol. The dose level recommendations will be made independently for Groups A (younger participants) and B (older participants).

Table 3 2 Study Cohorts, Groups, and Study Vaccine Administration (Part B)

Cohort	Vaccine	Dose Level	Group A Younger Adults ≥18 to <65 Years of Age (n range)	Total Cohort Sample Size
6	CV0501	3 µg	6a	15
7		6 µg	7a	15

Figure 3-1 Study Design Part A

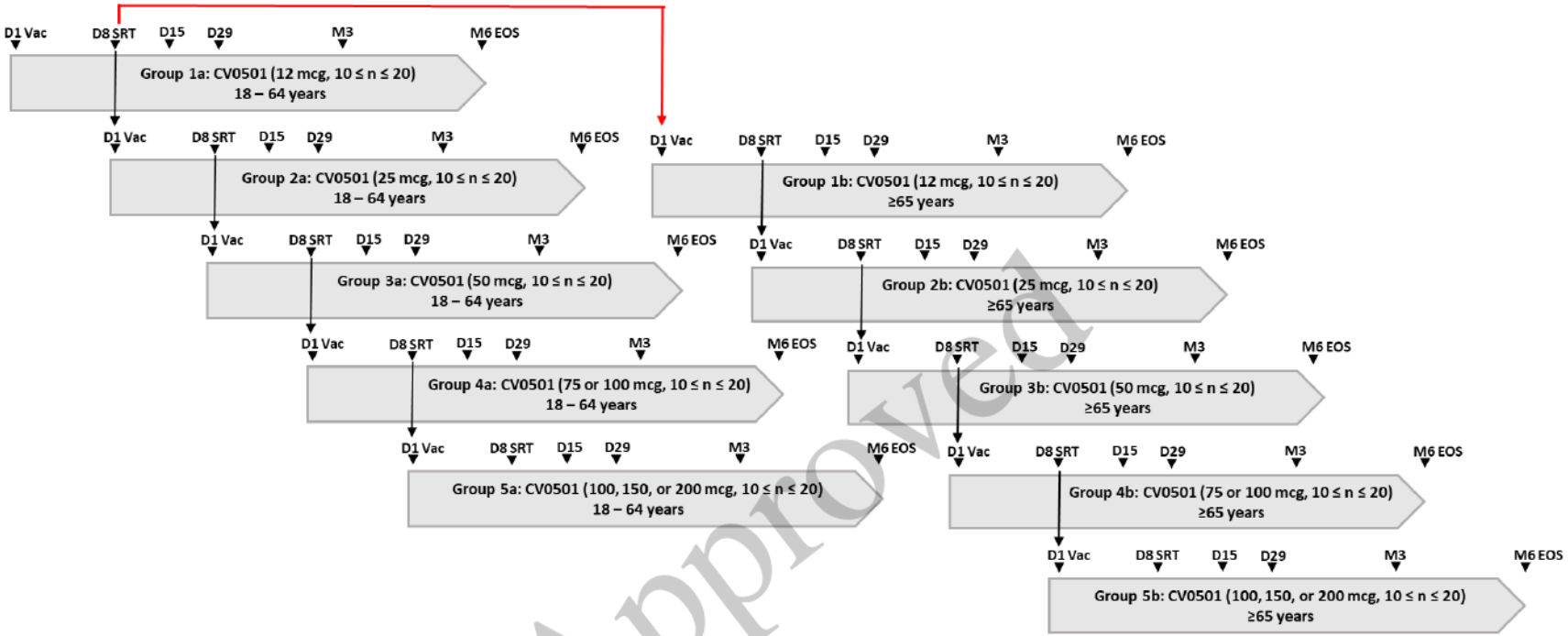
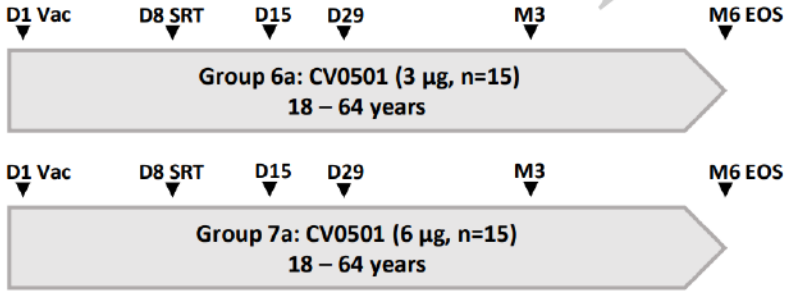


Figure 3-2 Study Design Part B



3.2. Study Endpoints

Please refer to Section 2.1 of this SAP.

3.3. Treatments

Investigational product (IP) in this Phase 1 study refers to the CV0501 vaccine, which is a formulation of modified mRNA encoding Omicron variant S protein microencapsulated in lipid nanoparticles (LNP) that will be administered during the study. CCI [redacted] The LNPs are composed of a CCI [redacted].

The following IP will be used in the study:

Intervention Name	**CV0501**
Type	Vaccine
Dose Formulation	Modified mRNA
Unit Dose Strength(s)	CCI µg mRNA/mL
Dosage Level(s)	3, 6, 12, 25, 50, 75, 100, 150, 200 µg
Route of Administration	Intramuscular injection
Diluent	0.9% sodium chloride
Use	Experimental
IMP or NIMP	IMP
Sourcing	Provided centrally by GSK Biologicals SA or CureVac GmbH
Packaging and Labeling	IP will be provided in a glass vial as a sterile colloidal dispersion in a frozen liquid formulation as open-label supply. Each vial will be labeled as required per country requirement.

3.4. Dose Adjustment/Modifications

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 adverse event (AE). Overdose participants will be included in the Safety Set and excluded from Per protocol Immunogenicity (PPI) 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% Confidence intervals (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, listing (TLF) is to be generated for any required item even where no data is available or reported. In such cases, the table, figure or listing 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.

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:

- study day prior to the injection will be calculated as: date of assessment – date of the injection
- 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 results released as below a value will be replaced by 0.5 × the value. Results released as above a value will be converted to the value. Missing results will not be imputed.

The lower limit of quantification (LLOQ) and upper limit of quantification (ULOQ) for WT 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 when available are described in Section 15.2

All safety data summaries/displays will be provided by dose group. Details will be included in the TLF shell.

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, 5 dose-level cohorts (Cohorts 1 to 5) each comprising 2 age groups. Cohorts 6 and 7 will comprise 1 age group (younger adults). 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. The sample size in Cohorts 6 and 7 is based on clinical feasibility rather than on statistical rationale. With 15 participants in each cohort, there is a 79.4% probability to observe at least one AE if the true incidence rate is 10%.

4.2. Randomization, Stratification, and Blinding

Participants in Part A will be assigned sequentially to a dose-level cohort by age group. Participants in Part B will be randomly assigned on day 1 to receive study vaccine by dose-level cohort.
The study will be open label.

4.3. Analysis Set

The following analysis sets have been defined: Enrolled Set, Per protocol Immunogenicity Set, and Safety Set.

4.3.1. Enrolled Set

The Enrolled Set will include all eligible participants who gave informed consent, regardless of the participants' treatment status in the study.

4.3.2. Per protocol Immunogenicity (PPI) Set

The PPI Set includes all eligible participants who received a dose of study IP per protocol and who have values for predose and Day 15 neutralizing Ab titers against pseudovirus bearing S protein from the Omicron BA1 variant of SARS-CoV-2. Results from a blood sample deviating from the dosing or blood sampling schedule and results from a blood sample after intercurrent conditions that may interfere with immunogenicity (e.g., laboratory-confirmed SARS-CoV-2 infections or immunosuppressive or immunodeficient conditions) or after a prohibited concomitant medication/vaccination (COVID-19 vaccination) will be excluded from the PPI Set. The data will be analyzed according to the dose that participants received at Visit 1.

The PPI Set will be used for the immunogenicity analyses.

4.3.3. Safety Set

All participants who receive 1 dose of IP. The Safety Set will be used for all analyses of safety. Data are analyzed according to treatment received.

5. Participant Disposition

5.1. Disposition

Participant disposition will be summarized by dose group for all participants. The number and percentage of participants for the following categories will be presented: participants who were enrolled, vaccinated, participants who discontinued from the study (i.e. did not complete the day 181 visit), participants in the Enrolled Set, PPI Set and Safety Set.

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

- Participant request.
- Investigator request.
- 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 is lost to follow-up.

- Death.
- The sponsor terminates 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
- 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 summary will also be provided which include participants who completed each visit, participants vaccinated with study vaccine, participants who had immunogenicity results at 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 reason for study discontinuation includes: Withdrawal due to AE, Lost To Follow-up, Physician Decision, Pregnancy, Site Terminated by Sponsor, Study Terminated by Sponsor, Withdrawal of Consent by Participant, Protocol Deviation, Vaccine Not Administered, Death, 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 and post-vaccination (day 15 and day 29) for neutralizing Abs against pseudovirus bearing S protein from Omicron BA.1 SARS-CoV-2
- Serological results available but results unreliable (e.g. wrong blood sample management)
- Intercurrent condition impacting immunogenicity

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. Major protocol deviation summary will be based on the Enrolled Set.

The major protocol deviations will be listed by age group, dose group, participant number and 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 in each age 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 study vaccine in each age group and overall.

The number and percentage of participants will be provided for gender at birth, ethnicity, race, 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 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 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 study vaccine is administered and:

- Within 6 months of Screening or
- Were taken first prior to the dosing and on-going after study vaccine 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):

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

(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 to list participants. 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 solicited local and systemic AE up to 7 days after study vaccination (day 1-7), unsolicited AEs up to 28 days after study vaccination (day 1-28), abnormal clinical safety laboratory finding up to 8 days after study vaccination (day 1-8) and non-serious Covid-19 adverse events (Day 1 – study end)

The percentages 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 clinical safety laboratory findings up to 8 days after study vaccination (day 1-8) and non-serious Covid-19 adverse events (day 1 – study end) will be computed by dose group.

8.1.2. 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

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. Participants AESIs from study vaccination through the end of the study (day 1-180) will be presented by dose group.

8.2. Analysis of Secondary Immunogenicity Endpoints

8.2.1. GMTs of neutralizing Ab titer against pseudotyped bearing S protein from SARS-CoV-2 WT, Omicron BA.1, BA.2 and BA.5 and GMI from baseline of neutralizing Ab titers against pseudotyped bearing S protein from SARS-CoV-2 WT, Omicron BA.1, BA.2 and BA.5 variants at each collection time point

For continuous variables and each dose group, summary statistics, geometric mean titer (GMT) and associated 95% CIs, and interquartile ranges will be provided. Listings will also be provided by age group, dose group, participant number and 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 15, 29, 91, 181). GMTs and GMIs from baseline will be summarized with descriptive statistics including a bar chart (on log scale) for each age group 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.

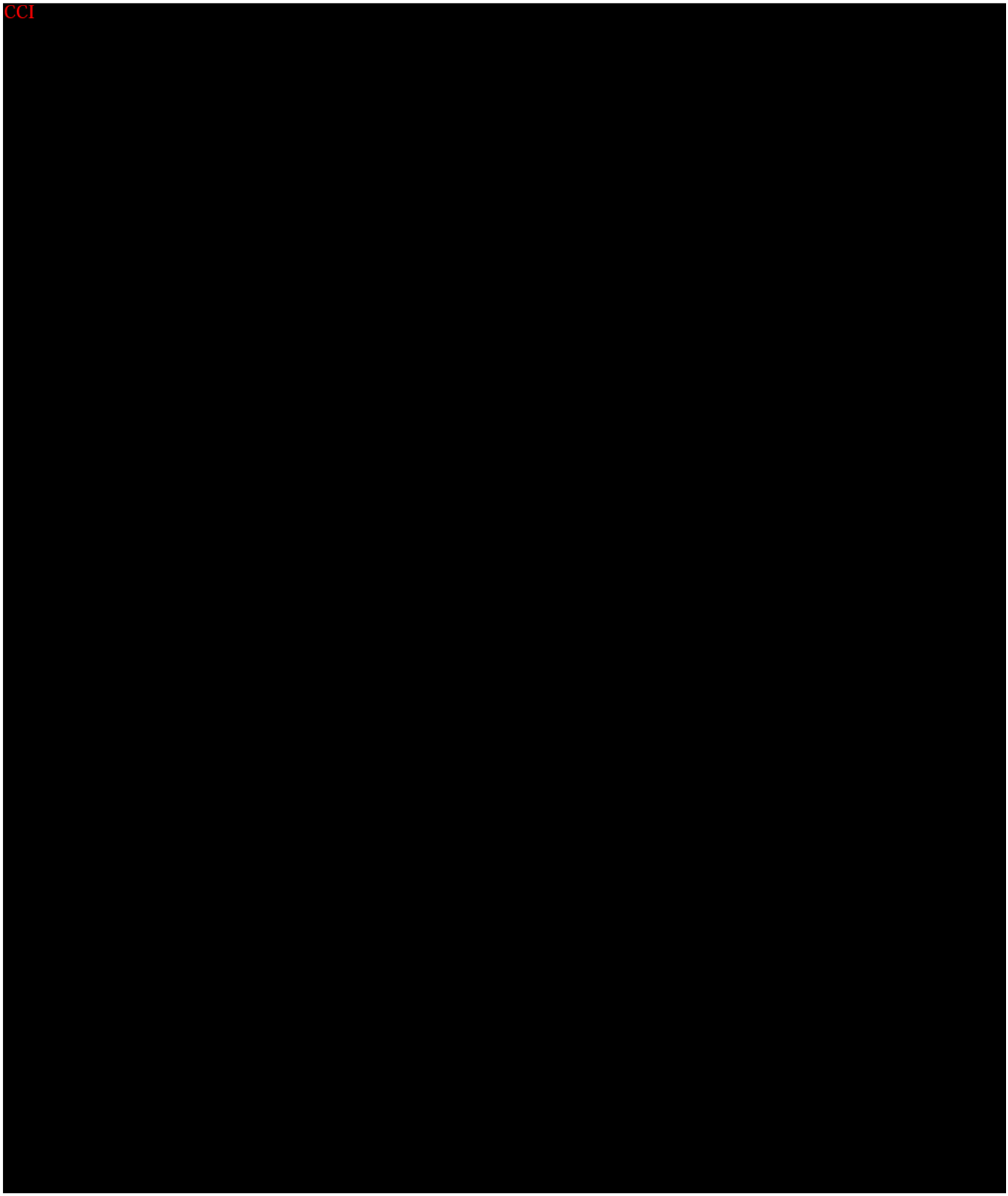
The GMT at each postvaccination time point, the GMI from baseline, and the 95% CIs in all cohorts will be analyzed using an ANCOVA model on log10 transformed titers with dose group and age group as fixed in the model and prior Covid-19 infection and prevaccination baseline value as covariables.

8.2.2. Seroresponse rate 28 days after the booster dose (day 29), based on neutralizing Ab titers against pseudoviruses bearing S protein from SARS-CoV-2 WT, Omicron BA.1, BA.2 and BA.5 variants at each collection timepoint, with seroresponse defined as postboost titers ≥ 4× preboost titers.

Proportion of participants with neutralizing seroresponse of serum SARS-CoV-2 WT, Omicron BA.1, BA.2 and BA.5 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



CCI

[redacted]

CCI

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 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 adverse events will be classified by SOC and PT according to the MedDRA.

Unless otherwise specified, AEs will be summarized by dose group based on 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, study vaccine, 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 from day 1 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 AE 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 overwrite the severity of AEs on the eDiary, if he believes the event grading has not been recorded, has been underestimated or overestimated, and provide his assessment. 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)

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 Covid-19 (see protocol section 6.4 for definitions)

- Potential immune-mediated disorders (see protocol section 13.4 for definitions)
- Anaphylaxis or severe hypersensitivity within 24 hours after study vaccine administration
- Myocarditis
- Pericarditis

AESIs will be identified using MedDRA queries and Investigator identification as per eCRF. Refer to appendix 15.3.MedDRA queries for identifying AESIs 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. All events of myocarditis and pericarditis will be considered important medical events and SAEs (see protocol section 6.1.3).

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 casuality 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 (eg, telephone call, physician's office visit, urgent care visit, emergency room visit or hospitalization). 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 1-180).

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:	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, total and direct bilirubin, blood urea nitrogen, and creatinine
SARS-CoV-2:	• SARS-CoV-2 serology (antibody) will include N protein for prevaccination and postvaccination timepoints. • SARS-CoV-2 RT-PCR (nasopharyngeal or mid-turbinate swab)
HIV/HBV/HCV	• Hepatitis B surface antigen test • HIV 4th generation antigen/Ab test • Anti-HCV Ab test (and RNA test if anti-HCV Ab positive)
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

Individual safety laboratory measurements for hematology, chemistry and coagulation laboratory panel will be provided. All listings will include the cohort, study vaccine, participants ID, 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 summary of patients with an abnormal laboratory value after study vacation (up to Day 8) will be presented. An abnormal laboratory is defined as any value outside of the normal range.

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, 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

At screening and at the Day 8 visit, all participants will be assessed by 12-lead ECG for evidence of asymptomatic myocarditis or pericarditis. The results of the electrocardiogram findings will be listed by participants and dose group, and sorted by age group, dose group and participant number.

10 Pharmacokinetics

Not applicable.

11 Pharmacodynamics

Not applicable.

12 Interim Analysis

There are 2 planned interim analyses of safety and immunogenicity data for at least neutralizing Ab titers against SARS-CoV-2 WT, Omicron BA.1 or BA.5 variant pseudoviruses. A first interim analysis of safety and immunogenicity data covering at least neutralizing Ab titers against pseudovirus bearing S protein from WT, Omicron BA.1 or BA.5 SARS-CoV-2 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 WT, Omicron BA.1, or BA.5 SARS-CoV-2 will be performed 14 days after participants in Cohorts 4 and 5 have received study vaccine including at least day 1 and day 15 data in Cohorts 4 and 5 and day 29 data in addition in Cohorts 1,2 and 3.

Further to the above the first interim will be based on the PNA data. Available binding IgG data at the time of the first interim will be included, but it is not requested to have 100% of these data at the time of the first interim analysis. For PNA, BA.1, BA.5 and Wuhan (ancestral strain, comparator with CV2CoV) will be prioritized (priority #1). BA.2 can be done as priority #2. Regarding cohort 6 and 7 (lowest doses), it is unsure at this stage whether these cohorts will be enrolled as it will depend on the data generated at 12 mcg.

The safety set will be used for the interim immunogenicity analyses.

13 Changes in the Planned Analysis

Because the assays are not fully validated values below LLOQ or above ULOQ they will be used as released. Results released as below a value will be assigned 0.5*the value. Results released as above a value will be assigned the value.

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[a]	D1	D4	D8	D15	D29	D91	D181 (EOS)	ET Visit	Unscheduled Visit for Suspected COVID19	Unscheduled COVID-19 Convalescent Visit
Window	**D–14 to –1**	**0**	**±1**	**±1**	**±3**	**±3**	**±5**	**±7**	**NA**	**NA**	**NA**
Visit	**1**	**2**	**Phone**	**3**	**4**	**5**	**6**	**7**	**NA**	**NA**	**NA**
Informed consent	X										
Inclusion/exclusion	X										
Reassess study vaccine eligibility[b]		X									
Demographics	X										
Medical history (including vaccination history)	X										
Pregnancy test[c]	X	X									
CCI											
Physical examination[f]	X	X		X	X	X	X	X	X	X	X
Vital sign measurements[g]	X	X		X	X	X	X	X	X	X	X
Viral screening assays[h]	X										
Hematology and serum chemistry[h]	X	X[d]		X							
CCI											
Group assignment for Part A/ Randomization for Part B		X									
CCI											
Initiate eDiary for solicited AEs[i]		X									
12-lead ECG examination	X			X							
Site staff review of eDiary			X	X							
CCI											
COVID-19 assessment[k]										X[k]	X[k]

Note: Due to the ongoing pandemic, follow-up visits may be completed via telephone calls, consistent with local regulations.

a. If the investigator believes there is a reasonable justification to do so, all screening procedures may be repeated (maximum 1 rescreening per participant is allowed). Only results from the rescreening visit, if it occurs, will be taken into consideration and recorded in the eCRF. The participant can only be vaccinated once the investigator receives the results and confirms the eligibility criteria.

b. Prior to study vaccine administration, participants will be reassessed for development of any new condition that would be considered exclusionary including acute illness or pregnancy. Assessment will be based on pregnancy test results, participant-reported symptomology, vital sign measurements, and physical examination findings.

c. A serum pregnancy test will be performed at screening in WOCBP. A urine pregnancy test by dipstick will be performed prior to study vaccination. Negative confirmation is required prior to study vaccine administration. Pregnancy test may be repeated at an unscheduled visit per investigator's discretion.

d. On day 1, the blood sample should be collected *before* study vaccine administration.

e. CCI [redacted]

f. 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.

g. Vital sign measurements (temperature, pulse rate, oxygen saturation by pulse oximetry, respiration rate, and blood pressure) should be collected before and after study vaccination on D1. Vital sign measurements should 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.

h. Clinical safety laboratory testing will include hematology and serum chemistry. Screening laboratory tests may be repeated once for enrollment requirements. At unscheduled visits, clinical safety laboratory testing may be performed per investigator's discretion. Viral screening assays include HIV1/2 Antigen/Ab, hepatitis B surface antigen (HBsAg) and hepatitis C virus antibodies (HCV Abs). Testing for HCV RNA will be performed in participants who test positive for HCV Ab.

i. An eDiary will be initiated for daily recording by the participant of solicited local and systemic adverse events.

j. Solicited local and systemic AEs will be collected during the 7 days after study vaccination via eDiaries. Unsolicited AEs will be collected for 28 days after study vaccination. SAEs, MAAEs, and AESIs will be collected for the duration of the study.

k. All suspected cases of COVID-19 in study participants will be diagnosed and clinically evaluated according to the definitions provided in Section 6.1.2. Such participants may have unscheduled study site visits and nasopharyngeal RT-PCR testing for SARS-CoV-2. An unscheduled visit may be performed for participants reporting symptoms consistent with COVID-19. An initial visit should be scheduled upon report of symptom onset, preferably within 3 days of symptom onset. Alternatively, an investigator may utilize participant medical records from non-study care providers to verify whether a participant was infected with SARS-CoV-2. An additional unscheduled, COVID-19 convalescent visit will be preferably conducted within the month after the participant is confirmed with COVID-19. At the convalescent visit, the investigator will seek medical records documenting any treatments and hospitalizations related to COVID-19.

CCI

[redacted]

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 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 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	10012305
		Intramyelinic oedema	10083038

Event Category	Immune-Mediated Disorder	MedDRA PT	PT Code
	demyelination (including site specific variants)	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

Event Category	Immune-Mediated Disorder	MedDRA PT	PT Code
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

Event Category	Immune-Mediated Disorder	MedDRA PT	PT Code
		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

Event Category	Immune-Mediated Disorder	MedDRA PT	PT Code
	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

Event Category	Immune-Mediated Disorder	MedDRA PT	PT Code
		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

Event Category	Immune-Mediated Disorder	MedDRA PT	PT Code
		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