Protocol Number: CV-NCOV-003

Official Title: A Phase 3 multicenter clinical trial to evaluate the safety, reactogenicity and immunogenicity of the investigational SARS-CoV-2 mRNA vaccine CVnCoV in adults 18 years of age and above with co-morbidities

NCT Number: NCT04860258

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Statistical Analysis Plan (SAP)

Protocol Title:	**COVID-19:** **A Phase 3 multicenter clinical trial to evaluate the safety, reactogenicity and immunogenicity of the investigational SARS-CoV-2 mRNA vaccine CVnCoV in adults 18 years of age and above with co-morbidities**
Protocol Version No./Date:	2.0/29-MAR-2021 and Protocol Amendment #1 27-JUL-2021
CRF Version No./Date:	2.0/28-JUL-2021
SAP Version No./Date:	2.0 /14-JAN-2022

1.0 Approvals

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

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

2.0 Change History

Version/Date	Change Log
1.0	Final version
2.0	Implementing changes to schedule of visits based on Protocol Amendment #1 – Section 6.1 and 6.2 Description of the reduced scope – Section 6.1 and 6.2 Definition of seroconversion changed to an increase above 1 regardless of a subjects serostatus at baseline – Section 10.8.1 Removal of any interim analysis – Section 11.1 List of detailed scope of analyses related to abbreviated CSR – Appendix 4 List of Abbreviated Scope Based on SAP Version 2.0

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-003.

5.0 Scope

The Statistical Analysis Plan (SAP) outlines the following:

- Trial Objectives
- Trial Design
- Trial Endpoints and Assessments
- Analysis Sets
- Conventions and Derivations
- 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-003.

The SAP should be read in conjunction with the

- Trial protocol version 2.0, 29-MAR-2021, and Protocol Amendment #1, 27-JUL-2021
- Electronic case report form (eCRF) version 2.0, 28-JUL-2021
- SAP Version 1, 01-JUL-2021
- Changes following approval of the first version of the SAP will be tracked in the SAP Change Log. A final version of the SAP V1.0 will be approved prior to final database lock.

Each version of the SAP requires approval by the Sponsor.

6.1 Amendment #1 to Protocol Version 2.0

Protocol Amendment #1 describes the changes to be implemented into protocol version 2.0 in the context of the pause of Trial CV-NCOV-003.

In line with protocol section 5.2.2 “Pausing of the Trial,” the DSMB convened to review the available CVnCoV data across ongoing trials, and notably the available safety data of the pivotal phase2b/3 trial CV-NCOV-004. The DSMB confirmed a favourable safety profile for CVnCoV. The second Interim Analysis data on efficacy from CV-NCOV-004 suggested age dependent efficacy with inconclusive efficacy data in the group > 60 years of age. In consultation with Investigators, a decision has been taken to stop further enrolment into CV-NCOV-003 and amend the current protocol version 2.0 to clarify that all subjects shall undergo safety and immunogenicity follow-up for 3 months following the last CVnCoV. Due to the change in risk/benefit profile, there is sufficient scientific and medical rationale to support an enrolment halt of all ages with comorbidities and for enrolled subjects to complete study activities, allowing standard of care COVID vaccination procedures to be followed by the Investigators or the subject’s primary care physician.

6.2 Description of changes to Trial CV-NCOV-003 Protocol Version 2.0

Subjects who already received at least 1 CVnCoV dose are requested to remain in the study for 3 months following their last CVnCoV dose for safety and immunogenicity follow-up. Subjects will follow the amended Schedule of Activities (Table 2) until they reach 3 months of follow-up post-CVnCoV last dose. The follow-up period including Visit 9/Day 211 and Phone Contact/Day 302 is removed. The previous End of Trial Visit/Day 393 is amended to 3 months post last injection of CVnCoV as described in Table 1.

Any subjects currently in screening will be considered screen failures and will not receive CVnCoV vaccination in line with the enrolment halt. No additional screenings will be performed.

Subjects will be provided with adequate information about the changes to the study, in accordance with applicable local regulations and in line with protocol section 12.4 “Informed Consent.” The original schedule of visit is contained in Protocol version 2.0.

Table 1 Summary of visits to be included in the 3-month follow-up

The last injection of CVnCoV was on:	The subject will perform the study visits as planned in the Schedule of Activities, up to:	The subject will additionally have an end of trial visit[a] at:
Day 1	Day 57	Day 91
Day 29	Day 120[b]	Day 120 [b]

NA: not applicable

a) At this visit, the procedures described for the End of Trial in Table 2 should be performed.
b) As Day 120 will be the end of trial visit, the procedures to be followed are those described for the End of Trial in Table 2.

Table 2 Amended Schedule of Activities

Visit		Safety contact[a]	Phone contact						End of Trial[c]
Trial Day	2 (D1 +1d)	9 (D1 +8d)	15 (D1+ 14d)	29 (D1 +28d)	30[b] (D29 +1d)	43 (D29 +14d)	57 (D29 +28d)	120 (D29 +91d)	
Visit Window (days)	-0/ +0	-0/ +7	-2/ +4	-3/ +14		-2/ +4	-2/ +4	-2/ +4	
Physical examination[d]									X
Symptom-directed physical examination	X			X	X	X	X		
Vital signs[d]	X			X	X	X	X		X
Diary retraining[e]	X				X	X			
Diary review[e]	X	X		X	X	X	X		
Solicited AEs collected by diary[e]	X	X		X	X				
Unsolicited AEs collected by diary[e]	X	X		X	X	X	X		
SAEs[f]	X	X	X	X	X	X	X	X	X
Intercurrent medical conditions[f]	X	X	X	X	X	X	X	X	X
AESIs[f]	X	X	X	X	X	X	X	X	X
Concomitant medication/vaccination	X	X	X	X	X	X	X	X	X
Safety laboratory (~8 mL)[g] – Up to 50 subjects per co-morbidity	X			X	X	(X)[h]	X	(X)[h]	
Nasopharyngeal swab collection for rapid diagnosis on site and PCR testing[i]	(X)								
Binding antibody to RBD of S (spike) protein of SARS-CoV-2 (~4mL blood)[j]				X		X		X	X
Binding antibody to the N (nucleocapsid) protein of SARS-CoV-2 (~4 mL blood)[j]						X		X	X
Subset of up to 25 subjects per co-morbidity: SARS-CoV-2 neutralizing activity (6 mL blood)[j,k]				X		X		X	X
Subset of up to 25 subjects per co-morbidity: Cell-mediated immunity (3 mL)[j,k]				X		X		X	
Maximum total blood volume (mL)	~8	-	-	~21	~8	~17	~8	~17	~14

Visit		Safety contact[a]	Phone contact						End of Trial[c]
Trial Day	2 (D1 +1d)	9 (D1 +8d)	15 (D1+ 14d)	29 (D1 +28d)	30[b] (D29 +1d)	43 (D29 +14d)	57 (D29 +28d)	120 (D29 +91d)	
Visit Window (days)	-0/ +0	-0/ +7	-2/ +4	-3/ +14		-2/ +4	-2/ +4	-2/ +4	
Trial end									X

AE: adverse event; AESI: adverse event of special interest; PCR: polymerase chain reaction; RBD: receptor-binding domain; SAE: serious adverse event.

a) The safety contact is only applicable for the subjects who were allocated to this assessment at the time of enrolment to collect diary card data. The safety/reactogenicity data entered in the week after the first vaccination (i.e. all data recorded until Day 8 inclusively) has to be received by site and entered into electronic data capture as soon as possible. The site and the subject should agree on the best way to transfer this data. It can be done via different means such as a site visit, phone call or a transfer of the diary to site.
b) Day 30 visit will be performed only for subjects who received their second CVnCoV injection.
c) The day when performing the end of trial procedures is presented in Table 1. This can be Day 91, Day 120, or at the time of Early Termination if the subject does not agree to continued follow-up as recommended but agrees to perform an Early Termination Visit.
d) Physical examination and vital signs must be performed/measured by a qualified healthcare professional. See Section 9.1.4 of Protocol version 2.0 for an overview of the required assessments.
e) Diary retraining, review, and recording of solicited and unsolicited AEs in diaries are applicable only to subjects who received their last dose of CVnCoV on either Day 1 or Day 29 (as applicable).
f) SAEs, AESIs (including COVID-19) and intercurrent medical conditions that may affect the immune response to vaccination will be collected throughout the trial.
g) Safety laboratory testing will be performed in the subjects who were allocated to this assessment at the time of enrolment. See Appendix 3 of Protocol version 2.0 for an overview of the safety laboratory assessments.
h) On Day 43 and Day 120, the safety laboratory only needs to be done if the previous result was abnormal.
i) Swabs for COVID-19 testing will be collected in case the subject displays symptoms of acute respiratory infection (including, but not limited to COVID-19) (see Section 9.3 of Protocol version 2.0).
j) No blood draws for immunogenicity will be performed after the subject receives their first dose of authorised vaccine.

Sites shall continue to collect blood for this immunogenicity testing from the subjects who were allocated to this assessment at the time of enrolment.

6.3 Changes to Planned Analysis according to SAP Version 1.0

The original planned analysis, definition and scope of outputs will remain in the version 2.0 of SAP. The changes to the planned analysis is described in Appendix 4 List of Abbreviated Scope Based on SAP Version 2.0 which contains the planned outputs. The N=1200 subjects will not be enrolled, instead the analysis is based on the N=129 enrolled at the time of the decision to pause the study.

6.4 Changes to Protocol from Version 2.0 to Protocol Amendment #1

- For this study an abbreviated CSR will be produced due to the reduced sample size. The CSR will be based on the reduced scope (see Appendix 4 List of Abbreviated Scope Based on SAP Version 2.0). For the primary safety endpoints, key analysis will be included related to summary/occurrence of solicited adverse events, duration of solicited adverse events, unsolicited adverse events, adverse events of special interest and adverse events leading to either study or vaccine withdrawal.
- The analysis of number and percentage of subjects with Grade 3 adverse reactions or SAE considered related to the trial vaccine according to the investigator with 95% credibility intervals on the beta (0.5, 1.5) prior distribution and estimate will not be performed due to the small number of subjects.
- For the secondary immunogenicity endpoints, the immunogenicity set was planned for Day 1 (baseline), Day 29, Day 120, Day 211 and Day 393. Instead, the analysis will be performed with per protocol immunogenicity set for all available time points (Day 1(baseline), Day 29, Day 43 and Day 120).
- Exploratory endpoints related to CMI response: these analyses will not be finalized due to invalid samples and small sample size.
- Exploratory endpoints related to occurrence of confirmed COVID-19 cases: analysis will not be performed.
- Only time points up to Day 120 will be included.

7.0 Trial Objectives

All objectives, with the exception of the exploratory objectives related to CMI response, will be analyzed in all subjects overall, as well as per underlying co-morbidity.

7.1 Primary Objectives

- To evaluate the safety and reactogenicity profile after 1 and 2 dose administrations of CVnCoV.
- To evaluate the humoral immune responses 14 days after 2 dose administrations of CVnCoV.

7.2 Secondary Objective

- To evaluate the humoral immune responses after 1 and 2 dose administrations of CVnCoV at different time points during the trial.

7.3 Exploratory Objectives

- To evaluate the occurrence of laboratory-confirmed cases of COVID-19 after 1 and 2 doses of CVnCoV.

8.0 Trial Design

8.1 Overall Design

This is a Phase 3 open-label, single-arm trial to assess the safety, reactogenicity and immunogenicity of CVnCoV in an adult population with co-morbidities known to increase the risk for (severe) COVID-19. The selected co-morbidities which will be investigated are obesity, chronic cardiovascular disease, chronic kidney disease, chronic obstructive pulmonary disease (COPD), human immunodeficiency virus (HIV) infection, type 2 diabetes mellitus and post-renal transplantation.

Male and female subjects ≥18 years of age with 1 or more of the above co-morbidities will be eligible for the trial, with a life expectancy of at least 1 year as per the Investigator's assessment. Eligible subjects at screening must have no overt clinical symptoms or signs of COVID-19.

Subjects will be enrolled into 1 trial group:

- CVnCoV (n = 1,200): CVnCoV 12 µg on Day 1 and Day 29.

The CVnCoV dose level to be administered in this trial was selected based on data from trial CV-NCOV-001 and confirmed in trial CV-NCOV-002. The 12-µg dose level is currently being investigated in large-scale Phase 2b/3 trials in subjects >18 years of age, both in subjects in the CV-NCOV-004 "Herald" trial and also in health care workers in the CV-NCOV-005 trial.

The trial contains 10 protocol-scheduled visits and 2 protocol-scheduled phone contacts. In addition, there will be a protocol-scheduled safety contact to collect diary card data on Day 9 for the first 25 subjects enrolled in the co-morbidities chronic kidney disease, COPD, chronic cardiovascular disease and diabetes mellitus (see below for details on the stratification).

Stratification Based on Co-Morbidities

For chronic kidney disease, COPD, chronic cardiovascular disease and diabetes mellitus, the first 25 subjects enrolled in each co-morbidity will be restricted to those with mild to moderate disease.

These first 25 subjects per co-morbidity will be followed up for safety and reactogenicity for at least 1 week after the first dose. An assessment of these data will be performed by CureVac's internal Safety Review Committee (iSRC) and DSMB Chair overviewing the clinical development program of CVnCoV. Once the safety of CVnCoV has been assessed in these 25 subjects and following iSRC and DSMB Chair approval, subjects with more severe forms of the co-morbidity may be enrolled as per the Investigator's decision.

For obesity, HIV and renal transplant, no distinction will be made between the initial 25 subjects that can be enrolled and any further enrollments. As described above, for subjects with multiple high-risk co-morbidities, the subject's main medical condition as determined by the Investigator will be used for enrollment stratification. A minimum of at least 50 subjects will be enrolled in each co-morbidity with a maximum of ~200 subjects.

8.2 Stopping/Pausing Rules for Safety

8.2.1 Individual Subjects Stopping Rules

Individual stopping adverse events (AE) rules will be applicable during the entire trial to ensure safe administration of the second dose to subjects vaccinated with the first vaccine dose.

Individual subject stopping rules are met in case any of the following events occur on the day of vaccination or the following 7 days (Days 1-8):

- An allergic/anaphylactic reaction considered as related to the trial vaccine.

- Any SAE considered as related to the trial vaccine.
- Any Grade 3 AE considered as related to the trial vaccine, with the following exceptions:
    - Transient Grade 3 systemic AE (fever, headache, fatigue, chills, myalgia, arthralgia, nausea/vomiting and diarrhea) considered as related to the trial vaccine that resolved within 24 hours to Grade ≤2

If any of these rules are met, the subject must not receive the second vaccine dose. The subject will be encouraged to continue participation until the end of the trial for safety and immunogenicity assessments.

8.2.2 Pausing of the Trial

The decision to pause the trial (i.e., temporary stopping of enrollment and vaccinations) due to a safety signal (see section 6.1 for more details for other reasons) will be based on a recommendation from the DSMB in consultation with the Sponsor. The DSMB may recommend pausing the trial for a safety concern following a review of accumulating safety data presented at the regularly scheduled DSMB meetings or from an ongoing review of AEs, which include but are not limited to, suspected unexpected serious adverse reactions (SUSARs); all SAEs judged as related to trial vaccine; concerning SAEs (e.g., adverse events of special interest (AESIs)); and all life-threatening SAEs and deaths. These events will be monitored by the DSMB (which is for entire COVID-19 vaccine clinical development trials encompassing CV-NCOV-001, -002, -004, -005 and -003) on a regular basis during the trial. The selected AEs and procedures for the safety review are described in detail in the DSMB Charter.

To ensure subject safety on an ongoing basis, a listing of the AEs as described above will be routinely monitored by the Chair of the DSMB (or designee) at regular intervals. For each review, the Chair [or designee(s)] will determine whether any single event or group of events constitute a new safety signal. If not, the Chair will inform the Trial Team that there are no safety concerns. Conversely, if there is a safety concern, the Chair may convene an ad-hoc DSMB meeting for further assessment of the event(s).

An iSRC will review the AEs across the clinical trials on a weekly basis and the meeting minutes will be shared with the DSMB Chair.

Based on the assessment of the benefit-risk ratio and biologic plausibility of a causal relationship of the AE(s) to the trial vaccine, the DSMB will make a recommendation to the Sponsor to either continue the trial as planned, modify its conduct, or pause the trial to allow further evaluation of the AE(s). If the latter, the Sponsor will make the decision to pause the trial in consultation with the DSMB.

Please refer to the DSMB Charter for additional discussion of the DSMB's role and responsibilities.

Details on the composition, objectives, and responsibilities of the DSMB, and the schedule and conduct of the DSMB meetings will be described in the DSMB Charter.

8.3 Sample Size Considerations

The sample size of the trial ensures that sufficient safety and immunogenicity data will be available in a population with co-morbidities. The aim is to enroll 1,200 subjects. Due to the reasons described in section 6.1 and 6.2 the trial was stopped prior reaching the 1,200 subjects; hence 129 subjects were enrolled in total.

The trial is designed to provide a reasonable precision for an estimate of the number of subjects seroconverting for SARS-CoV-2 S protein RBD-specific antibodies and an acceptable rate of Grade 3 adverse reactions (defined as solicited local Grade 3 AEs, and solicited systemic or unsolicited Grade 3 AEs considered as related to the trial vaccine). Table 3 provides the estimate and 95% credibility interval for the observed numbers of subjects seroconverting for SARS-CoV-2 S protein antibodies for sample sizes of 150 (providing characteristics for a pre-defined co-morbidity) and 1,200 assuming a Beta (1.9, 0.1) priors

for seroconversion for SARS-CoV-2 S protein antibodies and Beta (0.5, 1.5) priors for Grade 3 adverse reactions are assumed.

Table 3 Estimate of Number of Subjects Seroconverting for SARS-CoV-2 S Protein Antibodies and 95% Credibility Interval (CI)

Rate (%)	Sample Size			
	150		1200	
	N	95% CI	N	95% CI
80	120	80.2 (73.5 - 86.1)	960	80 (77.7 - 82.2)
85	128	85.5 (79.5 - 90.6)	1020	85 (82.9 - 87)
90	135	90.1 (84.9 - 94.3)	1080	90 (88.3 - 91.6)
95	142	94.7 (90.6 - 97.6)	1140	95 (93.7 - 96.2)
100	150	99.9 (99.4 - 100)	1200	100 (99.9 - 100)

CI: credibility interval; N: subjects seroconverting for SARS-CoV-2 S protein antibodies

Table 4 below provides probabilities (in %) that the following 2 conditions are simultaneously met for assumed true adverse reaction rates and for assumed true rates of subjects seroconverting for SARS-CoV-2 S protein antibodies and for different sample sizes:

- There is a ≥80% probability that the true rate of Grade 3 adverse reactions is ≤33%, and
- There is a ≥90% probability that the true rate of subjects seroconverting for SARS-CoV-2 S protein antibodies is >95%.

For example, assuming a true adverse reaction rate of 20% and a true rate of subjects seroconverting for SARS-CoV-2 S protein antibodies of 97.5%, the 2 conditions are met with a probability of 68% and 100% sample sizes of 150 and 1,200 respectively.

Table 4 Probabilities (in %) for Assumed True Adverse Reaction Rates and for Assumed True Rates of Subjects with Seroconverting for SARS-CoV-2 S Protein Antibodies and Different Sample Sizes

True adverse reaction rate (%)	Sample Size					
	150			1200		
	True rate of subjects with seroconverting for SARS-CoV-2 S protein antibodies (%)			True rate of subjects with seroconverting for SARS-CoV-2 S protein antibodies (%)		
	95	97.5	100	95	97.5	100
5	13	68	100	10	100	100
10	13	68	100	10	100	100
15	13	68	100	11	100	100
20	13	68	100	10	100	100
25	11	61	91	10	100	100
30	6	32	47	10	92	92
35	1	6	8	0	1	1

8.4 Justification for Dose

CVnCoV will be evaluated at the dose level of 12 µg, defined based on clinical data from the ongoing trials CV-NCOV-001 and CV-NCOV-002.

8.5 End of the Trial Definition

A subject is considered to have completed the trial when he/she has completed all visits.

End of Trial is defined as the point at which the last subject has completed the last visit.

8.6 Randomization and Blinding/Unblinding

Not applicable, since this is an open-label, single-arm trial.

8.7 Inclusion/Exclusion Criteria

See sections 6.1 and 6.2 in the trial protocol.

9.0 Trial Endpoints

Any immunogenicity samples may also be used for assay validation and additional studies of the mechanism of action of the vaccine.

9.1 Primary Endpoints

The primary endpoints are stated in section 9.4.

9.2 Secondary Endpoints

The secondary endpoints are stated in section 9.4.

9.3 Exploratory Endpoints

The exploratory endpoints are stated in section 9.4.

9.4 Estimands

Based on the Protocol Amendment #1, a subset of endpoints will be presented. See Section 6.1, 6.2, 6.3 and 6.4 and Appendix 4 List of Abbreviated Scope Based on SAP Version 2.0 for additional details.

ENDPOINTS (subject level)	ESTIMANDS (population level)
Primary Safety	
	In subjects who received at least one dose of CVnCoV vaccine and a post baseline vaccine safety assessment is available. Subjects receiving an authorized/licensed COVID-19 vaccine during the course of the trial will be censored at the day after intake. The primary safety will be analyzed with the safety analysis set.
The frequency, intensity, and duration of solicited local AEs on each vaccination day and the following 7 days. The frequency, intensity, duration, and relationship to trial vaccination of solicited systemic AEs on each vaccination day and the following 7 days. The occurrence, intensity and relationship to trial vaccination of unsolicited AEs on each vaccination day and the following 28 days. The occurrence and relationship to trial vaccination of SAEs and AESIs throughout the trial.	The number and percentage of subjects overall and by co-morbidity: Each solicited local AE within 7 days (after each trial vaccination by intensity and overall. Each solicited systemic AE within 7 days after each trial vaccination by intensity, by relationship to trial vaccine and overall. The mean duration in days by group with standard deviation of solicited AEs (within the solicited period, total duration). At least 1 unsolicited AEs, at least 1 grade unsolicited AEs and each unsolicited AEs by SOC/PT occurring within 28 days after each trial vaccination and overall by causal relationship to trial vaccine and overall. At least 1 SAE, or at least 1 AESI to vaccine overall by causal relationship to trial vaccine and overall.

ENDPOINTS (subject level)	ESTIMANDS (population level)
Primary Immunogenicity	
On Day 43: The proportion of subjects seroconverting for SARS-CoV-2 S protein RBD antibodies, as measured by an immunoassay. Individual SARS-CoV-2 S protein RBD-specific antibody levels in serum, as measured by an immunoassay. Geometric mean titers (GMTs) of serum SARS-CoV-2 S protein RBD antibodies, as measured by an immunoassay. *In a subset of subjects**: the proportion of subjects seroconverting for SARS-CoV-2 neutralizing antibodies, as measured by an activity assay. *In a subset of subjects**: individual SARS-CoV-2 neutralizing antibody levels in serum, as measured by an activity assay. *In a subset of subjects**: GMTs of serum SARS-CoV-2 neutralizing antibodies, as measured by an activity assay.	In subjects who received dose 1 and dose 2 of trial vaccine and for whom the baseline blood sample for immunogenicity assessment and day 43 are available for analysis and no major protocol deviations expected to impact the immunogenicity outcomes. Subjects receiving an authorized/ licensed vaccine during the course of the trial will be censored at the day after receiving the authorized/ licensed vaccine. The primary immunogenicity will be analyzed with the per protocol immunogenicity subset. Estimate of subjects seroconverted (SARS-CoV-2 spike protein-specific antibodies) with 95% credibility interval using prior beta (1.9, 0.1) Number and percentage with exact 95% confidence intervals of subjects for who a seroconversion is observed (SARS-CoV-2 spike protein-specific antibodies) Geometric mean of Fold Change from baseline with 95% CI of SARS-CoV-2 spike protein antibodiesEstimate of subjects seroconverted (SARS-CoV-2 neutralizing antibody levels in serum) with 95% credibility interval using prior beta(1.9, 0.1) Number and percentage with exact 95% confidence intervals of subjects for who a seroconversion is observed (SARS-CoV-2 neutralizing antibody levels in serum) Geometric mean of Fold Change from baseline with 95% CI of SARS-CoV-2 neutralizing antibody levels in serum
Secondary Immunogenicity	
On Day 29, Day 120, Day 211 and Day 393: The proportion of subjects seroconverting for	In subjects who received at least 1 dose of CVnCoV vaccine and for whom the baseline blood sample and at least 1 additional blood sample are available for analysis. Subjects receiving an authorized/licensed COVID-19 vaccine during the course of the trial will be censored at the day after intake. The secondary immunogenicity will be analyzed with the immunogenicity set. Day 211 and Day 393 will not be measured.

ENDPOINTS (subject level)	ESTIMANDS (population level)
SARS-CoV-2 S protein RBD antibodies, as measured by an immunoassay. Individual SARS-CoV-2 S protein RBD-specific antibody levels in serum, as measured by an immunoassay. GMTs of serum SARS-CoV-2 S protein RBD antibodies, as measured by an immunoassay. In a subset of subjects*, on Day 29 and Day 120: The proportion of subjects seroconverting for SARS-CoV-2 neutralizing antibodies, as measured by an activity assay. Individual SARS-CoV-2 neutralizing antibody levels in serum, as measured by an activity assay. GMTs of serum SARS-CoV-2 neutralizing antibodies, as measured by an activity assay.	Estimate of subjects seroconverted (SARS-CoV-2 spike protein-specific antibodies) with 95% credibility interval using prior beta(1.9, 0.1) Number and percentage with exact 95% confidence intervals of subjects for who a seroconversion is observed (SARS-CoV-2 spike protein-specific antibodies) Geometric mean of Fold Change from baseline with 95% CI of SARS-CoV-2 spike protein antibodiesEstimate of subjects seroconverted (SARS-CoV-2 neutralizing antibody levels in serum) with 95% credibility interval using prior beta(1.9, 0.1) Number and percentage with exact 95% confidence intervals of subjects for who a seroconversion is observed (SARS-CoV-2 neutralizing antibody levels in serum) Geometric mean of Fold Change from baseline with 95% CI of SARS-CoV-2 neutralizing antibody levels in serum
Exploratory	
Occurrence of confirmed COVID-19 cases Number of subjects with reverse transcription polymerase chain reaction (RT-PCR)-confirmed SARS-CoV-2 infection as measured by RT-PCR at clinically determined time points throughout the trial. Number of subjects with asymptomatic SARS-CoV-2 infection as measured by serological titers of nucleocapsid antibodies on Day 1, Day 43, Day 120 and Day 393.	In subjects who received at least one dose of CVnCoV vaccine and a post baseline vaccine safety assessment is available. Subjects receiving an authorized/licensed COVID-19 vaccine during the course of the trial will be censored at the day after intake. Number and percentage of subjects by co-morbidity at baseline and post-baseline time points with a positive RT-PCR result. This exploratory endpoint will be analyzed with the safety analysis set. Number and percentage of subjects by co-morbidity at baseline and post-baseline with a positive RT-PCR result and/or infection defined by SARS-CoV-2 N-antigen and no COVID-19 symptoms. This exploratory endpoint will be analyzed with the immunogenicity set. Day 211 and Day 393 will not be measured.
	CMI responses will not be analysed.

ENDPOINTS (subject level)	ESTIMANDS (population level)
CMI response On Day 1, Day 29, Day 43 and Day 120 in peripheral blood stimulated with antigen in a subset of subjects*: The SARS-CoV-2 S-specific T cell response, as measured by cytokine and chemokine expression after antigen stimulation using a standardized whole blood collection and culture system.	

* The subset of subjects to participate in neutralizing activity and CMI response testing shall consist of approximately 25 subjects for each co-morbidity (up to a maximum of 175 subjects).

9.5 Population Sets

9.5.1 Immunogenicity Set

The Immunogenicity set will include all subjects who received at least 1 dose of CVnCoV and for whom the baseline blood sample and at least 1 additional blood sample are available for analysis.

9.5.2 Per Protocol Immunogenicity Subset (PPI)

The Per Protocol Immunogenicity subset (PPI) will include all subjects who:

- Received both doses within the windows defined in the protocol.
- Have no important protocol deviations expected to impact the immunogenicity outcomes as specified in the statistical analysis plan (SAP).
- Have not received medical treatments (such as blood products, immunoglobulin therapy) that may interfere with any of the proposed immunogenicity measurements.
- Have at least 1 blood sample collected starting at 14 days (Day 43) post-second vaccination available for analysis.

The PPI will be the primary analysis population for SARS-CoV-2 RBD of S protein antibody responses and SARS-CoV-2 viral neutralizing antibody responses.

9.5.3 Safety Analysis Set (SAS)

The Safety Analysis Set will consist of all subjects who received at least 1 dose of CVnCoV and for whom any post-vaccination safety data are available.

10.0 Conventions and Derivations

All data obtained in this trial and documented in the eCRF will be listed and summarized with sample statistics or frequency tables as appropriate. In all tables, listings and figures (TLFs), the co-morbidities definitions - chronic kidney disease, chronic obstructive pulmonary disease (COPD), obesity, chronic cardiovascular disease, chronic HIV infection, type 2 diabetes mellitus and post-renal transplantation - will be reported in this order.

The statistical analyses will be reported using tables, listings, and figures (TLFs). Templates will be provided in a separate document (TFL shells).

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 = observed value at post-baseline time point – observed value at baseline

10.2 Fold Change from Baseline

Unless otherwise noted, fold change from baseline is defined as the ratio:

Post-baseline value/baseline value

10.3 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 will be calculated as

  Trial Day=Date of day – date of first dose + 1
- For days before first trial vaccination, trial day will be calculated as

  Trial Day=Date of day – date of first dose

10.4 Case Definitions of Co-morbidities

Subjects with the following selected co-morbidities are at increased risk of severe illness from COVID-19 and will be included in the trial. Life expectancy of at least 1 year as per the Investigators' assessment is required for inclusion of the subject into the trial.

- **Chronic kidney disease:** Kidney function will be ascertained from the serum creatinine measurement within the last 6 months, converted into estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, with impaired kidney function defined as eGFR <60 mL/min/1.73m².
  - Mild chronic kidney disease is defined as an eGFR between 60-89 mL/min/1.73 m^2.
  - Moderate chronic kidney disease is defined as an eGFR between 31-59 mL/min/1.73 m^2 with stable therapy and good maintenance over at least 6 months [1].
- **Chronic obstructive pulmonary disease** (COPD) (including emphysema and chronic bronchitis).
  - Mild COPD with or without cough or sputum production is defined as forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) <0.7 and FEV_1 ≥80% predicted.
  - Moderate COPD with or without cough or sputum production is defined as FEV_1/FVC <0.7 and FEV_1≥50%, but <80% predicted with stable treatment (GOLD Criteria for COPD severity).
- **Obesity** with body mass index >32 kg/m².
- **Chronic cardiovascular disease** (heart failure, structural heart disorder, coronary artery disease, cardiomyopathies, arterial hypertension), including the following:
  - Heart failures (according to New York Heart Association [NYHA] classification [2]):
    - Class I: No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
    - Class II: Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).

- A structural heart disorder
  - without symptoms
  - with symptoms.
- Coronary artery disease:
  - Mild with metabolic equivalent threshold (MET)[1] <3, stable with medication.
  - Moderate with MET >3 – 5.9, stable with medication.
- Cardiomyopathies of non-infective and metabolic origin:
  - Mild with MET <3, stable with medication.
  - Moderate with MET >3 – 5.9, stable with medication.
- Hypertension (National Institute for Health and Care Excellence [NICE] categorization [4]):
  - Stage 1 hypertension: Clinic blood pressure ranging from 140/90 mmHg to 159/99 mmHg and subsequent ambulatory blood pressure monitoring (ABPM) daytime average or home blood pressure monitoring (HBPM) average blood pressure ranging from 135/85 mmHg to 149/94 mmHg.
  - Stage 2 hypertension: Clinic blood pressure of 160/100 mmHg or higher but less than 180/120 mmHg and subsequent ABPM daytime average or HBPM average blood pressure of 150/95 mmHg or higher.

- **Chronic HIV infection with stable aviremia (<50 copies/mL) and CD4 count >350/mL** as documented by blood samples taken within 12 months before enrollment. Viral load <50 copies/mL over 12 months with transient changes of 50-350 copies/mL is allowed.
- **Type 2 diabetes mellitus**, controlled with medication [HbA1c <58 mmol/mol (7.45%)]; [(HbA1c in % - 2.15) x 10.929 = HbA1c in mmol/mol.
- **Subjects with a renal transplant** at least a year ago under stable conditions for at least 6 months with medications, categorized as low risk of rejection.

Following inclusion of 25 cases of mild to moderate conditions under chronic kidney disease, COPD, chronic cardiovascular disease and diabetes mellitus, more severe conditions can be included into the trial upon iSCR and DSMB Chair approval and subjected to the clinical Investigator's decision. Under cardiovascular disease, the following cases can be included:

- Heart failures (according to NYHA classification [2]) Class III: Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea (shortness of breath).
- Coronary artery disease: Severe with MET >6, stable with medication.
- Cardiomyopathies of non-infective and metabolic origin: Severe with MET >6, stable with medication.

[1] MET is defined as the amount of oxygen consumed while sitting at rest and is equal to 3.5 mL O_2 per kg body weight/min and is roughly equivalent to the expenditure of 1 kcal per kilogram of body weight per hour; 1 MET is the rate of energy expenditure while at rest. A 4 MET activity expends 4 times the energy used by the body at rest. Light MET is <3, moderate is 3 to 5.9 and vigorous is ≥6.0. MET 1 can take care of him/herself and may not maintain themselves and gets constraints on exertion. MET 4 can climb a flight of stairs or walk up a hill and can participate in other strenuous activities; >2-3 METs is fit normal person with well controlled with medication [3].

  - Hypertension (NICE categorization [4]): Stage 3 or severe hypertension: Clinic systolic blood pressure of 180 mmHg or higher or clinic diastolic blood pressure of 120 mmHg or higher.

- Under diabetes mellitus, cases of uncontrolled diabetes mellitus with recent HbA1c of >59 mmol/mol (7.45%) with medication can be included. For uncontrolled diabetes mellitus, HbA1c should be within <10% variation and the subject should not have any history of diabetic ketoacidosis or episode of severe symptomatic hypoglycemia within the past 3 months.

10.5 Missing Data

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

- For SARS-CoV-2 RBD of S protein antibodies, and viral neutralizing antibodies, concentration values marked as below the lower limit of quantification (LLOQ) will be 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 will be 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 will be 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 will be the time of vaccination start.
  - In all other cases, AE start time will be imputed as 00:00.

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

10.6 Prior/Concomitant Medication

Prior medications are medications with a start date prior first dose date of vaccination. Concomitant medications are those ongoing at or starting on or after first dose date of vaccination.

10.7 Adverse Events (AEs)

Since no control group is included in the trial, the subjects will serve as their own control for reactogenicity and safety assessments. For this purpose, the subjects will complete the pre-vaccination diary card on a daily basis as of Day -7 (i.e., during 1 week before the first vaccination) to give an indication of their normal life with co-morbidities. Solicited systemic AEs as well as unsolicited AEs will need to be collected similar to what is done during the 7 days after vaccination.

10.7.1 Treatment Emergent Adverse Events (TEAEs)

A 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 10.5 will be 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 will be considered treatment emergent.

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

10.7.2 Solicited Adverse Events

Solicited systemic AEs (fever, headache, fatigue, chills, myalgia, arthralgia, nausea/vomiting, and diarrhea) will be recorded from Day -7 until Day -1 using a paper diary. These records shall provide a baseline for reactogenicity and safety for each enrolled subject. See Table 5.

Solicited local AEs (injection site pain, redness, swelling, and itching) and solicited systemic AEs will be recorded on the days of vaccination (Day 1 and Day 29) and the following 7 days using a paper diary. See Table 6.

Body temperature should be measured orally and by using the thermometer provided to the subject at Visit 1.

Solicited AEs will be assessed on an intensity scale of absent, mild, moderate, and severe (5 and 6). In case of related Grade 3 solicited or unsolicited AEs reported for more than 1 day in the diary, the subject will be questioned to establish the total duration of the AE as exactly as possible and this information will be recorded in the eCRF.

Solicited systemic Grade 3 AEs and unsolicited Grade 3 AEs, except for solicited injection site reactions, must be reported to the medical monitor without delay, on the same day of awareness by the site.

By definition, all solicited local AEs occurring from the time of first vaccination are considered related to trial vaccination. For solicited systemic AEs, the Investigator will assess the relationship between trial vaccine and each occurrence of each AE.

Table 5 Intensity Grading for Solicited Local Adverse Events

Adverse Event	Grade	Definition
Pain at injection site	0	Absent
	1	Does not interfere with activity
	2	Interferes with activity and/or repeated use of non-narcotic pain reliever >24 hours
	3	Prevents daily activity and/or repeated use of narcotic pain reliever
Redness	0	<2.5 cm
	1	2.5 – 5 cm
	2	5.1 – 10 cm
	3	>10 cm
Swelling	0	<2.5 cm
	1	2.5 – 5 cm and does not interfere with activity
	2	5.1 – 10 cm or interferes with activity
	3	>10 cm or prevents daily activity
Itching	0	Absent
	1	Mild, no interference with normal activity
	2	Moderate, some interference with normal activity
	3	Significant, prevents normal activity

Based on the United States Food and Drug Administration toxicity grading scale [5].

Table 6 Intensity Grading for Solicited Systemic Adverse Events

Adverse Event	Grade	Definition
Fever	0	<38°C
	1	≥38 – 38.4°C
	2	≥38.5 – 38.9°C
	3	≥39°C
Headache	0	Absent
	1	Mild, no interference with normal activity
	2	Moderate, some interference with normal activity and/or repeated use of non-narcotic pain reliever >24 hours
	3	Significant; any use of narcotic pain reliever and/or prevents daily activity
Fatigue	0	Absent
	1	Mild, no interference with normal activity
	2	Moderate, some interference with normal activity
	3	Significant, prevents normal activity
Chills	0	Absent
	1	Mild, no interference with normal activity
	2	Moderate, some interference with normal activity
	3	Significant, prevents normal activity
Myalgia	0	Absent
	1	Mild, no interference with normal activity
	2	Moderate, some interference with normal activity
	3	Significant, prevents normal activity
Arthralgia	0	Absent
	1	Mild, no interference with activity
	2	Moderate, some interference with activity
	3	Significant, prevents 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 intravenous hydration
Diarrhea	0	Absent
	1	2 – 3 loose stools
	2	4 – 5 stools
	3	6 or more watery stools/over 24 hours or requires outpatient intravenous hydration

Based on the United States Food and Drug Administration toxicity grading scale [5].

10.7.2.1.1 Duration of Solicited Adverse Events

Duration of solicited local and systemic adverse events are defined as the sum consecutive days with local/systemic adverse events (days 1 to 8) for the same grade. For example, Fatigue with grade 1 occurring on day 2 and 3 and day 7 will be counted as two separate events with the duration 2 days and 1 day. For the duration of solicited local and systemic AEs ongoing beyond Day 8 the following definition is used:

If the AE is present on day 8 in the diary and the same AE is present on day 9 on the eCRF, the sum of days between the date of day 9 and end date for the AE on the eCRF is added to the consecutive days as collected on the diary. If the duration of any AE continues after the next dose and the subject experience an AE of the same type in the second dose, these two events will be presented separately.

10.7.3 Unsolicited Adverse Events and Serious Adverse Events

Diaries will also be used for collection of unsolicited AEs in the week before the first vaccination as well as on each vaccination day and the following 28 days. In addition, subjects will be contacted by phone to verify whether they had any health concerns since the last visit.

The occurrence of AEs (serious and non-serious) will be assessed by non-directive questioning of the subject at each visit. AEs volunteered by the subject during or between visits in the diary or detected through observation, physical examination, laboratory tests, or other assessments during the entire trial, will be recorded in the eCRF, if they fall within the reporting period. Subjects should be instructed to report immediately any AEs with serious symptoms, subjective complaints or objective changes in their well-being to the Investigator or the site personnel, regardless of the perceived relationship between the event and the trial vaccine.

The Investigator will assess the relationship between trial vaccine and each occurrence of AE/SAE.

SAEs and AEs leading to vaccine withdrawal or trial discontinuation will be collected throughout the trial.

10.7.4 Adverse Events of Special Interest (AESI)

The following events will be considered as AESIs during this trial:

- AEs with a suspected immune-mediated etiology (see Appendix 1 Potential Immune-Mediated Diseases).
- Other AEs relevant to SARS-CoV-2 vaccine development or the target disease (see Appendix 2 for the current list of AESIs and see the protocol for details on laboratory testing for COVID-19).
- Non-serious intercurrent medical conditions that may affect the immune response to vaccination will also be collected throughout the trial.

AESIs will be collected throughout the trial.

10.7.5 Medically-Attended Adverse Events

Medically-attended AEs will be collected on the eCRF throughout the trial.

10.7.6 Grade 3 Adverse Reactions

Adverse reactions are defined as solicited local Grade 3 AEs, and solicited systemic or unsolicited Grade 3 AEs considered as related to the trial vaccine.

10.7.7 Adverse Events Related to Standardised MedDRA Queries

Subjects' AEs are filtered with Standard MedDRA Query (SMQ) for the following SMQs:

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

In addition, two customized MedDRA queries are defined for taste and smelling disorder and events related to paraesthesia, hypoaesthesia, and hyperaesthesia. The related terms are listed in the Appendix 3 MedDRA Terms for CMQs. The MedDRA SMQs for the specific terms are not included in the appendix. See official MedDRA documentation.

10.7.8 Definition of Subjects with asymptomatic SARS-CoV-2 infection

Subjects without a AESI indicating COVID-19 infection and a positive SARS-CoV-2 N protein result and/or a positive PCR result.

10.7.9 Credibility Interval and related Estimate

The estimate, using Beta(α, β), is calculated as follows:

- (number of reactions + α) / (total number of subjects + α + β).

The lower and upper intervals are calculated as follows for a given number of reactions:

- In the programming language SAS: betainv(0.025, number of reactions + α , total number of subjects – number of reactions + β) and betainv(0.975, number of reactions + α , total number of subjects – number of reactions + β).

The SAS programming language function betainv returns a quantile from the beta distribution.

10.8 Immunogenicity Assessments

10.8.1 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 will apply.

10.8.1.1 SARS-CoV-2 RBD of S Protein Antibodies

Seroconversion is defined as a fold increase above 1 in antibody titer against SARS-CoV-2 RBD of S protein regardless of the serostatus at baseline. In addition, 2-fold and 4-fold increases will be presented.

10.8.1.2 SARS-CoV-2 Neutralizing Antibodies

Seroconversion is defined as a fold increase above 1 in SARS-CoV-2 neutralizing antibody titer regardless of the serostatus at baseline. In addition, 2-fold and 4-fold increases will be presented.

10.8.2 Geometric Mean

The SARS-CoV-2 spike RBD protein-specific antibody ELISA and SARS-CoV-2 neutralizing antibody are expressed as GMT [geometric mean of reciprocal duplicate dilutions]. It is assumed that the data is skewed hence the geometric mean (GM) and geometric standard deviation (GSD) will be presented. The GM is calculated as the anti-logarithm of the mean of the log-transformed data. The GSD will be calculated as the anti-logarithm transformation of the standard deviation of the log-transformed data.

10.9 Censoring Rules

Authorized/licensed vaccines are available to some subjects, and based on ethical reasons these subjects can decide whether they would like to receive the authorized/licensed vaccine. To avoid any study bias, subjects who are vaccinated with an authorized/licensed vaccine will be censored for safety and immunogenicity at the first day after receiving the authorized/licensed vaccine. The data collected from the censoring time point forward will be included and flagged in the listings output to identify corresponding data.

The following details are to be followed regarding censoring the day after receiving the authorized/licensed vaccine:

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

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

All incomplete or missing authorized/licensed vaccine dates need to be queried.

11.0 Interim Analyses and DSMB

11.1 Interim Analysis

There are no interim analyses planned for this study following Protocol Amendment #1. As this trial is of exploratory nature and no inferential statistics are planned, no adjustment for multiple testing will be done.

11.2 Safety Monitoring Committees

An independent DSMB will be convened to oversee the safety of subjects participating in this trial. The DSMB will perform a comprehensive review of all relevant safety and reactogenicity data before making a decision to pause the trial (i.e., temporary stopping of enrollment and vaccinations) due to a safety signal in consultation with the Sponsor. CureVac's Safety Review Team (SRT) also reviews the AEs reported across the CV-NCOV clinical trials on a weekly basis and the meeting minutes are shared with the DSMB Chair. For more details about the Protocol Amendment #1 and the description of the changes to the trial see sections 6.1 and 6.2.

For the co-morbidities chronic kidney disease, COPD, chronic cardiovascular disease and diabetes mellitus, the first 25 subjects per co-morbidity should include only mild to moderate cases. The iSRC and DSMB Chair will perform an assessment of the safety and reactogenicity data up to at least 1 week after the first dose, prior to proceeding with enrollment of subjects with more severe forms of the co-morbidity as per the Investigator's decision.

Details on the composition, objectives, and responsibilities of the DSMB, and the schedule and conduct of the DSMB meetings will be described in the DSMB Charter.

The DSMB analyses will be described in a separate SAP and TFL shells.

12.0 Statistical Methods

The SAP V1.0 will be prepared and finalized at the latest prior to database lock.

Subjects will be stratified post-hoc by pre-defined co-morbidities (see Section 10.4). Subjects with multiple co-morbidities will contribute to the different corresponding strata.

Data from this trial may be pooled with data from potential follow-up trials.

Due to the exploratory nature of this trial, only descriptive statistics will be used. No confirmatory statistical inference will be performed.

All data collected during this trial will be displayed in data listings, unless otherwise specified. Data listings will be sorted by co-morbidity definitions - chronic kidney disease, chronic obstructive pulmonary disease (COPD), obesity, chronic cardiovascular disease, chronic HIV infection, type 2 diabetes mellitus and post-renal transplantation and subject identifier. Screening failures will be excluded from all listings and tables if not otherwise stated. Listings will include all relevant assigned/derived variables.

Unless otherwise noted, categorical variables will be summarized using counts and percentages. Descriptive statistics (mean, median, standard deviation (SD), Q1, and Q3, minimum and maximum values) for continuous variable will be presented. Mean, median, Q1 and Q3 will be presented to 1 decimal more than original data. SD will be presented with 2 decimals more than original data. Minimum and maximum will match the decimal points in the original data. Maximum number of decimals will be 4, unless otherwise stated.

In general, all data summaries will be presented by (and in the following order):

- Chronic kidney disease,
- Chronic obstructive pulmonary disease (COPD),
- Obesity,
- Chronic cardiovascular disease,
- Chronic HIV infection,
- Type 2 diabetes mellitus,
- Post-renal transplantation and
- Overall

No imputation of missing data other than that described in Section 10.5 will be performed.

All data summaries and tabulations will be prepared using SAS Version 9.4 or higher.

12.1 Subject Disposition

The number and percentage of subjects who completed the 2-dose vaccination regimen, completed trial, and reason for discontinuing further vaccination and trial will be presented with a breakdown of the corresponding reasons for early termination and discontinuation.

The number and percentage of subjects included in each analysis set will be provided. Reasons for exclusion from each analysis set will not be tabulated, but will be listed.

Subjects not fulfilling one or more inclusion criterion or meeting any of the exclusion criteria will be listed only.

12.2 Demographic and Baseline Characteristics

Demographic characteristics to be summarized based on the Safety Analysis Set (SAS) will include gender, ethnicity, race, age at informed consent (years), age by group (18-60 years, >= 61 years), height, weight, Body Mass Index (BMI), height (cm), weight (kg), BMI (kg/m^2), childbearing potential. Subjects co-morbidities will be summarized by severity. Data collected related to the primary co-morbidities will be listed.

12.3 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1 or higher and will be summarized by Primary System Organ Class (SOC) and Preferred Term (PT) for the SAS. Medical history will also be listed.

12.4 Trial Vaccine Exposure

The number and percentage of subjects who received at least one vaccination on day 1 (dose 1), 29 (dose 2), including the reasons for not receiving a dose will be summarized using the SAS. The administrations of CVnCoV will be listed as well.

12.5 Important Protocol Deviations

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

Protocol deviation data will be reviewed prior to formal analysis (e.g. main, final) and important deviations leading to elimination of subjects from analysis sets will be identified. The detailed definitions of important protocol deviations leading to elimination of subjects from analysis sets will be provided in the final signed minutes of the data review meetings prior to each formal analysis.

A summary of important protocol deviation data will be created based on the SAS, displaying the number and percentage of subjects with any important protocol deviations and broken down by type of deviations. Protocol deviation data will also be listed.

12.6 Prior and Concomitant Medications and Vaccinations

Prior and concomitant medications and vaccinations will be coded using World Health Organization Drug Dictionary (WHODDRUG), Version September 2020 Global B3 or higher, and will be summarized based on the SAS.

Concomitant medications/vaccinations will be summarized by Anatomical Therapeutic Chemical (ATC) level 1 and WHODRUG Preferred Name as the number and percentage of subjects taking at least one medication within each medication group and subgroup.

Prior medications/vaccinations will be summarized by ATC level 1 and WHODRUG Preferred Name as the number and percentage of subjects taking at least one medication within each medication group and subgroup.

Medications with ATC level 2 code J07 are considered to be vaccinations.

Concomitant medications and vaccinations will be listed as well.

12.7 Analyses

The primary, secondary and exploratory endpoints will be analyzed overall, as well as per underlying co-morbidity.

Based on the Protocol Amendment #1, a subset of analyses will be presented. See Section 6.1, 6.2, 6.3, 6.4 and Appendix 4 List of Abbreviated Scope Based on SAP Version 2.0 for additional details. Below all planned analyses according to SAP version 1.0 will be described. Any analysis not performed according to the abbreviated scope will be described.

Any analysis marked with an asterisk * will not be part of the abbreviated scope described in detail in Appendix 4.

12.7.1 Primary Safety Endpoints

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

If not stated otherwise, all summaries/counts of unsolicited AEs will exclude solicited AEs.

For outputs presenting occurrence of AEs for a defined period after a dose, the following distinctions are made if not otherwise stated; by any dose, dose 1, and dose 2. Any dose is defined as a subject who received at least one dose of CVnCoV.

The primary and secondary safety endpoints will be analyzed using the safety set.

12.7.1.1 Analysis of Unsolicited AEs and Solicited AEs

An overall summary of unsolicited AEs will be prepared for AEs occurring within 28 days after each dose, within 28 days after any dose, and all reported AEs (including those reported at more than 28 days after any dose).

- Unsolicited AEs
- Related unsolicited AEs
- SAEs (includes solicited AEs)
- Related SAEs (includes solicited AEs)
- Grade 3 (severe) unsolicited AEs
- Grade 3 (severe) related unsolicited AEs
- Intercurrent medical conditions affecting immune response (includes solicited AEs)
- Medically attended AEs (includes solicited AEs)
- Related medically attended AEs (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)
- AESIs (includes solicited AEs)
- Related AESIs (includes solicited AEs)
- AEs leading to vaccine withdrawal
- AEs leading to withdrawal from trial

The overall summary will also be presented for overall and by sex (female/male)* and for any dose (dose 1 and dose 2) and include AEs for the duration of the trial.

The following summaries of unsolicited AEs by SOC and PT will further be 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 dose) if not otherwise stated:

- Occurrence of unsolicited AEs
- Occurrence of related unsolicited AEs*
- Occurrence of SAEs (includes solicited AEs)*
- Occurrence of related SAEs (includes solicited AEs) *
- Occurrence of unsolicited AEs by maximum severity (mild / moderate / severe)*
- Occurrence of related unsolicited AEs by maximum severity (mild / moderate / severe) *
- Occurrence of SAEs by maximum severity (mild / moderate / severe) (includes solicited AEs)*

- Occurrence of related SAEs by maximum severity (mild / moderate / severe) (includes solicited AEs)*
- Occurrence of AESIs (includes solicited AEs)
- Occurrence of related AESIs (includes solicited AEs)*
- Occurrence of intercurrent medical conditions affecting immune response (includes solicited AEs)*
- Occurrence of medically attended AEs (includes solicited AEs)*
- Occurrence of related medically attended AEs (includes solicited AEs)*
- Occurrence of AEs leading to withdrawal from trial (includes solicited AEs)
- Occurrence of AEs leading to vaccine withdrawal (includes solicited AEs)
- Occurrence of SMQs (Anaphylactic reaction, Convulsions, Embolic and thrombotic events, Hypersensitivity, Immune-mediated/autoimmune disorders, and Liver related investigations, signs and symptoms (Sub-SMQ)) (includes solicited AEs)*

A listing of all SAEs will further be provided by subject, including both unsolicited and solicited AEs.

Solicited AEs occurring on the day of vaccination and the following 7 days and unsolicited AEs will be listed together.

12.7.1.2 Analysis of Solicited AEs

The following summaries of solicited AEs within 7 days after each trial vaccination and within 7 days after any trial vaccination will be provided. If not stated otherwise the maximum grade will be presented (grade 0 to grade 3).

- Summary of solicited AEs, local AEs and systemic AEs, overall and by maximum grade
- Summary of local AEs, overall and by maximum grade
- Summary of systemic AEs, overall and by maximum grade (occurrence of systemic AEs will also be presented from day -7 until day -1)*
- Summary of related systemic AEs, overall and by maximum grade*
- Duration (days) of solicited AEs, overall and for Grade 3 events
- 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 (only for each dose)*
- Daily summary of systemic AEs (only for each dose)*
- Daily summary of related systemic AEs (only for each dose)*
- Summary of time of onset (Day) for grade 3 solicited AEs, any solicited AEs, local, systemic AEs, and related systemic AEs*
- Time of onset (Day) of local AEs*
- Time of onset (Day) of systemic AEs*
- Time of onset (Day) of related systemic AEs*
- Individual grade 3 solicited local and systemic adverse events will be presented in a figure.*

In addition, number and percentage of subjects with solicited Grade 3 adverse reaction(s) or SAEs considered as related to the trial vaccine according to the Investigator with the 95% credibility interval based on the Beta (0.5, 1.5) prior distribution will be calculated and summarized. This analysis is not part of the abbreviated scope.

Solicited AEs occurring on the day of vaccination and the following 7 days will be listed separately as well.

12.7.2 Primary and secondary Humoral Immune Response Endpoints

The primary humoral response endpoints will be analyzed with the per protocol immunogenicity subset population. The primary endpoint is subjects with seroconversion on day 43 compared to baseline (Day 1); the time points day 29, day 120 will be presented for the per protocol immunogenicity subset population as well. Seroconversion is defined as an increase above 1 from baseline (Day 1) (see Section 10.8.1), In addition conversion over 2 fold and 4 fold will be presented. Analysis based on the immunogenicity set will not be presented according to the abbreviated scope.

The following tables will be presented for SARS-CoV-2 S (RBD) protein antibodies, as measured by ELISA and SARS-CoV-2 neutralizing antibodies, as measured by an activity assay:

- The estimate and 95%-credibility intervals and proportion and Clopper-Pearson exact confidence intervals will be presented as well for seroconverted subjects.
- Geometric mean (GM), geometric standard deviation (GSD) and 95%- confidence intervals as well as fold change from baseline.

In addition, the following figures will be presented for the time points day 29, day 43, day 120, and for the per protocol immunogenicity population and immunogenicity set:

- Fold change from baseline for Individual subjects by co-morbidity presented in a line plot.
- Mean fold change from baseline by co-morbidity
- Individual line plots of GMTs by co-morbidity
- Line plot of GMTs with geometric mean and confidence intervals by co-morbidity
- Boxplots with median, Q1 and Q3, and whiskers representing minimum and maximum.

SARS-CoV-2 S (RBD) protein antibodies, and SARS-CoV-2 neutralizing antibodies results will be listed as well.

12.7.3 Exploratory Endpoints

The below mentioned exploratory endpoints will be included in the abbreviated scope. Cell-mediated immune response and cytokine concentrations will not be included.

- Number of subjects and percentages with RT-PCR-confirmed SARS-CoV-2 infection at clinically determined time points throughout the trial will be tabulated by time point. This table and listing will be presented for the safety set.
- Number of subjects and percentages with asymptomatic SARS-CoV-2 infection as measured by serological titers of nucleocapsid antibodies on day 1, day 43 and day 120 will be tabulated by time point. Subjects with COVID-19 symptoms are excluded.

12.7.4 Laboratory Data

Blood samples for determination of hematology, clinical biochemistry and coagulation will be analyzed at each trial visit they are collected by co-morbidity for SAS. In case of abnormal results additional analyses will take place.

All laboratory data will be summarized in International System (SI) units. The conversion factors from conventional to SI units will be documented in the Local Lab Conventions document for this trial.

Laboratory data will be graded according with the United States Food and Drug Administration (FDA) toxicity grading scale [5].

All laboratory data will be listed.

12.7.4.1 Hematology

Hematology parameters include Leukocytes (WBC), Erythrocytes (RBC), Hemoglobin, Hematocrit, Ery. Mean Corpuscular Hemoglobin (MCH), Ery. Mean Corpuscular HBG Concentration (MCHC), Ery. Mean Corpuscular Volume (MCV), Platelets, Neutrophils (Absolute), Lymphocytes (Absolute), Monocytes (Absolute), Eosinophils (Absolute), Basophils (Absolute), Reticulocytes (Absolute), Neutrophils/Leukocytes (%), Lymphocytes/Leukocytes (%), Monocytes/Leukocytes (%), Eosinophils/Leukocytes (%), Basophils/Leukocytes (%), Reticulocytes/Erythrocytes (%).

Hematology parameters will be summarized (n, mean, SD, median, Q1, Q3, minimum and maximum), including change from baseline at each visit. In addition, shift tables summarizing the shift including baseline, minimum and maximum post baseline values and last value will be presented. In addition, all parameters will be presented in a line plot for all planned visits.

12.7.4.2 Chemistry

Clinical Chemistry/Biochemistry parameters include Sodium, Potassium, Urea Nitrogen (BUN), Urea, Creatinine, Calcium, Total Protein, Albumin, Bilirubin (Total), Direct Bilirubin, Indirect Bilirubin, Aspartate Aminotransferase (AST; SGOT), Alanine Aminotransferase (ALT; SGPT), Gamma Glutamyl Transferase (GGT), Lactate Dehydrogenase (LDH), Alkaline Phosphatase (ALP), Magnesium, C-Reactive Protein (CRP).

Chemistry parameters will be summarized (n, mean, SD, median, Q1, Q3, minimum and maximum), including change from baseline at each visit. In addition, shift tables summarizing the shift including baseline, minimum and maximum post-baseline values and last value will be presented. In addition, all parameters will be presented in a line plot for all planned visits.

12.7.4.3 Coagulation

Coagulation parameters include Activated Partial Thromboplastin Time (aPTT), Prothrombin Intl. Normalized Ratio (INR), Prothrombin Time (PT).

All parameters will be summarized (n, mean, SD, median, Q1, Q3, minimum and maximum), including change from baseline at each visit. In addition, shift tables summarizing the shift including baseline, minimum and maximum post baseline values and last value will be presented. In addition, all parameters will be presented in a line plot for all planned visits.

12.7.4.4 Serum/Urine Pregnancy Test.

For subjects of childbearing potential, a pregnancy test will be performed on the day of enrollment and before any dose.

Pregnancy test results will be listed only.

12.7.5 Vital Signs

Vital signs will be summarized descriptively at each trial visit they are collected and by co-morbidity for SAS, including screening. Change from baseline values will be summarized for the post-vaccination visit. Vital

signs parameters to be summarized include systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (bpm) and body temperature (°C).

If the temperature is collected in Fahrenheit convert using the following formula: (°F– 32)X(5/9).

Vital signs will be listed as well.

12.7.6 Physical Examinations and ECGs

12.7.6.1 Physical Examinations

At specific trial visits a complete physical examination will be performed and the results collected if there are clinically significant results.

Physical examination results will be listed only.

12.7.6.2 Electrocardiogram

An electrocardiogram (ECG) with conventional 12-lead traces will be recorded on Day -7 for all subjects. Additionally, ECGs should be performed as clinically indicated.

ECG results will be listed only.

13.0 References

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4. National Institute for Health and Care Excellence (2019) Hypertension in adults: diagnosis and management NG136. Available at: https://www.nice.org.uk/guidance/ng136 Accessed 2 March 2021.
5. US Department of Health and Human Services. Food and Drug Administration (FDA). Guidance for Industry. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. 2007. [Available from: https://www.fda.gov/media/73679/download; Accessed 14 July 2020].

14.0 Glossary of Abbreviations

AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
BUN	Urea Nitrogen
CEPI	Coalition for Epidemic Preparedness Innovations
CMI	Cell-mediated immunity
COPD	Chronic obstructive pulmonary disease
CoV	Coronavirus
CRP	C-Reactive Protein
CVnCoV	Investigational SARS-CoV-2 mRNA vaccine
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
ELISA	Enzyme-linked immunosorbent assay
FDA	United States Food and Drug Administration
GGT	Gamma Glutamyl Transferase
GM	Geometric mean
GMT	Geometric mean titer
GSD	Geometric standard deviation
Ig	Immunoglobulin
INR	Prothrombin Intl. Normalized Ratio
IS	Immunogenicity Set
iSRC	Internal Safety Review Committee
LDH	Lactate Dehydrogenase
MCH	Ery. Mean Corpuscular Hemoglobin
MCHC	Ery. Mean Corpuscular HBG Concentration
MCV	Ery. Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities

mRNA	Messenger ribonucleic acid
N	Nucleocapsid
PCR	Polymerase chain reaction
pIMD	Potential immune-mediated disease
PPI	Per Protocol Immunogenicity Set
PT	Prothrombin Time
RBC	Erythrocytes
RBD	Receptor-binding domain
RNA	Ribonucleic acid
RT-PCR	Reverse transcription polymerase chain reaction
S	Spike
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	Safety Analysis Set
SD	Standard deviation
SGPT	Alanine Aminotransferase
SGOT	Aspartate Aminotransferase
SMQ	Standardized MedDRA Queries
SOC	System Organ Class
TBD	To be determined
TFL	Tables Figures Listings
WBC	Leukocytes
WHO	World Health Organization
WHODRUG	WHO Drug Dictionary

15.0 Appendices

Appendix 1 Potential Immune-Mediated Diseases

Current list of pIMDs:

Gastrointestinal disorders:

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

Liver disorders:

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

Metabolic diseases:

- o Addison's disease
- o Autoimmune thyroiditis (including Hashimoto thyroiditis)
- o Diabetes mellitus type I
- o Grave's or Basedow's disease

Musculoskeletal disorders:

- o Antisynthetase syndrome
- o Dermatomyositis
- o Juvenile chronic arthritis (including Still's disease)
- o Mixed connective tissue disorder
- o Polymyalgia rheumatic
- o Polymyositis
- o Psoriatic arthropathy
- o Relapsing polychondritis
- o Rheumatoid arthritis
- o Scleroderma, including diffuse systemic form and CREST syndrome
- o Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis
- o Systemic lupus erythematosus
- o Systemic sclerosis

Neuro-inflammatory disorders:

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

Skin disorders:

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

Vasculitides:

- o Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis and temporal arteritis
- o 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:

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

Appendix 2 Adverse Events of Special Interest for SARS-CoV-2 Vaccines

Current list of AESIs (based on Brighton Collaboration via CEPI's Safety Platform for Emergency vACcines [SPEAC] Project):

Immunological disorders:
- o Anaphylaxis
- o Vasculitides
- o Enhanced disease following immunization
- o Multisystem inflammatory syndrome in children

Respiratory disorders:
- o Acute respiratory distress syndrome
- o COVID-19 disease

Cardiac disorders:

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

Hematological disorders:
- o Thrombocytopenia

Coagulation disorder:
- o Deep vein thrombosis
- o Pulmonary embolus
- o Cerebrovascular stroke
- o Limb ischemia
- o Hemorrhagic disease

Renal disorders:
- o Acute kidney injury

Gastrointestinal disorders
- o Liver injury

Neurological disorders:
- o Generalized convulsion
- o Guillain-Barré Syndrome
- o Acute disseminated encephalomyelitis
- o Anosmia, ageusia
- o Meningoencephalitis

Dermatologic disorder:
- o Chilblain-like lesions
- o Single organ cutaneous vasculitis
- o Erythema multiforme

Other:
- o Serious local/systemic adverse reaction following immunization

** These are generally the conditions one encounters in normal subjects as AESI, but in this trial we use comorbid subjects and some of them may have coronary disease, arrhythmias or myocarditis to start with.

Appendix 3 MedDRA Terms for CMQs

MedDRA Version 24.1

A. Customized MedDRA Queries related to taste and smelling disorder

Preferred Term
Ageusia
Anosmia
Dysgeusia
Hypergeusia
Hypogeusia
Hyposmia
Parosmia
Taste disorder

B. Customized MedDRA Querie related to paraesthesia, hypoaesthesia, and hyperaesthesia

Preferred Term
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

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