Protocol Number: CV-NCOV-004

Official Title: COVID-19: A Phase 2b/3, Randomized, Observer-Blinded, Placebo-Controlled, Multicenter Clinical Study Evaluating the Efficacy and Safety of Investigational SARS-CoV-2 mRNA Vaccine CVnCoV in Adults 18 Years of Age and Older

NCT Number: NCT04652102

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Statistical Analysis Plan (SAP)

Protocol Title:	COVID-19: A Phase 2b/3, Randomized, Observer-Blinded, Placebo-Controlled, Multicenter Clinical Study Evaluating the Efficacy and Safety of Investigational SARS-CoV-2 mRNA Vaccine CVnCoV in Adults 18 Years of Age and Older.
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1.0 Approvals

Sponsor	
Sponsor Name:	CureVac AG
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(NOTE: Electronic Signatures should only be used if all parties have the ability to eSign.)

2.0 Change History

Version/Date	Change Log
0.1	Draft Version of the SAP
0.2	Second Draft Version of the SAP, including CureVac AG's Comments
1.0/14 Jan 2021	Final Version of the SAP
1.1/08FEB2021	Updates: • Minor modifications to Section 6.1 to clarify the main censoring rules following unblinding • Addition of a new section on censoring rules (Section 10.10) and deletion of censoring details from Section 9.5. Previous content of Section 10.10 moved to a new Section 10.11 • Additional instructions provided in Section 10.5.1 in case of missing AE start date • Re-arrangement and slight modifications to the imputation rules for missing or incomplete case onset dates in Section 10.7.2 • Asymptomatic cases of SARS-CoV-2 infections added to the section on adjudication (Section 10.7.5) • Update of the section on "Event Dates, Follow-Up Time, Time to Event Calculation and Censoring" (Section 10.11, previously 10.10) to take into consideration the unblinding context • Addition of the type of confidence interval (Wald) derived on the hazard ratio in Section 12.6.2.2
1.2/12APR2021	Updates: • Clarification on data handling for subjects who have been tested positive for COVID-19 in Section 9.5.6 • Adapted to protocol version 2.0 ○ The 1-year Extension study was removed from this protocol. It is now considered a separate trial, CV-NCOV-004Ext. ○ Based on feedback from Regulatory Authorities the secondary objective regarding reactogenicity for the Phase 2b part was changed to a primary objective. ○ Added exploratory objective "explore correlates of protective immunity induced by CVnCoV vaccination" ○ For positive RT-PCR tests performed at the central laboratory, the gene for the SARS CoV 2 S protein will be sequenced to identify mutations in this protein ○ Text regarding sample size adapted to apply also if the case accrual rate is higher than expected; in which case the DSMB may recommend a decrease in sample size. ○ COVID-19 is not to be recorded as an AE. ○ COVID-19 removed as an AESI • Adapted to protocol version 3.0 ○ The co-primary objective (and corresponding endpoint) regarding the efficacy of CVnCoV in the prevention of moderate to severe COVID 19 was changed to a key secondary objective. It is now generally accepted that a vaccine that protects against disease of any severity, will also (or even better) protect against more severe

	disease, therefore reducing the need to maintain this as a primary endpoint and thereby preserving the alpha. ○ Subsequently, the corresponding statistical calculations were also updated.. ○ Addition of a key secondary efficacy objective (and corresponding endpoint) to demonstrate the efficacy of CVnCoV in the prevention of COVID 19 caused by the "wild type" (i.e., WT/D614G lineages A.1 / B.1 without VOC B.1.1.7, B.1.351, B.1.429) and "UK" (B.1.1.7) strain. Various VOC strains have been identified since the original protocol and the efficacy to each individual VOC strain will also be evaluated as an exploratory objective. ○ Addition of an exploratory objective (and corresponding endpoint) to demonstrate the efficacy on any other VOC strains. ○ Decrease in the number of subjects needed for exploratory immunogenicity from 400 to 200. ○ Added further sensitivity analysis (subgroup analysis of primary efficacy endpoint by region). ○ Protocol deviation classification was changed from minor/major/critical to important/non-important • AE summary tables to be provided by gender.
1.3/13APR2021	Updates: • Added Section 12.7.6: Sensitivity Analysis on Safety Outputs (6 weeks post 2nd vaccination on Phase 2b subjects). This sensitivity analysis consists of a repeat of all safety outputs without censoring due to unblinding. • Added the following information in Section 10.7.6: Case onset date to be taken from EDC and not from the Adjudication Form.
2.0/14APR2021	Updates: • Updated Section 10.10 to account for subjects who received an alternate vaccination without or before unblinding. • Added Section 12.6.3.2 (Sensitivity Analysis for Key Secondary Efficacy Endpoints)
3.0/27MAY2021	Updates: • Section 8.2 Number evaluated for CMI changed from 400 to 200 • Updated Section 9.1.2/10.5: Changes in wording to be more precise for summaries until end of trial • Updated Section 9.5.2 to account for subjects who received an alternate vaccination and/or unblinding prior to Visit Day 43. • Updated Section 9.5.3: Change EASS definition and added supplementary criteria. No subset of EAS anymore. • Updated Section 9.5.5: Subjects who received an alternate vaccination prior to 15 days after the second vaccination will be excluded from IS. • Updated Section 10.6.1: Visit window was added for serology status at baseline and Day 43 • Updated Section 10.10: Reference for inclusion/exclusion rules were added • Updated Section 10.11: Table 7 - Added description for first episodes of VOC COVID-19 cases • Updated Section 11.0: CI from first IA was corrected

	• Updated Section 12.1: First part with screen failure information was removed; added additional summaries for unblinding and or alternate vaccine use before dose 2 and after dose 2 • Category for Adjudication Committee serostatus if available and lab based serostatus added in Section 12.2 • Precise description for using the adjudication information were added in Section 12.6.1.
4.0/17JUN2021	Updates: • Updated Section 6.1 • Updated Section 8.8: Note added that PRA will be unblinded at timepoint of the first data extraction for the final primary analysis. • Updated Section 9.1.2: Wording of two endpoints corrected. • Updated Section 9.4: Updated first sentence to clarify that the wording of endpoints and estimands does not exactly match with protocol. • Updated Section 9.5: Added clarification that analyses using all randomized subjects will be based on vaccination as randomized. • Insert Section 9.5.2: Added analysis set which is required for a sensitivity analysis. • Updated Section 9.5.3: Refer to 9.5.2 as basis for the analysis set and deleted bullet points which are not required. • Updated Section 9.5.8: Add EASU to primary efficacy endpoint, the analysis set is required for new sensitivity analysis. • Updated Section 10.7.4: Corrected formula so that it is consistent with protocol and definitions in this and other sections. • Update table 7: Corrected censoring date according to Section 10.10. • Insert Section 10.12: Describe derivation of age group. • Updated Section 12.1: Added text to cover additional/modified outputs which were agreed previously. • Updated Section 12.3: Clarified that summaries of medical history will also contain surgical history – data are collected collectively in eCRF. • Updated Section 12.5: Site-level protocol deviations will only be listed. • Updated Section 12.6.2.1: Clarified that repeats of primary analysis will not contain p-values and CIs in repeats will always be 95% CIs. • Updated Section 12.6.2.2: Add sensitivity analysis. • Updated Section 12.7.1.1 and added Section 12.7.1.3: Kept only analyses in Section 12.7.1.1 which are exclusively based on unsolicited AEs and moved analyses which are based on unsolicited as well as solicited AEs to Section 12.7.1.3. • “UK” SARS-CoV-2 variant has been replaced by “Alpha” SARS-Cov-2 variant to be consistent with updated WHO wording. • Definition of “wild type” and “Alpha” SARS-CoV-2 variants: Removed specific lineages from definition because it cannot be ruled out that these may change. The information will be provided by the vendor. • Replaced wordings “alternate vaccine”, “licensed vaccine” and “licensed/authorized vaccine” with “alternate licensed/authorized vaccine” to ensure that it is used consistently.
5.0/10Mar2022	Updates: • Several wording and grammar updates to clarify statements and to account for multiple analysis and decision timepoints throughout the document • Updated several signatories in Section 1.0

	• Added Section 6.1 for SAP version 5.0 specifities
	• Updated changes from protocol in Section 6.2
	• Introduced scenarios A and R to account for possible non-approval of protocol version 4.0 for single sites.
	• Introduced Open Label Phase and related divergence from schedule of events throughout the document. Added Section 8.3 providing specifics of the OL Phase. Added OL Trial Day definitions in Section 10.2.
	• Removed the following endpoints plus related definitions and analyses:
	  ○ Key Secondary Efficacy endpoint of seroconversion
	  ○ Other Secondary Efficacy endpoint of cases “with or without symptoms”
	  ○ Exploratory Efficacy endpoint of cases caused by individual VOCs
	  ○ Exploratory Efficacy endpoint of cases “regardless of baseline serostatus”
	  ○ Exploratory Efficacy endpoint of second episodes
	• Added the following analysis population
	  ○ Open-Label Set (OLS).
	• Removed the following analysis population
	  ○ Per Protocol Efficacy (PPE) Set.
	• Updated Section 10.7.6 to mention that case adjudication was stopped.
	• Added Section 10.10 defining individual and site-level unblinding.
	• Added Section 10.12 for unblinding of site AR009.
	• Added Section 12.7.7 containing new analyses to adapt to extensive unblinding and AV receipt.
	• Added Appendix 6 listing all reactogenicity analyses that have not been performed.

3.0 Table of Contents

4.0 Purpose

The SAP describes the statistical methods to be used during the reporting and analyses of data collected under CureVac AG Protocol CV-NCOV-004 (HERALD).

5.0 Scope

The SAP outlines the following:

- Trial Objectives
- Trial Design
- Trial Endpoints and Assessments
- Analysis Sets
- Conventions and Definitions
- Applicable Trial Definitions
- Statistical Methods

6.0 Introduction

The SAP describes the statistical methods to be used during the reporting and analyses of data collected under CureVac AG Protocol CV-NCOV-004.

The SAP should be read in conjunction with the trial protocol version 4.0 dated 25-NOV-2021 and Case Report Form (CRF) 6.0 dated 22-Oct-2021.

This SAP describes the statistical methods used for the final primary efficacy analysis (when at least 160 cases have been accrued), and a 1-year follow-up analysis (on all data up to Day 393 visit), as well as the planned interim analyses (when at least 56 and 111 cases have been accrued).

Changes performed on the SAP after approval of version 1.0 are tracked in the SAP Change Log.

Each version of the SAP requires approval by the Sponsor.

The SAP final versions 1.0 and 2.0 were finalized and approved prior to the first interim analysis (IA) (the IA when at least 56 cases had been accrued).

The SAP final versions 3.0 and 4.0 were finalized and approved prior to unblinding and the final primary efficacy analysis.

6.1 SAP Version 5.0: Background, Rationale and Specifics

After the final primary efficacy analysis but prior to the 1-year follow-up analysis, CureVac decided to withdraw CVnCoV from the current approval process with the European Medicines Agency (EMA). Due to availability of Authorized Vaccines (AVs) for preventing Coronavirus Disease 2019 (COVID-19) the trial was converted to an open-label design with the focus on safety monitoring. Protocol version 4.0 was issued in that context.

The main purpose of the protocol amendment is:

- To unblind all remaining blinded subjects and inform them of the treatment received.
- To monitor safety of the following subjects remaining in the open-label phase after unblinding:
    - Subjects who had received CVnCoV and received/will receive an AV through their national vaccination program.
    - Subjects who had received CVnCoV and continue follow-up in the trial as initially planned, without receiving an AV.

SAP version 5.0 is mainly required to cover the changes between protocol version 3.0 and 4.0

On agreement with the Sponsor SAP version 5.0 is created before approval of protocol version 4.0 by all authorities. In case protocol version 4.0 is rejected by any authority, protocol version 3.0 automatically applies. Therefore SAP version 5.0 provides separate wording for protocol version 4.0 changes that is conditional to the protocol version 4.0 being accepted. This prevents the requirement of a new SAP version in case protocol version 4.0 is rejected.

For ease of reading the condition of protocol 4.0 being fully approved is referred to as “Scenario A” (A referring to “Approved”) and the condition of protocol 4.0 being rejected/not approved by at least one of the authorities is referred to as “Scenario R” (R referring to “Rejected”). If only one of these 2 scenarios is mentioned this implies that the other scenario is reflected by the remaining text without any alterations required. If none of these scenarios is mentioned the related wording is applicable for the blinded phase under Scenario A and to the whole study under Scenario R. Also, “in the blinded study phase” might be used without mentioning that this is conditional to Scenario A. Under Scenario A “in the blinded study phase” applies to the blinded study phase. Under Scenario R “in the blinded study phase” applies to the whole study.

Important note: Some main stakeholders from the combined Sponsor and Contract Research Organization (CRO) study team, amongst others the full CRO study team and the Sponsor statistician, had already been unblinded at the time of the final primary efficacy analysis. The remaining Sponsor study team was unblinded on 25-Nov-21. As a consequence, the SAP version 5.0 is created and approved by an unblinded authorship/approval team.

6.2 Changes / Intended Divergence from Protocol Version 4.0

- The following selected Safety summary tables to be provided by gender:
  - Overall Summary of Unsolicited Adverse Events Occurring on the Day of Vaccination and the following 28 Days after any Dose
  - Overall Summary of Unsolicited Adverse Events Occurring on the Day of Vaccination and the following 28 Days after Dose 1
  - Overall Summary of Unsolicited Adverse Events Occurring on the Day of Vaccination and the following 28 Days after Dose 2
  - Summary of Solicited Adverse Events Overall and by Maximum Grade Occurring on the Day of Vaccination and the following 7 Days after any Dose
  - Summary of Solicited Adverse Events Overall and by Maximum Grade Occurring on the Day of Vaccination and the following 7 Days after Dose 1
  - Summary of Solicited Adverse Events Overall and by Maximum Grade Occurring on the Day of Vaccination and the following 7 Days after Dose 2
- The EAS excludes subjects who were unblinded prior to 15 days after the second vaccination or received an AV prior to 15 days after the second vaccination.
- Additional population set (EASU) are introduced to account for subjects receiving an AV during the course of the trial.
- The following deletion was performed on the definition of an exploratory safety endpoint:
  “Only for Cohort A: CVnCoV-AV: Occurrence of AEs leading to ~~**AV withdrawal or**~~ trial discontinuation after the first dose with an AV in the open-label phase until EOT.”
- Although not clearly determined in the protocol, no efficacy or reactogenicity analyses are performed at EOT analysis. Therefore some endpoints or parts of endpoints are not analyzed in this study. For reactogenicity, these are specified in Appendix 6, for efficacy these are:
  - All analyses on the PPE.
  - Occurrence of virologically-confirmed (RT-PCR positive) SARS-CoV-2 infection, with or without symptoms.

- Occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 caused by individual VOCs.
- Occurrence of supplemental oxygenation, mechanical ventilation, hospitalization and death due to COVID-19 at any time after the first trial vaccination in naïve subjects
- Occurrence of death due to any cause at any time after the first trial vaccination in naïve subjects.
- Occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity in all subjects, regardless of their baseline serostatus.
- Occurrence of second episodes of virologically-confirmed (RT-PCR positive) cases of COVID 19 of any severity in subjects who had a first episode of a virologically-confirmed (RT-PCR positive) case of COVID-19 of any severity meeting the case definition for the primary efficacy analysis.

7.0 Trial Objectives

Scenario A: For those sites where the protocol was accepted the objectives mentioned in Sections 7.1 – 7.3 are to be considered the objectives of the blinded study phase objectives and Section 7.4 becomes effective.

Scenario R: For those sites where the protocol was not accepted, the objectives mentioned in Sections 7.1 – 7.3 are considered the overall study objectives and Section 7.4 becomes redundant.

7.1 Primary Objectives:

7.1.1 Primary Efficacy Objective

- To demonstrate the efficacy of a 2-dose schedule of CVnCoV in the prevention of first episodes of virologically-confirmed cases of COVID-19 of any severity in Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) naïve subjects.

7.1.2 Primary Safety Objectives

- To evaluate the safety of CVnCoV administered as a 2-dose schedule to subjects 18 years of age and older.
- To evaluate the reactogenicity of CVnCoV administered as a 2-dose schedule to subjects 18 years of age and older participating in Phase 2b of the trial.

7.2 Secondary Objectives:

7.2.1 Key Secondary Efficacy Objectives

- To demonstrate the efficacy of a 2-dose schedule of CVnCoV in the prevention of first episodes of virologically-confirmed moderate to severe cases of COVID-19 in SARS-CoV-2 naïve subjects.
- To demonstrate the efficacy of a 2-dose schedule of CVnCoV in the prevention of first episodes of virologically-confirmed severe cases of COVID-19 in SARS-CoV-2 naïve subjects.
- To demonstrate the efficacy of a 2-dose schedule of CVnCoV in the prevention of first episodes of virologically-confirmed cases of COVID-19 of any severity caused by “wild type” and “Alpha” SARS-CoV 2 strains in SARS-CoV 2 naïve subjects.

7.2.2 Other Secondary Efficacy Objectives

To evaluate in SARS-CoV-2 naïve subjects:

- The efficacy of a 2-dose schedule of CVnCoV in the prevention of first episodes of virologically-confirmed cases of COVID-19 of any severity in subjects ≥ 61 years of age.
- The efficacy of a 2-dose schedule of CVnCoV in reducing the Burden of disease (BoD) from COVID-19.
- The efficacy of CVnCoV after the first dose in the prevention of first episodes of virologically-confirmed cases of COVID-19 of any severity.

7.2.3 Secondary Immunogenicity Objectives

- To assess antibody responses to the receptor binding domain (RBD) of spike (S) protein of SARS-CoV-2 after 1 and 2 doses of CVnCoV in a subset of subjects participating in Phase 2b of the trial.
- To assess SARS-CoV-2 viral neutralizing antibody responses after 1 and 2 doses of CVnCoV in a subset of subjects participating in Phase 2b of the trial.

7.3 Exploratory Objectives:

7.3.1 Exploratory Efficacy Objectives

To investigate in SARS-CoV-2 naïve subjects:

- If cases of COVID-19 are milder in severity in subjects receiving a 2-dose schedule of CVnCoV compared to those administered placebo.
- If the need for supplemental oxygenation due to COVID-19 is reduced in subjects receiving a 2-dose schedule of CVnCoV compared to those administered placebo.
- If the need for mechanical ventilation due to COVID-19 is reduced in subjects receiving a 2-dose schedule of CVnCoV compared to those administered placebo.
- If hospitalization due to COVID-19 is reduced in subjects receiving a 2-dose schedule of CVnCoV compared to those administered placebo.
- If mortality due to COVID-19 is reduced in subjects receiving a 2-dose schedule of CVnCoV compared to those administered placebo.
- If all-cause mortality is reduced in subjects receiving a 2-dose schedule of CVnCoV compared to those administered placebo.
- To investigate the cell-mediated immune (CMI) response of a 2-dose schedule of CVnCoV from approximately 200 subjects at selected site(s).

7.4 Open-Label Phase Objectives (Scenario A only)

7.4.1 Safety Objective:

- To evaluate safety in all subjects ≥ 18 years of age remaining in the trial after unblinding.

7.4.2 Exploratory Efficacy Objective:

- To describe the number of first episodes of symptomatic virologically-confirmed cases of mild, moderate, and severe COVID-19 as assessed by the Investigator.

8.0 Trial Design

Original Trial Design

Trial CV-NCOV-004 starts with an initial Phase 2b part followed by a large Phase 3 efficacy part. Both Phase 2b and Phase 3 parts are randomized, observer-blinded, and placebo-controlled. Adult subjects 18 years of age or older are enrolled at multiple trial sites globally and receive a 2-dose schedule of either CVnCoV at a dose level of 12 µg messenger Ribonucleic Acid (mRNA) or Placebo (normal saline [0.9% NaCl]) in a 1:1 ratio.

During the trial, subjects suspected of having COVID-19 undergo reverse transcription polymerase chain reaction (RT-PCR) testing for SARS-CoV-2 virus (for a virological confirmation). Both Phase 2b and Phase 3 parts of the trial are consistent in design, so that cases of COVID-19 occurring in Phase 2b can be pooled with those in Phase 3 for the primary analysis of vaccine efficacy (VE).

All subjects participating in the Phase 2b or Phase 3 parts of the trial have medically-attended adverse events (AE) collected for 6 months after the second vaccination (or End of Trial [EOT], whatever is earlier), and serious adverse events (SAE), adverse events of special interest (AESI) and AEs leading to vaccine withdrawal or trial discontinuation collected throughout the trial.

Two interim analyses for an early demonstration of high efficacy or futility were to be performed when 56 and 111 cases of COVID-19 of any severity (meeting the primary efficacy case definition) had been accrued (see Section 8.4). Independent of the demonstration of CVnCoV efficacy at either of the interim analyses or at the final primary efficacy analysis, trial CV-NCOV-004 was to continue and remain observer-blinded until the end of the trial (when the last subject has completed the last visit on Day 393), and the database is locked and unblinded for analysis. During this period, collection of placebo-controlled safety data and accrual of COVID-19 cases is to be continued.

Open-Label Phase

In view of the increasing availability of AVs in the countries where the trial is being conducted, multiple unblinding requests have been granted to trial subjects seeking access to these AVs during the blinded study phases. After approval of Protocol version 4.0, all trial subjects are thus planned to be unblinded and the trial is planned to shift to an open-label design.

8.1 Specifics of Phase 2b Design

The objective of Phase 2b is to further characterize the safety, reactogenicity and immunogenicity of CVnCoV prior to initiating Phase 3. Phase 2b is conducted in two age groups of adults: 18 to 60 years of age and ≥61 years of age, which represent the age range of the intended Phase 3 trial population.

Approximately 4,000 subjects were to be enrolled and randomized in a 1:1 ratio to receive 2 doses of either CVnCoV 12 µg mRNA or placebo, administered 28 days apart. Of the 4,000 subjects enrolled, approximately 800 to 1,000 (20% to 25%) were assumed to be ≥61 years of age. This percentage is just an ex ante assumption. No procedural intervention like e.g. any caps on the age strata are entailed to meet this percentage.

In addition to the general design aspects described in the Trial Design Introduction above, in Phase 2b the safety and reactogenicity of a 2-dose schedule of CVnCoV is assessed in detail by measuring the frequency and severity of solicited local and systemic reactions for 7 days after each vaccination, and unsolicited AEs for 28 days after each vaccination.

The immune response induced by vaccination with CVnCoV is evaluated in a subset of subjects (first 600 subjects enrolled in each age group; a total of 1200 subjects in the immunogenicity subset (IS), see also Section 9.6.5) by measuring:

- binding antibodies to the SARS-CoV-2 RBD of S protein by immunoassay and
- viral neutralizing antibodies directed against SARS-CoV-2 by a functional activity assay.

Further, CMI is evaluated in approximately 200 subjects from selected sites. 100 who receive CVnCoV and 100 who receive placebo. (First testing of samples is performed for a subset of these subjects and might be extended to 200 subjects if T-cell response is detectable).

An early safety review of the Phase 2b data is performed by an independent Data Safety Monitoring Board (DSMB, see Section 8.6). The safety review is conducted when approximately 1000 subjects have been enrolled in Phase 2b (25% of subjects) and have at least 1 week of safety follow-up after the first trial vaccination. If the safety profile is judged to be acceptable and there are no safety or tolerability concerns, it is anticipated that enrollment of subjects into Phase 3 can begin without interruption from Phase 2b. Another safety review by the DSMB is conducted when approximately 1,000 Phase 2b subjects have received their second trial vaccination and have at least 1 week of safety follow-up. All available first dose safety data is reviewed at this time.

8.2 Specifics of Phase 3 Design

The primary objective of the combined Phase 2b/3 trial is to demonstrate the efficacy of a 2-dose schedule of CVnCoV in the prevention of COVID-19 cases of any severity. The safety objective of Phase 3 is to generate a large-scale safety database to demonstrate the safety of CVnCoV.

Approximately 32,500 subjects, 18 years of age or older, are enrolled at multiple trial sites globally in Phase 3 and receive a 2-dose schedule of either CVnCoV 12 µg or placebo in a 1:1 ratio. Similar to Phase 2b, enrollment targets subjects ≥ 61 years of age to be approximately 20% to 25% of the Phase 3 trial population (6,500 to 8,125 subjects). Also here this percentage is just an ex ante assumption. No procedural intervention like e.g. any caps on the age strata are entailed to meet this percentage.

8.3 Specifics of Open-Label Phase (Scenario A only)

2 cohorts are defined for the open-label phase:

- Cohort A: CVnCoV-AV: Subjects ≥ 18 years who received at least 1 dose of CVnCoV and an AV before EOT.
- Cohort B: CVnCoV only: Subjects ≥ 18 years who received at least 1 dose of CVnCoV and no AV before EOT.

Placebo subjects do not require further follow-up. They are notified of the trial treatment they received by a Subject Information Letter and withdrawn after an EOT phone call. Subjects who received at least 1 dose of CVnCoV are asked to remain in the open-label phase of the trial for safety follow up. These subjects are notified of the trial treatment they received at the next planned trial visit/phone call. Subjects must provide additional written informed consent to be eligible for the open-label phase.

A simplification of the visit and calls schedule is implemented for the follow up of subjects who received CVnCoV until EOT: No blood samples are to be collected; home visits are no longer to be performed, and clinic visits may be replaced with phone calls. The open-label phase provides additional safety data, including data from subjects who receive an AV after CVnCoV receipt. Subjects participating in the open label (OL) phase of the trial continue to be evaluated for symptomatic COVID-19 cases (passive surveillance for COVID-19) No confirmatory efficacy analyses are planned, only a descriptive summary of cases. The electronic diary (eDiary) is no longer used during the open-label phase.

Trial unblinding and transition from the randomized observer-blinded phase to the open-label phase is conducted on a country/site level and starts immediately after full competent authority and Ethics Committee approval of Protocol version 4.0 in the respective country/site.

The open-label phase visits (OL-1 and OL-2) are scheduled according to the originally scheduled visits/phone calls in the Phase 2b/3 schedule: Day 302 (-3/+21 days) and Day 393 (-0/+21 days). They are to be conducted as phone calls. Only if the Informed Consent Form (ICF) cannot be signed remotely a clinic visit may be performed.

8.4 Interim Analysis

Due to the uncertain incidence rate of COVID-19 cases in a pandemic setting, the trial is conducted as a case-driven trial, which includes two formal interim analyses and a final primary efficacy analysis both triggered by achieving a predefined number of cases for each analysis. As described in Section 8.0, cases of COVID-19 occurring in Phase 2b are pooled with those in Phase 3 for the primary analysis of VE. As such, subjects participating in Phase 2b contribute to the sample size for the final and interim analyses of VE.

The interim analyses for an early demonstration of high efficacy or futility are to be performed when 56 and 111 cases of COVID-19 meeting the primary efficacy case definition have been accrued. The assessment of the interim analyses is performed by the DSMB and the outcome is communicated without unblinding the trial team or the Sponsor.

Additionally, at or near the completion of enrollment, an unblinded review of the incidence rate of cases is to be performed by the DSMB. If the case accrual rate is lower than the planned 0.15% per month in placebo subjects, the DSMB may recommend an increase in sample size. If needed, another unblinded review by the DSMB may be performed later in the trial to further adjust the sample size.

8.5 End of Trial

A subject is considered to have completed the trial when he/she has completed all visits applicable for the group to which he/she was randomized to at trial entry.

For placebo subjects only: Scenario A: If the respective site has been unblinded and the subject had not yet completed or discontinued the trial the subject is considered to have completed the trial when he/she has completed the EOT phone call.

EOT is defined as the point at which the last subject has completed the last visit on Day 393 or prematurely discontinued the trial. This applies for both the blinded Phase 2b/3 and the OL phase (if applicable), whatever is later.

8.6 Independent Data Safety Monitoring Board

An independent DSMB is convened to oversee the safety of subjects participating in the trial, to assess the progress and conduct of the trial, to review the cumulative safety data from the trial, and to make recommendations to CureVac whether to continue, modify, or stop the trial.

The DSMB has regularly scheduled meetings to perform these responsibilities. During these meetings, the DSMB is informed on the safety data generated throughout the current CVnCoV portfolio. In addition to safety data, the DSMB is asked to review efficacy data at the interim analyses and possibly at other time points during the trial for a continued assessment of the risk-benefit of the trial. As part of the risk-benefit analysis, the DSMB periodically monitors COVID-19 cases for signals of Vaccine Dependent Disease Enhancement (VDE). The DSMB is also asked to perform an unblinded review(s) of the incidence rate of COVID-19 cases to recommend an increase(s) in sample size, if needed.

The DSMB Charter describes the details of the composition and objectives of the DSMB, the responsibilities of the DSMB, CureVac and Pharmaceutical Research Associates, Inc. (PRA), the schedule and conduct of the DSMB meetings, the datasets to be reviewed, and the stopping criteria for the trial. The Charter contains the DSMB-SAP.

8.7 Sample Size Considerations

This is an event-driven trial. Sample size and power considerations are based on the primary objective for demonstrating efficacy of CVnCoV in the prevention of virologically-confirmed cases of COVID-19 of any severity meeting the primary case definition.

8.7.1 Sample Size Considerations for the Primary Objective

A group sequential design with two interim analyses for demonstrating a high level of efficacy or reaching futility is planned using O'Brien and Fleming type error-spending-function [1] and the sample size is based on the test for one single proportion (i.e. the proportion of cases coming from CVnCoV group among all cases). The interim analyses for high efficacy or futility based on the primary endpoint of COVID-19 cases of any severity was to be performed once 56 and 111 cases have been accrued (approximately 35% and 69% of the final number of cases).

With a 2-sided alpha of 5%, a total of 160 COVID-19 cases of any severity (meeting the primary efficacy case definition for COVID-19 cases of any severity) are needed at final primary efficacy analysis, to have a power of 90% to demonstrate the VE is above 30% based on the lower bound of the confidence interval (CI) for VE when assuming that the VE under the alternative hypothesis is 60%. Note that this is equivalent to demonstrating that the proportion of cases coming from CVnCoV group is below 0.4118 based on the upper bound of the CI for the proportion when assuming that the proportion under the alternative hypothesis is equal to 0.2857.

Assuming an incidence rate of COVID-19 of 0.15% per month in placebo subjects, an overall non-evaluable rate of 20% (corresponding to subjects excluded from the Efficacy Analysis Set and drop-outs) and a VE of 60%, 36,500 subjects enrolled over approximately 3 months (18,250 per vaccine group) accrue 160 COVID-19 cases of any severity around 9 months after the first vaccination. A lower incidence rate, a longer enrollment duration, or a higher non-evaluable rate or VE delay the acquisition of the 160 cases and the time of final primary efficacy analysis.

Subjects are randomized to receive either CVnCoV or placebo in a 1:1 ratio, stratified by country and age group (18 to 60 and ≥ 61 years of age).

8.7.2 Sample Size Considerations for the Key Secondary Objectives

For the key secondary efficacy objective evaluating the prevention of virologically-confirmed moderate to severe cases of COVID-19, a lower number of cases has accrued at the time of final primary efficacy analysis compared to the primary endpoint. If one third of cases of any severity are moderate to severe, then 53 moderate to severe cases can be expected when the total number of COVID-19 cases is 160. The trial then has 91.5% power to obtain a lower limit (LL) of the 95% CI of the VE above 20% when assuming the true VE is 70%.

For the key secondary efficacy objective evaluating the prevention virologically-confirmed severe cases of COVID-19 an analysis of a large database by Verity et al. [2], suggests approximately 20% of COVID-19 cases can be clinically defined as severe or critical, the latter requiring intensive care.

With 32 cases of severe COVID-19 (20% of 160 cases), the trial has 81.5% power to detect a LL of the 95% CI of the VE above 10% when assuming the VE is 70%. The power increases to 91% if the VE against severe cases is 75%.

For the key secondary endpoint the prevention of first episodes of virologically-confirmed cases of COVID-19 of any severity caused by "wild type", if 50% of COVID-19 cases of any type are "wild type" and "Alpha", then 80 such cases can be expected when the total number of COVID-19 cases is 160. The trial then has 90.7% power to obtain a LL of the 95% CI of the VE above 30% when assuming the true VE is 70%.

8.8 Randomization and Blinding

Phase 2b and Phase 3 are randomized, observer-blinded, and placebo-controlled. The difference in appearance of the investigational CVnCoV vaccine and placebo requires the trial to be conducted in an observer-blinded manner.

The pharmacist at the site is not blinded to the identity of the trial vaccine being administered to the subject. However, the vaccinator, Investigator and all site personnel involved in the conduct of the trial (including follow-up of safety and COVID-19 case ascertainment) are blinded to trial vaccine and subject treatment assignments. All personnel at PRA and Sponsor directly involved in the conduct of the trial are also initially

blinded. There are certain individuals at PRA and Sponsor whose function requires them to be unblinded during the trial (e.g., unblinded monitoring for trial vaccine accountability in the pharmacy; unblinded independent statistician assisting the DSMB; review of immunogenicity data). These unblinded individuals are identified and their responsibilities documented.

At the timepoint of the first data extraction for the final primary analysis the complete study team at the designated CRO and some Sponsor designees become unblinded.

As the immunogenicity results would unblind the subject's treatment assignment, an independent laboratory performing the assays keeps the results in strict confidence. An unblinded person, named at the start of the trial and independent of the conduct of the trial, has the responsibility of reviewing the quality of the immunogenicity data as it is being generated. This person maintains the results in strict confidence. To maintain the blind, the immunogenicity data is only merged with the clinical database at Clinical Data Interchange Standards Consortium (CDISC) level following unblinding of the trial at the final primary analysis. As the trial vaccine is not affecting the N antibody status, the N antibody laboratory data is not considered unblinding information.

Subjects 18 years of age or older are enrolled at multiple trial sites globally and are randomized in a 1:1 ratio to receive a 2-dose schedule of either CVnCoV or placebo. The randomization is performed centrally and stratified by country and by age group (18 to 60 and ≥61 years of age).

Initiation of subject enrollment into the two target age groups of Phase 2b is flexible: Depending on the timing of data from the Phase 1 and Phase 2a studies, enrollment into the two age groups of Phase 2b would have been allowed to be staggered, initially starting with subjects 18 to 60 years of age followed by subjects ≥ 61 years of age. As the older age group was expected to comprise only 20% to 25% of the total number of subjects in Phase 2b, this staggered start was not expected to impact overall enrollment of the Phase 2b cohort.

The randomization scheme is generated and maintained by an Independent Statistical group at PRA. Subjects are enrolled into the trial online and randomized using an interactive web response system (IWRS).

9.0 Trial Endpoints

9.1 Primary Endpoints

9.1.1 Primary Efficacy Endpoint

- Occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity meeting the case definition for the primary efficacy analysis.

9.1.2 Primary Safety Endpoints

All safety endpoints are analyzed in all subjects, in subjects seronegative at baseline, and in subjects seropositive at baseline

- Occurrence, intensity and relationship of medically-attended AEs collected to 6 months after the second trial vaccination in all subjects.
- Occurrence, intensity and relationship of SAEs and AESIs collected through EOT Visit in all subjects.
- Occurrence of fatal SAEs through EOT Visit in all subjects.
- Occurrence, intensity and duration of each solicited local AE within 7 days after each trial vaccination in Phase 2b subjects.

- Occurrence, intensity, and duration of each solicited systemic AE within 7 days after each trial vaccination in Phase 2b subjects.
- Occurrence, intensity and relationship of unsolicited AEs occurring within 28 days after each trial vaccination in Phase 2b subjects.
- Occurrence of AEs leading to vaccine withdrawal or trial discontinuation through to EOT Visit in all subjects.

9.2 Secondary Endpoints

9.2.1 Key Secondary Efficacy Endpoints

- Occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of moderate to severe COVID-19 meeting the case definition for the primary efficacy analysis
- Occurrence of first episodes of virologically-confirmed (RT-PCR positive) severe cases of COVID-19 meeting the case definition for the primary efficacy analysis.
- Occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity meeting the case definition due to infection with “wild type” and “Alpha” SARS-CoV-2 strains in SARS-CoV-2 naïve subjects.

9.2.2 Other Secondary Efficacy Endpoints

- In subjects ≥ 61 years of age, occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity meeting the case definition for the primary efficacy analysis.
- BoD scores calculated based on first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity meeting the case definition for the primary efficacy analysis.
    - BoD #1 – no disease (not infected or asymptomatic infection) = 0; mild or moderate disease = 1; severe disease = 2.
    - BoD #2 – no disease (not infected or asymptomatic infection) = 0; disease without hospitalization = 1; disease with hospitalization = 2; death = 3.
- Occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity with symptom onset at any time after the first trial vaccination.

9.2.3 Secondary Immunogenicity Endpoints (Phase 2b Immunogenicity Subset)

Scenario A: Exclude Day 57.

- SARS-CoV-2 RBD of the S protein antibody responses on Days 1, 29, 43, 57, 120 and 211:
    - Serum antibodies to SARS-CoV-2 RBD of the S protein, as measured by immunoassay.
    - Occurrence of seroconversion to SARS-CoV-2 RBD of S protein.

      Thereby, seroconversion is defined as detectable SARS-CoV-2 RBD of S protein antibodies in the serum of subjects who tested seronegative at Day 1 (baseline), see Section 10.6.1 and Section 10.6.2.1 for details.
- SARS-CoV-2 viral neutralizing antibody responses on Days 1, 29, 43, 57, 120 and 211:

- Serum viral neutralizing antibodies to SARS-CoV-2 virus, as measured by a functional activity assay.
- Occurrence of seroconversion to SARS-CoV-2 virus.

  Thereby, seroconversion is defined as detectable SARS-CoV-2 viral neutralizing antibodies in the serum of subjects who tested seronegative at Day 1 (baseline), see Section 10.6.1 and Section 10.6.2.2 for details.

9.3 Exploratory Endpoints

9.3.1 Exploratory Efficacy Endpoints

- Severity assessment of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 meeting the case definition for the primary efficacy analysis.
- The following endpoints are analyzed as occurring ≥ 15 days after the second trial vaccination (full VE).
  - In SARS-CoV-2 naïve subjects:
    - Occurrence of supplemental oxygenation due to COVID-19.
    - Occurrence of mechanical ventilation due to COVID-19.
    - Occurrence of hospitalization due to COVID-19.
    - Occurrence of death due to COVID-19.
    - Occurrence of death due to any cause.

  Thereby, the start date of the COVID-19 case leading to occurrence of any of the above must be ≥ 15 days after second trial vaccination.

9.3.2 Exploratory Immunogenicity Endpoints

On Days 1, 29, 43, 120, and 211 in peripheral blood mononuclear cells (PBMCs) from approximately 200 subjects at selected site(s):

- The frequency and functionality of SARS-CoV-2 RBD of S-specific T-cell response after antigen stimulation by intracellular cytokine staining (ICS) to investigate Th1 response and expression of Th2 markers.
- The proportion of subjects with a detectable increase in SARS-CoV-2 RBD of S-specific T-cell response.

Thereby, testing of samples collected on Day 120 and Day 211 is done only in subjects categorized as T-cell responders on Day 29 and/or Day 43. First testing of samples is performed for a subset of these 200 subjects and might be extended to 200 subjects if T-cell response is detectable.

9.4 Open-label Endpoints (Scenario A only)

9.4.1 Safety Endpoints

- Occurrence, intensity, and relationship to CVnCoV of SAEs and AESIs collected throughout the trial until the EOT.
- Occurrence of fatal SAEs throughout the trial until EOT.

- Only for Cohort A: CVnCoV-AV: Occurrence of AEs leading to trial discontinuation after the first dose with an AV in the open-label phase until EOT.

9.4.2 Exploratory Efficacy Endpoint

- Occurrence of first episodes of symptomatic virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity as assessed by the Investigator.

9.5 Estimands

Table 1 presents the study endpoints and corresponding estimands based on the study protocol, Section 4.3.

Table 1: Study Endpoints and Estimands for the Blinded Phase

ENDPOINTS (subject level)	ESTIMANDS (population level)
Primary Efficacy	
• Occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity meeting the case definition for the primary efficacy analysis.	In naïve evaluable subjects (complying with the definition of Efficacy Analysis Set) at least 15 days following second vaccination: VE = 1- RR with exact 95% CI Where RR (relative risk) is the ratio of attack rates of COVID-19 cases per 100 person-month in the CVnCoV vaccine group over the placebo group.
Primary Safety	
• Occurrence, intensity and relationship of medically-attended AEs collected through 6 months after the second trial vaccination in all subjects. • Occurrence, intensity and relationship of SAEs and AESIs collected through EOT Visit in all subjects. • Occurrence of fatal SAEs through EOT Visit in all subjects.	In subjects who received at least one dose of CVnCoV or placebo vaccine, the number and percentage of subjects by group reporting at least 1 and at each type (by System Organ Class [SOC]/Preferred Term [PT]) of: • Medically-attended AE in the 6 months after the last vaccination overall, by intensity and by causal relationship to trial vaccine. • SAE in the year after the last vaccination overall and by causal relationship to trial vaccine. • AESI in the year after the last vaccination overall, by intensity and by causal relationship to trial vaccine. • Fatal SAE in the year after the last vaccination.
• Occurrence, intensity and duration of each solicited local AE within 7 days after each trial vaccination in Phase 2b subjects. • Occurrence, intensity, duration of each solicited systemic AE within 7 days after each trial vaccination in Phase 2b subjects • Occurrence, intensity and relationship of unsolicited AEs occurring within 28 days after each trial vaccination in Phase 2b subjects.	In phase 2b subjects who received at least one dose of CVnCoV or placebo vaccine: The number and percentage of subjects by group reporting: • Each solicited local AE within 7 days after each trial vaccination by intensity and overall • Each solicited systemic AE within 7 days after each trial vaccination by intensity, by relationship to trial vaccine and overall. At least 1 unsolicited AE, at least 1 grade 3 unsolicited AE and each

ENDPOINTS (subject level)	ESTIMANDS (population level)
• Occurrence of AEs leading to vaccine withdrawal or trial discontinuation through EOT Visit in all subjects.	unsolicited AE by SOC/PT occurring within 28 days after each trial vaccination and overall by causal relationship to trial vaccine and overall • At least 1 AE leading to vaccine withdrawal or trial discontinuation in the year after the last trial vaccination The mean duration in days by group with standard deviation (SD) of solicited AEs (within the solicited period, total duration).
Key Secondary Efficacy	
• Occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of moderate to severe COVID-19 meeting the case definition for the primary efficacy analysis.	In naïve evaluable subjects (complying with the definition of Efficacy Analysis Set) at least 15 days following second vaccination: VE = 1- RR with exact 95% CI Where RR is the ratio of attack rates of COVID-19 cases per 100 person month in the CVnCoV vaccine group over the placebo group.
• Occurrence of first episodes of virologically-confirmed (RT-PCR positive) severe cases of COVID-19 meeting the case definition for the primary efficacy analysis.	In naïve evaluable subjects (complying with the definition of Efficacy Analysis Set) at least 15 days following second vaccination: VE = 1- RR with exact 95% CI Where RR is the ratio of attack rates of severe COVID-19 cases per 100 person-month in the CVnCoV vaccine group over the placebo group
• Occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of “wild type” and “Alpha” SARS CoV 2 strains in SARS CoV 2 naïve subjects.	In naïve evaluable subjects (complying with the definition of Efficacy Analysis Set) at least 15 days following second vaccination: VE = 1- RR with exact 95% CI Where RR is the ratio of attack rates of COVID-19 cases per 100 person month in the CVnCoV vaccine group over the placebo group.
Other Secondary Efficacy	
• In subjects ≥ 61 years of age, occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity meeting the case definition for the primary efficacy analysis.	In naïve evaluable subjects ≥ 61 years of age at randomization (complying with the definition of Efficacy Analysis Set) at least 15 days following second vaccination: VE = 1- RR with exact 95% CI Where RR is the ratio of attack rates of COVID-19 cases per 100 person-month in the CVnCoV vaccine group over the placebo group
• BoD scores calculated based on first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity	In naïve evaluable subjects (complying with the definition of Efficacy Analysis Set) at least 15 days following second trial vaccination:

ENDPOINTS (subject level)	ESTIMANDS (population level)
meeting the case definition for the primary efficacy analysis. ○ BoD #1 – no disease (not infected or asymptomatic infection) = 0; mild or moderate disease = 1; severe disease = 2. ○ BoD #2 – no disease (not infected or asymptomatic infection) = 0; disease without hospitalization = 1; disease with hospitalization = 2; death = 3.	VE_{BOD} = 1- SV/SP with exact 95% CI Where SV denotes the ratio of mean BoD score in the CVnCoV group and the mean follow-up time (years) in the CVnCoV group and SP denotes the ratio of mean BoD score in the placebo group and the mean follow-up time (years) in the placebo group.
• Occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity with symptom onset at any time after the first trial vaccination.	In naïve subjects who received at least one dose of CVnCoV or placebo vaccine at any time after the first vaccination: VE = 1- RR with exact 95% CI Where RR is the ratio of attack rates of COVID-19 cases per 100 person-month in the CVnCoV vaccine group over the placebo group
Secondary Immunogenicity	
SARS-CoV-2 RBD of S protein antibody responses on Days 1, 29, 43, (57,) 120 and 211: • Serum antibodies to SARS-CoV-2 RBD of S protein, • Occurrence of seroconversion to SARS-CoV-2 RBD of S protein. Seroconversion is defined as detectable SARS-CoV-2 RBD of S protein antibodies in the serum of subjects who tested seronegative at baseline.	In phase 2b subjects belonging to the IS and evaluable (complying with the definition of per-protocol immunogenicity set): On Days 1, 29, 43, (57,) 120 and 211: • Geometric mean of titers (GMT) with 95% CI of SARS-CoV-2 RBD of S protein antibody responses by group and by baseline sero-status and group. On Days 29, 43, (57,) 120, 211 (and 393) for subjects seropositive at baseline: • Geometric Mean (GM) of Fold Change (FC) from baseline with 95% CI of SARS-CoV-2 RBD S protein antibody responses by group. On Days 29, 43, (57,) 120, 211 (and 393) for subjects seronegative at baseline: • Number and percentage with exact 95%CI of subjects by group for who a seroconversion is observed (detectable SARS-CoV-2 RBD of S protein antibodies in the serum)
SARS-CoV-2 viral neutralizing antibody responses on Days 1, 29, 43, (57,) 120 and 211: • Serum viral neutralizing antibodies to SARS-CoV-2 virus. • Occurrence of seroconversion to SARS-CoV-2 virus. Seroconversion is defined as detectable SARS-CoV-2 viral neutralizing antibodies in	In phase 2b subjects belonging to the IS and evaluable (complying with the definition of per-protocol immunogenicity set): On Days 1, 29, 43, (57,) 120, 211 and: • GMT with 95% CI of neutralizing antibodies to SARS-CoV-2 virus by group and by baseline serostatus and group

ENDPOINTS (subject level)	ESTIMANDS (population level)
the serum of subjects who tested seronegative at baseline.	On Days 29, 43, (57,) 120 and 211 for subjects seropositive at baseline: • GM of FC from baseline with 95% CI of neutralizing antibodies to SARS-CoV-2 virus by group. On Days 29, 43, (57,) 120 and 211 for subjects seronegative at baseline: • Number and percentage with exact 95%CI of subjects by group for who a seroconversion is observed (detectable neutralizing antibodies to SARS-CoV-2 virus in the serum).
Exploratory Efficacy	
• Severity assessment of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 meeting the case definition for the primary efficacy analysis	In naïve evaluable subjects (complying with the definition of Efficacy Analysis Set) who had a first episode of a virologically-confirmed (RT-PCR positive) case of COVID-19 of any severity meeting the case definition for the primary efficacy analysis: • The proportions of mild, moderate and severe COVID-19 cases among all cases by severity group

ENDPOINTS (subject level)	ESTIMANDS (population level)
The following endpoints are analyzed as occurring ≥ 15 days following the second trial vaccination (full VE). • Occurrence of supplemental oxygenation due to COVID-19. • Occurrence of mechanical ventilation due to COVID-19. • Occurrence of hospitalization due to COVID-19. • Occurrence of death due to COVID-19. • Occurrence of death due to any cause.	In naïve evaluable subjects (complying with the definition of Efficacy Analysis Set) at least 15 days following second vaccination: Number and percentages by group of subjects who: • Need supplemental oxygenation due to COVID-19. • Need mechanical ventilation due to COVID-19. • Were hospitalized due to COVID-19. • Deceased due to COVID-19. • Deceased due to any cause.
Exploratory Immunogenicity	
On Days 1, 29, 43, 120, and 211 in PBMCs from up to 200 subjects at selected site(s): • The frequency and functionality of SARS-CoV-2 RBD of S-specific T-cell response after antigen stimulation by ICS to investigate Th1 response and expression of Th2 markers. • The proportion of subjects with a detectable increase in SARS-CoV-2 RBD of S-specific T-cell response. Thereby, testing of samples collected on Day 120 and Day 211 is done only in subjects categorized as T-cell responders on Day 29 and/or Day 43. First testing of samples is performed for a subset of these subjects and might be extended to 200 subjects if T-cell response is detectable.	In subjects belonging to the Immunogenicity/Reactogenicity subset and selected to take part of the CMI subset: • The number and percentage of subjects for whom a SARS CoV-2 RBD of S-specific T-cell response is observed • The number and percentage of subjects with a detectable increase in SARS-CoV-2 RBD of S-specific T-cell response

Table 2: Study Endpoints and Estimands for the Open Label Phase (Scenario A only)

Safety	
• Occurrence, intensity and relationship of SAEs and AESIs collected throughout the trial until the EOT. • Occurrence of fatal SAEs throughout the trial until the EOT. • Occurrence of AEs leading to trial discontinuation.	In subjects who received at least 1 dose of CVnCoV and participate in the open-label phase of the trial: • SAE after the first dose with an AV in the open-label phase until the EOT. • AESI after the first dose with an AV in the open-label phase until the EOT. • Fatal SAE in the open-label phase through EOT. • At least 1 AE leading to trial discontinuation.
Exploratory Efficacy	
• Occurrence of first episodes of symptomatic virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity as assessed by the Investigator.	In naïve subjects from the Open-Label Set (OLS) at any time after the first vaccination: VE = 1- RR with exact 95% CI Where RR is the ratio of attack rates of COVID-19 cases per 100 person-month in Cohort A: CVnCoV-AV over Cohort B: CVnCoV only.

9.6 Population Sets

In the Safety Analysis Set (SAS), the Safety Analysis Set 2 (SAS 2) and in the Solicited AEs Safety Analysis Set (SASsol), subjects are analyzed in the group they actually received ("as treated"). Based on the number of subjects receiving treatment not as randomized, selected efficacy analyses performed on the SAS "as treated" may be repeated on the SAS, analyzing subjects under the treatment they were actually randomized to.

If a subject received both the active vaccine and the placebo (i.e. at the two different vaccination timepoints or the same vaccination timepoint), subjects are analyzed in the active vaccine group for "as treated" analyses.

Following the intent-to-treat principle, in the Efficacy Sets and Per-Protocol Sets, subjects are analyzed in the group to which they were randomized ("as randomized").

Any analyses using all randomized subjects are based on vaccination "as randomized".

Clarifying notes regarding immunogenicity analyses: There are no analyses (tables or figures) performed on the full IS (only on the Per Protocol Immunogenicity [PPI] Set which is a subset of the IS). Listings based on the IS are displayed by actual treatment received. As described above, analyses on the PPI Set are performed "as randomized". As correct treatment allocation is an eligibility criterion for any per protocol (PP) set in this study, "as randomized" and "as treated" are identical for PP sets.

9.6.1 Safety Analysis Sets (SAS, SAS 2, SASsol)

- The SAS includes all subjects randomized in phase 2b or 3 who received at least one dose of CVnCoV or placebo
- The SASsol includes all phase 2b subjects of the SAS with at least one diary collection indicating the occurrence or lack of occurrence of solicited AEs. See Section 10.5.2 for further details.
- The SAS 2 includes all phase 2b subjects of the SAS

9.6.2 Efficacy Analysis Set Disregarding Unblinding (EASU)

The EASU includes all subjects randomized in Phase 2b or Phase 3 who:

- Received both doses of trial vaccine according to their randomization (two doses of CVnCoV if randomized to CVnCoV or two doses of placebo if randomized to placebo).
- Had not developed a virologically-confirmed case of COVID-19 before trial entry (based on exclusion criteria 1, see Trial Protocol).
- Had not developed a virologically-confirmed case of COVID-19 (definition in Section 10.7.2) or an asymptomatic case of SARS-CoV-2 (definition in Section 10.8) before 15 days after the second vaccination.
- Had not stopped the trial before 15 days after the second vaccination.
- Were SARS-CoV-2 naïve at baseline and Visit Day 43 (based on seronegativity to N protein in the blood sample taken at baseline and Visit Day 43, see Section 10.6.1 for details).
- Did not receive an AV for preventing COVID-19 prior to 15 days after the second vaccination (See Section 10.11)

Where available the information assessed by the independent Adjudication Committee of clinicians (Section 10.7.6) is used.

9.6.3 Efficacy Analysis Set (EAS)

The EAS includes all subjects of the EASU but excluding subjects who:

- Were unblinded prior to 15 days after the second vaccination (See Section 10.11)

Where available, the information assessed by the independent Adjudication Committee of clinicians (Section 10.7.6) is used.

9.6.4 Efficacy Analysis Set for Seroconversion for N Protein Antibody (EASS)

Not further applicable.

9.6.5 Immunogenicity Subset (IS)

The IS is defined as all Phase 2b subjects from the immunogenicity cohort as indicated on the CRF (i.e. ~the first 600 subjects enrolled into each of the two age groups in Phase 2b [18-60 and ≥ 61 years of age]).

9.6.6 Per Protocol Immunogenicity (PPI) Set

The PPI Set includes all Phase 2b subjects who belong to IS and who:

- Received both doses as randomized and within the windows defined in the protocol.
- Have no important protocol deviations that are expected to impact the immunogenicity outcomes as specified in Section 12.5.
- Have not received medical treatments (such as blood products, immunoglobulin therapy or an AV) that may interfere with one or both of the proposed immunogenicity measurements.
- Have at least one blood sample collected at baseline and starting at 14 days (Visit Day 43) post-second vaccination available for analysis.

Subjects who have been tested positive for COVID-19 have their data included up to the point of a positive test result.

Subjects to be excluded from the PPI Set are identified and reviewed at the Blinded Data Review Meeting held before any formal analysis (interim or final). See Section 12.5 for further details.

9.6.7 Open-Label Set (OLS)

The OLS includes all study subjects who

- Received at least 1 dose of CVnCoV.
- Provided additional written informed consent to attend the OL phase.

This implies that, to be eligible for the OLS, participants must be ongoing study subjects at the time protocol version 4.0 is approved for their site.

Participants of the open-label phase and the OLS are to be considered synonymous.

9.6.8 Cohorts in the Open-Label Phase

All subjects who rolled over to the open-label phase are allocated to 1 of these 2 cohorts:

- Cohort A: CVnCoV-AV: OL participants who received an AV before EOT.
- Cohort B: CVnCoV only: OL participants who received no AV before EOT.

Some further clarification notes on subjects who continue in the open-label phase:

- OLS subjects who were already individually unblinded during the randomized observer-blinded phase and who received CVnCoV but – according to their concomitant medication data – did not receive an AV before implementation of Protocol version 4.0 and – according to their concomitant medication data – do not receive an AV until EOT are included in cohort B.
- OLS subjects who were already individually unblinded and – according to their concomitant medication data –either received an AV during the OL phase or already any time during the blinded study phase are included in Cohort A.
- OLS subjects who intended to receive an AV but – according to their concomitant medication data – have not received an AV before EOT are in Cohort B, irrespective of their intention recorded on the CRF.
- OLS subjects who initially intended to participate in the open-label phase without receiving an AV but – according to their concomitant medication data – nevertheless receive(d) an AV (within the open-label phase or already during the blinded study phase) are in Cohort A, irrespective of their intention recorded on the CRF.
- OLS subjects who were not individually unblinded but nevertheless received an AV in the blinded phase are included in Cohort A.

Allocation to cohorts is performed retrospectively. This means: At the time of analysis the concomitant medication data of open-label participants is checked for AV receipt. If the subject has an AV application recorded for any timepoint between first study dose and EOT the subject is eligible for Cohort A. All other open-label phase participants are allocated to Cohort B.

9.6.9 Summary of Analysis Sets to be Used per Analysis

Table 3Table 4 and Table 4**Error! Reference source not found.** below provide an overview on the Analysis Sets used for the analyses of each endpoint.

Table 3: Summary of Analysis Sets to be Used per Analysis - Efficacy Endpoints

ENDPOINT TYPE	ENDPOINT SHORT DESCRIPTION	ANALYSIS SET
PRIMARY EFFICACY ENDPOINT	First episodes of COVID-19 cases.	EAS
KEY SECONDARY EFFICACY ENDPOINT	First episodes of moderate to severe COVID-19 cases.	EAS
	First episodes of severe COVID-19 cases.	EAS
	"Wild type" and "Alpha" SARS-CoV-2 strains	EAS
OTHER SECONDARY EFFICACY ENDPOINT	First episodes of COVID-19 cases in subjects ≥ 61 years of age	EAS*
	First episodes of SARS-CoV-2 infection, with or without symptoms.	EAS
	BoD Scores	EAS
	First episodes of COVID-19 cases with symptom onset at any time after the first trial vaccination	SAS#
EXPLORATORY EFFICACY ENDPOINT	Severity assessment of first episodes of COVID-19 cases	EAS
	Any strain COVID-19	EAS
	Supplemental oxygenation, mechanical ventilation, hospitalization, death (cases ≥ 15 days after second vaccination)	EAS
	Supplemental oxygenation, mechanical ventilation, hospitalization, death (cases after first dose)	SAS
	First episodes of COVID-19 cases with symptom onset ≥ 15 days after second vaccination, regardless of baseline serostatus	SAS$
	First episodes of COVID-19 cases with symptom onset at any time after the first vaccination, regardless of baseline serostatus	SAS

ENDPOINT TYPE	ENDPOINT SHORT DESCRIPTION	ANALYSIS SET
	Second episodes of COVID-19 cases	EAS

*** RESTRICTED TO SUBJECTS ≥61 YEARS OF AGE**
 # RESTRICTED TO SUBJECTS WITH NEGATIVE BASELINE SEROSTATUS
$ RESTRICTED TO SUBJECTS WHO RECEIVED BOTH DOSES AS RANDOMIZED, DID NOT DEVELOP A COVID-19 CASE OR DISCONTINUED TRIAL PRIOR TO 15 DAYS AFTER SECOND VACCINATION

Table 4: Summary of Analysis Sets to be Used per Analysis - Safety and Immunogenicity Endpoints

ENDPOINT TYPE	ENDPOINT SHORT DESCRIPTION	ANALYSIS SET
PRIMARY SAFETY ENDPOINT$	Occurrence, intensity and relationship of medically-attended AEs	SAS
	Occurrence, intensity and relationship of SAEs and AESIs	SAS
	Occurrence of fatal SAEs	SAS
	Occurrence, intensity and duration of solicited local AEs	SASsol
	Occurrence, intensity and duration of solicited systemic AEs	SASsol
	Occurrence, intensity and relationship of unsolicited AEs	SAS 2
	Occurrence of AEs leading to vaccine withdrawal or trial discontinuation	SAS
SECONDARY IMMUNOGENICITY ENDPOINT	Serum antibodies to SARS-CoV-2 RBD of S protein	PPI
	Seroconversion to SARS-CoV-2 S RBD protein	PPI#
	Serum viral neutralizing antibodies to SARS-CoV-2 virus	PPI
	Seroconversion to SARS-CoV-2 virus	PPI#

ENDPOINT TYPE	ENDPOINT SHORT DESCRIPTION	ANALYSIS SET
EXPLORATORY IMMUNOGENICITY ENDPOINT	Frequency and functionality of SARS-CoV-2 RBD of S-specific T-cell response after ICS	PPI*
	Proportion of subjects with a detectable increase in SARS-CoV-2 RBD of S-specific T-cell response.	PPI*

 # RESTRICTED TO SUBJECTS SERONEGATIVE TO THE N PROTEIN AT BASELINE.
*** RESTRICTED TO SUBJECTS WITH CMI ASSESSMENTS PERFORMED**
$ ALL SAFETY ENDPOINTS ARE ANALYSED FOR ALL SUBJECTS, IN SUBJECTS SERONEGATIVE AT BASELINE, AND IN SUBJECTS SEROPOSITIVE AT BASELINE

10.0 Conventions and Derivations

10.1 Baseline and Change from Baseline

Unless otherwise stated, baseline is defined as the last non-missing measurement at Visit 1 (Day 1), prior to administration of the first dose of trial vaccine.

Change from baseline at any post baseline timepoint is defined as:

$$\text{Change from baseline} = \text{Observed Value at post baseline timepoint} - \text{Observed value at baseline.}$$

10.2 Trial Day

Throughout this trial, trial days are defined as follows:

- Day 1 is the day of first trial vaccination.
- For days after first trial vaccination, trial day in the blinded study phase is calculated as

$$Trial\ Day = Date\ of\ day - Date\ of\ first\ vaccination + 1\ .$$

- For days before first trial vaccination, trial day is calculated as

$$Trial\ Day = Date\ of\ day - Date\ of\ first\ vaccination.$$

- Day 1 of the open-label phase (OL-1) and EOT Day of the open-label phase (OL-2):

  The protocol defines OL-1 as Trial Day 302 (-3/+21) and OL-2 as Trial Day 393 (-0/+21) for OLS subjects.

Table 5: Replacement by OL-1 and OL-2 Visits for OLS Subjects

Site Unblinding Timepoint	Day 302 Replaced?	Clinical Visit 7/Day 393 Replaced?
By Day 302	By OL-1	By OL-2
After Day 393	No	No
After Day 302 but before Day 393	No	By OL-2

10.3 Missing Data

In general, no imputation of missing values is done except for the following:

- Imputation of missing onset date for confirmed COVID-19 cases as specified in Section 10.7.2.
- For SARS-CoV-2 RBD of S protein antibodies, and viral neutralizing antibodies, concentration values marked as below the lower limit of quantification (LLOQ) are set to 0.5*LLOQ for computation purposes.
- Imputation of (partially) missing AE start dates:
    - If start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if year value is missing, the imputed AE start date is set to missing.
    - If start date year value is before the vaccination start date year value, then the AE started before the vaccination. Therefore:
        - If month is missing, the imputed start date is set to the mid-year point (i.e., 01JULYYYY).
        - If month is not missing, the imputed start date is set to the mid-month point (i.e., 15MONYYYY).
    - If start date year value is equal to the vaccination start date year value, the start date month needs to be compared against the vaccination start date month, to determine the imputation rule to apply. Therefore:
        - If month is missing, the imputed month and imputed day is the same as start of vaccination
        - If month is lower than vaccination start date month and start date day is missing, the imputed start date is set to the mid-month point (i.e. 15MONYYYY).
        - If month is equal to the vaccination start date month and start date day is missing, the start day is set to the start day of vaccination.
        - If month is greater than the vaccination start date month and start date day is missing, the imputed start date is set to the beginning of the month (i.e., 01MONYYYY).
    - If start date year value is greater than the vaccination start date year value, the AE started after vaccination. Therefore:
        - If month is missing, the imputed start date is set to the year start point (i.e., 01JANYYYY).
        - If start date month is not missing and start date day is missing, the imputed start date is set to the beginning of the month (i.e., 01MONYYYY).
    - If after imputation of start and resolution date (see below) a start date is after the resolution date (for example if a missing day of a start date is set to 15 and the resolution date is before the 15th of the same month and year) then the start date is set to the resolution date.
- Imputation of (partially) missing AE end dates:
    - If date of resolution is completely missing, and it is assumed that it resolved at the date of the end of the trial, the date of the end of the trial is used as the AE end date.
    - If year is present, it is assumed that it resolved on 31 December of that year (i.e., 31DECYYYY), or at the end of the trial if this is earlier and in the same year.
    - If year and month are present, it is assumed that it resolved on the last day of that month, or at the end of the trial if this is earlier and in the same month/year.
- Imputation of missing AE start times:
    - If the (recorded or imputed) AE start date is equal to the vaccination start date, then the AE start time is the time of vaccination start.
    - In all other cases, AE start time is imputed as 00:00.

If not stated otherwise, the original or incomplete data is presented in listings rather than the imputed one.

10.4 Prior and Concomitant Medications

Medications are categorized as prior medication or concomitant medication based on the following rules:

- Any medication taken prior to blinded study phase start (first ICF signature) as recorded by the investigator is considered prior medication.
- Any medication **not** taken prior to blinded study phase start as recorded by the investigator is considered concomitant medication.
- Any medication taken prior to blinded study phase start as recorded by the investigator and for which “Ongoing” is ticked as “Yes” or “Unknown” is considered concomitant medication.

Note: A medication can be both prior and concomitant if it starts prior to trial start and is ongoing.

10.5 AEs

An AE is any untoward medical occurrence in a subject which does not necessarily have to have a causal relationship with the investigational product. In this trial, confirmed non-fatal cases of COVID-19 and complications/sequelae are not considered as AEs as they are captured on the CRF pages for COVID-19 illness which are expected outcomes of the trial and are analyzed as efficacy endpoints. Only for any complications and sequelae of COVID-19 illness not mentioned on the COVID-19 summary form in the electronic Case Report Form (eCRF), an AE form needs to be completed.

In this trial, for Phase 2b subjects, information on solicited local and systemic AEs occurring within 7 days after each CVnCoV vaccination and on unsolicited AEs occurring within 28 days after each CVnCoV vaccination are collected.

For all Phase 2b and Phase 3 subjects, information on medically attended AEs up to 6 months after second CVnCoV vaccination and SAEs, AESIs and AEs leading to vaccine withdrawal or trial discontinuation after the second CVnCoV vaccination to EOT Visit are recorded.

No other AEs require recording in the CRF.

The recording of AEs remains unchanged, irrespective of the subject rolling over to the OL-phase or not.

10.5.1 Treatment Emergent Adverse Events (TEAE)

A TEAE is any AE that first occurs or increases in severity or relationship to trial vaccine (CVnCoV/placebo) after the first dose of CVnCoV/placebo vaccine. AEs which change in severity or relationship to trial vaccine (CVnCoV/placebo) are assigned a new start date and captured as a new record in the CRF. Hence, an AE is defined as TEAEs if the start date/time is after the date/time of first CVnCoV/placebo vaccination. Imputed AE start date/time as defined in Section 10.3 is considered when assessing if an AE is treatment emergent. If the AE start date is still missing after applying imputation rules (i.e. missing year), the AE is considered treatment emergent and is assumed to occur within 28 days after any CVnCoV/placebo vaccination. However, it is not possible to link this event to a specific CVnCoV/placebo dose.

All Solicited AEs are considered treatment emergent, even in the case that (partially) missing or conflicting date/time information is recorded or imputed.

10.5.2 Solicited AEs

Solicited local AEs (injection site pain, redness, swelling and itching) and solicited systemic AEs (chills, fever, nausea/vomiting, diarrhea, headache, fatigue, myalgia and arthralgia) information is collected for Phase 2b subjects for each day of CVnCoV/placebo vaccination (i.e. dose 1 and dose 2) and for the following 7 days after each CVnCoV/placebo dose. Subjects record any occurrence of an AE, grading of severity, and medication for treatment of the AE in an eDiary.

Subjects' eDiaries are reviewed by the investigator and available information on solicited local and systemic AEs with a grade > 0 is integrated into the CRF, including assessment of severity on an intensity scale of mild, moderate, and severe (Grade 1 – Grade 3), see Table 6 and Table 7. Note that events with a severity Grade 0 are not recorded as AEs in the CRF.

Additional solicited AEs may be recorded by the investigator based on CRF review if the recording within the diary is deemed incomplete.

In case there is more than one solicited AE with the same relationship to study treatment on a specific day with the same type of reaction (e.g. myalgia, injection site pain, nausea/vomiting) but recorded as different events, records are collapsed for that specific diary day. Thereby, if there are overlapping events with the same relationship on a given diary day, they are collapsed and reported with the highest severity grade on that day. Overlapping events with different relationship to study treatment are not collapsed.

Solicited events reported as "Nausea" and "Vomiting" are considered to be of the same reaction type "Nausea/Vomiting".

Table 6: Intensity Grading* for Solicited Local Adverse Events

AE	GRADE	DEFINITION
PAIN AT INJECTION SITE	0	Absent
	1	Does not interfere with activity
	2	Interferes with activity and/or repeated use of non-narcotic pain reliever >24 hours
	3	Prevents daily activity and/or repeated use of narcotic pain reliever
REDNESS	0	<2.5 cm
	1	2.5 – 5 cm
	2	5.1 – 10 cm
	3	>10 cm
SWELLING	0	<2.5 cm
	1	2.5 – 5 cm and does not interfere with activity
	2	5.1 – 10 cm or interferes with activity
	3	>10 cm or prevents daily activity
ITCHING	0	Absent
	1	Mild, no interference with normal activity
	2	Moderate, some interference with normal activity
	3	Significant, prevents normal activity

*** FDA TOXICITY GRADING SCALE**

Solicited AEs are assigned to first or second CVnCoV/placebo dose based on the (reported or imputed) AE date. Solicited AEs occurring before dose 2 are assigned to dose 1. Solicited AEs occurring on or after dose 2, are assigned to dose 2.

Solicited local AEs are always considered related to trial vaccine. Relationship to trial vaccine for solicited systemic AEs is assessed by the investigator and recorded on the CRF.

If not stated otherwise, data as recorded on the CRF is used for analysis of solicited AEs. However, subject's diary data is used to assess their eligibility for the SASsol (see Section 9.6.1) as follows:

- If at least one question on occurrence of a local or systemic AE is answered with either “Yes” or “No”, then the subject is included in the SASsol.
- If no question on occurrence of a local or systemic AE is answered with either “Yes” or “No”, then the subject is **not** included in the SASsol.

It should be noted that the inclusion in the SASsol is defined overall, not by trial vaccine dosing. I.e. if a subject provided information on solicited AEs for the time period after the second CVnCoV/placebo vaccination, but not for the time period after the first CVnCoV/placebo vaccination, the subject is still included in the SASsol.

Table 7: Intensity Grading* for Solicited Systemic Adverse Events

AE	GRADE	DEFINITION
FEVER	0	<38°C
	1	≥38.0 – 38.4°C
	2	≥38.5 – 38.9°C
	3	≥39°C
HEADACHE	0	Absent
	1	Mild, no interference with normal activity
	2	Moderate, some interference with normal activity and/or repeated use of non-narcotic pain reliever >24 hours
	3	Significant; any use of narcotic pain reliever and/or prevents daily activity
FATIGUE	0	Absent
	1	Mild, no interference with normal activity
	2	Moderate, some interference with normal activity
	3	Significant, prevents normal activity
CHILLS	0	Absent
	1	Mild, no interference with normal activity
	2	Moderate, some interference with normal activity
	3	Significant, prevents normal activity
MYALGIA	0	Absent
	1	Mild, no interference with normal activity
	2	Moderate, some interference with normal activity
	3	Significant, prevents normal activity
ARTHRALGIA	0	Absent
	1	Mild, no interference with normal activity
	2	Moderate, some interference with normal activity
	3	Significant, prevents normal activity
NAUSEA/ VOMITING	0	Absent
	1	Mild, no interference with activity and/or 1 – 2 episodes/ 24 hours
	2	Moderate, some interference with activity and/or >2 episodes/ 24 hours
	3	Significant, prevents daily activity, requires outpatient i.v. hydration
DIARRHEA	0	Absent
	1	2 – 3 loose stools over 24 hours
	2	4 – 5 stools over 24 hours

AE	GRADE	DEFINITION
	3	6 or more watery stools or >800 g/24 hours or requires outpatient IV hydration

*** FDA TOXICITY GRADING SCALE; I.V. = INTRAVENOUS.**

10.5.3 Duration and Time of Onset for Solicited AEs

Duration of solicited local and systemic AEs is defined as the number of **consecutive** days with a recorded local/systemic AE regardless of grade. For example, Fatigue with Grade 1 occurring on day 2 and 3 and day 7 is counted as two separate events with the duration 2 days and 1 day.

The duration of solicited local and systemic AEs ongoing beyond Day 8 after vaccination is defined as

$$Duration = AE\ end\ date - AE\ start\ date + 1.$$

The AE end date as recorded on the CRF is used in the above formula, except for instances where the recorded date is incomplete in which case the imputed date is used.

The time of onset (Day) of a solicited AE is defined as the day of first occurrence of the AE after the trial vaccination it was assigned to (dose 1 or dose 2, see also Section 10.5.2), regardless of the severity (Grade 1 – Grade 3). The time of onset (Day) of a Grade 3 solicited AE is defined as the first day after the trial vaccination it was assigned to (dose 1 or dose 2, see also Section 10.5.2), on which the AE was first graded as severe (Grade 3), regardless of an earlier occurrence with a lower severity.

Durations are not calculated separately for each grade but rather only for any grade >0 (no matter how often it might transition up and down between grades 1 through 3) or grade=3. Only the longest consecutive duration determined this way is displayed.

Duration and time of onset are calculated separately for events recorded after each trial vaccination.

10.5.4 Unsolicited AEs

Information on unsolicited AEs occurring on each CVnCoV/placebo vaccination day (i.e. dose 1 and 2) and the following 28 days after each CVnCoV/placebo dose are collected for Phase 2b subjects. Data is recorded in the eDiary by the subject to aid AE reporting. The investigator reviews the eDiary and records information on any AEs on the CRF.

Unsolicited AEs are assigned to first or second CVnCoV/placebo dose based on the (reported or imputed) AE date. Unsolicited AEs occurring before dose 2 are assigned to dose 1. Unsolicited AEs occurring after dose 2, are assigned to dose 2. Unsolicited AEs occurring on the day of dose 2 are assigned to either dose 1 or dose 2 as per the following rules:

- If the AE occurred on the day of dose 2 but before vaccination with dose 2, the AE is assigned to dose 1.
- If the AE occurred on the day of dose 2 but on or after vaccination with dose 2, it is assigned to dose 2.
- If the AE occurred on the day of dose 2 and it cannot be determined whether it occurred before, on or after vaccination with dose 2, it is assigned to dose 2.

10.5.5 Adverse Events of Special Interest

The following events are considered and collected as AESIs throughout the trial:

- AEs with a suspected immune-mediated etiology (pIMDs, see Appendix 1)
- Other AEs relevant to SARS-CoV-2 vaccine development or the target disease (see Appendix 2)

AESI are identified as recorded by the investigator in the eCRF. No additional programming is performed to identify (potential) AESIs.

Note: Since it is to be expected that some trial subjects vaccinated with an AV remain in the study, the AESIs collected do not necessarily have to originate from the investigational product but might also have been caused by the AV. For details how this is handled in the analyses please see Section 12.7.1.

10.5.6 Medically Attended AEs

Up to 6 months after second CVnCoV/placebo vaccination (or up to EOT, whatever is earlier), subjects are asked to confirm if they sought medical attention for an AE. Medically attended AEs are defined as AEs with medically-attended visits that are not routine visits for physical examination or vaccination, such as visits for hospitalization, an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason. The start of a medically attended AE is defined by its start date, irrespective of the date medical attention was sought. A medically attended AE is considered as occurring up to 6 months after second trial vaccination if

$$Start\ Date\ of\ AE - (Scheduled)\ date\ of\ second\ vaccination + 1 \leq 180\ days.$$

I.e. one month is defined as 30 days and the date of the scheduled second vaccination (Day 29) is used in case a subject only received the first vaccination.

Although the 6 months of medically attended AE recording are not re-started when the subject receives an AV, the subject might have received an AV while still being inside the 6 months window after CVnCoV/placebo administration. Thus the medically attended AEs collected might have been caused by an AV. For details how this is handled in the analyses please see Section 12.7.1.

10.5.7 Adverse Events Related to Standardised and Customized MedDRA Queries

Subjects' AEs are filtered with Standardised Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQs) and Customized MedDRA Queries (CMQs) for the following SMQs/CMQs:

- Anaphylactic reaction (SMQ)
- Convulsions (SMQ)
- Embolic and thrombotic events
- Hypersensitivity (SMQ)
- Immune-mediated/autoimmune disorders (SMQ)
- Liver related investigations, signs and symptoms (Sub-SMQ)
- Paraesthesia, Hypoaesthesia, Hyperaesthesia (CMQ)
- Taste and smell disorders (CMQ)

The related terms are listed in Appendix 3.

Although rather unlikely it might happen that study subjects receive an AV during the 28 day post-CVnCoV/placebo injection window where SMQs/CMQs are recorded. Thus the SMQs/CMQs collected do not necessarily have to originate from the investigational product but might also have been caused by an AV or the association of CvnCoV and AV. For details how this is handled in the analyses please see Section 12.7.1.

10.6 Immunogenicity Assessments

Immunogenicity assessments to assess the immune response induced by vaccination with CVnCoV are only performed in a subset of Phase 2b subjects, the IS, and are evaluated in 2 ways:

- Binding antibodies to the SARS-CoV-2 RBD of the S protein Immunoglobulin G (IgG) measured in serum by immunoassay.

- Viral neutralizing antibodies directed against SARS-CoV-2 (MN 25 TCID50) measured in serum by a functional activity assay.

Results from the two assays are quantitative. Measures below the LLoQ are presented as half the LLoQ in the data.

Assessments for serology status to natural SARS-CoV-2 infection (SARS-CoV-2 N protein) are performed by immunoassay in all subjects. The N protein is not a component of the CVnCoV vaccine, but is measured to determine the serostatus of subjects to the SARS-CoV-2 virus and the occurrence of SARS-CoV-2 infections during the trial. Data provided is qualitative (positive/negative).

Additionally, CMI is evaluated in 200 (100 per treatment group) subjects in selected sites.

As some immunogenicity results could potentially unblind the subject's treatment assignment, the laboratory performing the concerned assays (IgG and MN 25 TCID50) keeps the results in strict confidence. The SARS-CoV-2 N protein data is not considered unblinding information.

10.6.1 SARS-CoV-2 Serology Status

For all subjects in the Phase 2b and Phase 3 parts of the trial, measurement of binding antibodies to the SARS-CoV-2 N protein are performed by immunoassay. Blood samples are taken on Day 1 (pre-vaccination baseline), Visit Day 43, Visit Day 211 and Visit Day 393 of the trial. (Day 393 assessments are only taken until the Urgent Safety Measure (USM) was implemented on 30-November-21.)

The (retrospective) SARS-CoV-2 serology status is defined based on levels of antibodies to the SARS-CoV-2 N protein. Subjects are defined as naïve to SARS-CoV-2 infection at baseline and Day 43, respectively, if there are no detectable SARS-CoV-2 N protein antibodies in the blood samples taken at baseline and Day 43, respectively.

Serology status at baseline is based on blood samples taken at Clinic Visit 1 (Visit Day 1) up to 2 days after 1st CVnCoV/placebo vaccination. The baseline definition for serology status is differing from the general baseline definition in this study (see Section 10.1).

Serology status at Visit Day 43 is based on blood samples taken at Clinic Visit 3 (Visit Day 43) 14 days after 2nd CVnCoV/placebo vaccination +/- 3 days.

For safety analyses, N antibody serostatus at baseline is used to define the seronegative and seropositive safety populations.

For the primary efficacy analyses, the subject must be seronegative/naïve to N protein at baseline and Visit Day 43 to be considered naïve when COVID-19 cases are being counted ≥ 15 days after second trial vaccination. For endpoints where cases are counted at any time after the 1st trial vaccination, these subjects only have to be seronegative/naive at baseline.

The same definition as given above is applied to assess the SARS-CoV-2 serology status of subjects at any other timepoint where a respective blood sample was taken; to measure infections with SARS-CoV-2 during the course of the trial.

Nota bene: Although the N antibody serostatus is to be considered an immunogenicity assessments, these values are not censored due to AV receipt.

10.6.2 Seroconversion

Seroconversion is defined by a relevant increase in antibody titer compared to baseline. The titer is the highest dilution factor that still yields a positive reading for the antibodies, i.e. larger titers correspond to larger concentration of antibodies. Depending on the type of antibodies and previous exposure of a subject to SARS-CoV-2 (as measured by antibodies to the SARS-CoV-2 N protein), different definitions of seroconversion apply:

10.6.2.1 SARS-CoV-2 RBD of S Protein Antibodies

In subjects who tested seronegative to the N protein for SARS-CoV-2 at baseline (see Section 10.6.1), seroconversion is defined as a fold increase above 1 in antibody titer against SARS-CoV-2 RBD of S protein.

In subjects who tested seropositive to the N protein for SARS-CoV-2 at baseline (see Section 10.6.1), the definition for seroconversion is a fold increase above 2 in antibody titer against SARS-CoV-2 RBD of S protein versus baseline.

10.6.2.2 SARS-CoV-2 Neutralizing Antibodies

In subjects who tested seronegative to the N protein for SARS-CoV-2 at baseline (see Section 10.6.1), seroconversion is defined as a fold increase above 1 in SARS-CoV-2 neutralizing antibody titer.

In subjects who tested seropositive to the N protein for SARS-CoV-2 at baseline (see Section 10.6.1), the definition for seroconversion is a fold increase above 2 in SARS-CoV-2 neutralizing antibody titer versus baseline.

10.6.3 Cell-mediated Immunity

CMI is evaluated in approximately 200 subjects in selected sites.

The frequency and functionality of SARS-CoV-2 RBD of S-specific T-cell response after antigen stimulation is determined in PBMC in comparison to baseline. CMI assessment is performed on Day 1 (baseline), Day 29, Day 43, Day 120 and Day 211. Note that testing on Day 120 and Day 211 is only performed on subjects who are determined as T-cell responders on Day 29 and/or Day 43.

10.7 COVID-19 Cases

COVID-19 case ascertainment occurs in an identical manner in both the Phase 2b and Phase 3 parts of the trial. Case detection begins with the identification of subjects reporting at least one symptom from a standardized list of symptoms. Based on a scripted phone interview with trial staff, subjects suspected of having COVID-19 undergo testing for SARS-CoV-2 virus. Details of the tests performed and, in case of confirmed COVID-19 cases, details on the COVID-19 cases are recorded on the CRF.

Scenario A: For consistency reasons, although the efficacy analysis has already been completed, the reporting procedure for COVID 19 cases in the open-label phase remains the same as in the randomized observer blinded phase (however, a reduced list of symptoms is used).

10.7.1 Case Detection

10.7.1.1 Routine Surveillance

During all clinic visits and phone calls, subjects are reminded to contact the trial site if they have any of the following symptoms [4]:

- **Fever** or Chills
- **Shortness of breath** or difficulty breathing
- **New loss of smell or taste**
- **Cough**
- Fatigue
- Muscle or body aches
- Headache
- Sore throat
- Congestion or runny nose

- Nausea or vomiting
- Diarrhea

Scenario A: Only symptoms in bold underline are effective.

In addition, subjects are messaged up to twice a week to provide a yes or no response to having COVID-19 symptoms.

Scenario A: Mobile Health Platform (MHP) is switched off, only passive surveillance is performed (subject to call site in case of symptoms).

Those who report symptoms either at the clinic visit or by phone call, or respond “yes” to having symptoms by messaging are contacted by trial staff for a follow-up interview(s) to determine the probability of the subject having COVID-19. If the subject is suspected of having COVID-19 illness, he/she undergoes testing for SARS-CoV-2 infection, consisting of a rapid antigen test performed locally by the trial staff and a molecular-based RT-PCR test performed at a designated central laboratory.

The result of both the antigen test and the central RT-PCR test are recorded on the CRF as positive or negative.

10.7.1.2 Non-Routine Surveillance for COVID-19 (Positive Test Outside of Trial Site)

Subjects are reminded to contact the trial site immediately if he/she has a positive SARS-CoV-2 test performed outside of the trial site, and they were symptomatic (COVID-19 illness) or asymptomatic at the time of the test.

The subject should be retested as soon as feasible to have the result confirmed by the central laboratory. This RT-PCR test result is considered definitive as a virologically-confirmed case of COVID-19. If the subject is not virologically-confirmed by RT-PCR testing, he/she returns to routine surveillance for COVID-19 as a subject who is naïve to SARS-CoV-2 infection (unless determined otherwise by a seropositive test to the N protein).

If the subject was symptomatic, trial staff use the scripted interview to collect information about the subject’s COVID-19 symptoms and medical condition.

Scenario A: No RT-PCR confirmation of positive test results that were performed outside the trial site is to be performed. Neither on suspected symptomatic or on suspected asymptomatic infections.

10.7.2 Definition of Virologically-Confirmed COVID-19 Case and Onset Date

A virologically-confirmed case of COVID-19 is defined as a positive SARS-CoV-2 specific RT-PCR test performed at a designated central laboratory in a person with clinically symptomatic disease consisting of one or more of the symptoms listed in Section 10.7.1.The onset date of a virologically confirmed COVID-19 case (identified during routine surveillance or outside of the trial) is defined as the date of symptom onset as recorded on the CRF. If the date of symptom onset is partially or completely missing, the following imputation rules are applied:

1. If the date is present but incomplete and it can be confirmed, based on the available date parts, that the onset was before first vaccination, then the missing date parts are imputed as the earliest possible date.
2. If a present but incomplete date is still incomplete after checking point 1, and it can be confirmed, based on the available date parts, that the onset was before 15 days after second vaccination, the missing date parts are imputed with the earliest possible date on or after first vaccination.
3. If a present but incomplete date is still incomplete after checking points 1 and 2, it is imputed with the earliest possible date ≥ 15 days after second vaccination.
4. If the symptom onset date is completely missing, the date of first positive RT-PCR test is used instead.

a) If the first positive RT-PCR test is incomplete then points 1-3 above should be applied on the first positive RT-PCR test date.

10.7.3 Definition of Mild, Moderate and Severe COVID-19 Cases

Mild COVID-19 cases are defined as virologically (RT-PCR) confirmed cases fulfilling **all** of the following:

- Symptomatic,
- No shortness of breath or difficulty breathing,
- No hypoxemia, i.e. oxygen saturations in arterial blood (SpO2) saturation ≥ 95% on room air at sea level; SpO2 should be adjusted according to altitude.
- Does not meet the case definition of moderate or severe COVID-19.

Moderate COVID-19 cases are defined as virologically (RT-PCR) confirmed cases fulfilling **any** of the following criteria:

- Shortness of breath or difficulty breathing
- Respiratory rate ≥ 20 to < 30 breaths per minute
- Abnormal SpO2, but still > 93% on room air at sea level; SpO2 should be adjusted according to altitude.
- Clinical or radiographic evidence of lower respiratory tract disease
- Radiologic evidence of deep vein thrombosis (DVT)

Severe COVID-19 cases are defined as virologically (RT-PCR) confirmed cases fulfilling **any** of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, SpO2 ≤ 93% on room air at sea level or arterial oxygen partial pressure/fractional inspired oxygen [PaO2/FIO2] < 300 mmHg). SpO2 should be adjusted according to altitude.
- Respiratory failure (defined as needing high flow-oxygen, noninvasive ventilation, mechanical ventilation or Extracorporeal membrane oxygenation [ECMO])
- Evidence of shock (systolic blood pressure [SBP] < 90 mmHg, diastolic blood pressure [DBP] < 60 mmHg, or requiring vasopressors)
- Significant renal, hepatic, or neurologic dysfunction
- Admission to Intensive Care Unit (ICU)
- Death

A fourth category of “moderate to severe” cases is further defined, combining cases of moderate severity and cases of severe severity.

10.7.4 COVID-19 Case Definition for Primary Efficacy Analysis

A case of COVID-19 meeting the case definition for primary efficacy analysis is defined as follows:

- Virologically-confirmed case of COVID-19 (of any severity) defined as a positive SARS-CoV-2 specific RT-PCR test in a person with clinically symptomatic COVID 19, see Section 10.7.2.
- Symptom onset ≥ 15 days after second trial vaccination, i.e.

$$Start\ date\ of\ symptoms - date\ of\ second\ vaccination\ \geq 15\ days.$$

See Section 10.7.2 for further details on definition of symptom onset.

- First episode of virologically-confirmed COVID-19, i.e. the subject must not have a history of virologically-confirmed COVID-19 illness at enrollment or have developed a case of virologically-confirmed COVID-19 before 15 days after the second trial vaccination.
- Subject is SARS-CoV-2 naïve at baseline and Day 43 (defined as seronegative to N protein in the blood samples collected at baseline and Day 43). See Section 10.6.1 for further details.

10.7.5 SARS-CoV-2 Genome Lineage Characterization

The characterization of SARS-CoV-2 variants are implemented as per Protocol Section 9.2.1.6. The following phylogenetic clustering is applied:

1. “Wild type” virus
2. “Alpha” variant of concern (VOC)
3. All other VOCs.

In this trial, the primary efficacy endpoint is based on all strains, the “wild type” virus and all SARS-CoV-2 variants (as defined under numbers 1, 2 and 3 above); the key secondary efficacy endpoint is based on the “wild type” virus and the Alpha variant (as defined under numbers 1 and 2 above); and the exploratory efficacy endpoint is based on disease caused by individual VOCs (as defined under numbers 2 and 3 above).

Genome lineage characterization of the SARS-CoV-2 viruses has been requested to stop on 01-Sep-2021.

10.7.6 Adjudication of COVID-19 Cases

An independent Committee of clinicians is formed to adjudicate all COVID-19 cases, and asymptomatic cases of SARS-CoV-2 infections (Section 10.8) . The Committee is blinded to the treatment assignments of the subjects. The cases are adjudicated by the members with respect to the following questions:

- Is the case a virologically-confirmed case of COVID-19 defined as a positive SARS-CoV-2 specific RT-PCR test in a person with clinically symptomatic COVID-19 with one or more of the symptoms listed in Section 10.7.1?
- Was the RT-PCR test performed at the CureVac designated central laboratory?
- Was the symptom onset of the case ≥ 15 days following the second vaccination? Or did it occur before 15 days following the second trial vaccination?
- Was the subject naïve or non-naïve to SARS-CoV-2 at baseline and Day 43? (defined as being seronegative or seropositive to the SARS-CoV-2 N protein at baseline and Day 43).
- Was the subject 18 to 60 years of age or ≥ 61 years of age?
- Was the subject asymptomatic? If asymptomatic, was the RT-PCR test positive ≥ 15 days following the second vaccination or before?
- Was it a mild, moderate or severe case of COVID-19 based on the provided clinical definitions?
- Did the subject require supplemental oxygenation? What type of oxygen support did the subject receive?
- Was the subject hospitalized? Was the subject admitted to the ICU?
- Did the subject die? Due to COVID-19 or another cause?

COVID-19 case summary data as provided by the Adjudication Committee is used for all relevant definitions and analyses, i.e. especially all primary efficacy cases have to be confirmed by the Adjudication Committee. Where the adjudicated data conflicts with other data recorded on the CRF (e.g. severity of the event, or

baseline serology status), the adjudication data generally overrules the other data available. This applies to both COVID-19 cases and asymptomatic cases of SARS-CoV-2 infections.

Exceptions:

1. For the analysis of COVID-19 cases by age group, the age at trial entry as recorded on the CRF rather than the age at onset (as assessed by the Adjudication Committee) is used.
2. The case onset date is also taken from the CRF, irrespective of the onset date recorded on the Adjudication Form.

COVID-19 case adjudication stopped on 18-Jun-2021 (cut-off date for the final efficacy analysis) and is not to be re-started again, also not in a possible open-label phase. The determining factor for the adjudication cut-off was the central PCR test date.

10.8 Definition of Asymptomatic Cases of SARS-CoV-2 Infection and Onset Date

In this trial no active surveillance for asymptomatic SARS-CoV-2 infections is foreseen. Subjects are reminded to contact the trial site immediately if he/she had a positive SARS-CoV-2 test performed outside of the trial site, whether or not they were symptomatic (COVID-19 illness) or asymptomatic at the time of the test.

If the subject was asymptomatic, trial staff contacts the subject immediately to collect information about the positive SARS-CoV-2 test the subject reported. The subject should be retested as soon as feasible to confirm the result. A positive RT-PCR test result is considered definitive as a virologically-confirmed case of SARS-CoV-2 infection.

If the subject is confirmed to have SARS-CoV-2 infection, the subject is followed by trial staff for at least 2 weeks for the development of any COVID-19 symptoms, to ensure that this is an asymptomatic infection. If the subject develops COVID-19, he/she is followed up as a COVID-19 case. If the subject is confirmed to be an asymptomatic infection, information is collected by the trial staff and documented on the appropriate CRF page.

The onset date of an asymptomatic infection is defined as the date of the positive RT-PCR test result performed by a central laboratory.

Scenario A: Asymptomatic cases are not collected in the OL Phase.

10.9 Burden of Disease

Two different BoD scores are calculated for each subject, based on their first episode of virologically confirmed COVID-19 case meeting the case definition for primary efficacy analysis.

BoD Score #1 is assigned as follows (considering only first episodes):

- No disease (i.e. not infected or only asymptomatic infection): Score = 0
- Mild or moderate disease (as defined in Section 10.7.3): Score = 1
- Severe disease (as defined in Section 10.7.3): Score = 2

BoD Score #2 is assigned as follows (considering only first episodes):

- No disease (i.e. not infected or only asymptomatic infection): Score = 0
- Disease without hospitalization: Score = 1
- Disease with hospitalization: Score = 2
- Death: Score = 3.

10.10 Individual and Site-Level Unblinding Date

Although some members of the combined Sponsor and CRO study team were unblinded before EOT (e.g. the full CRO study team and selected members of the Sponsor study team were unblinded at the time of the primary efficacy analysis delivery), study subjects and site personnel were originally supposed to remain blinded until EOT.

Transition from the randomized observer-blinded phase to the open-label phase and related unblinding procedures of study subjects and site personnel before EOT are conducted on country/site level and start immediately after full competent authority and Ethics Committee approval of Protocol version 4.0 in the respective country/site. This is referred to as site-level unblinding. If subjects were individually unblinded before site-level unblinding this is referred to as individual unblinding.

Unblinding date (individual unblinding): The date and time stamp created by the IWRS system when the site entered the individual unblinding request.

Unblinding date (site-level unblinding): The date and time created by a preconceived script run by the IWRS provider on the IWRS system. This date and time are the date and time that the script is run by the designated person from the CRO. In case the IWRS data does not provide one consolidated unblinding date as described in Table 8, the below logic is implemented in CDISC.

Table 8: Logic Behind the Unblinding Date in IWRS

Individual Unblinding Date is	Site Unblinding Date is	IWRS Unblinding Date Shows
None	Not before EOT	Empty
Available	Not before EOT	Individual unblinding date
None	Before EOT	Site Unblinding Date
Available	Before EOT	Min(Individual unblinding date; Site Unblinding Date)

10.11 Censoring Rules for Subjects Unblinded and/or Treated with Authorized/Licensed Vaccine for Preventing COVID-19

The following was decided based on ethical reasons and requests from health authorities and applies to the blinded study phase already: If during the conduct of study CV-NCOV-004 an AV becomes available to subjects, these subjects can request to be individually unblinded from the study treatment to decide whether they would like to receive the AV. The following censoring rules are applied to these subjects to avoid any study bias. Further inclusion/exclusion rules are specified in the relevant analysis populations (See Section 0).

- Subjects who are unblinded are censored for the primary efficacy and safety endpoints and all related efficacy and safety endpoints at the first day after unblinding. Any related follow-up data that is collected from censoring time point forward is included in the listings output.
- Subjects who are unblinded but decide not to receive the AV and to stay in the study are analyzed for immunogenicity as planned.
- Subjects who are unblinded, but decide to receive the AV, have their immunogenicity data censored at the first day after receiving the AV. However any related follow-up data that is collected from this time point forward is included in the listings output.

- Subjects who are treated with an AV without or before being unblinded are censored for efficacy, safety and immunogenicity at the first day after receiving the AV. As described above, data collected from the censoring timepoint forward is included in the listings output.

This is summarized in Table 9.

Table 9: Censoring Rules for Subjects Unblinded and/or Treated with AV

Analysis	Treatment Received in CV-NCOV-004	AV Received?	Unblinded?	Censoring Rule
Efficacy/Safety	CVnCoV	No	No	Analyzed as planned
			Yes	Censored at the first day after unblinding or at the first day after receiving the AV, whichever is earlier.
		Yes	No	
			Yes	
	Placebo	No	No	Analyzed as planned
			Yes	Censored at the first day after unblinding or at the first day after receiving the AV, whichever is earlier.
		Yes	No	
			Yes	
Immunogenicity	CVnCoV	No	No	Analyzed as planned
			Yes	
		Yes	No	Censored at the first day after receiving the AV.
			Yes	
	Placebo	No	No	Analyzed as planned
			Yes	
		Yes	No	Censored at the first day after receiving the AV
			Yes	

The following details are to be followed regarding censoring the day after unblinding:

- Unblinding day (= Pacific Time Zone) must be adjusted to the subject's time zone.
- Unblinding time does not matter for anything apart from the above time zone normalization. (As case start time is not collected.)
- If the case start day and the unblinding day occur on the same day the case counts for the analysis. (Censoring starts at the day after the unblinding.)

The following details are to be followed regarding censoring the day after receiving the AV:

- Times are not relevant as neither AV time nor case start time are collected.
- If AV date is complete then censoring starts at first day after the AV day.
- If AV date is incomplete (only day missing) then censoring starts after this month.
- If AV date is incomplete (month missing, year available) then censoring starts after this year.
- If AV date is completely missing then no censoring can be made.

As these imputations of incomplete AV dates are not an ideal solution this is only to be considered as a fallback solution in case complete AV dates cannot be retrieved and as an interim workaround for unclean data during study conduct.

All incomplete or missing AV dates need to be queried.

Site level unblinding:

As each of these subjects receives an unblinding date and time that feeds into the analysis data exactly like the individual unblinding date and time, no difference in censoring process needs to be made for these subjects.

If the subject has never received a CVnCoV dose in this study the subject is discontinued after site-level unblinding, so only the related EOT assessments are censored if performed after the day of unblinding. (Provided the subject has not received an AV before unblinding. In that case the above rules for individual unblinding with AV receipt also apply.)

If the subject has received at least 1 dose of CVnCoV in this study the subject is not automatically discontinued and the subject's data is censored as specified above for individually unblinded subjects.

10.12 Unblinding of Site AR009

Due to accidental unblinding at Site AR009 between 09 April 2021 and 16 Apr 2021 the following unblinding dates are created in CDISC:

Table 10 Unblinding Date for Subjects from Site AR009

Subject Randomization Date	Unblinding Date in IWRS Database	Consequence on Unblinding Date
Before or on 09-Apr-2021	None	Set to 09-Apr-2021
	Before 09-Apr-2021 (incl.)	Leave as is
	After 09-Apr-2021	Set to 09-Apr-2021
After 09-Apr-2021 and until 16-Apr-2021 (inclusively)	None	Set to randomization date
	Before 16-Apr-2021 (incl.)	Set to randomization date
	After 16-Apr-2021	Set to randomization date
After 16-Apr-2021	None	Leave as is
	Before 16-Apr-2021 (incl.)	N/A
	After 16-Apr-2021	Leave as is

10.13 Event Dates, Follow-Up Time, Time to Event Calculation and Censoring

Subject's follow-up time and rules for time to event calculations and censoring are dependent on the definition of the endpoint analyzed.

General formulae for the calculation of follow-up time and time to event are provided below. Table 11 further summarizes the definitions and derivations for the dates to be included in the respective formulae based on the endpoint analyzed.

- For each subject, the follow-up time (days) is defined as:

$$Follow\ Up\ Time\ (days) = End\ date\ of\ Follow\ Up - Start\ date\ of\ Follow\ Up + 1.$$

- For each event type, the total follow-up time within each vaccine group is calculated as the sum of all single follow-up times in that group. The total follow-up (years) is calculated as

$$Total\ Follow\ Up\ Time\ (years) = \frac{Total\ Follow\ Up\ time\ (days)}{365.25}$$

- The time to event (days) for both subjects with an event and censored subjects is calculated as follows:

$$Time\ to\ Event\ (days) = \text{Event/Censoring Date} - \text{Start Date} + 1.$$

Table 11: Event Dates, Censoring and Follow-Up Time Calculation

ENDPOINT SHORT DESCRIPTION	START DATE	EVENT DATE*	CENSORING DATE#	END DATE OF FOLLOW-UP
FIRST EPISODES OF COVID-19 CASES+	2nd vac. + 15 days	Date of symptoms onset	Min (unblinding date + 1; date AV + 1; trial termination date; cut-off date^)	Min (Event date; Censoring date; 18-Jun-2021§)
FIRST EPISODES OF MODERATE TO SEVERE COVID-19 CASES	2nd vac. + 15 days	Date of symptoms onset	Min (first episode of mild COVID-19 case date; unblinding date + 1; date AV + 1; trial termination date; cut-off date^)	Min (Event date; Censoring date; 18-Jun-2021)
FIRST EPISODES OF SEVERE COVID-19 CASES	2nd vac. + 15 days	Date of symptoms onset	Min (first episode of mild or moderate COVID-19 case date; unblinding date + 1; date AV + 1; trial termination date; cut-off date^)	Min (Event date; Censoring date; 18-Jun-2021)
FIRST EPISODES OF COVID-19 CASES IN SUBJECTS ≥ 61 YEARS OF AGE	2nd vac. + 15 days	Date of symptoms onset	Min (unblinding date + 1; date AV + 1; trial termination date; cut-off date^)	Min (Event date; Censoring date; 18-Jun-2021)
BURDEN OF DISEASE SCORES	2nd vac. + 15 days	Date of symptom onset of corresponding COVID-19 case	Min (unblinding date + 1; date AV + 1; trial termination date; cut-off date^)	Min (Event date; Censoring date; 18-Jun-2021)
FIRST EPISODES OF MILD COVID-19 CASES	2nd vac. + 15 days	Date of symptoms onset	Min (first episode of moderate or severe COVID-19 case date; unblinding date + 1; date AV + 1; trial termination date; cut-off date^)	Min (Event date; Censoring date; 18-Jun-2021)

ENDPOINT SHORT DESCRIPTION	START DATE	EVENT DATE*	CENSORING DATE#	END DATE OF FOLLOW-UP
FIRST EPISODES OF MODERATE COVID-19 CASES	2nd vac. + 15 days	Date of symptoms onset	Min (first episode of mild or severe COVID-19 case date; unblinding date + 1; date AV + 1; trial termination date; cut-off date^)	Min (Event date; Censoring date; 18-Jun-2021)
FIRST EPISODES COVID-19 CASES WITH SYMPTOM ONSET AT ANY TIME AFTER THE FIRST TRIAL VACCINATION+	1st vac.	Date of symptoms onset	Min (unblinding date + 1; date AV + 1; trial termination date; cut-off date^)	Min (Event date; Censoring date; 18-Jun-2021)

VAC = VACCINATION
+ FOR ENDPOINTS ASSESSED IN NAÏVE SUBJECTS AS WELL AS ENDPOINT ASSESSED IN SUBJECTS REGARDLESS OF THEIR BASELINE SEROLOGY STATUS
*** ONLY EVENTS WITH AN ONSET DATE ≥ START DATE ARE CONSIDERED**
 # ONLY FOR SUBJECTS WITHOUT AN EVENT WITH AN ONSET DATE ≥ START DATE
^ E.G. IN CASE OF AN INTERIM ANALYSIS
$ DATE OF SYMPTOM ONSET OF A VIROLOGICALLY-CONFIRMED COVID-19 CASE. AFTER SUCH A CASE, SUBJECT CAN NO LONGER BE CONSIDERED AN "ASYMPTOMATIC" SUBJECT.
€ XXX IS A PLACEHOLDER FOR THE ANALYZED VARIANT/CLUSTER (E.G. ALPHA)
§ 18TH JUN-2021 CUT-OFF DATE FOR PRIMARY EFFICACY ANALYSIS

10.14 Age Group

Subjects are assigned to age groups "18 to 60 years" and "≥ 61 years" based on their age recorded in IWRS. If age is missing in IWRS then age group is assigned based on the age derived from year of birth recorded in IWRS and date of first informed consent (age = year of date of first informed consent – year of birth).

11.0 Interim Analyses

Two interim analyses are performed for this trial by an unblinded independent statistician with no previous involvement in the trial and reviewed by the DSMB when 56 and 111 cases of COVID-19 (meeting the primary efficacy case definition) are observed. These analyses aim to assess early high efficacy or futility on the primary efficacy endpoint of COVID-19 cases of any severity and are done on the EAS only. The safety data that is available at this time point is be described.

For the analysis of early demonstration of high efficacy or futility, cumulative O'Brien-Fleming type error-spending-function [1] is used to provide statistical stopping rules for high efficacy (α-boundaries) and futility (β-boundaries) for the interim analyses, based on the information accumulated until that specific interim stage.

At the interim stage, if the p-value for the test of the primary endpoint of COVID-19 cases of any severity is lower than the α-boundary, a high level of efficacy for CVnCoV is declared. Conversely, demonstration of futility occurs if the p-value is higher than the β-boundary.

The interim analyses are planned to occur when 56 and 111 cases of any severity, meeting the primary case definition have been observed. The analysis of this primary endpoint is performed as described in detail in Section 12.6.1 and Section 12.6.2.1. If the interim analyses are performed exactly after 56/111 cases have been reported, a 1-sided p-value lower than 0.00015/0.00707 (i.e. LL of the 2-sided

99.97%/98.586% CI > 30%) for the test on the primary endpoint of COVID-19 cases of any severity leads to the conclusion of high efficacy, while a 1-sided p-value higher than 0.66345/0.12356 results in the demonstration of futility. Otherwise, the final primary efficacy analysis is performed at 160 cases.

Table 12 below shows the boundaries for demonstrating high efficacy or futility based on 56 and 111 cases, calculated on a one-sided p-value scale using the cumulative error spending function.

Table 12: Decision rules for interim and final analyses based on 56, 111 and 160 cases

	Interim Analysis 1	*Interim Analysis 2*	*Final Analysis*
Number of cases	56	111	160
Efficacy α-Boundary on p-value scale (1-sided)	0.00015	0.00707	0.02281
Futility β-Boundary on p-value scale (1-sided)	0.66345	0.12356	NA

It should be noted that the actual boundaries used for decision making depend on the exact number of cases accrued at the time of each analysis. At the time of the interim analysis, actual boundaries are re-derived based on the actual number of cases accrued and are displayed in the IA outputs. The boundaries are applied in a non-binding way as there may be other factors that are part of the decision-making process.

A list of Tables, Figures and Listings (TFL) that is prepared for the IA can be found in a separate document CV-NCOV-004 Statistical Analysis Plan – Appendix 4 List of TFLs.

12.0 Statistical Methods

Unless otherwise noted, categorical variables are summarized using counts and percentages. Percentages are presented with one decimal place, except for 100% which is displayed without any decimal places and percentages are not displayed for zero counts. Continuous variables are summarized using the number of observations (n), mean, median, SD, 1st Quartile (Q1), and 3rd Quartile (Q3), minimum and maximum values. Mean, median, Q1 and Q3 are presented to 1 decimal more than original data. SD is presented with 2 decimals more than original data. Minimum and maximum match the decimal points in the original data. The maximum number of decimals is 4, unless otherwise stated.

In general, for the blinded study phase, all data summaries are presented overall and by vaccine group. Summaries are further repeated by age group (18 to 60 years and ≥ 61 years) and vaccine group. Efficacy outputs do not have an overall column presented. Selected outputs are **additionally** presented using further subsetting of the data. This is specified explicitly in the respective sections. Data summaries for the OL-phase are generally presented by cohort, unless otherwise stated.

If not stated otherwise, p-values from statistical tests are two-sided and CIs are calculated using a 95% confidence level.

The factors used for stratification of randomization are age group and country. The primary and key secondary efficacy analyses are **not** adjusted for these factors, but the analyses are repeated by age group (18 to 60 years and ≥ 61 years) and by country separately. The sensitivity analyses for the primary endpoint using time to event methodology includes both stratification factors in the statistical model.

No imputation of missing data other than that described in Section 10.3 is performed.

All data collected during this trial is displayed in data listings, unless otherwise specified. Screening failures are excluded from all listings and tables if not otherwise stated. Listings include all relevant assigned/derived variables. If not explicitly stated, listings do not show imputed data, but present data as reported.

All data summaries and tabulations are prepared using SAS® Version 9.4 or higher.

12.1 Subject Disposition

A summary of enrollment by region (Latin America vs Europe), country and site is provided for all randomized subjects. This summary is repeated on the OL Set.

The number and percentage of subjects who prematurely withdrew from treatment, prematurely withdrew from the trial before entering the OL phase, rolled over to the OL phase, prematurely withdrew from the trial during the OL phase and a breakdown of the corresponding reasons for treatment withdrawal and early trial discontinuation (summarized separately for blinded and OL phase) is provided.

The number and percentage of subjects randomized and treated is presented with the number and percentage of subjects included in each analysis set. Reasons for exclusion from each analysis set is not tabulated, but listed.

The number of subjects whose data is censored due to unblinding and/or AV application are provided for unblinding and/or AV use before dose 2 and after dose 2. The output is provided for the SAS and for all randomized subjects. A separate listing is provided indicating the date a subject was unblinded / received an AV. Subjects who have received an AV without being unblinded are also included in that listing.

The number and percentage of subjects who were not stratified correctly is presented along with the number of subjects who received an incorrect vaccine at first and/or second vaccination. The summary is done for all randomized subjects. These subjects are also listed.

12.2 Demographic and Baseline Characteristics

The following demographic data collected at baseline is summarized for the SAS, EAS and OL Set. The data used for the OL Set summary is the same as for SAS and EAS (ie. the data collected at Day 1):

- Age at first informed consent (years),
- Age group (18 to 60 years / ≥ 61 years),
- Gender (Female / Male / Undifferentiated / Unknown),
- Ethnicity (Hispanic or Latino / Not Hispanic or Latino / Not Reported / Unknown),
- Race (American Indian or Alaska Native / Asian Indian/ Black or African American / Chinese / Filipino / Japanese / Korean / Native Hawaiian or Pacific Islander / Vietnamese / White / Other / Not reported / Unknown),
- Baseline and Visit Day 43 serology status (Seronegative / Seropositive), see Section 10.6.1 for details.
- Baseline and Visit Day 43 serology status, overruled by independent committee adjudication if available (Seronegative / Seropositive), see Section 10.7.6 for details.
- Height (cm),
- Weight (kg),
- Body Mass Index (BMI) (kg/m^2).
- Smoking Status (Never / Current / Former)
- Duration of Smoking (within the group of former and current smokers)

12.3 Medical and Surgical History

Medical/surgical history is coded using the MedDRA Version 23.1 or higher and is summarized by Primary SOC and PT for the SAS and EAS. Medical/surgical history is listed for the SAS.

The number and percentage of subjects with any co-morbidity and a breakdown of the corresponding co-morbidities is provided for the SAS and EAS.

12.4 Trial Treatment

12.4.1 Trial Vaccine Exposure

A summary of doses administered, including reasons for doses not administered is provided for the SAS.

12.4.2 Prior and Concomitant Medications and Vaccinations

Prior and concomitant medications and vaccinations are coded using World Health Organization Drug Dictionary (WHODRUG), Version September 2020 Global B3 or higher, and are summarized based on the SAS and EAS. The summary of concomitant medications/vaccinations is repeated on the OL Set.

Concomitant medications/vaccinations (see Section 10.4) are summarized by Anatomical Therapeutic Chemical (ATC) level 1 and WHODRUG PN as the number and percentage of subjects taking at least one medication within each medication group and subgroup.

Prior medications/vaccinations (see Section 10.4) are summarized by ATC level 1 and WHODRUG PT as the number and percentage of subjects taking at least one medication within each medication group and subgroup.

12.5 Important Protocol Deviations

Per PRA processes, protocol deviations data are entered into PRA system of records (PSO). The trial team and the Sponsor conduct ongoing reviews of the deviation data from PSO and the resulting set of evaluable subjects throughout the trial, adjusting the deviation criteria as seems appropriate.

Protocol deviation data are reviewed prior to each formal analysis (i.e. interim analyses or final analyses) and important deviations leading to elimination of subjects from analysis sets are identified. Detailed definitions and further guidance on programmatic approaches for identification of protocol deviations and/or other criteria leading to exclusion from the analysis sets are provided in an Appendix to the SAP (see Appendix 5). The detailed definitions of important protocol deviations leading to elimination of subjects from analysis sets are provided in the final version of the SAP and/or in the final signed minutes of the data review meetings prior to each formal analysis and prior to database lock.

A summary of important subject-level protocol deviation data (conjoinedly for the blinded and the OL phase) is created based on the SAS, displaying the number and percentage of subjects with any important protocol deviations and broken down by type of deviations.

Site- and subject-level protocol deviation data is listed conjoinedly for the blinded and the OL phase.

12.6 Efficacy Analyses

12.6.1 Hypothesis Testing Strategy and Multiplicity

The overall 2-sided significance level of 5% is applied to the primary endpoint (or equivalently, a 1-sided 2.5% level of significance).

The primary endpoint of COVID-19 cases of any severity is evaluated at two interim analyses (see Section 11.0) and - if the trial is not stopped due to futility or early high efficacy at either of the interim analyses - at the final primary efficacy analysis (when 160 cases have accrued). A cumulative O'Brien-Fleming type error spending function [1] is utilized to provide statistical stopping rules for the interim analyses. The related outputs are not planned to be re-run at the EOT analysis. Due to the fact that the unblinding dates for site AR009 were only corrected after the final delivery for the primary analysis was done it might nevertheless be decided to re-run some of the related outputs together with the EOT analysis.

Assuming the interim analyses are based on 56 and 111 cases and the final primary efficacy analysis based on 160 cases, the two-sided significance level to be considered for the primary analysis of the first primary endpoint of COVID-19 cases of any severity is 4.562% (based on the error spending function used

for the interim analyses). This level may change depending on the number of cases accrued at the time of each analysis.

Analysis of the key secondary efficacy endpoints is performed according to a conditional hierarchical testing procedure using the order defined in endpoints sections, see Section 9.2.1. Moreover, efficacy of CVnCoV in regard to the key secondary efficacy endpoints is demonstrated only if there is successful demonstration of the primary efficacy objective. Otherwise, these endpoints are analyzed as exploratory endpoints without success criteria testing.

The analyses of the key secondary endpoints are performed at the final primary efficacy analysis only, using a two-sided 5% significance level. They are not planned to be re-run at the EOT analysis. Due to the fact that the unblinding dates for site AR009 were only corrected after the final delivery for the primary analysis was done it might nevertheless be decided to re-run some of the related outputs together with the EOT analysis.

For any analyses requiring the serostatus at baseline or Visit Day 43 the information of the adjudication of COVID-19 cases is used, if available (Section 10.7.6). Otherwise the information of the N protein blood samples taken at baseline and Visit Day 43 is used (Section 10.6.1).

12.6.2 Primary Efficacy Endpoint Analysis

12.6.2.1 Primary Efficacy Analysis

The primary endpoint in this trial is the occurrence of first episodes of virologically-confirmed cases of COVID-19 of any severity meeting the case definition for the primary efficacy analysis (see Section 10.7.4).

From the number of occurrences of COVID-19 cases in each vaccine group, the VE corresponding to the endpoint is calculated as follows:

$$VE = 1 - \frac{p}{1-p} * \frac{1}{r}$$

Thereby, p denotes the proportion of cases coming from the CVnCoV group among all cases and r is the ratio of total follow-up time of subjects in the CVnCoV group over the total follow-up time of subjects in the placebo group (see Section 10.13).

The statistical hypothesis for the primary efficacy endpoints is:

$$H_{0A}: VE \leq 30\% \; vs. \; H_{1A}: VE > 30\%$$

Or, equivalently:

$$H_{0A}: p \geq \frac{0.7}{\frac{1}{r} + 0.7} vs. H_{1A}: p < \frac{0.7}{\frac{1}{r} + 0.7}$$

Thereby, A refers to the endpoint of COVID-19 cases of any severity.

It should be noted that the above reduces to

$$H_{0A}: p \geq 0.4118 \; vs. \; H_{1A}: p < 0.4118 \, ,$$

if the total follow-up time is the same in both groups, i.e. if r equals 1.

For the primary analysis, the above hypotheses are tested via an exact test for Binomial proportions on p. with an overall 2-sided significance level of 5% (or equivalently, a 1-sided 2.5% level of significance).

Given the IA stopping rules for the primary endpoint of COVID-19 cases of any severity, if the final primary efficacy analysis is performed at 160 cases, the tests are performed with a 1-sided 2.281% level of significance, to keep the type I error rate for this endpoint at 5% (2-sided). See also Section 11.0 for further details.

An exact two-sided 95.438% Pearson-Clopper CI for p is calculated. From this, the LL and Upper Limit (UL) of the 95.438% CI for the VE is calculated from the UL and LL of the CI for p as:

$$LL_{VE} = 1 - \frac{UL_p}{(1 - UL_p) * r};\ UL_{VE} = 1 - \frac{LL_p}{(1 - LL_p) * r}$$

Efficacy on this primary endpoint is demonstrated at the final primary efficacy analysis if the UL of the 95.438% CI for p is below 0.4118. Note that this is equivalent to the LL of the 95.438% CI for the VE being above 30%.

The trial is successful if efficacy is demonstrated on the primary endpoint.

The following is presented for the analysis of the primary endpoint:

- Number and percentage of subjects with a respective COVID-19 case (any severity) meeting the case definition for the primary efficacy analysis in each vaccine group,
- Total follow-up time (years) in each vaccine group,
- Calculated proportion of cases coming from the CVnCoV group among all cases (p),
- Ratio of total follow-up time of subjects in the CVnCoV group over the total follow-up time of subjects in the placebo group (r),
- Estimated VE based on p and r,
- 1-sided p-value from the exact Binomial test for the above hypotheses on p,
- 95.438% CIs for p and VE for the primary endpoint of COVID-19 cases of any severity.

The primary analysis set for the primary analysis is the EAS. Any repeated analyses using an analysis set other than EAS or analyses by subgroup present 95% CIs and no p-values are presented.

12.6.2.2 Sensitivity Analyses

As a sensitivity analysis, the time to first occurrence of virologically-confirmed COVID-19 case of any severity according to the primary case definition is analyzed. Calculation of the time to first occurrence and censoring rules are applied according to Section 10.11.

Kaplan-Meier (KM) estimates for the probability of not developing COVID-19 (hereafter referred to as “survival”) are computed for each vaccine group. Estimates for Q1, median and Q3 of the survival times are presented. A log rank test comparing the vaccine groups is performed. The summaries are provided by vaccine group and by age group and vaccine group.

KM curves by vaccine group are presented, displaying the estimated survival probabilities over time. These figures are also repeated by age group and vaccine group.

A Cox Proportional Hazard model is used to model the time to first occurrence of virologically-confirmed COVID-19 cases according to primary case definition (any severity). The model includes the vaccine group as a factor and is adjusted for the stratification factors age at baseline (18 to 60 and ≥61 years) and country. The estimated Hazard Ratios (HR) for the CVnCoV vaccine group versus placebo and corresponding 95% CI as well as the 97.5% CI is presented. The CIs are derived based on the Wald test. This analysis is repeated by age group, but the corresponding model does not include the age group as a factor.

A subgroup analysis of region (LATAM vs EUROP) on the primary endpoint is also performed.

These sensitivity analyses are performed on the EAS.

12.6.3 Secondary Efficacy Analyses

12.6.3.1 Key Secondary Efficacy Analyses

The key secondary efficacy endpoints in this trial are:

- The occurrence of first episodes of virologically-confirmed moderate to severe cases of COVID-19 meeting the case definition for the primary efficacy analysis
- The occurrence of first episodes of virologically-confirmed severe cases of COVID-19 meeting the case definition for the primary efficacy analysis. For details on the definition of moderate and severe COVID-19 cases see 10.7.3.
- The occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity meeting the case definition due to infection with “wild type” and “Alpha” SARS-CoV-2 strains in SARS-CoV-2 naïve subjects. For details on the definition of VOC see Section 10.7.5

For the above endpoints, the analysis approach as described for the primary endpoint in Section 12.6.2.1 are conducted in a similar manner. For details regarding events to be considered in each analysis and for calculation of follow-up time, refer to Section 10.13.

As the key secondary efficacy endpoints are not part of the interim analysis, the significance level does not require an adjustment and – following successful demonstration of efficacy in the primary endpoints - the full 5% level of significance is used for statistical testing. Different success thresholds are also defined for these endpoints. Consequently:

- Efficacy based on moderate to severe cases of COVID-19 is demonstrated if the LL of the exact two-sided 95% Pearson-Clopper CI for the VE based on moderate to severe cases is above 20%
- Efficacy based on severe cases of COVID-19 is demonstrated if the LL of the exact two-sided 95% Pearson-Clopper CI for the VE based on severe cases is above 10%.
- Efficacy based on first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity meeting the case definition due to infection with “wild type” and “Alpha” SARS-CoV-2 strains in SARS-CoV-2 naïve subjects is demonstrated if the LL of the exact two-sided 95% Pearson-Clopper CI for the VE based on severe cases is above 30%.

Note that the hierarchical testing procedure outlined in Section 12.6.1 has to be considered when assessing if efficacy has been demonstrated based on each of the four key secondary efficacy endpoints.

The following is presented for the key secondary efficacy analyses:

- Number and percentage of subjects with a respective case,
- Total follow-up time (years) in each vaccine group,
- Calculated proportion of cases coming from the CVnCoV group among all cases (p),
- Ratio of total follow-up time of subjects in the CVnCoV group over the total follow-up time of subjects in the placebo group (r),
- Estimated VE based on p and r,
- 95% CIs for p and VE.

The analyses of the key secondary efficacy endpoint is performed on the EAS.

12.6.3.2 Sensitivity Analyses

The sensitivity analyses described in Section 12.6.2.2 for the primary efficacy endpoint is also performed on the 3 key secondary efficacy endpoints.

12.6.3.3 Other Secondary Efficacy Analyses

Other secondary efficacy endpoints in this trial are:

- Occurrence of first episodes of virologically-confirmed cases of COVID-19 of any severity meeting the case definition for the primary efficacy analysis in subjects ≥ 61 years of age.
- BoD scores calculated based on first episodes of virologically-confirmed cases of COVID-19 of any severity meeting the case definition for the primary efficacy analysis.
- Occurrence of first episodes of virologically-confirmed cases of COVID-19 of any severity with symptom onset at any time after the first trial vaccination.

For the above endpoints, excluding BoD scores, the analysis approach as described for the primary endpoints in Section 12.6.2.1 is conducted in a similar manner, but no confirmative testing is performed. For details regarding events to be considered in each analysis and for calculation of follow-up time, refer to Section 10.13.

The following is presented for the secondary efficacy analyses:

- Number and percentage of subjects with a respective case,
- Total follow-up time (years) in each vaccine group,
- Calculated proportion of cases coming from the CVnCoV group among all cases (p),
- Ratio of total follow-up time of subjects in the CVnCoV group over the total follow-up time of subjects in the placebo group (r),
- Estimated VE based on p and r,
- 95% CIs for p and VE.

For the BoD endpoints, the number and percentage of subjects in each category is summarized descriptively for both of the two scores.

Additionally, VE measures based on each of the calculated BoD Scores (referred to as "VE_{BoD}") are derived. VE_{BoD} is defined as the relative reduction in the BoD score in the CVnCoV group compared to Placebo and is calculated as:

$$VE_{BoD} = 1 - \frac{SV}{SP}$$

Thereby, SV denotes the ratio of mean BoD score in the CVnCoV group and the mean follow-up time (years) in the CVnCoV group and SP denotes the ratio of mean BoD score in the Placebo group and the mean follow-up time (years) in the Placebo group (see Section 10.13).

The VE_{BoD} and corresponding 95% CI based on the Normal distribution are presented for each of the two BoD scores defined. The analysis tables also present the calculated mean BoD scores in the CVnCoV and Placebo groups and the total follow-up time (months) in each group.

The analyses of the other secondary efficacy endpoint of COVID-19 cases in subjects 61 years or older are performed on the EAS, thereby restricting to subjects with age at trial entry ≥ 61 years. This analysis is not repeated by age group.

The analysis of the other secondary efficacy endpoint of BoD categories is performed on the EAS.

The analysis of the other secondary efficacy endpoint COVID-19 cases after first vaccination is performed on the SAS, restricted to subjects with a negative baseline serology (see Section 10.6.1).

All secondary efficacy endpoints mentioned in this section are provided for the interim analyses and for the primary efficacy delivery.

All applicable cases available in the respective data cut are used for the respective analyses.

12.6.4 Exploratory Efficacy Analyses

12.6.4.1 Severity Assessment of COVID-19 Cases

All COVID-19 cases meeting the primary efficacy case definition are classified as mild, moderate or severe. An additional category “moderate to severe” is created, combining moderate and severe cases. The number and percentage of subjects with mild, moderate, severe and moderate to severe cases is summarized descriptively.

These summaries and analyses are provided based on the EAS and are provided for the interim analyses and the primary efficacy delivery.

The analysis contains all applicable cases available in the respective data cut.

12.6.4.2 Hospitalizations, Oxygenations, Mechanical Ventilations and Deaths

A summary table presents the number and percentage of subjects with any of the following events:

- Need for supplemental oxygenation due to COVID-19,
- Need for mechanical ventilation due to COVID-19,
- Hospitalization due to COVID-19,
- Death due to COVID-19,
- Death due to any cause.

This table is provided considering only virologically confirmed COVID-19 cases with an onset ≥ 15 days after second vaccination. Thereby, the start date of the COVID-19 case leading to occurrence of any of the above must be ≥ 15 days after second trial vaccination.

The summary for events with a start date ≥ 15 days after second vaccination is based on the EAS.

The summary based on the EAS is provided for the second interim analyses and the primary efficacy delivery and contains all applicable cases available in the respective data cut.

12.6.5 Open-Label Analyses

In agreement with the Sponsor it was decided to not analyze the exploratory OL efficacy endpoint.

12.7 Safety Analyses

12.7.1 Adverse Events

Unsolicited AEs, including SAEs, and AESIs and solicited AEs integrated to or recorded on the CRF are coded using MedDRA Version 23.1 or higher, by SOC and PT.

Only TEAEs as defined in Section 10.5.1 are included in AE summaries. In AE listings, all AEs are included.

Solicited AEs occurring on the day of vaccination and the following 7 days are generally included in summaries if not otherwise stated.

Summaries of medically attended AEs only include those AEs that started up to 6 months after the second trial vaccination, see Section 10.5.6 for further details.

Note that for all summaries by SOC and PT, counting is by subject, not event and subjects are only counted once within each SOC and PT. However, if not stated otherwise, all summaries of unsolicited AEs include the number of AEs reported in each category and all events of a subject are then counted.

All AE summary tables are provided overall, by vaccine group, and by age group and vaccine group and are repeated separately in subjects seronegative at baseline and in subjects seropositive at baseline for SARS-CoV-2 N protein antibody levels (see Section 10.6.1).

In general, percentages are based on the number of subjects in the respective analysis set. In summary tables for AEs after the second vaccination, percentages are based on the number of subjects in the respective analysis set who have received the second vaccination.

12.7.1.1 Analysis of Unsolicited AEs

The following summaries of unsolicited AEs by SOC and PT are provided, separately for AEs occurring within the first 28 days after each vaccination, within the 28 days after any vaccination, and all reported AEs (including those reported later than 28 days after any vaccination):

- Occurrence of unsolicited AEs,
- Occurrence of related unsolicited AEs,
- Occurrence of unsolicited AEs by maximum severity (mild / moderate / severe),
- Occurrence of related unsolicited AEs by maximum severity (mild / moderate / severe)

Additionally, a summary of unsolicited AEs (excluding solicited AEs) occurring within the first 28 days after each vaccination and within 28 days after any dose that have a frequency of > 5% in at least one treatment arm (on PT level) by SOC and PT is provided. The summary is repeated for all reported AEs (including those reported later than 28 days after any vaccination).

Summaries of unsolicited AEs occurring within 28 days after each vaccination and within 28 days after any vaccination are provided based on the SAS 2. Summaries of all reported unsolicited AEs (including those reported later than 28 days after any vaccination) are provided based on the SAS.

Listings of unsolicited AEs and related unsolicited AEs are produced. These listings are excluding solicited AEs and flagging treatment emergent events.

12.7.1.2 Analysis of Solicited AEs

The following summaries of solicited AEs within 7 days after each trial vaccination and within 7 days after any trial vaccination are planned:

- Summary of local and systemic AEs, overall and by maximum grade (mild / moderate / severe)
    - Also provided by gender (female/male) for any vaccination, vaccination 1, and vaccination 2.
- Occurrence of local AEs, overall and by maximum grade (mild / moderate / severe)
- Occurrence of systemic AEs, overall and by maximum grade (mild / moderate / severe)
- Occurrence of related systemic AEs, overall and by maximum grade (mild / moderate / severe)
- Duration (days) of local AEs, overall and for grade 3 events
- Duration (days) of systemic AEs, overall and for grade 3 events
- Duration (days) of related systemic AEs, overall and for grade 3 events
- Daily summary of local AEs overall and by maximum grade (mild/moderate/severe) (only for each dose)
- Daily summary of systemic AEs overall and by maximum grade (mild/moderate/severe) (only for each dose)
- Daily summary of related systemic AEs overall and by maximum grade (mild/moderate/severe) (only for each dose)
- Summary of time of onset (Day) overall and for grade 3 solicited AEs, any solicited AEs, local, systemic AEs, and related systemic AEs

- Time of onset (Day) of local AEs, overall and for grade 3 events
- Time of onset (Day) of systemic AEs, overall and for grade 3 events.
- Time of onset (Day) of related systemic AEs, overall and for grade 3 events

All analyses of solicited AEs are provided based on the SASsol.

Before EOT is was decided to not provide any analyses on solicited AEs in the EOT analysis. Therefore some of the above analyses were never performed. For details, please refer to Appendix 6.

12.7.1.3 Analysis of AEs (Combined Unsolicited and Solicited)

An overall summary of unsolicited AEs, SAEs, intercurrent medical conditions affecting immune response, AESIs, medically attended AEs, AEs leading to vaccine withdrawal, AEs leading to withdrawal from trial and AEs with fatal outcome is prepared for AEs occurring within 28 days after each CVnCoV vaccination, within 28 days after any CVnCoV vaccination, and all reported AEs (including those reported later than 28 days after any CVnCoV vaccination), presenting the number and percentage of subjects with

- any unsolicited AEs ,
- related unsolicited AEs,
- grade 3 (severe) unsolicited AEs
- grade 3 (severe) related unsolicited AEs
- SAEs (includes solicited AEs),
- related SAEs (includes solicited AEs),
- intercurrent medical conditions affecting immune response (includes solicited AEs),
- AESIs (includes solicited AEs),
- related AESIs (includes solicited AEs),
- medically attended AEs (includes solicited AEs),
- related medically attended AEs (includes solicited AEs),
- AEs leading to vaccine withdrawal (includes solicited AEs),
- AEs leading to withdrawal from trial (includes solicited AEs),
- AEs with fatal outcome (includes solicited AEs),
- related AEs with fatal outcome (includes solicited AEs).

The overall summary is also provided by gender (male/female) for any CVnCoV vaccination, CVnCoV vaccination 1 and CVnCoV vaccination 2.

The following summaries of AEs by SOC and PT are further provided, separately for AEs occurring within the first 28 days after each CVnCoV vaccination, within the 28 days after any CVnCoV vaccination, and all reported AEs (including those reported at more than 28 days after any CVnCoV vaccination):

- Occurrence of SAEs,
- Occurrence of related SAEs,
- Occurrence of SAEs by maximum severity (mild / moderate / severe),
- Occurrence of related SAEs by maximum severity (mild / moderate / severe),
- Occurrence of intercurrent medical conditions affecting immune response,

- Occurrence of AESIs,
- Occurrence of related AESIs,
- Occurrence of medically attended AEs,
- Occurrence of related medically attended AEs,
- Occurrence of AEs leading to vaccine withdrawal,
- Occurrence of AEs leading to withdrawal from trial,
- Occurrence of AEs with fatal outcome,
- Occurrence of related AEs with fatal outcome,
- Occurrence of SMQs and CMQs (as specified in Section 10.5.7). (The SMQ/CMQ tables is only provided for all reported AEs, not by vaccination 1 and vaccination 2 separately and only by PT, not by SOC.)

Overall summaries of AEs occurring within 28 days after each CVnCoV vaccination and within 28 days after any CVnCoV vaccination are provided based on the SAS and the SAS 2. Summaries of SMQs and CMQs are provided based on the SAS and the SAS 2. All other summaries and listings are provided based on the SAS.

A listing of all SAEs and all SAEs with fatal outcome is further provided by subject, including both unsolicited and solicited AEs.

Further AE listings supporting the AE tables described above include both relevant solicited and unsolicited AEs.

12.7.1.4 Repeats of AE Analyses without Censoring

In the EOT analysis the following outputs are repeated without applying any censoring rules due to subject unblinding or AV receipt:

- Overall summary of unsolicited AEs occurring through EOT Visit
- Unsolicited AEs, SAEs, unsolicited AESIs and AEs with fatal outcome, by SOC and PT occurring through EOT Visit

12.7.2 Deaths and Serious Adverse Events

Description of analyses of SAEs and fatal AEs are included in Section 12.7.1.3.

12.7.3 Laboratory Data

A urine sample for pregnancy testing is taken from women of childbearing potential on Day 1 prior to trial vaccination to establish eligibility. A urine pregnancy test is also performed before the second trial vaccination on Day 29 to continue to determine eligibility. Urine pregnancy test result data is listed only.

No other standard laboratory tests are performed.

12.7.4 Vital Signs

Vital signs are recorded at each clinic visit (i.e. Day 1, Day 29, Day 43, Day 57, Day 120, Day 211, and Day 393 / EOT). Thereby, phase 2b subjects not included in the IS do not have vital signs collected at day 57 and phase 3 subjects do not have vital signs data collected on day 57 and 120.

Scenario A: Vital signs are not collected at EOT visit.

Body temperature (°C), SBP/DBP (mmHg) and pulse (beats per minute) at baseline and each post-baseline timepoint as well as change from baseline at each post-baseline timepoint are summarized.

Vital Signs data are summarized based on the SAS.

12.7.5 Physical Examinations, ECGs, and Other Observations Related to Safety

General physical examinations are performed at Day 1 and Day 393 / EOT. Symptom-directed examinations are performed Day 29, Day 43, Day 57, Day 120, and Day 211.

Scenario A: Physical examinations are not performed at EOT visit.

Physical examination data is listed only.

12.7.6 Sensitivity Analysis on Safety Outputs

12.7.6.1 Safety Delivery when Phase 2b is 6 Weeks post Second Dose

For the safety delivery when all Phase 2b subjects are 6 weeks post 2nd vaccination all safety outputs are repeated without applying any censoring due to subject unblinding.

12.7.7 Adapting the Safety Analyses to the Requirements of Extensive Unblinding

If not explicitly exempted, all safety analyses described in Sections 12.7.1 – 12.7.6 are performed under the conditions of data censoring (described in Section 10.11).

In order to maximally maintain the previous analysis setup while nevertheless aiming at optimally evaluating the collected data the following approach is introduced regarding safety analyses.

1. The above-mentioned analyses (Sections 12.7.1 – 12.7.6) remain unchanged, regardless of extensive individual or site-level unblinding or subjects rolling-over to the OL phase. All definitions still correctly apply and analyses are conducted as originally planned and described above.
2. Additional outputs are planned to account for the massive loss of data due to censoring.
    a. These additional outputs are closely following the above mentioned safety analyses.
    b. As far as possible, endpoint definitions and analysis sets are maintained as described in Sections 12.7.1 – 12.7.6.
    c. No censoring due to unblinding and/or AV receipt is performed.
    d. AEs/vital sign values are divided into 4 groups: Placebo-only, CVnCoV-only, CVnCoV-AV, AV-only.

       AEs/vital sign values are allocated to treatment groups as follows:

       - Placebo-only: Only placebo has been administered before AE start date / vital signs date. No CVnCoV and no AV must have been administered until then.
       - CVnCoV-only: At least one dose of CVnCoV and no AV has been administered before AE start date / vital signs date. Placebo might have been administered as well.
       - CVnCoV-AV: At least one dose of CVnCoV and at least one dose of AV has been administered before AE start date / vital signs date. Placebo might have been administered as well.
       - AV-only: At least one dose of AV and no CVnCoV has been administered before AE start date / vital signs date. Placebo might have been administered as well.

Treatments are considered “as received”, not “as randomized”.

The following analyses are repeated as described above. All repeat analyses are based on the SAS.

- Overall summary of unsolicited AEs occurring through EOT Visit
- Unsolicited AEs, SAEs, unsolicited AESIs and AEs with fatal outcome, by SOC and PT occurring through EOT Visit

The analyses in this section substitute the analyses of the OL safety endpoints.

12.8 Immunogenicity Analyses

12.8.1 Secondary Immunogenicity Analyses

For Phase 2b subjects participating in the IS, blood samples for SARS-CoV-2 viral neutralizing activity and antibody to SARS-CoV-2 RBD of S protein testing are collected on Day 1, Day 29, Day 43, Day 57, Day 120 and Day 211.

Scenario A: Results from Day 57 are not included in the analyses, although perhaps available.

Scenario R: Results from Day 57 are included for those sites where Protocol 4.0 was not approved before EOT analysis. For sites where protocol 4.0 was approved before EOT analysis, Day 57 results are not included.

All analyses of SARS-CoV-2 RBD to S protein antibodies and SARS-CoV-2 viral neutralizing antibody levels are performed based on the PPI Set, overall and separately in subjects seronegative to the N protein at baseline and in subjects seropositive to the N protein at baseline (see Section 10.6.1). Summary statistics presented include the GM with corresponding geometric SD and 95% CI, as well as the Median, Min, Max, Q1 and Q3. Total columns (or respective sections in graphs) are provided for immunogenicity outputs.

SARS-CoV-2 RBD of S protein antibodies and SARS-CoV-2 viral neutralizing antibodies (both expressed as GMT) are summarized descriptively. Summaries are provided at baseline and each post-baseline sampling timepoint. The FC from baseline is further computed and summarized for each post-baseline sampling timepoint.

For each post-baseline timepoint, the number and percentage of subjects seroconverting with any fold increase, a 2-fold increase and a 4-fold increase are presented together with the exact 95% Pearson-Clopper CIs for the proportion of seroconverting subjects. This analysis is only done for subjects seronegative to the N protein at baseline and not censored.

GMTs of SARS-CoV-2 RBD of S protein antibodies and SARS-CoV-2 viral neutralizing antibody levels over time are presented in the following figures:

- Line plot of GM FC from baseline and 95% CIs,
- Line plot of GMTs with geometric mean/titers and 95% CIs,
- Boxplots of GMTs with median, Q1 and Q3, and whiskers representing minimum and maximum by vaccine group.

All Secondary Immunogenicity analyses are based on the PPI Set.

Immunogenicity data is also listed based on the IS. In these listings, all values that were censored from the analyses due to earlier AV receipt will be flagged.

For the EOT analysis, Immunogenicity Tables on subjects seronegative at baseline are repeated on the subset of subjects accounted for the primary efficacy analysis (228 subjects) and a subset of 350 further interesting subjects, selected by the Sponsor.

The analysis to explore correlates of protective immunity induced by CVnCoV vaccination is described in a separate SAP.

12.8.2 Exploratory Immunogenicity Analyses

CMI assessments are performed in IS subjects from selected sites. The frequency of immune cell populations induced by the vaccine is summarized at each post-baseline timepoint.

Further characterization of the T-cell immune response may be done with other technologies like ELISpot, CyTOF and/or analysis of genomic biomarkers.

All relevant data is presented in listings.

13.0 References

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[3] Daniel P, Oren AM, Topol EJ. Prevalence of asymptomatic SARS-CoV-2 Infection. Ann. Intern. Med. 2020. doi:10.7326/M20-3012.

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14.0 Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomic Therapeutic Chemical
AV	Authorized Vaccine
BMI	Body Mass Index
BoD	Burden of Disease
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CMI	Cell-mediated Immune/Immunity
CMQ	Customized MedDRA Queries
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CRO	Contract Research Organization
DBP	Diastolic Blood Pressure
DSMB	Data Safety Monitoring Board
DVT	Deep Vein Thrombosis
EAS	Efficacy Analysis Set
EASS	Efficacy Analysis Set for Seroconversion
EASU	Efficacy Analysis Set Disregarding Unblinding
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
EMA	European Medicines Agency
EOT	End of Trial
FC	Fold Change
FiO2	Fractional Inspired Oxygen
GM	Geometric Mean
GMT	Geometric Mean of Titers
HR	Hazard Ratio
ICS	Intracellular cytokine staining
ICU	Intensive Care Unit

Glossary of Abbreviations:	
IgG	Immunoglobulin G
IS	Immunogenicity Subset
IWRS	Interactive Web Response System
KM	Kaplan Meier
LL	Lower Limit
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
MHP	Mobile Health Platform
mRNA	Messenger Ribonucleic Acid
N	Nucleocapsid
OL	Open-Label
O2	Oxygen
PaO2	Arterial Oxygen Partial Pressure
PBMC	Peripheral blood mononuclear cell
pIMD	Potential Immune-mediated Disease
PP	Per Protocol
PPE	Per Protocol Efficacy
PPI	Per Protocol Immunogenicity
PRA	Pharmaceutical Research Associates, Inc.
PSO	PRA System of Records
PT	Preferred Term
Q1	1st Quartile
Q3	3rd Quartile
RBD	Receptor-binding domain
RR	Relative Risk
RT-PCR	Reverse Transcription Polymerase Chain Reaction
S	Spike
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAS	Safety Analysis Set
SASsol	Safety Analysis Set for Solicited Adverse Events
SBP	Systolic Blood Pressure

Glossary of Abbreviations:	
SD	Standard Deviation
SMQ	Standardised MedDRA Query
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TFL	Tables, Figures and Listings
UL	Upper Limit
VDE	Vaccine Dependent Disease Enhancement
VE	Vaccine Efficacy
VOC	Variant of Concern
WHODRUG	World Health Organization Drug Dictionary

15.0 Appendices

Appendix 1 Potential Immune-Mediated Diseases

Gastrointestinal disorders:

- Celiac disease
- Crohn's disease
- Ulcerative colitis
- Ulcerative proctitis

Liver disorders:

- Autoimmune cholangitis
- Autoimmune hepatitis
- Primary biliary cirrhosis
- Primary sclerosing cholangitis

Metabolic diseases:

- Addison's disease
- Thyroiditis (including autoimmune [Hashimoto's disease] and subacute thyroiditis)
- Diabetes mellitus type I
- Grave's or Basedow's disease

Musculoskeletal disorders:

- Antisynthetase syndrome
- Dermatomyositis
- Juvenile chronic arthritis (including Still's disease)
- Mixed connective tissue disorder
- Polymyalgia rheumatic
- Polymyositis

- Psoriatic arthropathy
- Relapsing polychondritis
- Rheumatoid arthritis
- Scleroderma, including diffuse systemic form and CREST syndrome
- Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis
- Systemic lupus erythematosus
- Systemic sclerosis

Neuro-inflammatory disorders:

- Acute disseminated encephalomyelitis, including site specific variants (e.g., non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculomyelitis)
- Cranial nerve disorders, including paralyses/paresis (e.g., Bell's palsy)
- Guillain-Barré syndrome, including Miller Fisher syndrome and other variants
- Immune-mediated peripheral neuropathies, Parsonage-Turner syndrome and plexopathies, including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, and polyneuropathies associated with monoclonal gammopathy
- Multiple sclerosis
- Narcolepsy
- Optic neuritis
- Transverse Myelitis

Skin disorders:

- Alopecia areata
- Autoimmune bullous skin diseases, including pemphigus, pemphigoid and dermatitis herpetiformis
- Cutaneous lupus erythematosus
- Erythema nodosum
- Morphoea
- Lichen planus
- Psoriasis
- Sweet’s Syndrome
- Vitiligo

Vasculitides:

- Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis and temporal arteritis
- Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg-Strauss syndrome (allergic granulomatous angiitis), Buerger's disease thromboangiitis obliterans, necrotizing vasculitis and anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis

Others:

- Antiphospholipid syndrome

- Autoimmune hemolytic anemia
- Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis)
- Autoimmune myocarditis/cardiomyopathy
- Autoimmune thrombocytopenia
- Goodpasture syndrome
- Idiopathic pulmonary fibrosis
- Pernicious anemia
- Raynaud's phenomenon
- Sarcoidosis
- Sjörgen's syndrome
- Stevens-Johnson syndrome
- Uveitis

Appendix 2 AESIs for SARS-CoV-2 Vaccines*

Immunological disorders:

- Anaphylaxis
- Vasculitides
- Enhanced disease following immunization
- Multisystem inflammatory syndrome in children (MIS) and adults

Respiratory disorders:

- Acute respiratory distress syndrome

Cardiac disorders:

- Acute cardiac injury including:
  - Microangiopathy
  - Heart failure and cardiogenic shock
  - Stress cardiomyopathy
  - Coronary artery disease
  - Arrhythmia
  - Myocarditis, pericarditis

Hematological disorders:

- Thrombocytopenia

Coagulation disorder:

- Deep vein thrombosis
- Pulmonary embolus
- Cerebrovascular stroke
- Limb ischemia
- Hemorrhagic disease

Renal disorders:

- Acute kidney injury

Gastrointestinal disorders

- Liver injury
- Acute pancreatitis

Neurological disorders:

- Generalized convulsion
- Guillain-Barré Syndrome
- Acute disseminated encephalomyelitis
- Anosmia, ageusia
- Meningoencephalitis

Dermatologic disorder:

- Chilblain-like lesions
- Single organ cutaneous vasculitis
- Erythema multiforme

Other:

- Serious local/systemic AR following immunization

* based on Brighton Collaboration via CEPI's Safety Platform for Emergency vaccines (SPEAC) Project

Appendix 3 Terms for Selected Standardised and Customized MedDRA Queries

Anaphylactic Reaction (SMQ)

Narrow

- Anaphylactic reaction
- Anaphylactic shock
- Anaphylactic transfusion reaction
- Anaphylactoid reaction
- Anaphylactoid shock
- Circulatory collapse
- Dialysis membrane reaction
- Kounis syndrome
- Procedural shock
- Shock
- Shock symptom
- Type I hypersensitivity

Broad

- Acute respiratory failure
- Asthma
- Bronchial oedema
- Bronchospasm
- Cardio-respiratory distress
- Chest discomfort
- Choking
- Choking sensation
- Circumoral oedema
- Cough
- Cough variant asthma
- Cyanosis
- Dyspnoea
- Hyperventilation
- Irregular breathing
- Laryngeal dyspnoea
- Laryngeal oedema
- Laryngospasm
- Laryngotracheal oedema
- Mouth swelling
- Nasal obstruction
- Oedema mouth
- Oropharyngeal oedema
- Oropharyngeal spasm
- Oropharyngeal swelling
- Pharyngeal oedema

- Pharyngeal swelling
- Respiratory arrest
- Respiratory distress
- Respiratory failure
- Reversible airways obstruction
- Sensation of foreign body
- Sneezing
- Stridor
- Swollen tongue
- Tachypnoea
- Throat tightness
- Tongue oedema
- Tracheal obstruction
- Tracheal oedema
- Upper airway obstruction
- Wheezing
- Acquired C1 inhibitor deficiency
- Allergic oedema
- Angioedema
- Circumoral swelling
- Erythema
- Eye oedema
- Eye pruritus
- Eye swelling
- Eyelid oedema
- Face oedema
- Flushing
- Hereditary angioedema with C1 esterase inhibitor deficiency
- Injection site urticaria
- Lip oedema
- Lip swelling
- Nodular rash
- Ocular hyperaemia
- Oedema
- Oedema blister
- Periorbital oedema
- Periorbital swelling
- Pruritus
- Pruritus allergic
- Rash
- Rash erythematous
- Rash pruritic
- Skin swelling
- Swelling
- Swelling face
- Swelling of eyelid
- Urticaria
- Urticaria papular
- Blood pressure decreased
- Blood pressure diastolic decreased
- Blood pressure systolic decreased
- Cardiac arrest
- Cardio-respiratory arrest
- Cardiovascular insufficiency
- Diastolic hypotension
- Hypotension
- Hypotensive crisis
- Post procedural hypotension

Convulsions (SMQ)

Narrow

- 1p36 deletion syndrome
- 2-Hydroxyglutaric aciduria
- Acquired epileptic aphasia
- Acute encephalitis with refractory, repetitive partial seizures
- Alcoholic seizure
- Alpers disease
- Aspartate-glutamate-transporter deficiency
- Atonic seizures
- Atypical benign partial epilepsy
- Automatism epileptic
- Autonomic seizure
- Baltic myoclonic epilepsy
- Benign familial neonatal convulsions
- Benign rolandic epilepsy
- Biotinidase deficiency
- CDKL5 deficiency disorder
- CEC syndrome
- Change in seizure presentation
- Clonic convulsion
- Congenital bilateral perisylvian syndrome
- Convulsion in childhood

- Convulsions local
- Convulsive threshold lowered
- CSWS syndrome
- Deja vu
- Double cortex syndrome
- Dreamy state
- Drug withdrawal convulsions
- Early infantile epileptic encephalopathy with burst-suppression
- Eclampsia
- Epilepsy
- Epilepsy surgery
- Epilepsy with myoclonic-atonic seizures
- Epileptic aura
- Epileptic psychosis
- Faciobrachial dystonic seizure
- Febrile convulsion
- Febrile infection-related epilepsy syndrome
- Focal dyscognitive seizures
- Frontal lobe epilepsy
- Gelastic seizure
- Generalised onset non-motor seizure
- Generalised tonic-clonic seizure
- Glucose transporter type 1 deficiency syndrome
- GM2 gangliosidosis
- Grey matter heterotopia
- Hemimegalencephaly
- Hyperglycaemic seizure
- Hypocalcaemic seizure
- Hypoglycaemic seizure
- Hyponatraemic seizure
- Idiopathic generalised epilepsy
- Infantile spasms
- Jeavons syndrome
- Juvenile myoclonic epilepsy
- Lafora's myoclonic epilepsy
- Lennox-Gastaut syndrome
- Migraine-triggered seizure
- Molybdenum cofactor deficiency
- Multiple subpial transection
- Myoclonic epilepsy
- Myoclonic epilepsy and ragged-red fibres
- Neonatal epileptic seizure
- Neonatal seizure
- Partial seizures
- Partial seizures with secondary generalisation
- Petit mal epilepsy
- Polymicrogyria
- Post stroke epilepsy
- Post stroke seizure
- Postictal headache
- Postictal paralysis
- Postictal psychosis
- Postictal state
- Post-traumatic epilepsy
- Schizencephaly
- Seizure
- Seizure anoxic
- Seizure cluster
- Seizure like phenomena
- Severe myoclonic epilepsy of infancy
- Simple partial seizures
- Status epilepticus
- Sudden unexplained death in epilepsy
- Temporal lobe epilepsy
- Tonic clonic movements
- Tonic convulsion
- Tonic posturing
- Topectomy
- Transient epileptic amnesia
- Tuberous sclerosis complex
- Uncinate fits

Broad

- Amygdalohippocampectomy
- Aura
- Corpus callosotomy
- Drop attacks
- Foaming at mouth
- Focal cortical resection
- Narcolepsy
- Preictal state
- Seizure prophylaxis
- Tongue biting

Embolic and thrombotic events, arterial (SMQ)

Narrow

- Acute aortic syndrome
- Acute myocardial infarction
- Amaurosis
- Amaurosis fugax
- Angioplasty
- Aortic bypass
- Aortic embolus
- Aortic surgery
- Aortic thrombosis
- Aortogram abnormal
- Arterectomy
- Arterectomy with graft replacement
- Arterial angioplasty
- Arterial bypass occlusion
- Arterial bypass operation
- Arterial bypass thrombosis
- Arterial graft
- Arterial occlusive disease
- Arterial revascularisation
- Arterial stent insertion
- Arterial therapeutic procedure
- Arterial thrombosis
- Arteriogram abnormal
- Arteriogram carotid abnormal
- Arteriotomy
- Atherectomy
- Atherosclerotic plaque rupture
- Atrial appendage closure
- Atrial appendage resection
- Basal ganglia infarction
- Basilar artery occlusion
- Basilar artery thrombosis
- Blindness transient
- Brachiocephalic artery occlusion
- Capsular warning syndrome
- Carotid angioplasty
- Carotid arterial embolus
- Carotid artery bypass
- Carotid artery occlusion
- Carotid artery stent insertion
- Carotid artery thrombosis
- Carotid endarterectomy
- Cerebellar artery occlusion
- Cerebellar artery thrombosis
- Cerebral artery embolism
- Cerebral artery occlusion
- Cerebral artery stent insertion
- Cerebral artery thrombosis
- Cerebral hypoperfusion
- Cerebrovascular insufficiency
- Cerebrovascular stenosis
- Coeliac artery occlusion
- Coronary angioplasty
- Coronary arterial stent insertion
- Coronary artery bypass
- Coronary artery embolism
- Coronary artery occlusion
- Coronary artery reocclusion
- Coronary artery surgery
- Coronary artery thrombosis
- Coronary endarterectomy
- Coronary revascularisation
- Coronary vascular graft occlusion
- Embolia cutis medicamentosa
- Embolism arterial
- Endarterectomy
- Femoral artery embolism
- Hepatic artery embolism
- Hepatic artery occlusion
- Hepatic artery thrombosis
- Hypothenar hammer syndrome
- Iliac artery embolism
- Iliac artery occlusion
- Internal capsule infarction
- Intra-aortic balloon placement
- Intraoperative cerebral artery occlusion
- Ischaemic cerebral infarction
- Ischaemic stroke
- Lacunar infarction
- Leriche syndrome
- Mesenteric arterial occlusion
- Mesenteric arteriosclerosis
- Mesenteric artery embolism
- Mesenteric artery stenosis

- Mesenteric artery stent insertion
- Mesenteric artery thrombosis
- Myocardial infarction
- Myocardial necrosis
- Ophthalmic artery thrombosis
- Papillary muscle infarction
- Penile artery occlusion
- Percutaneous coronary intervention
- Peripheral arterial occlusive disease
- Peripheral arterial reocclusion
- Peripheral artery angioplasty
- Peripheral artery bypass
- Peripheral artery occlusion
- Peripheral artery stent insertion
- Peripheral artery surgery
- Peripheral artery thrombosis
- Peripheral embolism
- Peripheral endarterectomy
- Popliteal artery entrapment syndrome
- Post procedural myocardial infarction
- Postinfarction angina
- Precerebral artery occlusion
- Precerebral artery thrombosis
- Profundaplasty
- Pulmonary artery occlusion
- Pulmonary artery therapeutic procedure
- Pulmonary artery thrombosis
- Pulmonary endarterectomy
- Pulmonary tumour thrombotic microangiopathy
- Renal artery angioplasty
- Renal artery occlusion
- Renal artery thrombosis
- Renal embolism
- Retinal artery embolism
- Retinal artery occlusion
- Retinal artery thrombosis
- Silent myocardial infarction
- Spinal artery embolism
- Spinal artery thrombosis
- Splenic artery thrombosis
- Splenic embolism
- Stress cardiomyopathy
- Subclavian artery embolism
- Subclavian artery occlusion
- Subclavian artery thrombosis
- Thromboembolectomy
- Thrombotic microangiopathy
- Thrombotic thrombocytopenic purpura
- Transient ischaemic attack
- Truncus coeliacus thrombosis
- Vascular pseudoaneurysm thrombosis
- Vertebral artery occlusion
- Vertebral artery thrombosis
- Visual acuity reduced transiently

Embolic and thrombotic events, venous (SMQ)

Narrow

- Aseptic cavernous sinus thrombosis
- Axillary vein thrombosis
- Brachiocephalic vein occlusion
- Brachiocephalic vein thrombosis
- Budd-Chiari syndrome
- Catheterisation venous
- Cavernous sinus thrombosis
- Central venous catheterisation
- Cerebral venous sinus thrombosis
- Cerebral venous thrombosis
- Compression garment application
- Deep vein thrombosis
- Deep vein thrombosis postoperative
- Embolism venous
- Hepatic vein embolism
- Hepatic vein occlusion
- Hepatic vein thrombosis
- Homans' sign positive
- Iliac vein occlusion
- Inferior vena cava syndrome
- Inferior vena caval occlusion
- Jugular vein embolism
- Jugular vein occlusion
- Jugular vein thrombosis
- Mahler sign
- May-Thurner syndrome
- Mesenteric vein thrombosis
- Mesenteric venous occlusion

- Obstetrical pulmonary embolism
- Obstructive shock
- Ophthalmic vein thrombosis
- Ovarian vein thrombosis
- Paget-Schroetter syndrome
- Pelvic venous thrombosis
- Penile vein thrombosis
- Peripheral vein occlusion
- Peripheral vein thrombus extension
- Phlebectomy
- Portal vein cavernous transformation
- Portal vein embolism
- Portal vein occlusion
- Portal vein thrombosis
- Portosplenomesenteric venous thrombosis
- Post procedural pulmonary embolism
- Post thrombotic syndrome
- Postoperative thrombosis
- Postpartum venous thrombosis
- Pulmonary embolism
- Pulmonary infarction
- Pulmonary microemboli
- Pulmonary thrombosis
- Pulmonary vein occlusion
- Pulmonary veno-occlusive disease
- Pulmonary venous thrombosis
- Renal vein embolism
- Renal vein occlusion
- Renal vein thrombosis
- Retinal vein occlusion
- Retinal vein thrombosis
- Septic pulmonary embolism
- SI QIII TIII pattern
- Splenic vein occlusion
- Splenic vein thrombosis
- Subclavian vein occlusion
- Subclavian vein thrombosis
- Superior sagittal sinus thrombosis
- Superior vena cava occlusion
- Superior vena cava syndrome
- Thrombophlebitis
- Thrombophlebitis migrans
- Thrombophlebitis neonatal
- Thrombophlebitis superficial
- Thrombosed varicose vein
- Thrombosis corpora cavernosa
- Transverse sinus thrombosis
- Vena cava embolism
- Vena cava filter insertion
- Vena cava filter removal
- Vena cava thrombosis
- Venogram abnormal
- Venoocclusive disease
- Venoocclusive liver disease
- Venous angioplasty
- Venous occlusion
- Venous operation
- Venous recanalisation
- Venous repair
- Venous stent insertion
- Venous thrombosis
- Venous thrombosis in pregnancy
- Venous thrombosis limb
- Venous thrombosis neonatal
- Visceral venous thrombosis

Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (SMQ)

Narrow

- Administration site thrombosis
- Adrenal thrombosis
- Angiogram abnormal
- Angiogram cerebral abnormal
- Angiogram peripheral abnormal
- Antiphospholipid syndrome
- Application site thrombosis
- Arteriovenous fistula occlusion
- Arteriovenous fistula thrombosis
- Arteriovenous graft thrombosis
- Artificial blood vessel occlusion
- Atrial thrombosis
- Basal ganglia stroke
- Bone infarction
- Brain stem embolism
- Brain stem infarction

- Brain stem stroke
- Brain stem thrombosis
- Cardiac ventricular thrombosis
- Catheter site thrombosis
- Cerebellar embolism
- Cerebellar infarction
- Cerebral congestion
- Cerebral infarction
- Cerebral infarction foetal
- Cerebral ischaemia
- Cerebral microembolism
- Cerebral microinfarction
- Cerebral septic infarct
- Cerebral thrombosis
- Cerebral vascular occlusion
- Cerebrospinal thrombotic tamponade
- Cerebrovascular accident
- Cerebrovascular accident prophylaxis
- Cerebrovascular disorder
- Cerebrovascular operation
- Choroidal infarction
- Collateral circulation
- Coronary bypass thrombosis
- Device embolisation
- Device occlusion
- Device related thrombosis
- Diplegia
- Directional Doppler flow tests abnormal
- Disseminated intravascular coagulation
- Disseminated intravascular coagulation in newborn
- Embolic cerebellar infarction
- Embolic cerebral infarction
- Embolic pneumonia
- Embolic stroke
- Embolism
- Eye infarction
- Fluorescence angiogram abnormal
- Foetal cerebrovascular disorder
- Gastric infarction
- Graft thrombosis
- Haemorrhagic adrenal infarction
- Haemorrhagic cerebral infarction
- Haemorrhagic infarction
- Haemorrhagic stroke
- Haemorrhagic transformation stroke
- Haemorrhoids thrombosed
- Hemiparesis
- Hemiplegia
- Heparin-induced thrombocytopenia
- Hepatic infarction
- Hepatic vascular thrombosis
- Implant site thrombosis
- Incision site vessel occlusion
- Infarction
- Infusion site thrombosis
- Injection site thrombosis
- Inner ear infarction
- Instillation site thrombosis
- Intestinal infarction
- Intracardiac mass
- Intracardiac thrombus
- Lambl's excrescences
- Medical device site thrombosis
- Mesenteric vascular insufficiency
- Mesenteric vascular occlusion
- Microembolism
- Monoparesis
- Monoplegia
- Optic nerve infarction
- Pancreatic infarction
- Paradoxical embolism
- Paraneoplastic thrombosis
- Paraparesis
- Paraplegia
- Paresis
- Peripheral revascularisation
- Pituitary infarction
- Placental infarction
- Pneumatic compression therapy
- Portal shunt procedure
- Post procedural stroke
- Postpartum thrombosis
- Prosthetic cardiac valve thrombosis
- Prosthetic vessel implantation
- Quadriparesis
- Quadriplegia
- Renal infarct

- Renal vascular thrombosis
- Retinal infarction
- Retinal vascular thrombosis
- Revascularisation procedure
- Shunt occlusion
- Shunt thrombosis
- Spinal cord infarction
- Spinal stroke
- Splenic infarction
- Splenic thrombosis
- Stoma site thrombosis
- Stroke in evolution
- Strokectomy
- Surgical vascular shunt
- Testicular infarction
- Thalamic infarction
- Thrombectomy
- Thromboangiitis obliterans
- Thrombolysis
- Thrombosis
- Thrombosis in device
- Thrombosis mesenteric vessel
- Thrombosis prophylaxis
- Thrombotic cerebral infarction
- Thrombotic stroke
- Thyroid infarction
- Tumour embolism
- Tumour thrombectomy
- Tumour thrombosis
- Ultrasonic angiogram abnormal
- Ultrasound Doppler abnormal
- Umbilical cord occlusion
- Umbilical cord thrombosis
- Vaccination site thrombosis
- Vascular access site thrombosis
- Vascular device occlusion
- Vascular graft
- Vascular graft occlusion
- Vascular graft thrombosis
- Vascular operation
- Vascular stent insertion
- Vascular stent occlusion
- Vascular stent thrombosis
- Vasodilation procedure
- Vessel puncture site occlusion
- Vessel puncture site thrombosis
- Visual midline shift syndrome

Hypersensitivity (SMQ)

Narrow

- Acquired C1 inhibitor deficiency
- Acute generalised exanthematous pustulosis
- Administration related reaction
- Administration site dermatitis
- Administration site eczema
- Administration site hypersensitivity
- Administration site rash
- Administration site recall reaction
- Administration site urticaria
- Administration site vasculitis
- Allergic bronchitis
- Allergic colitis
- Allergic cough
- Allergic cystitis
- Allergic eosinophilia
- Allergic gastroenteritis
- Allergic hepatitis
- Allergic keratitis
- Allergic oedema
- Allergic otitis externa
- Allergic otitis media
- Allergic pharyngitis
- Allergic reaction to excipient
- Allergic respiratory disease
- Allergic respiratory symptom
- Allergic sinusitis
- Allergic stomatitis
- Allergic transfusion reaction
- Allergy alert test positive
- Allergy test positive
- Allergy to immunoglobulin therapy
- Allergy to surgical sutures
- Allergy to vaccine

- Anal eczema
- Anaphylactic reaction
- Anaphylactic shock
- Anaphylactic transfusion reaction
- Anaphylactoid reaction
- Anaphylactoid shock
- Anaphylaxis treatment
- Angioedema
- Antiallergic therapy
- Antiendomysial antibody positive
- Anti-neutrophil cytoplasmic antibody positive vasculitis
- Application site dermatitis
- Application site eczema
- Application site hypersensitivity
- Application site rash
- Application site recall reaction
- Application site urticaria
- Application site vasculitis
- Arthritis allergic
- Aspirin-exacerbated respiratory disease
- Atopic cough
- Atopy
- Blepharitis allergic
- Blood immunoglobulin E abnormal
- Blood immunoglobulin E increased
- Bromoderma
- Bronchospasm
- Bullous haemorrhagic dermatosis
- Catheter site dermatitis
- Catheter site eczema
- Catheter site hypersensitivity
- Catheter site rash
- Catheter site urticaria
- Catheter site vasculitis
- Chronic eosinophilic rhinosinusitis
- Chronic hyperplastic eosinophilic sinusitis
- Circulatory collapse
- Circumoral oedema
- Circumoral swelling
- Conjunctival oedema
- Conjunctivitis allergic
- Contact stomatitis
- Contrast media allergy
- Contrast media reaction
- Corneal oedema
- Cutaneous vasculitis
- Dennie-Morgan fold
- Dermatitis
- Dermatitis acneiform
- Dermatitis allergic
- Dermatitis atopic
- Dermatitis bullous
- Dermatitis contact
- Dermatitis exfoliative
- Dermatitis exfoliative generalised
- Dermatitis herpetiformis
- Dermatitis infected
- Dermatitis psoriasiform
- Device allergy
- Dialysis membrane reaction
- Distributive shock
- Documented hypersensitivity to administered product
- Drug eruption
- Drug hypersensitivity
- Drug provocation test
- Drug reaction with eosinophilia and systemic symptoms
- Eczema
- Eczema infantile
- Eczema nummular
- Eczema vaccinatum
- Eczema vesicular
- Eczema weeping
- Encephalitis allergic
- Encephalopathy allergic
- Eosinophilic granulomatosis with polyangiitis
- Epidermal necrosis
- Epidermolysis
- Epidermolysis bullosa
- Epiglottic oedema
- Erythema multiforme
- Erythema nodosum
- Exfoliative rash
- Eye allergy
- Eye oedema

- Eye swelling
- Eyelid oedema
- Face oedema
- Fixed eruption
- Giant papillary conjunctivitis
- Gingival oedema
- Gingival swelling
- Gleich's syndrome
- Haemorrhagic urticaria
- Hand dermatitis
- Henoch-Schonlein purpura
- Henoch-Schonlein purpura nephritis
- Heparin-induced thrombocytopenia
- Hereditary angioedema
- Hereditary angioedema with C1 esterase inhibitor deficiency
- Hypersensitivity
- Hypersensitivity myocarditis
- Hypersensitivity pneumonitis
- Hypersensitivity vasculitis
- Idiopathic urticaria
- Immediate post-injection reaction
- Immune thrombocytopenia
- Immune tolerance induction
- Implant site dermatitis
- Implant site hypersensitivity
- Implant site rash
- Implant site urticaria
- Incision site dermatitis
- Incision site rash
- Infusion related hypersensitivity reaction
- Infusion related reaction
- Infusion site dermatitis
- Infusion site eczema
- Infusion site hypersensitivity
- Infusion site rash
- Infusion site recall reaction
- Infusion site urticaria
- Infusion site vasculitis
- Injection related reaction
- Injection site dermatitis
- Injection site eczema
- Injection site hypersensitivity
- Injection site rash
- Injection site recall reaction
- Injection site urticaria
- Injection site vasculitis
- Instillation site hypersensitivity
- Instillation site rash
- Instillation site urticaria
- Interstitial granulomatous dermatitis
- Intestinal angioedema
- Iodine allergy
- Kaposi's varicelliform eruption
- Kounis syndrome
- Laryngeal oedema
- Laryngitis allergic
- Laryngospasm
- Laryngotracheal oedema
- Limbal swelling
- Lip oedema
- Lip swelling
- Mast cell degranulation present
- Medical device site dermatitis
- Medical device site eczema
- Medical device site hypersensitivity
- Medical device site rash
- Medical device site recall reaction
- Medical device site urticaria
- Mouth swelling
- Mucocutaneous rash
- Multiple allergies
- Nephritis allergic
- Nikolsky's sign
- Nodular rash
- Nutritional supplement allergy
- Oculomucocutaneous syndrome
- Oculorespiratory syndrome
- Oedema mouth
- Oral allergy syndrome
- Oropharyngeal blistering
- Oropharyngeal oedema
- Oropharyngeal spasm
- Oropharyngeal swelling
- Palatal oedema
- Palatal swelling
- Palisaded neutrophilic granulomatous dermatitis

- Palpable purpura
- Pathergy reaction
- Perioral dermatitis
- Periorbital oedema
- Periorbital swelling
- Pharyngeal oedema
- Pharyngeal swelling
- Procedural shock
- Pruritus allergic
- Radioallergosorbent test positive
- Rash
- Rash erythematous
- Rash follicular
- Rash macular
- Rash maculo-papular
- Rash maculovesicular
- Rash morbilliform
- Rash neonatal
- Rash papulosquamous
- Rash pruritic
- Rash pustular
- Rash rubelliform
- Rash scarlatiniform
- Rash vesicular
- Reaction to azo-dyes
- Reaction to colouring
- Reaction to excipient
- Reaction to food additive
- Reaction to preservatives
- Red man syndrome
- Rhinitis allergic
- Scleral oedema
- Scleritis allergic
- Scrotal dermatitis
- Scrotal oedema
- Serum sickness
- Serum sickness-like reaction
- Shock
- Shock symptom
- SJS-TEN overlap
- Skin necrosis
- Skin reaction
- Skin test positive
- Solar urticaria
- Solvent sensitivity
- Stevens-Johnson syndrome
- Stoma site hypersensitivity
- Stoma site rash
- Swelling face
- Swelling of eyelid
- Swollen tongue
- Symmetrical drug-related intertriginous and flexural exanthema
- Therapeutic product cross-reactivity
- Tongue oedema
- Toxic epidermal necrolysis
- Toxic skin eruption
- Tracheal oedema
- Type I hypersensitivity
- Type II hypersensitivity
- Type III immune complex mediated reaction
- Type IV hypersensitivity reaction
- Urticaria
- Urticaria cholinergic
- Urticaria chronic
- Urticaria contact
- Urticaria papular
- Urticaria physical
- Urticaria pigmentosa
- Urticaria vesiculosa
- Urticarial dermatitis
- Urticarial vasculitis
- Vaccination site dermatitis
- Vaccination site eczema
- Vaccination site exfoliation
- Vaccination site hypersensitivity
- Vaccination site rash
- Vaccination site recall reaction
- Vaccination site urticaria
- Vaccination site vasculitis
- Vaccination site vesicles
- Vaginal ulceration
- Vasculitic rash
- Vernal keratoconjunctivitis
- Vessel puncture site rash
- Vessel puncture site vesicles
- Vulval eczema

- Vulval ulceration
- Vulvovaginal rash
- Vulvovaginal ulceration
- Vulvovaginitis allergic

Broad

- Acute respiratory failure
- Administration site photosensitivity reaction
- Airway remodelling
- Allergy to chemicals
- Allergy to fermented products
- Alpha tumour necrosis factor increased
- Alveolitis
- Antibody test abnormal
- Antibody test positive
- Anti-insulin antibody increased
- Anti-insulin antibody positive
- Anti-insulin receptor antibody increased
- Anti-insulin receptor antibody positive
- Application site photosensitivity reaction
- Asthma
- Asthma late onset
- Asthma-chronic obstructive pulmonary disease overlap syndrome
- Asthmatic crisis
- Auricular swelling
- Blister
- Blister rupture
- Blood immunoglobulin A abnormal
- Blood immunoglobulin A increased
- Blood immunoglobulin D increased
- Blood immunoglobulin G abnormal
- Blood immunoglobulin G increased
- Blood immunoglobulin M abnormal
- Blood immunoglobulin M increased
- Bronchial hyperreactivity
- Bronchial oedema
- Bullous impetigo
- Caffeine allergy
- Capillaritis
- Charcot-Leyden crystals
- Cheilitis
- Childhood asthma
- Choking
- Choking sensation
- Complement factor C1 decreased
- Complement factor C2 decreased
- Complement factor C3 decreased
- Complement factor C4 decreased
- Complement factor decreased
- Conjunctivitis
- Corneal exfoliation
- Cough variant asthma
- Cytokine release syndrome
- Cytokine storm
- Ear swelling
- Eosinophil count abnormal
- Eosinophil count increased
- Eosinophil percentage abnormal
- Eosinophil percentage increased
- Eosinophilia
- Eosinophilia myalgia syndrome
- Eosinophilic bronchitis
- Eosinophilic oesophagitis
- Eosinophilic pneumonia
- Eosinophilic pneumonia acute
- Eosinophilic pneumonia chronic
- Erythema
- Flushing
- Gastrointestinal oedema
- Generalised oedema
- Genital rash
- Genital swelling
- Haemolytic transfusion reaction
- HLA marker study positive
- Human anti-hamster antibody increased
- Human anti-hamster antibody positive
- Immune complex level increased
- Immunoglobulins abnormal
- Immunoglobulins increased
- Immunology test abnormal
- Implant site photosensitivity
- Infusion site photosensitivity reaction
- Injection site panniculitis
- Injection site photosensitivity reaction
- Interstitial lung disease
- Laryngeal dyspnoea

- Laryngeal obstruction
- Leukotriene increased
- Lip exfoliation
- Localised oedema
- Macrophage inflammatory protein-1 alpha increased
- Mechanical urticaria
- Medical device site photosensitivity reaction
- Mesenteric panniculitis
- Monocyte chemotactic protein-2 increased
- Mouth ulceration
- Mucocutaneous ulceration
- Mucosa vesicle
- Mucosal erosion
- Mucosal exfoliation
- Mucosal necrosis
- Mucosal ulceration
- Nasal crease
- Necrotising panniculitis
- Neurodermatitis
- Neutralising antibodies positive
- Noninfective conjunctivitis
- Non-neutralising antibodies positive
- Occupational asthma
- Occupational dermatitis
- Oedema mucosal
- Oral mucosal exfoliation
- Orbital oedema
- Panniculitis
- Penile exfoliation
- Penile oedema
- Penile rash
- Penile swelling
- Perineal rash
- Perivascular dermatitis
- Photosensitivity reaction
- Pneumonitis
- Prurigo
- Pruritus
- Pulmonary eosinophilia
- Reactive airways dysfunction syndrome
- Respiratory arrest
- Respiratory distress
- Respiratory failure
- Respiratory tract oedema
- Reversible airways obstruction
- Rhinitis perennial
- Scrotal exfoliation
- Scrotal swelling
- Seasonal allergy
- Septal panniculitis
- Skin erosion
- Skin exfoliation
- Skin oedema
- Skin swelling
- Sneezing
- Status asthmaticus
- Stomatitis
- Streptokinase antibody increased
- Stridor
- Suffocation feeling
- Sunscreen sensitivity
- Throat tightness
- Tongue exfoliation
- Tracheal obstruction
- Tracheostomy
- Transplantation associated food allergy
- Upper airway obstruction
- Vaccination site photosensitivity reaction
- Vaginal oedema
- Visceral oedema
- Vulval oedema
- Vulvovaginal exfoliation
- Vulvovaginal swelling
- Wheezing

Immune-Mediated/Autoimmune Disorders (SMQ)

Narrow

- Acute cutaneous lupus erythematosus
- Acute motor axonal neuropathy
- Acute motor-sensory axonal neuropathy
- Addison's disease

- Administration site vasculitis
- Alloimmune hepatitis
- Alopecia areata
- Alveolar proteinosis
- Amyloid arthropathy
- Amyloidosis
- Amyloidosis senile
- Ankylosing spondylitis
- Anti-glomerular basement membrane disease
- Anti-myelin-associated glycoprotein associated polyneuropathy
- Anti-neutrophil cytoplasmic antibody positive vasculitis
- Antiphospholipid syndrome
- Antisynthetase syndrome
- Aplasia pure red cell
- Application site vasculitis
- Arthritis enteropathic
- Autoimmune anaemia
- Autoimmune aplastic anaemia
- Autoimmune arthritis
- Autoimmune blistering disease
- Autoimmune cholangitis
- Autoimmune colitis
- Autoimmune demyelinating disease
- Autoimmune dermatitis
- Autoimmune disorder
- Autoimmune encephalopathy
- Autoimmune endocrine disorder
- Autoimmune enteropathy
- Autoimmune eye disorder
- Autoimmune haemolytic anaemia
- Autoimmune heparin-induced thrombocytopenia
- Autoimmune hepatitis
- Autoimmune hyperlipidaemia
- Autoimmune hypothyroidism
- Autoimmune inner ear disease
- Autoimmune lung disease
- Autoimmune lymphoproliferative syndrome
- Autoimmune myocarditis
- Autoimmune myositis
- Autoimmune nephritis
- Autoimmune neuropathy
- Autoimmune neutropenia
- Autoimmune pancreatitis
- Autoimmune pancytopenia
- Autoimmune pericarditis
- Autoimmune retinopathy
- Autoimmune thyroid disorder
- Autoimmune thyroiditis
- Autoimmune uveitis
- Autoinflammation with infantile enterocolitis
- Autoinflammatory disease
- Axial spondyloarthritis
- Basedow's disease
- Behcet's syndrome
- Bickerstaff's encephalitis
- Birdshot chorioretinopathy
- Butterfly rash
- C1q nephropathy
- Caplan's syndrome
- Cardiac amyloidosis
- Cardiac sarcoidosis
- Central nervous system lupus
- Central nervous system vasculitis
- Cerebral amyloid angiopathy
- Cholangitis sclerosing
- Chronic autoimmune glomerulonephritis
- Chronic cutaneous lupus erythematosus
- Chronic gastritis
- Chronic inflammatory demyelinating polyradiculoneuropathy
- Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids
- Chronic recurrent multifocal osteomyelitis
- Clinically isolated syndrome
- Coeliac disease
- Cogan's syndrome
- Cold type haemolytic anaemia
- Colitis ulcerative
- Collagen disorder
- Collagen-vascular disease
- Concentric sclerosis
- Coombs positive haemolytic anaemia

- CREST syndrome
- Crohn's disease
- Cryofibrinogenaemia
- Cryoglobulinaemia
- Cutaneous amyloidosis
- Cutaneous lupus erythematosus
- Cutaneous sarcoidosis
- Cutaneous vasculitis
- Cystitis interstitial
- De novo purine synthesis inhibitors associated acute inflammatory syndrome
- Demyelinating polyneuropathy
- Dermatomyositis
- Dialysis amyloidosis
- Diffuse vasculitis
- Digital pitting scar
- Dressler's syndrome
- Encephalitis allergic
- Encephalitis autoimmune
- Encephalitis post immunisation
- Endocrine ophthalmopathy
- Enteropathic spondylitis
- Eosinophilic fasciitis
- Eosinophilic granulomatosis with polyangiitis
- Eosinophilic oesophagitis
- Evans syndrome
- Felty's syndrome
- Fibrillary glomerulonephritis
- Gastrointestinal amyloidosis
- Giant cell arteritis
- Glomerulonephritis
- Glomerulonephritis rapidly progressive
- Goodpasture's syndrome
- Granulomatosis with polyangiitis
- Granulomatous dermatitis
- Guillain-Barre syndrome
- Haemophagocytic lymphohistiocytosis
- Haemorrhagic vasculitis
- Hashimoto's encephalopathy
- Hashitoxicosis
- Henoch-Schonlein purpura
- Henoch-Schonlein purpura nephritis
- Heparin-induced thrombocytopenia
- Hepatic amyloidosis
- Hypogammaglobulinaemia
- IgA nephropathy
- IgM nephropathy
- Immune thrombocytopenia
- Immune-mediated adverse reaction
- Immune-mediated cholangitis
- Immune-mediated cholestasis
- Immune-mediated cytopenia
- Immune-mediated encephalitis
- Immune-mediated encephalopathy
- Immune-mediated endocrinopathy
- Immune-mediated enterocolitis
- Immune-mediated gastritis
- Immune-mediated hepatic disorder
- Immune-mediated hepatitis
- Immune-mediated hyperthyroidism
- Immune-mediated hypothyroidism
- Immune-mediated myocarditis
- Immune-mediated myositis
- Immune-mediated nephritis
- Immune-mediated neuropathy
- Immune-mediated pancreatitis
- Immune-mediated pneumonitis
- Immune-mediated renal disorder
- Immune-mediated thyroiditis
- Immune-mediated uveitis
- Immunoglobulin G4 related disease
- Inclusion body myositis
- Inflammatory bowel disease
- Injection site vasculitis
- Insulin autoimmune syndrome
- Interstitial granulomatous dermatitis
- IPEX syndrome
- Juvenile idiopathic arthritis
- Juvenile polymyositis
- Juvenile psoriatic arthritis
- Juvenile spondyloarthritis
- Kawasaki's disease
- Keratoderma blenorrhagica
- Laryngeal rheumatoid arthritis
- Latent autoimmune diabetes in adults
- Leukoencephalomyelitis
- Lewis-Sumner syndrome

- Limbic encephalitis
- Linear IgA disease
- Liver sarcoidosis
- Lupoid hepatic cirrhosis
- Lupus cystitis
- Lupus encephalitis
- Lupus endocarditis
- Lupus enteritis
- Lupus hepatitis
- Lupus myocarditis
- Lupus myositis
- Lupus nephritis
- Lupus pancreatitis
- Lupus pleurisy
- Lupus pneumonitis
- Lupus vasculitis
- Lymphocytic hypophysitis
- MAGIC syndrome
- Marburg's variant multiple sclerosis
- Marine Lenhart syndrome
- Metastatic cutaneous Crohn's disease
- Microscopic polyangiitis
- Mixed connective tissue disease
- Morphoea
- Morvan syndrome
- Multifocal motor neuropathy
- Multiple sclerosis
- Multiple sclerosis relapse
- Multisystem inflammatory syndrome in children
- Muscular sarcoidosis
- Myasthenia gravis
- Myasthenia gravis crisis
- Myasthenia gravis neonatal
- Myasthenic syndrome
- Myelitis transverse
- Neonatal Crohn's disease
- Neonatal lupus erythematosus
- Neuralgic amyotrophy
- Neuromyelitis optica pseudo relapse
- Neuromyelitis optica spectrum disorder
- Neuropsychiatric lupus
- Neurosarcoidosis
- Nodular vasculitis
- Noninfectious myelitis
- Noninfective encephalitis
- Noninfective encephalomyelitis
- Ocular myasthenia
- Ocular pemphigoid
- Ocular sarcoidosis
- Ocular vasculitis
- Overlap syndrome
- Palindromic rheumatism
- Palisaded neutrophilic granulomatous dermatitis
- Palpable purpura
- Pericarditis lupus
- Peritonitis lupus
- Pernicious anaemia
- POEMS syndrome
- Polyarteritis nodosa
- Polychondritis
- Polyglandular autoimmune syndrome type I
- Polyglandular autoimmune syndrome type II
- Polyglandular autoimmune syndrome type III
- Polymyalgia rheumatica
- Postpericardiotomy syndrome
- Primary amyloidosis
- Primary biliary cholangitis
- Primary progressive multiple sclerosis
- Proctitis ulcerative
- Progressive facial hemiatrophy
- Progressive multiple sclerosis
- Progressive relapsing multiple sclerosis
- Psoriasis
- Psoriatic arthropathy
- Pulmonary renal syndrome
- Pulmonary sarcoidosis
- Pulmonary vasculitis
- Pyoderma gangrenosum
- Pyostomatitis vegetans
- Radiologically isolated syndrome
- Rasmussen encephalitis
- Raynaud's phenomenon
- Reactive capillary endothelial proliferation

- Relapsing multiple sclerosis
- Relapsing-remitting multiple sclerosis
- Renal amyloidosis
- Renal arteritis
- Renal vasculitis
- Retinal vasculitis
- Retroperitoneal fibrosis
- Reynold's syndrome
- Rheumatic brain disease
- Rheumatic disorder
- Rheumatoid arthritis
- Rheumatoid lung
- Rheumatoid neutrophilic dermatosis
- Rheumatoid nodule
- Rheumatoid scleritis
- Rheumatoid vasculitis
- SAPHO syndrome
- Sarcoidosis
- Satoyoshi syndrome
- Sclerodactylia
- Scleroderma
- Scleroderma associated digital ulcer
- Scleroderma renal crisis
- Scleroderma-like reaction
- Secondary amyloidosis
- Secondary cerebellar degeneration
- Secondary progressive multiple sclerosis
- Segmented hyalinising vasculitis
- Shrinking lung syndrome
- Sjogren's syndrome
- SLE arthritis
- Stiff leg syndrome
- Stiff person syndrome
- Still's disease
- Stoma site vasculitis
- Subacute cutaneous lupus erythematosus
- Subacute inflammatory demyelinating polyneuropathy
- Susac's syndrome
- Sympathetic ophthalmia
- Systemic lupus erythematosus
- Systemic lupus erythematosus rash
- Systemic scleroderma
- Systemic sclerosis pulmonary
- Takayasu's arteritis
- Terminal ileitis
- Testicular autoimmunity
- Thromboangiitis obliterans
- Thrombocytopenic purpura
- Thrombotic thrombocytopenic purpura
- Tongue amyloidosis
- Toxic oil syndrome
- Tubulointerstitial nephritis and uveitis syndrome
- Tumefactive multiple sclerosis
- Type 1 diabetes mellitus
- Type III immune complex mediated reaction
- Ulcerative keratitis
- Undifferentiated connective tissue disease
- Vaccination site vasculitis
- Vasculitic rash
- Vasculitic ulcer
- Vasculitis
- Vasculitis gastrointestinal
- Vasculitis necrotising
- Vitiligo
- Vogt-Koyanagi-Harada disease
- Warm type haemolytic anaemia

Broad

- Acoustic neuritis
- Acute febrile neutrophilic dermatosis
- Acute flaccid myelitis
- Acute macular outer retinopathy
- Anosmia
- Antiacetylcholine receptor antibody positive
- Anti-actin antibody positive
- Anti-aquaporin-4 antibody positive
- Anti-basal ganglia antibody positive
- Anti-cyclic citrullinated peptide antibody positive
- Anti-epithelial antibody positive
- Anti-erythrocyte antibody positive

- Anti-exosome complex antibody positive
- Anti-GAD antibody negative
- Anti-GAD antibody positive
- Anti-ganglioside antibody positive
- Antigliadin antibody positive
- Anti-glomerular basement membrane antibody positive
- Anti-glycyl-tRNA synthetase antibody positive
- Anti-HLA antibody test positive
- Anti-IA2 antibody positive
- Anti-insulin antibody increased
- Anti-insulin antibody positive
- Anti-insulin receptor antibody increased
- Anti-insulin receptor antibody positive
- Anti-islet cell antibody positive
- Antimitochondrial antibody positive
- Anti-muscle specific kinase antibody positive
- Anti-myelin-associated glycoprotein antibodies positive
- Antimyocardial antibody positive
- Anti-neuronal antibody positive
- Antineutrophil cytoplasmic antibody increased
- Antineutrophil cytoplasmic antibody positive
- Anti-NMDA antibody positive
- Antinuclear antibody increased
- Antinuclear antibody positive
- Antiphospholipid antibodies positive
- Anti-platelet antibody positive
- Anti-prothrombin antibody positive
- Antiribosomal P antibody positive
- Anti-RNA polymerase III antibody positive
- Anti-saccharomyces cerevisiae antibody test positive
- Anti-sperm antibody positive
- Anti-SRP antibody positive
- Anti-thyroid antibody positive
- Anti-transglutaminase antibody increased
- Anti-VGCC antibody positive
- Anti-VGKC antibody positive
- Anti-vimentin antibody positive
- Anti-zinc transporter 8 antibody positive
- Aortitis
- Aplastic anaemia
- Arteritis
- Arteritis coronary
- Arthritis
- Atrophic thyroiditis
- Autoantibody positive
- Autonomic nervous system imbalance
- Axonal and demyelinating polyneuropathy
- Axonal neuropathy
- Beta-2 glycoprotein antibody positive
- Bulbar palsy
- Capillaritis
- Cardiolipin antibody positive
- Cerebral arteritis
- Chronic spontaneous urticaria
- Cold agglutinins positive
- Colitis
- Colitis erosive
- Colitis microscopic
- Complement factor abnormal
- Complement factor C1 decreased
- Complement factor C2 decreased
- Complement factor C3 decreased
- Complement factor C4 decreased
- Complement factor decreased
- Cranial nerve disorder
- Cranial nerve palsies multiple
- Cranial nerve paralysis
- CSF oligoclonal band present
- Demyelination
- Dermatitis
- Dermatitis bullous
- Dermatitis herpetiformis
- Diabetes mellitus
- Diabetic ketoacidosis
- DNA antibody positive
- Double stranded DNA antibody positive
- Encephalitis
- Encephalitis brain stem
- Encephalitis haemorrhagic

- Encephalomyelitis
- Encephalopathy
- Endocrine disorder
- Enteritis
- Enterocolitis
- Erythema induratum
- Erythema multiforme
- Erythema nodosum
- Expanded disability status scale score decreased
- Expanded disability status scale score increased
- Facial paresis
- Fulminant type 1 diabetes mellitus
- Glomerulonephritis membranoproliferative
- Glomerulonephritis membranous
- Glossopharyngeal nerve paralysis
- Haemolytic anaemia
- Hepatitis
- Histone antibody positive
- Hyperthyroidism
- Hypoglossal nerve paralysis
- Hypoglossal nerve paresis
- Hypothyroidism
- Idiopathic interstitial pneumonia
- Idiopathic pulmonary fibrosis
- IIIrd nerve paralysis
- IIIrd nerve paresis
- Immunoglobulins abnormal
- Infected vasculitis
- Interstitial lung disease
- Intrinsic factor antibody abnormal
- Intrinsic factor antibody positive
- IRVAN syndrome
- IVth nerve paralysis
- IVth nerve paresis
- LE cells present
- Lichen planopilaris
- Lichen planus
- Lichen sclerosus
- Lupus-like syndrome
- Mastocytic enterocolitis
- Mesangioproliferative glomerulonephritis
- Miller Fisher syndrome
- Mononeuritis
- Mononeuropathy multiplex
- Myelitis
- Myocarditis
- Myositis
- Narcolepsy
- Nephritis
- Neuritis
- Neuritis cranial
- Neuronal neuropathy
- Neuropathy peripheral
- Noninfective oophoritis
- Oculofacial paralysis
- Oesophageal achalasia
- Optic neuritis
- Optic neuropathy
- Optic perineuritis
- Oral lichen planus
- Palmoplantar keratoderma
- Pancreatitis
- Panencephalitis
- Paresis cranial nerve
- Parietal cell antibody positive
- Pemphigoid
- Pemphigus
- Pericarditis
- Pityriasis lichenoides et varioliformis acuta
- Pleuroparenchymal fibroelastosis
- Polyglandular disorder
- Polymyositis
- Polyneuropathy idiopathic progressive
- Premature menopause
- Pulmonary amyloidosis
- Pulmonary fibrosis
- Radiculitis brachial
- Retinopathy
- Rheumatoid factor increased
- Rheumatoid factor positive
- Rheumatoid factor quantitative increased
- Rheumatoid nodule removal
- Scleritis

- Silent thyroiditis
- Smooth muscle antibody positive
- Spondylitis
- Spondyloarthropathy
- Stevens-Johnson syndrome
- Subacute endocarditis
- Systemic lupus erythematosus disease activity index abnormal
- Systemic lupus erythematosus disease activity index decreased
- Systemic lupus erythematosus disease activity index increased
- Thromboplastin antibody positive
- Thyroid disorder
- Thyroid stimulating immunoglobulin increased
- Thyroiditis
- Toxic epidermal necrolysis
- Trigeminal nerve paresis
- Trigeminal palsy
- Urticarial vasculitis
- Uveitis
- Vagus nerve paralysis
- Vascular purpura
- VIth nerve paralysis
- VIth nerve paresis
- Vocal cord paralysis
- Vocal cord paresis
- XIth nerve paralysis

Liver-related investigation, signs and symptoms (sub-SMQ)

Narrow

- Alanine aminotransferase abnormal
- Alanine aminotransferase increased
- Ammonia abnormal
- Ammonia increased
- Ascites
- Aspartate aminotransferase abnormal
- Aspartate aminotransferase increased
- AST/ALT ratio abnormal
- Bacterascites
- Bile output abnormal
- Bile output decreased
- Biliary ascites
- Bilirubin conjugated abnormal
- Bilirubin conjugated increased
- Bilirubin urine present
- Biopsy liver abnormal
- Blood bilirubin abnormal
- Blood bilirubin increased
- Blood bilirubin unconjugated increased
- Bromosulphthalein test abnormal
- Child-Pugh-Turcotte score abnormal
- Child-Pugh-Turcotte score increased
- Computerised tomogram liver abnormal
- Congestive hepatopathy
- Foetor hepaticus
- Galactose elimination capacity test abnormal
- Galactose elimination capacity test decreased
- Gamma-glutamyltransferase abnormal
- Gamma-glutamyltransferase increased
- Guanase increased
- Hepaplastin abnormal
- Hepaplastin decreased
- Hepatic artery flow decreased
- Hepatic enzyme abnormal
- Hepatic enzyme decreased
- Hepatic enzyme increased
- Hepatic function abnormal
- Hepatic hydrothorax
- Hepatic hypertrophy
- Hepatic hypoperfusion
- Hepatic mass
- Hepatic pain
- Hepatic sequestration
- Hepatic vascular resistance increased
- Hepatic venous pressure gradient abnormal
- Hepatic venous pressure gradient increased
- Hepatobiliary scan abnormal
- Hepatomegaly

- Hepatosplenomegaly
- Hyperammonaemia
- Hyperbilirubinaemia
- Hypercholia
- Hypertransaminasaemia
- Kayser-Fleischer ring
- Liver function test abnormal
- Liver function test decreased
- Liver function test increased
- Liver induration
- Liver palpable
- Liver scan abnormal
- Liver tenderness
- Magnetic resonance imaging liver abnormal
- Magnetic resonance proton density fat fraction measurement
- Mitochondrial aspartate aminotransferase increased
- Molar ratio of total branched-chain amino acid to tyrosine
- Oedema due to hepatic disease
- Perihepatic discomfort
- Retrograde portal vein flow
- Total bile acids increased
- Transaminases abnormal
- Transaminases increased
- Ultrasound liver abnormal
- Urine bilirubin increased
- White nipple sign
- X-ray hepatobiliary abnormal

Broad

- 5'nucleotidase increased
- AST to platelet ratio index increased
- Blood alkaline phosphatase abnormal
- Blood alkaline phosphatase increased
- Blood cholinesterase abnormal
- Blood cholinesterase decreased
- Deficiency of bile secretion
- Glutamate dehydrogenase increased
- Glycocholic acid increased
- Haemorrhagic ascites
- Hepatic fibrosis marker abnormal
- Hepatic fibrosis marker increased
- Hepatic lymphocytic infiltration
- Hypoalbuminaemia
- Leucine aminopeptidase increased
- Liver iron concentration abnormal
- Liver iron concentration increased
- Liver opacity
- Model for end stage liver disease score abnormal
- Model for end stage liver disease score increased
- Periportal oedema
- Peritoneal fluid protein abnormal
- Peritoneal fluid protein decreased
- Peritoneal fluid protein increased
- Pneumobilia
- Portal vein flow decreased
- Portal vein pressure increased
- Retinol binding protein decreased
- Urobilinogen urine decreased
- Urobilinogen urine increased

Paraesthesia, Hypoaesthesia, Hyperaesthesia (CMQ)

- Anal hypoaesthesia
- Anal paraesthesia
- Dental paraesthesia
- Eye paraesthesia
- Genital hyperaesthesia
- Genital hypoaesthesia
- Genital paraesthesia
- Hemihyperaesthesia
- Hemiparaesthesia
- Hyperaesthesia
- Hyperaesthesia eye
- Hyperaesthesia teeth
- Hypoaesthesia
- Hypoaesthesia eye
- Hypoaesthesia oral
- Hypoaesthesia teeth
- Intranasal hypoaesthesia
- Intranasal paraesthesia

- Oral hyperaesthesia
- Paraesthesia
- Paraesthesia ear
- Paraesthesia mucosal
- Paraesthesia oral
- Pharyngeal hypoaesthesia
- Pharyngeal paraesthesia
- Thermohyperaesthesia
- Thermohypoaesthesia

Taste and smell disorders (CMQ)

- Ageusia
- Anosmia
- Dysgeusia
- Hypergeusia
- Hypogeusia
- Hyposmia
- Parosmia
- Taste disorder

Appendix 4 List of TFLs

A complete list of all TFLs is provided in a separate document CV-NCOV-004 Statistical Analysis Plan – Appendix 4 List of TFLs. TFLs for the interim analyses are indicated therein. The document is managed outside of this SAP.

Appendix 5 Identification of Protocol Deviations Leading to Exclusion from Analysis Sets

Details on the identification of protocol deviations leading to exclusion of subjects from analysis sets are described in a separate document CV-NCOV-004 Statistical Analysis Plan – Appendix 5 Protocol Deviations Leading to Exclusion from Analysis sets. The document is maintained outside of this SAP

Appendix 6 Analyses on Solicited Adverse Events that have not been performed

Table 14.3.3.1.5 Summary of Solicited Adverse Events Overall and by Maximum Grade Occurring on the Day of Vaccination and the following 7 Days after Dose 1 in subjects Seronegative at Baseline

Table 14.3.3.1.6 Summary of Solicited Adverse Events Overall and by Maximum Grade Occurring on the Day of Vaccination and the following 7 Days after Dose 1 in subjects Seropositive at Baseline

Table 14.3.3.1.8 Summary of Solicited Adverse Events Overall and by Maximum Grade Occurring on the Day of Vaccination and the following 7 Days after Dose 2 in subjects Seronegative at Baseline

Table 14.3.3.1.9 Summary of Solicited Adverse Events Overall and by Maximum Grade Occurring on the Day of Vaccination and the following 7 Days after Dose 2 in subjects Seropositive at Baseline

Table 14.3.3.2.2 Summary of Local Solicited Adverse Events Overall and by Maximum Grade Occurring on the Day of Vaccination and the following 7 Days after any Dose in subjects Seronegative at Baseline

Table 14.3.3.2.3 Summary of Local Solicited Adverse Events Overall and by Maximum Grade Occurring on the Day of Vaccination and the following 7 Days after any Dose in subjects Seropositive at Baseline

Table 14.3.3.2.5 Summary of Local Solicited Adverse Events Overall and by Maximum Grade Occurring on the Day of Vaccination and the following 7 Days after Dose 1 in subjects Seronegative at Baseline

Table 14.3.3.2.6 Summary of Local Solicited Adverse Events Overall and by Maximum Grade Occurring on the Day of Vaccination and the following 7 Days after Dose 1 in subjects Seropositive at Baseline

Table 14.3.3.2.8 Summary of Local Solicited Adverse Events Overall and by Maximum Grade Occurring on the Day of Vaccination and the following 7 Days after Dose 2 in subjects Seronegative at Baseline

Table 14.3.3.2.9 Summary of Local Solicited Adverse Events Overall and by Maximum Grade Occurring on the Day of Vaccination and the following 7 Days after Dose 2 in subjects Seropositive at Baseline

Table 14.3.3.14.8 Time of Onset for Related Systemic Solicited Adverse Events Overall and for Grade 3 Occurring on the Day of Vaccination and the following 7 Days after Dose 2 in subjects Seronegative at Baseline

Table 14.3.3.14.9 Time of Onset for Related Systemic Solicited Adverse Events Overall and for Grade 3 Occurring on the Day of Vaccination and the following 7 Days after Dose 2 in subjects Seropositive at Baseline