Protocol Number: CV-NCOV-005

Official Title: COVID-19: A Phase 3, Randomized, Observer-Blinded, Placebo-Controlled Clinical Study Evaluating the Safety and Immunogenicity of Investigational SARS-CoV-2 mRNA Vaccine CVnCoV in Adult Health Care Workers in Mainz (Germany)

NCT Number: NCT04674189

Document Date: 08 April 2022

Statistical Analysis Plan (SAP)

Protocol Title:	COVID-19: A Phase 3, Randomized, Observer-Blinded, Placebo-Controlled Clinical Study Evaluating the Safety and Immunogenicity of Investigational SARS-CoV-2 mRNA Vaccine CVnCoV in Adult Health Care Workers in Mainz (Germany)
Protocol Versions No./Date:	1.0 / 19-Nov-2020 2.0 / 19-Mar-2021 3.0 / 23-Jul-2021 4.0 / 11-Aug-2021 5.0 / 22-Dec-2021
CRF Version No./Date:	4.0 / 10-Jun-2021
SAP Version No./Date:	4.0 / 08-Apr-2022

1.0 Approvals

Sponsor	
Sponsor Name:	CureVac AG
Representative/ Title:	[redacted]
Signature/ Date:	
Representative/ Title:	[redacted]
Signature/ Date:	
Representative/ Title:	[redacted]
Signature/ Date:	
Representative/ Title:	[redacted]
Signature/ Date:	
PRA/ICON	
Biostatistician / Title:	[redacted]
Signature/ Date:	

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

Statistical Analysis Plan (SAP)

Protocol Title:	COVID-19 A Phase 3 Randomized Observer-Blinded, Placebo-Controlled Clinical Study Evaluating the Safety and Immunogenicity of Investigational SARS-CoV-2 mRNA Vaccine CVnCoV in Adult Health Care Workers in Mainz (Germany)
Protocol Versions No./Date:	1.0 / 19-Nov-2020 2.0 / 19-Mar-2021 3.0 / 23-Jul-2021 4.0 / 11-Aug-2021 5.0 / 22-Dec-2021
CRF Version No./Date:	4.0 / 10-Jun-2021
SAP Version No./Date.	4.0 / 08-Apr-2022

Approvals

Sponsor

Sponsor Name: CureVac AG

Representative/ Title

Signature/ Date:

Representative/ Title

Signature/ Date:

Representative/ Title

Signature/ Date:

Representative/ Title:

Signature/ Date:

PRA/ICON

Biostatistician / Title:

Signature/ Date:

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

[redacted]

2.0 Change History

Version/Date	Change Log
0.1	Draft Version of the SAP
1.0 / 14 Jan 2021	Final Version of the SAP
1.1 / 21 Apr 2021	Updates: • Minor modifications to Section 6.1 to clarify the main censoring rules following unblinding • Clarification on data handling for subjects who have been tested positive for COVID-19 in Section 9.5.4 • 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 12.8.1.4 • Addition of SMQ/CMQ in Section 10.5.7, reporting thereof (Section 12.6.1.1) and list of term (Appendix 3) • Addition of sensitivity analysis on Safety outputs to account for censoring rules in main analyses (Section 12.6.6) • Addition of reporting of selected solicited local and systemic AEs by Gender (Section 12.6.1.2)
2.0 / 29-Apr 2021	Finalization of Draft 1.1 without any further changes

3.0 (2.1) / 15-Jul-2021	Updates
	• Overall: Harmonized nomenclature around alternate vaccine to read "alternate / licensed / authorized"
	• Overall: Changed naming of endpoints containing "through 1 year after second trial vaccination" to read "through EOT Visit".
	• Section 8.2:
	  ○ Removed planned interim analysis.
	  ○ Early immunogenicity delivery and related unblinding of designated CRO added.
	• Section 8.6 Added unblinding timepoint of designated CRO.
	• Section 9.4: Modified introductory sentence to allow for changes from protocol in the estimand table.
	• Section 9.5: Added that analyses using all randomized subjects will be based on vaccination "as randomized".

	• Section 9.5.2 Added that Subjects who received an alternate / licensed / authorized vaccine prior to 15 days after the second vaccination will be excluded from IS.
	• Section 9.5.5:
	  ○ Reworded the EAS definition to make it clearer.
	  ○ Added unblinding and alternate / licensed / authorized vaccine receipt.
	  ○ Added use of adjudication data.
	• Section 9.5.6: Modified EASS definition to not exclude subjects after unblinding.
	• Section 10.6.1: Added serology status at baseline and serology status at Visit Day 43 definition.
	• Section 10.7.4: Corrected formula for Symptom onset ≥ 15 days after second trial vaccination.
	• Section 10.11: Added date of alternate / licensed / authorized vaccine + 1 to the censoring date formula.
	• Section 10.12: Added section regarding age groups.
	• Section 11:
	  ○ Removed planned interim analysis.
	  ○ Added possible ad-hoc analyses around early conditional approval in Europe.
	• Section 12.1:
	  ○ Screen failures were removed.
	  ○ Description of tables was adapted to match the required outputs.
	  ○ Summary of censored subjects was added.
	  ○ Summary of stratification and treatment errors was added.
	• Section 12.2: Added combined (adjudication + EDC) serology status variable
	• Section 12.3:
	  ○ Adapted analysis description of medical/surgical history to match required analyses.
	  ○ Added co-morbidities analysis.
	• Section 12.5: Added subject- and site-level for protocol deviations.
	• Section 12.6.1.1 Re-arranged solicited and unsolicited AE analysis descriptions to reflect the required analyses, added Section 12.6.1.3.
	• Section 12.7: Added that no “Total” summaries will be provided for immunogenicity.
	• Section 12.8.1.1: Added usage of adjudication data for serostatus at baseline and Visit Day 43.
	• Section 12.8.1.4: Added sensitivity analysis for one secondary endpoint.
	• Appendix 2:
	  ○ Removed Multisystem inflammatory syndrome in children from AESI list
	  ○ Removed COVID-19 disease from AESI list

4.0 / 08 Apr 2022	• Section 1.0: Updated signatories details • Section 6.0: Added info that main stakeholders are unblinded at time of SAP update • Section 6.1: Changes from protocol were updated

	• Section 7.2.1: Secondary efficacy objective on asymptomatic cases was deleted. • Section 7.2.2: Secondary immunogenicity objective on lot-to-lot consistency was deleted. • Section 7.3: All exploratory objectives were deleted. • Section 8.2: Added EOT wording for placebo subjects after study unblinding. • Section 8.5.2: Adapted Sample information on primary immunogenicity objective to new analysis scope. • Section 8.6: Updated unblinding information according to protocol 3.0 and study development. • Section 9.1.2: Reduced timepoints for immunogenicity analyses to Days 1, 29 and 43. • Section 9.2.1: Reduced secondary efficacy endpoints according to scope reduction in EOT delivery. • Section 9.2.2: Reduced timepoints for immunogenicity analyses to Days 1, 29 and 43. Reduced secondary immunogenicity endpoints according to scope reduction in EOT delivery. • Section 9.3: Deleted all exploratory endpoints. • Section 9.4: Updated “Estimands” table to match study. • Section 9.5.2: Updated IS definition to not exclude subjects who had received an AV prior to 15 days after 2nd vaccination. • Section 9.5.4: Reduced PPI Set to 250 subjects. • Section 9.5.6: Mentioned that EASS is not further applicable. • Section 9.5.7: Updated and corrected Summary of Analysis Sets • Section 10.5.5: Corrected AESI definition • Section 10.5.8: Added Section defining overreported AEs. • Section 10.6, and 10.6.1: Updated wording according to protocol v 3.0 and for clarity reasons • Section 10.6.2.3 and 10.6.3: Deleted Sections on seroconversion to N protein antibodies and CMI. • Section 10.7.1.1 and 10.7.2 and 10.7.5: Provided for a local instead of a central laboratory being used • Section 10.10: Added unblinding column to censoring table. • Section 10.11: Updated overview table to match analysis updates. • Section 11.0: Updated IA info to match study development. • Section 12.0 and 12.2 and 12.4.2 and 12.6.1.2: Updated to match study development and reduced EOT analysis. • Section 12.6.1.4: Added section on repeats of AE analyses without censoring • Section 12.6.7: Added section on adapting the safety analyses to the requirements of extensive unblinding • Section 12.7 and 12.7.1: Reduced timepoints for immunogenicity analyses to Days 1, 29 and 43. • Section 12.7.2 and 12.8.1.1 – 12.8.1.4: Adapted to account for reduced EOT analyses. • Section 12.7.3 and 12.8.2: Deleted to account for endpoint deletion.

3.0 Table of Contents

4.0 Purpose

The Statistical Analysis Plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under CureVac AG Protocol CV-NCOV-005.

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-005.

The SAP should be read in conjunction with the trial protocol version 5.0 dated 22-Dec-2021 and Case Report Form (CRF) v4.0 dated 10-Jun-2021.

This SAP describes the statistical methods used for the final analysis. The SAP v1.0 is approved prior to the first relevant delivery[1]. Changes following approval of the first version of the SAP are tracked in the SAP Change Log and the last final SAP version is approved prior to final database lock.

Each version of the SAP requires approval by the Sponsor.

It must be noted that all main stakeholders from the combined Sponsor and designated Contract Research Organization (CRO) (PRA/ICON) study team have been unblinded between approval of SAP versions 3.0 and 4.0. As a consequence, the SAP version 4.0 is created and approved by an unblinded authorship/approval team.

6.1 Changes from Protocol

1) Addition of sensitivity analysis on Safety outputs for Safety Interim Analysis (IA) to account for censoring rules in main analyses (Section12.6.6)
2) Inclusion of Adverse Events (AEs) Related to Standardized and Customized Medical Dictionary for Regulatory Activities (MedDRA) Queries (CMQs)
3) The planned IA to obtain early conditional approval in Europe was removed.
4) An early immunogenicity delivery and related unblinding of PRA/ICON was added.
5) Update to analysis sets (Section 9.5) to account for unblinding and/or Authorized Vaccine (AV) application.
6) Protocol deviations are classified in site- and subject-level protocol deviations.
7) A sensitivity analysis on a secondary endpoint was added, according to what was done in the CV-NCOV-004 study.

[1] This was the safety delivery for the rolling submission when subjects randomized by (including) 11-Feb-2021 had reached 6 weeks post 2nd dose.

8) Multisystem inflammatory syndrome in children was removed from Adverse Event of Special Interest (AESI) list

9) The Efficacy Analysis Set (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

10) In the protocol synopsis the definition of the efficacy endpoint does no longer require the subject to be N negative. This is considered an erroneous deletion and is ignored.

11) "Non-serious intercurrent medical conditions that may affect the immune response to vaccination will also be collected throughout the trial." is taken out of the AESI definition.

12) The secondary immunogenicity endpoint lot to lot consistency is not to be analyzed.

13) From the secondary efficacy endpoint "Occurrence of first episodes of virologically-confirmed (RT-PCR positive) symptomatic cases of COVID-19 meeting the case definition for the efficacy analysis by severity (mild, moderate, severe and moderate to severe COVID-19)" only the mild cases are analyzed .

14) No repeat of any of the secondary efficacy analyses on the Safety Analysis Set (SAS) is done.

15) Protocol Section 10.3.7.1 requires the secondary efficacy analyses of prevention or reduction of asymptomatic infections as measured by seroconversion to the N protein to be performed, although this was deleted from all other sections in the protocol. This is considered an oversight and therefore this analysis is not performed.

16) The Vaccine Efficacy (VE) analysis of Burden of Disease (BoD) is not performed.

17) The sensitivity analysis by Kaplan-Meier (KM) curves for the time to first occurrence of virologically-confirmed COVID-19 case of any severity is not performed. No sensitivity analysis of this endpoint on the SAS is performed either.

7.0 Trial Objectives

7.1 Primary Objectives:

7.1.1 Primary Safety Objective

- To evaluate the safety (in all subjects) and reactogenicity (in a subset of subjects) of CVnCoV administered as a 2-dose schedule to adults 18 years of age or older.

7.1.2 Primary Immunogenicity Objective

- To assess antibody responses to the receptor-binding domain (RBD) of S protein of SARS-CoV-2 after 1 and 2 doses of CVnCoV in adults 18 years of age or older included in a subset of subjects.

7.2 Secondary Objectives:

7.2.1 Secondary Efficacy Objectives

- To assess the efficacy of a 2-dose schedule of CVnCoV in the prevention of first episodes of virologically-confirmed symptomatic cases of COVID-19 of any severity in SARS-CoV-2 naïve subjects.
- To describe the severity of first episodes of virologically-confirmed symptomatic cases of COVID-19 in SARS-CoV-2 naïve subjects, receiving a 2-dose schedule of CVnCoV compared to those administered placebo.
- To assess the efficacy of a 2-dose schedule of CVnCoV in reducing the BoD from COVID-19.

7.2.2 Secondary Immunogenicity Objectives

- To assess SARS-CoV-2 virus neutralizing antibody responses after 1 and 2 doses of CVnCoV in adults 18 years of age or older included in a subset of subjects.

8.0 Trial Design

8.1 Overall Design

Trial CV-NCOV-005 is conducted as a randomized, observer-blinded, and placebo-controlled trial. Subjects 18 years of age or older previously enrolled in the non-interventional trial performed at the Mainz University, Germany (COVID19-5-P-002), other health care workers (HCW) and potentially students in clinical training are enrolled. Subjects receive a 2-dose schedule, 28 days apart, of either one of two lots of CVnCoV at a dose level of 12 µg mRNA or placebo (normal saline [0.9% NaCl] for injection) in a 1:1:1 ratio. Approximately 2,520 subjects (840 per randomization group) are enrolled.

The safety, reactogenicity and immunogenicity of a 2-dose schedule of CVnCoV in HCWs is assessed descriptively.

The primary safety objective is to expand the safety database that demonstrates the safety profile of CVnCoV. 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 AEs (on the day of vaccination and for the following 7 days after each vaccination) and unsolicited AEs on the day of vaccination and for the following 28 days after each vaccination, both in a subset of subjects (Immunogenicity/Reactogenicity Subset i.e. the first 1,260 subjects enrolled). Medically-attended AEs through 6 months after the second trial vaccination and AESIs, Serious Adverse Events (SAEs) and AEs leading to vaccine withdrawal or trial discontinuation for 1 year after the second trial vaccination are collected for all subjects.

An independent Data Safety Monitoring Board (DSMB, see Section 8.4) performs a review of the available safety data of both CV-NCOV-004 and CV-NCOV-005 at regular meetings.

The immunogenicity of CVnCoV after 1 and 2 doses is evaluated in a subset of subjects (Immunogenicity/Reactogenicity Subset, the first 1,260 subjects enrolled) by measuring:

- binding antibodies to the SARS-CoV-2 RBD of S protein
- viral neutralizing antibodies directed against SARS-CoV-2

During the trial, subjects undergo active surveillance for COVID-19. Subjects suspected of having COVID-19 undergo testing for SARS-CoV-2 virus.

8.2 Interim Analysis

No formal IA is done. In August 2021 a first immunogenicity delivery is provided. PRA/ICON who is to create that analysis is unblinded on that occasion.

8.3 End of Trial

A subject is considered to have completed the trial when he/she has completed all visits, procedures, and tests applicable for the group to which he/she was randomized to at trial entry. Exception: Placebo subjects discontinue the trial once study protocol version 3.0 and 4.0 are approved. The corresponding wording from the protocol is as follows: "*After trial unblinding, i.e. after approval of study protocol version 3.0 and 4.0, all placebo subjects should be withdrawn at the earliest possible timepoint, if their originally planned End of Trial visit is later than February 2022 and will undergo the same procedures as for the End of Trial visit at their withdrawal visit. If a withdrawal visit cannot be scheduled for placebo subjects due to the pandemic setting, the end of trial assessment, i.e. collection of final safety data, can also be done by phone. In the e-*

CRF, the withdrawal reason for placebo subjects should be documented as "placebo subject withdrawn after trial unblinding"."

End of Trial (EOT) is defined as the point at which the last subject has completed the last visit on Day 393 or (prematurely) discontinued the trial.

8.4 Independent Data Safety Monitoring Board

An independent DSMB is convened to oversee the safety of subjects participating in this trial and trial CV-NCOV-004, to assess the progress and conduct of the trials, to review the cumulative safety data from the trials, and to make recommendations to CureVac whether to continue, modify, or stop the trials.

The DSMB has regularly scheduled meetings to perform these responsibilities. During these meetings, the DSMB is informed of the safety data being generated in other ongoing clinical trials of CVnCoV. 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 Charter describes in detail the composition and objectives of the DSMB, the responsibilities of the DSMB, CureVac and PRA/ICON, the schedule and conduct of the DSMB meetings, the datasets to be reviewed, and the stopping criteria for the trial. The Charter contains the SAP for the DSMB.

8.5 Sample Size Considerations

8.5.1 Sample Size Considerations for the Primary Safety Objective

While solicited vaccine reactions are expected, AEs that would limit product development may arise. Table 1 below indicates the probability of observing at least 1 AE in the trial when the true incidence of the AE with CVnCoV is 1:1000, 5:1000 or 1:100.

Table 1 Probability of Observing at least one Adverse Event Given a True Incidence Rate

True AE Incidence	All Subjects Pooled Lots (N=1,680)	Subset for solicited/ unsolicited AE By Lot (N=420)	Subset for solicited/ unsolicited AE Pooled Lots (N=840)
1:1000	81.4%	34.3%	56.8%
5:1000	100.0%	87.8%	98.5%
1:100	100.0%	98.5%	100.0%

N = Number of Subjects receiving CVnCoV

With a total of 1,680 subjects receiving CVnCoV (840 per lot), AEs with a true incidence of 1:1000 are likely observed in this trial, with a 81.4% probability of observing at least one. Additionally, observation of 0 AEs in 1,680 subjects would be associated with a 95% confidence that the true incidence rate of this AE is below 1.8:1000. With a total of 840 subjects included in the Immunogenicity/Reactogenicity subset and receiving CVnCoV (420 per lot), solicited/unsolicited AEs with a true incidence of 5:1000 are likely observed in this trial with a 98.5% probability of observing at least one. Observation of 0 AE in 840 subjects would be associated with a 95% confidence that the true incidence rate of this AE is below 3.6:1000.

8.5.2 Sample for the Primary Immunogenicity Objective

The primary analysis for SARS-CoV-2 RBD of S protein antibody response performed on data collected on Days 1, 29 and 43 is done on 250 subjects (200 on verum, i.e. 100 per lot and 50 on placebo) from the Per Protocol Immunogenicity (PPI) analysis set.

8.6 Randomization and Blinding

The trial is 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/personnel preparing the trial vaccine 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 are blinded to trial vaccine and subject treatment assignments. To maintain the blinding of the vaccinator, the unblinded pharmacist/site personnel provide the dose of trial vaccine to the vaccinator prefilled in a syringe with a label covering the liquid contents so that it is not visible. All personnel at PRA/ICON and Sponsor directly involved in the conduct of the trial is also blinded. There are certain individuals at PRA/ICON 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.

As the immunogenicity results would unblind the subject's treatment assignment, an independent laboratory performing the assays keep 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 CDISC level following unblinding of the trial.

The first immunogenicity analysis is scheduled for August 2021. PRA/ICON who is to perform this analysis is unblinded on that occasion.

Approximately 2,520 subjects 18 years of age or older are enrolled at the site at Mainz University, Germany and are randomized in a 1:1:1 ratio (840 per randomization group) to receive either one of two different lots of a 2-dose schedule of CVnCoV or placebo. The randomization is performed centrally and stratified by age group (18 to 60 and ≥61 years of age).

The randomization scheme is generated and maintained by an independent statistical group at PRA/ICON. Subjects are enrolled into the trial online and randomized using an Interactive Web Response System (IWRS). The first 1,260 subjects enrolled are planned to be included in the Immunogenicity/Reactogenicity Subset.

See Section 10.10 for handling of cases where a subject becomes eligible to receive an AV during the course of the trial.

In Study Protocol 3.0 the following decision regarding unblinding was added: "*Since the efficacy results from the HERALD study for CVnCoV are available and all subjects in the CV-NCOV-005 study are currently eligible to receive an authorized vaccine, all subjects in this CV-NCOV-005 study will be unblinded.*" This unblinding is performed on a by-subject level via IWRS and therefore does not require any additional programmatic or planning attention.

In July 2021, on the occasion of Herald CV-NCOV-004 study primary efficacy analysis delivery, selected members from the Sponsor and PRA/ICON study teams (i.e. both Biostatistics teams) were unblinded for CV-NCOV-005. In December 2021 the full Sponsor and PRA/ICON study teams were unblinded.

9.0 Trial Endpoints

9.1 Primary Endpoints

9.1.1 Primary Safety Endpoints

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

9.1.2 Primary Immunogenicity Endpoints

SARS-CoV-2 RBD of the S protein antibody responses on Days 1, 29 and 43 in a subset of 250 subjects (Per Protocol Immunogenicity Set (PPI)) :

- Serum antibodies to SARS-CoV-2 RBD of the S protein
- 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 10.6.2.1 and Section 10.6.1 for details.

9.2 Secondary Endpoints

9.2.1 Secondary Efficacy Endpoints

- Occurrence of first episodes of virologically-confirmed (RT-PCR positive) symptomatic cases of COVID-19 of any severity meeting the case definition for the efficacy analysis.
- Occurrence of first episodes of virologically-confirmed (RT-PCR positive) symptomatic mild cases of COVID-19 meeting the case definition for the efficacy analysis as defined in Section 10.7.3.
- 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 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.

9.2.2 Secondary Immunogenicity Endpoints

- SARS-CoV-2 viral neutralizing antibody responses on Days 1, 29 and 43 in the PPI subset of 250 subjects:
    - Serum viral neutralizing antibodies to SARS-CoV-2 virus, as measured by a virus neutralizing assay.

- Occurrence of seroconversion to SARS-CoV-2 virus as measured by a virus neutralizing assay.

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

9.3 Exploratory Endpoints

9.3.1 Exploratory Efficacy Endpoint

In agreement with the sponsor it was decided not to analyze the exploratory efficacy endpoint in this study.

9.3.2 Exploratory Immunogenicity Endpoints

Exploratory Immunogenicity Endpoints are voided since protocol version 5.0. They have never been analyzed in this study.

9.3.3 Exploratory Efficacy Endpoints (pooled analysis of trial COVID19-5-P-002 and trial CV-NCOV-005)

The exploratory efficacy endpoints related to the pooled analysis of COVID19-5-P-002 and CV-NCOV-005 are voided since protocol version 5.0. They have never been analyzed in this study.

9.4 Estimands

Table 2**Error! Reference source not found.** presents the study endpoints and corresponding Estimands based on the study protocol, Section 4.3.

Table 2: Study Endpoints and Estimands

ENDPOINTS (subject level)	ESTIMANDS (population level)
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. • Occurrence of AEs leading to vaccine withdrawal or trial discontinuation through EOT Visit in all subjects. • Occurrence, intensity and duration of each solicited local AE within 7 days after each trial vaccination in a subset of subjects. • Occurrence, intensity, duration and relationship of each solicited systemic AE within 7 days after each trial vaccination in a subset of subjects.	In subjects who received at least 1 dose of CVnCoV or placebo vaccine, the number and percentage of subjects by group reporting at least 1 and of each type {by System Organ Class (SOC)/ Preferred Term (PT)} of: • Medically-attended AE collected through 6 months after the second trial vaccination overall, by intensity and by causal relationship to trial vaccine. • SAE collected through EOT Visit overall and by causal relationship to trial vaccine. • AESI collected through EOT Visit overall, by intensity and by causal relationship to trial vaccine. • Fatal SAE collected through EOT Visit. • At least 1 AE leading to vaccine withdrawal or trial discontinuation through EOT Visit. In subjects who received at least 1 dose of CVnCoV or placebo vaccine, and belong to the Immunogenicity/Reactogenicity subset, the number and percentage of subjects by group reporting: • Each solicited local AE within 7 days after each trial vaccination by intensity and overall.

ENDPOINTS (subject level)	ESTIMANDS (population level)
• Occurrence, intensity and relationship of unsolicited AEs occurring within 28 days after each trial vaccination in a subset of subjects.	• 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 unsolicited AE by SOC/PT occurring within 28 days after each trial vaccination and overall by causal relationship to trial vaccine and overall. The mean duration in days by group with standard deviation (SD) of solicited AEs is described.
Primary Immunogenicity	
SARS-CoV-2 RBD of S protein antibody responses On Days 1, 29 and 43: • 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 subjects belonging to the Immunogenicity/Reactogenicity subset and evaluable {complying with the definition of PPI Subset}: On Days 1, 29 and 43: • Geometric Mean of Titers (GMTs) with 95% Confidence Interval (CI) of SARS-CoV-2 RBD of S protein antibody responses by group and by baseline serostatus. On Days 29 and 43 for subjects seronegative at baseline: • Number and percentage with exact 95%CI of subjects by group for whom a seroconversion is observed (detectable SARS-CoV-2 RBD of S protein antibodies in the serum).
Secondary Efficacy	
• Occurrence of first episodes of virologically-confirmed (RT-PCR positive) symptomatic cases of COVID-19 of any severity meeting the case definition for the efficacy analysis.	In naïve evaluable subjects {complying with the definition of EAS} at least 15 days following second vaccination: • VE = 1- RR with exact 95% CI Where Relative Risk (RR) is the ratio of attack rates of COVID-19 cases per 100 person-month in the CVnCoV vaccine groups (pooled lots) over the placebo group.
• Occurrence of first episodes of virologically-confirmed (RT-PCR positive) symptomatic cases of COVID-19 meeting the case definition for the efficacy analysis by severity (mild, moderate, severe and moderate to severe COVID-19) as defined in the protocol.	In naïve evaluable subjects (complying with the definition of EAS) at least 15 days following second vaccination: • The number and percentage of subjects who developed a first episode of virologically-confirmed (RT-PCR positive) cases of COVID-19 meeting the case definition for the efficacy analysis, by severity (mild, moderate, severe and moderate to severe, as defined in Section 10.7.3.) •
• BoD scores calculated based on first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any	Descriptive summaries in naïve evaluable subjects (complying with the definition of EAS) at least 15 days following second trial vaccination:

ENDPOINTS (subject level)	ESTIMANDS (population level)
severity meeting the case definition for the 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.	
Secondary Immunogenicity	
SARS-CoV-2 virus neutralizing antibody responses in a subset of subjects On Days 1, 29 and 43: • Serum neutralizing antibodies to SARS-CoV-2 virus, as measured by a virus neutralizing assay. • Occurrence of seroconversion to SARS-CoV-2 virus, as measured by a virus neutralizing assay. - Seroconversion is defined as detectable SARS-CoV-2 virus neutralizing antibodies in the serum of subjects who tested seronegative at baseline.	In subjects belonging to the Immunogenicity/Reactogenicity subset and evaluable (complying with the definition of the PPI): On Days 1, 29 and 43: • GMT with 95% CI of neutralizing antibodies to SARS-CoV-2 virus by group and by baseline sero-status On Days 29 and 43 for subjects seronegative at baseline: • Number and percentage with exact 95%CI of subjects by group for whom a seroconversion is observed (detectable neutralizing antibodies to SARS-CoV-2 virus in the serum).

9.5 Population Sets

For analyses on the Safety Analysis Sets (SAS, SAS 2, and SAS for Solicited Adverse Events [SASsol]), subjects are analyzed in the group of treatment 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 had actually been randomized to.

If a subject received both the active vaccine and the placebo (i.e. at the two different vaccinations), 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".

9.5.1 Safety Analysis Set

The SAS includes all subjects randomized in the trial who received at least one dose of any lot of CVnCoV or placebo vaccine.

9.5.2 Immunogenicity/Reactogenicity Subset

The Immunogenicity/Reactogenicity Subset is defined as all subjects from the immunogenicity/reactogenicity cohort as indicated on the CRF (i.e. the first 1260 subjects enrolled into the study).

9.5.3 Safety Analysis Subsets (SAS 2 and SASsol)

- The SAS 2 includes all subjects of the SAS who belong to the Immunogenicity/Reactogenicity cohort.
- The SASsol includes all subjects of the SAS who belong to the Immunogenicity/Reactogenicity cohort with at least 1 diary collection indicating the occurrence or lack of occurrence of solicited AEs (see Section 10.5.2).

9.5.4 Per Protocol Immunogenicity (PPI) Set

The PPI set includes 250 subjects (100 per lot and 50 placebo subjects) from the Immunogenicity/Reactogenicity Subset who:

- Received both doses as randomized and within the windows defined in the protocol.
- Have no major protocol deviations expected to impact the immunogenicity outcomes as specified in Section 12.5.
- Have not received medical treatments (such as blood products, immunoglobulin therapy) that may interfere with one or both of the proposed immunogenicity measurements.
- Have at least one blood sample collected at baseline and at 14 days (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.

The selection of the 250 applicable subjects is performed by the Sponsor and communicated at the Blinded Data Review Meeting performed before the EOT analysis.

9.5.5 Efficacy Analysis Set (EAS)

The EAS includes all subjects of the SAS who:

- Received both trial doses according to their randomization (two doses of the same lot of CVnCoV if randomized to that lot 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 (Visit Day 1) and Visit Day 43 (based on seronegativity to N protein in the blood sample).
- Were not unblinded or in receipt of AV prior to 15 days after the second vaccination (See Section 10.10)

Where available the information assessed by the independent adjudication Committee of clinicians (Section 10.7.5) is used.

9.5.6 Efficacy Analysis Set for Seroconversion for N Protein Antibodies (EASS)

Not further applicable.

9.5.7 Summary of Analysis Sets to be Used per Analysis

Table 3 and

Table 4 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 - 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 of AEs leading to vaccine withdrawal or trial discontinuation	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
Primary Immunogenicity Endpoint	Serum antibodies to SARS-CoV-2 RBD of S protein	PPI
	Seroconversion to SARS-CoV-2 S RBD protein	PPI#
Secondary Immunogenicity Endpoint	Serum neutralizing antibodies to SARS-CoV-2 virus	PPI
	Seroconversion to SARS-CoV-2 virus	PPI#
	Lot-to-Lot consistency of 2 CVnCoV lots, based on antibodies to the SARS-CoV-2 RBD of S protein	PPI#

restricted to subjects naïve to SARS-CoV-2 N protein ant bodies at baseline

Table 4: Summary of Analysis Sets to be Used per Analysis - Efficacy Endpoints

Endpoint Type	Endpoint Short Description	Primary Analysis Set	Supportive Analysis Set
Secondary Efficacy Endpoint	First episodes of COVID-19 cases.	EAS	SAS#
	Severity assessment of first episodes of COVID-19 cases.	EAS	SAS#
	BoD Scores	EAS	SAS#
	Second episodes of COVID-19 cases	EAS	SAS
Exploratory Efficacy Endpoint	Second episodes of COVID-19 cases	EAS	SAS

#Including all subjects whatever their serological status at baseline and considering all events occurring at any time after the first trial vaccination.

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 is calculated as

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

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

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

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 trial start (informed consent signature) as recorded by the investigator is considered prior medication.
- Any medication **not** taken prior to trial start as recorded by the investigator is considered concomitant medication.
- Any medication taken prior to trial 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 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.

In this trial, for subjects in the Immunogenicity/Reactogenicity Subset, information on solicited local and systemic AEs occurring within 7 days after each vaccination and on unsolicited AEs occurring within 28 days after each vaccination are collected.

For all trial subjects, information on medically attended AEs through 6 months after second vaccination and SAEs, AESIs and AEs leading to vaccine withdrawal or trial discontinuation through EOT are recorded.

Non-serious intercurrent medical conditions that may affect the immune response to vaccination are also collected as AEs throughout the trial.

No other AEs require recording in the CRF.

10.5.1 Treatment Emergent Adverse Events (TEAE)

A Treatment Emergent Adverse Event (TEAE) is any AE that first occurs or increases in severity or relationship to trial vaccine after the first dose of vaccine. AEs which change in severity or relationship to trial vaccine 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 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 vaccination. However, it is not possible to link this event to a specific 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 subjects in the Immunogenicity/Reactogenicity Subset for each day of vaccination (i.e. dose 1 and dose 2) and for the following 7 days after each dose. Subjects record any occurrence of an AE, grading of severity, and medication for treatment of the AE in an electronic diary (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 5 and Table 6. 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 5: 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

AE	Grade	Definition
	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 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 9.5.3) 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 vaccination, but not for the time period after the first vaccination, the subject is still included in the SASsol.

Table 6: 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

AE	Grade	Definition
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
	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 vaccination day (i.e. dose 1 and 2) and the following 28 days after each dose is collected for subjects in the Immunogenicity/Reactogenicity subset. 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 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 AESI 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 (electronic CRF). No additional programming is performed to identify (potential) AESIs.

10.5.6 Medically Attended AEs

Up to 6 months after second 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

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

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.

10.5.7 Adverse Events Related to Standardized and Customized MedDRA Queries

Subjects' AEs are filtered with Standardized 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 for MedDRA Version 23.1 are listed in Appendix 3.

10.5.8 Overreported AEs

The definition of overreported AEs consists of the following 6 items:

No overreporting restrictions exist for:

1. (Treatment emergent) AESIs
2. (Treatment emergent) SAEs
3. (Treatment emergent) non-serious intercurrent medical condition that may affect the immune response to vaccination
4. (Treatment emergent) AEs leading to vaccine withdrawal or trial discontinuation

Overreporting restrictions:

5. Medically attended TEAEs not matching any of the above 4 categories that have started later than 6 months after 2nd dose
6. TEAEs not matching any of the above 5 categories that have started later than 28 days after any dose. (I.e. An AE starting between Day 29 and 49 when dose 2 was given on Day 50 is also an overreported AE.)

In the output, overreported AEs are displayed in listings but are not included in tables.

10.6 Immunogenicity Assessments

Immunogenicity assessments are only performed in subjects from the Immunogenicity/Reactogenicity Subset to assess the immune response induced by vaccination with CVnCoV and are evaluated in 2 ways:

- Binding antibodies to the SARS-CoV-2 RBD of the S protein (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.

Further assessments for serology status to natural SARS-CoV-2 infection (SARS-CoV-2 N protein) are performed in all subjects by immunoassay. 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 (see also Section **Error! Reference source not found.**). Data provided is qualitative (positive/negative).

As the immunogenicity results would potentially unblind the subject's treatment assignment, the laboratory performing the assays keeps the results in strict confidence. The SARS-CoV-2 N protein data is not considered unblinding information.

After approval of protocol v3.0 immunogenicity assessments are no longer performed.

10.6.1 SARS-CoV-2 Serology Status

In all trial subjects, measurement of binding antibodies to the SARS-CoV-2 N protein is performed by immunoassay. Blood samples are taken on Day 1 (pre-vaccination baseline), Day 43 and Day 211 of the trial.

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, 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 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 vaccination +/- 3 days.

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

For the efficacy analyses, the subject must be seronegative/naïve to N protein at baseline and 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 assessment, 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.

10.7 COVID-19 Cases

COVID-19 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.

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 [1]:

- 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

In addition, subjects are messaged up to twice a week to provide a yes or no response to having COVID-19 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 molecular-based RT-PCR test performed at a designated local laboratory.

The result of the local RT-PCR test is 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, whether or not they were symptomatic (COVID-19 illness) or asymptomatic at the time of the test.

The subject should be retested as soon as feasible to confirm the result. The 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 uses the scripted interview to collect information about the subject’s COVID-19 symptoms and medical condition.

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 the designated local 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

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 Efficacy Analysis

A case of COVID-19 meeting the case definition for 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 Adjudication of COVID-19 Cases

An independent Committee of clinicians is formed to adjudicate some COVID-19 cases, and asymptomatic cases of SARS-CoV-2 infections (Section 10.8). The Committee is blinded to the treatment assignment of the subject. 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 other cause?

NB: The Adjudication questionnaire uses the term “CureVac designated central laboratory” although in this study the local laboratory had been designated by CureVac to perform the RT-PCR test.

COVID-19 case summary data as provided by the Adjudication Committee is used for all relevant definitions and analyses, i.e. especially all 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 from the onset date recorded on the Adjudication Form.

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

There is no active surveillance in this trial for asymptomatic SARS-CoV-2 infections. 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.

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 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 Censoring Rules for Unblinded Subjects and/or Treated with AV

If during the conduct of study CV-NCOV-005 an AV becomes available to subjects, these subjects can request to be 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 9.5).

- Subjects who are unblinded are censored for the safety and efficacy endpoints at the first day after unblinding. However 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 a 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 7.

Table 7: Censoring Rules for Unblinded Subjects 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 an interim workaround for unclean data during study conduct.

All incomplete or missing AV dates need to be queried.

10.11 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 8 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 are calculated as follows:

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

Table 8: 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)
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; date AV + 1; unblinding date + 1; trial termination date; cut-off date^)	Min (Event date; Censoring date)
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; date AV + 1; unblinding date + 1;	Min (Event date; Censoring date)

Endpoint Short Description	Start Date	Event Date*	Censoring Date#	End Date of Follow-Up
			trial termination date; cut-off date^)	
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; date AV + 1; unblinding date + 1; trial termination date; cut-off date^)	Min (Event date; Censoring date)
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; date AV + 1; unblinding date + 1; trial termination date; cut-off date^)	Min (Event date; Censoring date)
BoD 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)
Second episode of Covid-19	Resolution date of first primary case episode	Date of symptoms onset of a second COVID-19 case	Min (unblinding date + 1; date AV + 1; trial termination date; cut-off date^)	Min (Event date; Censoring date)

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 IA
$ Date of symptom onset of a virologically-confirmed COVID-19 case. After such a case, subject can no longer be considered an "asymptomatic" subject.

10.12 Age Group

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

11.0 Interim Analyses

No formal IA is done. In August 2021 a first immunogenicity delivery is provided.

12.0 Statistical Methods

Unless otherwise noted, categorical variables are summarized using counts and percentages. Percentages are presented with one decimal place, except 100% 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, all data summaries are presented overall and by vaccine group. Thereby, the CVnCoV data is presented for pooled CVnCoV lots and split by lot. Efficacy outputs are not split by lot and 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.

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

Age group is used as a factor for stratification of randomization. The efficacy analyses are in general **not** adjusted for this factor.

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.

In agreement with the sponsor it was decided to not perform some of the analyses in the EOT analysis. Therefore some of the below analyses were never performed. For details, please refer to Appendix 4

12.1 Subject Disposition

The number and percentage of subjects who prematurely withdraw from treatment, prematurely withdraw from the trial and a breakdown of the corresponding reasons for treatment withdrawal and early trial discontinuation is provided. Reasons for withdrawal are listed for subjects who prematurely withdraw from treatment or prematurely withdraw from the trial.

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 are not tabulated, but are listed.

Subjects whose data is censored due to unblinding for AV treatment being available, are summarized for unblinding and / or AV use before dose 2 and after dose 2 for SAS and 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. Subjects are also listed accordingly.

12.2 Demographic and Baseline Characteristics

The following demographic data collected at baseline is summarized for the SAS (and PPI at the Immunology IA):

- 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 10.7.5 for details.
- Height (cm),
- Weight (kg),
- Body Mass Index (kg/m2).

12.3 Medical and Surgical History

Medical/surgical history is coded using the MedDRA Version 23.1 or higher. 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 are provided for the SAS.

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. Concomitant medications are summarized based on the SAS. .

Concomitant medications/vaccinations (see Section 10.4) are summarized by Anatomical Therapeutic Chemical (ATC) level 1 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 provided in a data listing along with the concomitant medications/vaccinations.

12.5 Important Protocol Deviations

Per PRA/ICON processes, protocol deviations data is entered into PRA/ICON system of record (PSO). The trial team and the Sponsor conduct on-going 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 is 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 a separate Appendix to the SAP (see 5). The detailed definitions of important protocol deviations leading to exclusion 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 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.

12.6 Safety Analyses

12.6.1 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 (placebo, pooled CVnCoV lot, and split by lot), 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.

12.6.1.1 Analysis of Unsolicited AEs

The following summaries of unsolicited AEs by SOC and PT are further provided, separately for AEs occurring within the first 28 days after each vaccination, within 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 exclude solicited AEs and flag treatment emergent event.

12.6.1.2 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)
    - Are 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.

In agreement with the sponsor was decided to not provide any analyses on solicited AEs in the EOT analysis. Therefore some of the above analyses are never performed. For details, please refer to Appendix 4.

12.6.1.3 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 vaccination, within 28 days after any vaccination, and all reported AEs (including those reported at more than 28 days after any 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 vaccination, vaccination 1 and 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 vaccination, within the 28 days after any vaccination, and all reported AEs (including those reported at more than 28 days after any 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 are only provided for all reported AEs, not by vaccination 1 and vaccination 2 separately and only by PT, not by SOC.)

All summaries and listings above 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.

12.6.1.4 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 28 days after any dose
- Unsolicited AEs, SAEs, unsolicited AESIs and AEs with fatal outcome, by SOC and PT occurring through EOT Visit

12.6.2 Deaths and Serious Adverse Events

Description of analyses of SAEs and fatal AEs are included in Section 12.6.1.1.

12.6.3 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.

12.6.4 Vital Signs

Vital signs are recorded at each clinic visit (i.e. Day 1, Day 29, Day 43, Day 57 [Immunogenicity/Reactogenicity Subset only], Day 120 [Immunogenicity/Reactogenicity Subset only], Day 211, and Day 393 / EOT). 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 is summarized.

Vital Signs data is summarized based on the SAS.

12.6.5 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. Physical examination data is listed only.

12.6.6 Sensitivity Analysis on Safety Outputs

For the safety delivery when the first 1037 subjects are 6 weeks post 2nd vaccination all safety outputs are repeated without applying any censoring due to AV-prone subject use or unblinding.

12.6.7 Adapting the Safety Analyses to the Requirements of Extensive Unblinding

If not explicitly exempted, all safety analyses described in Sections 12.6.1 – 12.6.6 are performed under the conditions of data censoring (described in Section 10.10).

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 12.6.1 – 12.6.6) remain unchanged, regardless of extensive unblinding. 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. The concerned analyses are explicitly listed at the end of this Section 12.6.7.
    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 12.6.1 – 12.6.6.
    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

12.7 Immunogenicity Analyses

For subjects in the Immunogenicity/Reactogenicity Subset, 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 and Day 43.

In general, 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, for the pooled CVnCoV lots, split by lot and for placebo, 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 Geometric Mean (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 not provided for immunogenicity outputs.

12.7.1 Primary Immunogenicity Analyses

SARS-CoV-2 RBD of S protein antibodies (expressed as GMT) are summarized descriptively. Summaries are provided at baseline and each post-baseline sampling timepoint. The fold change (FC) from baseline is further computed and summarized for Day 29 and Day 43.

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. For a definition of seroconversion for subjects seronegative at baseline, see Section 10.6.2.

GMTs of SARS-CoV-2 RBD of S protein 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 GM and 95% CIs,
- Boxplots of GMTs with median, Q1 and Q3, and whiskers representing minimum and maximum by vaccine group.

12.7.2 Secondary Immunogenicity Analyses

The analyses described for the primary immunogenicity endpoints detailed above in Section 12.7.1, are repeated for the secondary immunogenicity endpoints related to viral neutralizing antibodies to SARS-CoV-2 (expressed as GMT).

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

12.7.3 Exploratory Immunogenicity Analyses

Exploratory immunogenicity endpoints were deleted from the study protocol from version 5.0 onwards.

12.8 Efficacy Analyses

All efficacy analyses are presented for pooled CVnCoV lots and Placebo.

12.8.1 Secondary Efficacy Endpoint Analysis

12.8.1.1 First Episodes of Covid-19 Cases

Occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity meeting the case definition for the efficacy analysis is analyzed as follows:

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

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

Thereby, p denotes the proportion of cases coming from the pooled CVnCoV group among all cases and r is the ratio of total follow-up time of subjects in the pooled CVnCoV group over the total follow-up time of subjects in the placebo group (see Section 10.11).

An exact two-sided 95% Pearson-Clopper CI for p is calculated. From this, the Lower Limit (LL) and Upper Limit (UL) of the 95% CI for the VE is calculated from the UL and LL of the CI for p as:

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

The following is presented for the analysis of these secondary efficacy endpoints:

- Number and percentage of subjects with a respective case (COVID-19 case or seroconversion)
- Total follow-up time (years) in each vaccine group,
- Calculated proportion of cases coming from the pooled CVnCoV group among all cases (p),
- Ratio of total follow-up time of subjects in the pooled 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

This secondary efficacy analysis is performed on the EAS.

For any analysis requiring the serostatus at baseline or Visit Day 43 the information of the adjudication of COVID-19 cases is used, if available (Section 10.7.5). Otherwise the information of the N protein blood samples taken at baseline and Visit Day 43 is used (Section 10.6.1).

12.8.1.2 Severity Assessment of COVID-19 Cases

All COVID-19 cases meeting the 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.

Additionally, VE efficacy is analyzed based on first occurrence of mild COVID-19 cases meeting the efficacy case definition in a similar way as for the analysis of first episodes of COVID-19 cases of any severity.

The following is presented for these cases:

- Number and percentage of subjects with a respective case,
- Total follow-up time in each vaccine group (years),
- Calculated proportion of cases coming from the pooled CVnCoV group among all cases (p),
- Ratio of total follow-up time of subjects in the pooled 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.

All summaries and analyses are provided based on the EAS.

12.8.1.3 BoD Scores

BoD scores are calculated based on first episodes of virologically-confirmed cases of COVID-19 of any severity meeting the case definition for the efficacy analysis (see Section 10.7.4).

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

These analysis is provided for the EAS.

12.8.1.4 Sensitivity Analyses

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

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

A Cox Proportional Hazard model is used to model the time to first occurrence of virologically-confirmed COVID-19 cases according to the efficacy case definition. The model includes the vaccine group (pooled CVnCoV or Placebo) as a factor and is adjusted for the stratification factor age at baseline (18 to 60 and ≥61 years). The estimated Hazard Ratios for the CVnCoV vaccine group versus placebo and corresponding 95% CI is presented. The CIs are derived based on the Wald test.

These sensitivity analyses are performed on the EAS.

13.0 References

[1] Development and Licensure of Vaccines to Prevent COVID-19, FDA Guidance for Industry, June 2020.

14.0 Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomic Therapeutic Chemical
AV	Authorized Vaccine
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
EAS	Efficacy Analysis Set
EASS	Efficacy Analysis Set for Seroconversion
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
EOT	End of Trial
FC	Fold Change
FiO2	Fractional Inspired Oxygen
GM	Geometric Mean
GMT	Geometric Mean of Titers
HCW	Health Care Workers
IA	Interim Analysis
ICU	Intensive Care Unit
IgG	Immunoglobulin G
IS	Immunogenicity Subset
IWRS	Interactive Web Response System
KM	Kaplan Meier
LL	Lower Limit

Glossary of Abbreviations:	
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger Ribonucleic Acid
N	Nucleocapsid
O2	Oxygen
PaO2	Arterial Oxygen Partial Pressure
PBMC	Peripheral blood mononuclear cell
pIMD	Potential Immune-mediated Disease
PPI	Per Protocol Immunogenicity
PRA/ICON	Pharmaceutical Research Associates, Inc.
PSO	PRA/ICON 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
SD	Standard Deviation
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SpO2	Oxygen saturations in arterial blood
TEAE	Treatment Emergent Adverse Event
TFL	Tables, Figures and Listings
UL	Upper Limit
VDE	Vaccine Dependent Disease Enhancement
VE	Vaccine Efficacy

Glossary of Abbreviations:	
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
- Autoimmune thyroiditis (including Hashimoto 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

Respiratory disorders:

- Acute respiratory distress syndrome
- COVID-19

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

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

From MedDRA version 23.1

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 Tables, Figures and Listings (TFLs) is provided in a separate document CV-NCOV-005 Statistical Analysis Plan – Appendix 4 List of TFLs. TFLs to be provided at the different interim and final delivery timepoints are indicated therein. The document is maintained 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-005 Statistical Analysis Plan – Appendix 5 Protocol Deviations Leading to Exclusion from Analysis sets. The document is maintained outside of this SAP.