Protocol Number: CV-NCOV-002

Official Title: COVID-19: A Phase 2a, partially observer-blind, multicenter, controlled, dose-confirmation clinical trial to evaluate the safety, reactogenicity and immunogenicity of the investigational SARS-CoV-2 mRNA vaccine CVnCoV in adults >60 years of age and 18 to 60 years of age

NCT Number: NCT04515147

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Statistical Analysis Plan (SAP)

Protocol Title:	**A Phase 2a, partially observer-blind, multicenter, controlled, dose-confirmation clinical trial to evaluate the safety, reactogenicity and immunogenicity of the investigational SARS-CoV-2 mRNA vaccine CVnCoV in adults >60 years of age and 18 to 60 years of age**
Protocol Version No./Date:	3.0./03-DEC-2021
eCRF Version No./Date:	5.0/17-AUG-2021
SAP Version No./Date:	3.0/18-FEB-2022

1.0 Approvals

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

2.0 Change History

Version/Date	Change Log
1.0/22-JAN-2021	Created as new
2.0/01-APR-2021	Section 9.4 Estimands – Added new tables and updated wording. Section 10.5.9 Adding definition of SMQ; 6 pre-defined and 2 customized. Section 10.8 Censoring rules of unblinded subjects. Section 12.0 Changing to use MedDRA 24.0 instead of 23.1. Section 12.8 Adding outputs occurrence of AEs related to SMQs. Section 12.8.1.2 Adding of Summary of Solicited AEs by gender for dose 1, dose 2 and booster dose. Section 12.8.1.2 Adding of Estimate and Credibility intervals for seroconverted subjects. Section 12.9.4 Adding of Cytokine parameters Appendix 6 MedDRA terms.
3.0/18-FEB-2022	Section 8.8 and 10.8 with the protocol version 3.0 all subjects will be unblinded. Section 9.1, 9.2 and 9.3 Endpoints are now described in the Estimands table (Section 9.4). Section 9.4 removal of endpoint related to asymptomatic infections with SARS-CoV-2 Section 12.9.4 Adding of CMI analysis- data to be listed Section 10.6.4 and 12.9.5 Adding of definition and Analysis of Evaluation of Asymptomatic SARS-CoV-2 infection

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-002.

5.0 Scope

The Statistical Analysis Plan outlines the following:

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

6.0 Introduction

The SAP should be read in conjunction with the

- Study protocol version 3.0, 03-DEC-2021.
- Electronic case report form (eCRF) version 5.0, 17-AUG-2021.

Changes following approval of the first version of the SAP will be tracked in the SAP Change Log and a final version of the amended SAP will be approved prior to final database lock.

Each version of the SAP requires approval by the Sponsor.

6.1 Changes from Protocol

CMI response On Day 1, Day 29, and Day 43 in peripheral blood mononuclear cells (PBMCs) in a subset of subjects, will not be analyzed as part of this SAP, but listed only.

Evaluation of asymptomatic SARS-CoV-2 infection will be summarized by time point based on retrospective serology and RT-PCR results.

7.0 Study Objectives

All objectives will be analyzed in all subjects, in subjects retrospectively SARS-CoV-2 seronegative at baseline, and in subjects retrospectively SARS-CoV-2 seropositive at baseline.

7.1 Primary Objectives

- To evaluate the safety and reactogenicity profile after 1 and 2 dose administrations of CVnCoV at different dose levels.
- To evaluate the humoral immune response after 1 and 2 dose administrations of CVnCoV.

7.2 Secondary Objectives

- To evaluate the safety and reactogenicity profile after a booster dose administration of CVnCoV at different dose levels.
- To evaluate the humoral immune response after a booster dose administration of CVnCoV at different dose levels.

7.3 Exploratory Objectives

- To evaluate the cell-mediated immune (CMI) response after 1 and 2 dose administrations of CVnCoV at different dose levels in a subset of subjects.
- To evaluate the innate immune response after the first dose administration of CVnCoV at different dose levels in a subset of subjects.
- To identify and assess cases of COVID-19 disease.

8.0 Study Design

8.1 Overall Design

This is a Phase 2a, partially blind, active-controlled, dose-confirmation trial to assess the safety and immunogenicity of provisionally selected CVnCoV dose levels of 6 and 12 µg in an older adult population. The design of the trial will allow an increase or decrease in dose based on data from Trial CV-NCOV-001 and this trial. An overview of the planned number of subjects to be enrolled per trial group and the vaccination schedule is provided in Table 1.

Subjects will be recruited independent of their SARS-CoV-2 serology status. Their serostatus will be determined retrospectively by a blood sample drawn at baseline and analyzed to allow post hoc stratified analyses of subjects who are SARS-CoV-2 seronegative or seropositive at baseline.

In the initial phase, subjects will be enrolled in 3 cohorts divided into 6 groups:

- 6 µg dose level cohorts
    - Group 1 (observer-blind): CVnCoV 6 µg on Day 1 and 6 µg on Day 29 (in subjects 18 to 60 years of age)
    - Group 2 (observer-blind): CVnCoV 6 µg on Day 1 and 6 µg on Day 29 (in subjects >60 years of age [i.e., 61 years or older])
- 12 µg dose level cohorts
    - Group 3 (observer-blind): CVnCoV 12 µg on Day 1 and 12 µg on Day 29 (in subjects 18 to 60 years of age)
    - Group 4 (observer-blind): CVnCoV 12 µg on Day 1 and 12 µg on Day 29 (in subjects >60 years of age [i.e., 61 years or older])
- Active control cohort
    - Group 5 (observer-blind): licensed hepatitis A vaccine on Day 1 and on Day 29 (in subjects 18 to 60 years of age)
    - Group 6 (observer-blind): licensed pneumococcal vaccine on Day 1 and on Day 29 (in subjects >60 years of age [i.e., 61 years or older])

A subgroup of subjects in Group 3 will receive a booster dose of CVnCoV on Day 180 and a subgroup of subjects in Group 4 will receive a booster dose of CVnCoV on Day 57 or Day 180, each in an open-label manner.

The 6 µg and 12 µg groups will be enrolled sequentially, i.e., enrollment in the 12 µg groups will only be initiated once Groups 1 and 2 have been fully enrolled. Group 2 (subjects >60 years, for 6 µg) will be initiated in 4 sentinel subjects. These subjects should be vaccinated at least 60 minutes apart. Safety and reactogenicity data reported during an observation period of at least 24 hours after vaccination will be collected and reviewed by an iSRC. In this review, the iSRC will review all available safety data, but focus

specifically on Grade 3 adverse reactions. Based on this review, the iSRC will decide on continuation of enrollment of subjects at this dose level. In a next step, 8 additional sentinel subjects will be enrolled. Safety and reactogenicity data reported during an observation period of at least 24 hours after vaccination will be collected and reviewed by the iSRC. In this review, the iSRC will review all available safety data, but focus specifically on Grade 3 adverse reactions. The same procedure will be followed for Group 4 (subjects >60 years, 12 µg) and the iSRC will decide on continuation of enrollment of subjects at this dose level after review of the first 12 sentinel subjects.

In the initial phase, subjects will be randomized according to a 10:1 ratio to receive CVnCoV or the active control in an observer-blinded manner.

Table 1 Trial Groups and Vaccination Schedule

Cohort	Age (years)	Group	Vaccination Schedule				Blinding
			Primary Doses			Booster Dose	
			Day 1	Day 29	Day 57	Day 180	
CVnCoV 6 µg	18-60	Group 1 (n=11)	CVnCoV 6 µg	CVnCoV 6 µg	-	-	Primary doses: Observer-blind
CVnCoV 6 µg	>60	Group 2 (n=12)	CVnCoV 6 µg	CVnCoV 6 µg	-		Primary doses: Observer-blind
CVnCoV 12 µg	18-60	Group 3 (n=90)	CVnCoV 12 µg	CVnCoV 12 µg	-	CVnCoV 12 µg (n=30)	Primary doses: Observer-blind Booster dose: Open-label
CVnCoV 12 µg	>60	Group 4 (n=90)	CVnCoV 12 µg	CVnCoV 12 µg	CVnCoV 12 µg (n=30)	-	Primary doses: Observer-blind Booster dose: Open-label
					-	CVnCoV 12 µg (n=30)	
Active control	18-60	Group 5 (n=9) n=1 against Group 1	Hepatitis A vaccine	Hepatitis A vaccine	-	-	Observer-blind
	>60	Group 6 (n=9) n=1 against Group 2	Pneumococcal vaccine	Pneumococcal vaccine	-	-	Observer-blind

Cohort	Age (years)	Group	Vaccination Schedule				Blinding
			Primary Doses			Booster Dose	
			Day 1	Day 29	Day 57	Day 180	
Expansion	18-60	n=200	CVnCoV 12 µg	CVnCoV 12 µg	-	-	Observer-blind
		n=20	Hepatitis A vaccine	Hepatitis A vaccine	-	-	
	>60	n=200	CVnCoV 12 µg	CVnCoV 12 µg	-	-	Observer-blind
		n=20	Pneumococcal vaccine	Pneumococcal vaccine	-	-	

8.2 Change in Dose Level

Other possible dose levels to be administered in this trial will continuously be assessed based on the ongoing Trial CV-NCOV-001 in adults aged 18 to 60 years. In case additional dose levels are investigated in this trial, such a dose level will be initiated in additional sentinel subjects.If the dose level of 12 µg is considered too reactogenic for adults aged 18 to 60 years in the CV-NCOV-001 trial, the dose level in this trial would be reduced from 12 µg to 8 µg.

In case of any dose increases, the next dose level will only be given to subjects once initial data from the previous dose level have been reviewed by the iSRC.

In case the starting dose level is not well tolerated, a decrease in the dose level may occur and the lower dose levels will be assessed in the same manner as described above.

8.3 Expansion Cohorts

Following the initial phase, a separate expansion cohort of 220 subjects aged 18 to 60 years and 220 subjects aged >60 years (i.e., 61 years or older) will be enrolled to be vaccinated on Days 1 and 29.

Expansion for subjects 18 to 60 years of age may start once the final dose for subjects in this age category has been selected based on the data from Trial CV-NCOV-001. Expansion for subjects >60 years of age may start once the final dose for these subjects has been selected based on data from this trial.

Subjects in the expansion cohorts will be randomized according to a 10:1 ratio to receive either the selected dose of CVnCoV or the active control in an observer-blinded manner.

8.4 Stopping Rules

8.4.1 Individual Stopping Rules

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

The stopping rules are met in case any of the following events occur on the day of vaccination or following 7 days:

- An allergic/anaphylactic reaction considered as related to the trial vaccine.
- Any serious AE (SAE) considered as related to the trial vaccine.
- Any Grade 3 AE considered 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 related to the trial vaccine that resolved within 48 hours to Grade ≤2.
  - Transient Grade 3 local AE that resolved within 48 hours to Grade ≤2.

If any of these rules are met, the subject must not receive the second vaccine dose (or booster). The subject will be encouraged to continue participation until the end of the trial for safety and immunogenicity assessments, but only relevant visits need to be conducted for any such subjects.

8.4.2 Trial Suspension Rule

A trial suspension rule will be applicable during the entire trial. This rule is met if a subject vaccinated with CVnCoV experiences an SAE considered related to the trial vaccine by the Investigator or Sponsor.

If this rule is met, enrollment and vaccination with CVnCoV will be suspended within 24 hours after reporting to the trial team. An ad-hoc Data Safety Monitoring Board (DSMB) meeting will be held to review all safety data per the DSMB charter. Depending on the DSMB assessment of the benefit-risk ratio, including the relationship of the SAE to the trial vaccine, enrollment and vaccination with CVnCoV might be temporarily halted and only be re-started upon approval by the DSMB and competent authority.

8.4.3 Justification for Dose

Two provisional CVnCoV dose levels (6 and 12 µg) will be evaluated. Based on favorable immunogenicity data and tolerable safety/reactogenicity data administered with 12 µg in Trial CV-NCOV-001, the DSMB endorsed the decision to implement the 12 µg dose in this phase 2a trial. Refer to the Investigator's Brochure for an overview of the CVnCoV non-clinical data.

Additional higher, lower, and/or intermediate dose levels might be evaluated depending on the outcomes of Trial CV-NCOV-001, as well as data from Trial CV-NCOV-002. Identification of immunogenic dose levels with lower mRNA content might be of particular importance for efficient vaccination in a worldwide viral outbreak setting

8.4.4 End of Trial Definition

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

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

8.5 Sample Size Considerations

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

8.5.1 Sample Size Determination

The sample size of the trial ensures that sufficient safety and immunogenicity data will be available for the selected CVnCoV dosage(s) prior to initiation of Phase 3 clinical trials. Approximately 200 subjects will be enrolled in the initial phase to investigate different dose levels and 20 subjects as control. Furthermore, 440 subjects will be enrolled in an expansion phase (400 will receive CVnCoV and 40 the active control). Overview in Table 2.

Table 2 Sample Size

Open-label	**Randomized**									
Dose escalation[a]	Group 1 6 µg Age 18-60	Group 2 6 µg Age >60	Group 3 12 µg Age 18-60	Group 4 12 µg Age >60	Expansion Age 18-60	Expansion Age >60	Total CVnCoV	Group 5 Active control Age 18-60	Group 6 Active control Age >60	Expansion Active control Age ≥18
4	**11**	**12[c]**	**90**	**90**	**200**	**200**	**603**	**10[b]**	**10[b]**	**40**

a. Only if the dose level was previously untested.
b. Includes 1 control subject from Group 1 and 1 control subject from Group 2.
c. Includes the 4 subjects from the dose escalation.

The trial is designed to provide a reasonable precision for an estimate of the number of subjects with seroconverting for nCoV spike protein antibodies and an acceptable rate of Grade 3 adverse reactions (ARs). Table 3 provides the estimate and 95% credibility interval for the observed numbers of subjects with seroconverting for nCoV spike protein antibodies for different sample sizes assuming a Beta (1.9,0.1) prior for seroconverting for nCoV spike protein antibodies and a Beta (0.5,1.5) prior for Grade 3 adverse reactions.

Table 3 Estimate of Number of Subjects with Seroconverting for nCoV Spike Protein Antibodies and 95% Credibility Interval

	Sample Size					
	90		200		603	
Rate (%)	N	95% CI	N	95% CI	N	95% CI
80	72	80.3 (71.7 - 87.7)	160	80.1 (74.4 - 85.3)	482	80 (76.7 - 83.1)
85	76	84.7 (76.7 - 91.2)	170	85.1 (79.9 - 89.7)	513	85 (82.2 - 87.8)
90	81	90.1 (83.3 - 95.3)	180	90 (85.6 - 93.8)	543	90.1 (87.6 - 92.3)
95	86	95.5 (90.5 - 98.7)	190	95 (91.6 - 97.6)	573	95 (93.2 - 96.6)
100	90	99.9 (98.9 - 100)	200	100 (99.5 - 100)	603	100 (99.8 - 100)

CI: credibility interval; N: subjects with seroconverting for nCoV spike protein antibodies

Table 4 provides probabilities (in %) that the following 2 conditions are simultaneously met for assumed true adverse reaction rates and for assumed true rates with seroconverting for nCoV spike protein antibodies and for different sample sizes:

- there is a ≥80% probability that the true rate of Grade 3 AR(s) is ≤33%, and
- there is a ≥90% probability that the true rate of subjects seroconverting for nCoV spike protein antibodies>95%.

For example, for a sample size of 200, assuming a true AR rate of 20% and a true rate of subjects seroconverting for nCoV spike protein antibodies of 97.5%, the 2 conditions are met with a probability of 76%.

Table 4 Probabilities (in %) for Assumed True Adverse Reaction Rates and for Assumed True Rates of Subjects with Seroconverting for nCoV Spike Protein Antibodies and Different Sample Sizes

	Sample Size								
	90			200			603		
	True rate of subjects with seroconverting for nCoV spike protein antibodies (%)			True rate of subjects with seroconverting for nCoV spike protein antibodies (%)			True rate of subjects with seroconverting for nCoV spike protein antibodies (%)		
True adverse reaction rate (%)	**95**	**97.5**	**100**	**95**	**97.5**	**100**	**95**	**97.5**	**100**
5	17	61	100	12	76	100	10	98	100
10	17	61	100	12	76	100	10	98	100
15	17	61	100	12	76	100	10	98	100
20	16	60	98	12	76	100	10	98	100
25	14	51	83	12	73	96	10	98	100
30	8	28	46	7	41	54	8	78	79
35	2	8	13	1	6	8	0	3	3

8.6 Randomization

The first part of the trial will be conducted with 4 CVnCoV groups versus 2 active controls. In the initial phase, subjects will be randomized according to a 10:1 ratio to receive CVnCoV or the active control in an observer-blinded manner.

Subjects in the expansion cohorts will be randomized according to a 10:1 ratio to receive either the selected dose of CVnCoV or the active control in an observer-blinded manner; 200 subjects per age category will receive CVnCoV and 20 subjects will receive the active control.

8.7 Blinding/Unblinding

The Sponsor and safety monitoring committees will be unblinded for data from the randomized groups, but will take appropriate measures to ensure subject blinding is kept at site level until database lock. Subjects may request to be unblinded in case they are eligible for an authorized/licensed SARS-CoV-2 vaccine.

8.8 Licensed/Authorized Vaccine

Since the efficacy results from Trial CV-NCOV-004 are available and all subjects in this trial are currently eligible to receive a licensed/authorized vaccine, all subjects in this trial will be unblinded.

Each subject will be informed by the study physician of the available efficacy results from Trial CV-NCOV-004 and whether he/she received CVnCoV or an active control. All subjects will be asked to remain in the trial to allow safety follow-up. For details related to the censoring rules for the analysis see section 10.8.

9.0 Study Endpoints

The endpoints will be analyzed in all subjects, in subjects retrospectively SARS-CoV-2 seronegative at baseline, and in subjects retrospectively SARS-CoV-2 seropositive at baseline.

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

ENDPOINTS (subject level)	ESTIMANDS (population level)
Primary Safety	
The frequencies, intensities, and duration of solicited local AEs on Day 1 and Day 29 and the following 7 days by dose and group. The frequencies, intensities, duration, and relationship to trial vaccination of solicited systemic AEs on Day 1 and Day 29 and the following 7 days by dose and group. The occurrence, intensity and relationship to trial vaccination of unsolicited AEs on each vaccination day and the following 28 days by dose and group. The occurrence and relationship to trial vaccination of SAEs and AESIs throughout the trial.	Safety set. Subjects who were unblinded and/or received an authorized/licensed COVID-19 vaccine will be censored at the day after unblinding and/or vaccination receipt. The number and percentage of subjects overall and by dose level: 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 29 and Day 43 • The proportion of subjects seroconverting for SARS-CoV-2 spike protein antibodies, as measured by ELISA. • Individual SARS-CoV-2 spike protein-specific antibody levels in serum, as measured by ELISA. • Geometric mean titers (GMTs) of serum SARS-CoV-2 spike protein antibodies, as measured by ELISA. • 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. • GMTs of serum SARS-CoV-2 neutralizing antibodies, as measured by an activity assay.	Immunogenicity set. Subjects receiving an authorized/licensed COVID-19 vaccine during the course of the trial will be censored at the day after intake. Sensitivity analysis: in addition, the primary immunogenicity analysis will be repeated for subjects who received dose 1 and dose 2 (and if eligible and received a booster dose at day 57 or day 180) of trial vaccine and for whom the baseline blood sample for immunogenicity assessment was seronegative and day 43 are available for analysis and no major protocol deviations expected to impact the immunogenicity outcomes. Subjects exposed to SARS-CoV-2 prior to the trial will be excluded. Subjects will be excluded at the time point they have been exposed to SARS-CoV-2. 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 (SARS-CoV-2 spike protein antibodies) Estimate 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 (SARS-CoV-2 neutralizing antibody levels in serum)
Secondary Safety	
	Safety set. Applicable for subjects who received a booster dose at day 57 or day 180. Subjects unblinded and/or received an authorized/ licensed vaccine during the course of the trial will be censored at the day after unblinding or receipt of authorized/ licensed vaccine (whichever is earlier).

ENDPOINTS (subject level)	ESTIMANDS (population level)
• The frequencies, intensities, and duration of solicited local AEs on the day of the booster administration and the following 7 days by group. • The frequencies, intensities, duration, and relationship to trial vaccination of solicited systemic AEs on the day of the booster administration and the following 7 days by group. • The occurrence, intensities and relationship to trial vaccination of unsolicited AEs on the day of the booster administration and the following 28 days by group.	The number and percentage of subjects by group reporting: • Each solicited local AE within 7 days after each trial booster vaccination by intensity and overall • Each solicited systemic AE within 7 days after each trial booster vaccination by intensity, by relationship to trial vaccine and overall. • At least 1 unsolicited AEs, at least 1 grade 3 unsolicited AEs and each unsolicited AEs by SOC/PT occurring within 28 days after each trial booster vaccination and overall by causal 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).
Secondary Immunogenicity	
Day 57 (only for subjects receiving the booster dose on Day 57), Day 85 (only for subjects receiving the booster dose on Day 57), Day 180 (only for subjects receiving the booster dose on Day 57 or Day 180), Day 208 (only for subjects receiving the booster dose on Day 180), and Day 393 (only for subjects receiving the booster dose on Day 180):: • The proportion of subjects seroconverting for SARS-CoV-2 spike protein antibodies, as measured by ELISA. • Individual SARS-CoV-2 spike protein-specific antibody levels in serum, as measured by ELISA. • GMTs of serum SARS-CoV-2 spike protein antibodies, as measured by ELISA.	Immunogenicity set. Applicable for subjects who received a booster dose at day 57 or day 180. Subjects receiving an authorized/licensed COVID-19 vaccine during the course of the trial will be censored at the day after intake. Sensitivity analysis: In addition, the secondary immunogenicity endpoint will be repeated for subjects who received dose 1 and dose 2 (and if eligible and received a booster dose at day 57 or day 180) 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. Subjects exposed to SARS-CoV-2 prior to the trial will be excluded. Subjects will be excluded at the time point they have been exposed to SARS-CoV-2. 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

ENDPOINTS (subject level)	ESTIMANDS (population level)
• 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.	observed (SARS-CoV-2 spike protein-specific antibodies) Geometric mean of Fold Change from baseline with 95% CI of SARS-CoV-2 spike protein antibodies Estimate 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 (SARS-CoV-2 neutralizing antibody levels in serum)
Exploratory	
<u>*Innate immune response*</u> *On Day 1 and Day 2 in a subset of subjects:* • Serum cytokine concentrations, including but not limited to IFN-α, IFN-γ, IL-6, chemokine ligand (CCL) 2, and IFN-γ-induced protein 10 (IP-10). <u>*CMI response*</u> *On Day 1, Day 29, and Day 43 in peripheral blood mononuclear cells (PBMCs) in a subset of subjects:* • The frequency and functionality of SARS-CoV-2 spike-specific T-cell response after antigen stimulation.	Immunogenicity set. A subset of subjects (approximately 20 subjects per CVnCoV group). Subjects receiving an authorized/licensed COVID-19 vaccine during the course of the trial will be censored at the day after intake. Minimum, Q1, Median, Q3, Mean and change from baseline with 95% CI. Immunogenicity set. A subset of subjects (approximately 20 subjects per CVnCoV group). Subjects receiving an authorized/licensed COVID-19 vaccine during the course of the trial will be censored at the day after intake. The CMI data will be listed.
<u>*Evaluation of infection*</u> • Number of subjects with virologically-confirmed SARS-CoV-2 infection as measured by RT-	Subjects who were unblinded and/or received an authorized/licensed COVID-19 vaccine will be censored at the day after unblinding and/or vaccination receipt. Excluding subjects who had a COVID-19 infection at baseline. Safety set. The number and percentage of subjects by group at baseline and by post-baseline time points with a positive RT-PCR result

ENDPOINTS (subject level)	ESTIMANDS (population level)
PCR at clinically determined time points throughout the trial. • Number of subjects with asymptomatic SARS-CoV-2 infection as measured by serology at predefined time points.	Immunogenicity set. The number and percentage of subjects by group 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.

9.5 Population Sets

9.5.1 Safety Analysis Set

The safety set will consist of all subjects who received at least 1 dose of trial vaccine and for whom any post-vaccination safety data are available. All safety data will be analyzed using the safety set, if not otherwise stated.

9.5.2 Immunogenicity Analysis Set

The immunogenicity set will include all subjects who received at least 1 dose of trial vaccine and for whom the baseline blood sample for immunogenicity assessment and at least 1 additional blood sample for immunogenicity assessment are available for analysis. All immunogenicity data will be analyzed using the immunogenicity set, if not otherwise stated.

9.5.3 Dose-determining Set

In case a dose-level has not been previously administered in Trial CV-NCOV-001, a dose-determining set (DDS) is defined and will consist of 4 additional subjects in the respective dose level and will be part of the safety set, who have either experienced Grade 3 adverse reactions or SAEs considered as related to the trial vaccine according to the Investigator at any time during the first 24 hours, or completed the 24-hour observation period without experiencing Grade 3 adverse reactions or SAEs considered as related to the trial vaccine according to the Investigator. The DDS will be used to confirm the safety on untested dose level prior to enrollment into the randomized part at the particular dose level. The minimum vaccination and safety evaluation requirements will have been met if the subject has received the planned dose of CVnCoV, has been observed for at least 24 hours following the first vaccine administration and has completed the required safety evaluation. Subjects who do not meet these requirements will be regarded as ineligible for inclusion in the DDS. Since DDS is only used to confirm safety prior to randomization, the DDS is not reported in the tables but Grade 3 adverse reactions and SAEs considered as related to the trial vaccine according to the Investigator used for the analyses are marked in the listings.

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 dose groups will be reported from the lowest to the highest dose. The safety and immunogenicity analyses will be done overall and by age group and baseline serology status for SARS-CoV-2.

The statistical analyses will be reported using tables, listings, and figures (TLFs).

10.1 Baseline and Change from Baseline

Unless otherwise noted, baseline is defined as the last valid measurement at Visit 1: Day 1 prior to administration of the trial vaccine.

Change from Baseline is defined as:

Observed result at nominal time point – observed result 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 Missing Data

Analysis of vaccination data will be done on a valid case basis, i.e., for missing observations, no imputation for missing data, such as last observation carried forward, will be applied. For nCoV spike protein antibodies and Virus Neutralization, concentration values marked as below the cut point (CP) will be set to 0.5*CP.

No imputation of missing values will be done for any analysis (except the imputation for missing partial dates of AEs and concomitant medication). Reasons for discontinuation from the trial or trial vaccination will be listed and summarized.

Currently no replacement of drop-out subjects is foreseen.

For unsolicited AEs, solicited AEs occurring after Day 8 and concomitant medications, some missing or partially missing variables will be imputed as follows:

For AE or concomitant medication start date:

- 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, 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 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, 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

For resolution date:

- If date of resolution is completely missing, it is assumed that it resolved at the date of the end of the trial.
- 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 earlier.
- 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 earlier.

No other safety variables will be imputed. In case the number of missing/partial dates for solicited local AEs, solicited systemic AEs or individual solicited AEs is higher than expected for the analysis of durations (in days), a sensitivity analysis will be conducted to assess the impact on the primary endpoint.

10.4 Prior and Concomitant Medications

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

10.5 Adverse Events (AEs)

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this vaccination.

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, dose 2 and booster at day 57 and day 180. Any dose is defined as a subject who received at least one dose of either CVnCoV or active control.

10.5.1 Treatment Emergent Adverse Events (TEAE)

A TEAE is any AE that first occurs or increases in severity or relationship to trial vaccine 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 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.

10.5.2 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) will be collected on the day of vaccination and the following 7 days for dose 1, dose 2 and booster dose on a specific diary and after that together with all AEs occurring throughout the trial.

The severity and relatedness for each separate solicited AE should be assessed by the investigator and recorded on the AE form in the eCRF. The severity will be assessed for each day and the relatedness will be assessed overall.

The investigator's assessments on the CRF for severity assessment will be used.

Relatedness will be set to related for solicited local AEs on day 1 to 8 with a non-missing grade > 0 even if it was assessed as not related by the investigator.

For solicited systemic AEs the assessment of relatedness by the investigator will be used for all AEs on day 1 to 8 with a non-missing grade > 0.

Relatedness will be set to missing for all solicited AEs on day 1 to 8 with a missing grade or grade 0.

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

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

*FDA toxicity grading scale [1].

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 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 IV hydration
Diarrhea	0	Absent
	1	2 – 3 loose stools or <400 g/24 hours
	2	4 – 5 stools or 400 – 800 g/24 hours
	3	6 or more watery stools or >800 g/24 hours or requires outpatient IV hydration

*FDA toxicity grading scale [1]; IV = Intravenous.

10.5.3 Unsolicited Adverse Events

Unsolicited AEs occurring on the day of vaccination and the following 28 days will be collected. For unsolicited AEs occurring on the day of dose 2 and the booster dose the following rule will be used:

If the AE is occurring on the day of dose 2 but before vaccination the AE will be presented with AEs for dose 1, if the AE is occurring on day of dose 2 but on or after vaccination it will be presented with AEs for dose 2. If this rule cannot be applied (for example, if the start time of the AE is missing) but the AE occurred on the day of vaccination for dose 2 it will be presented with the AEs for dose 2. The same rule applies for any unsolicited AE occurring on the day of the booster dose.

10.5.4 Serious Adverse Events

SAEs are defined as any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent disability/incapacity, is a congenital anomaly/birth defect in the offspring of the subject, or is an important medical event.

SAEs and AEs leading to vaccine withdrawal or trial discontinuation will be collected throughout the trial. Non-serious intercurrent medical conditions that may affect the immune response to vaccination will also be collected throughout the trial.

10.5.5 Adverse Events of Special Interest

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

- AEs with a suspected immune-medicated etiology (pIMDs, see Appendix 1),
- COVID-19 disease,
- other AEs relevant to SARS-CoV-2 vaccine development or the target disease (see Appendix 2).

AESIs will be collected on eCRF throughout the trial

10.5.6 Medically Attended Adverse Events

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

10.5.7 Duration 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 experiences an AE of the same type after the second dose, or booster dose, these two events will be presented separately.

10.5.8 Adverse Reactions

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

10.5.9 Adverse Events Related to Standardized 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 4. The MedDRA SMQs for the specific terms are not included in the appendix. See official MedDRA documentation.

10.5.10 Credibility Interval and 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:

- Using 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 function betainv returns a quantile from the beta distribution.

10.6 Immunogenicity Assessments

If a subject receives a licensed/authorized vaccine, no further immunogenicity samples will be collected/analyzed after receipt of the licensed/authorized vaccine. Immunogenicity samples on Day 393 will only be collected from subjects who attend this visit at the site, ie, subjects who received the Day 180 booster AND who had not received a licensed/authorized vaccine before this visit.

10.6.1 Humoral Immune Response

In addition to evaluation of vaccine-induced immune responses, ELISA to SARS-CoV-2 N-antigen (not contained in the vaccine construct) will be performed to determine the subject's serology status to natural infection, to retrospectively identify the baseline serology status, and to detect and/or confirm natural infection during the trial. The SARS-CoV-2 N-antigen ELISA will be performed at the specified time points for humoral immune response testing to SARS-CoV-2 S-protein. See section 10.8 for more details related to censoring.

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. That is, 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.

10.6.2.1 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 10.6.3), 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 10.6.3), 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 10.6.3), 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 10.6.3), the definition for seroconversion is a fold increase above 2 in SARS-CoV-2 neutralizing antibody titer versus baseline.

10.6.3 Retrospective SARS-CoV-2 Serology Baseline Status and during the Trial

The retrospective SARS-CoV-2 status at baseline and throughout the trial is based on Anti-SARS-CoV-2 NCP ELISA (IgG) EI 2606-9601-2 G by Euroimmun.

Serology status for baseline:

- A ratio below 0.8 is defined as seronegative
- A ratio equal and above 0.8 and below 1.1 is a borderline case and will therefor also be defined as seronegative.
- A ratio equal and above 1.1 is defined as seropositive

If either the swab PCR performed at baseline is seropositive or the local ELISA serology assessment is seropositive, the subject is seropositive at baseline independently of the above cut-off values.

Serology status during the trial:

A subject categorized as seropositive at baseline will remain seropositive independently of later assessments, per the algorithm detailed for baseline assessment. A subject categorized as seronegative at baseline but assessed as seropositive at any post-baseline sample will be categorized as seropositive at this sample visit and beyond.

If either the PCR swab performed post-baseline or the local ELISA serology assessment collected post-baseline is seropositive, the subject is seropositive at that visit and beyond independently of the above cut-off values.

The baseline sample is defined as the sample taken at the screening/clinic visit 1 – day 1.

For subjects in which the retrospectively baseline/post-baseline serology status cannot be determined these will not be included in the counts of seroconverted subjects.

This definition is used throughout the endpoints for the sub-analysis.

10.6.4 Evaluation of Infection

Virologically-confirmed SARS-CoV-2 infections are measured by RT-PCR at clinically determined time points throughout the trial.

Subjects with asymptomatic SARS-CoV-2 infections will be measured by retrospective serology at predefined time points (see section 10.6.3 for additional details) and RT-PCR results. The selection of asymptomatic subjects will be based on the exclusion of subjects with adverse of events of special interest indicating COVID-19 disease.

10.6.5 Cell-Mediated Immunity

CMI will only be evaluated in approximately 20 subjects per CVnCoV group at assigned site(s).
The frequency and functionality of SARS-CoV-2 spike-specific T-cell response after antigen stimulation will be determined in PBMC in comparison to baselineInnate Immune Response

The innate immune response will only be evaluated in approximately 20 subjects per CVnCoV group at assigned site(s) by measuring serum cytokines, including but not limited to IFN-α, IFN-γ, IL-6, CCL 2, and IP 10.

10.7 Geometric Mean

The RBD IgG ELISA and virus neutralizing antibodies 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.

10.8 Censoring Rules for Subjects Unblinded and/or Treated with Alternate Licensed/Authorized Vaccine

Since the efficacy results from Trial CV-NCOV-004 are available and all subjects in this trial are currently eligible to receive a licensed/authorized vaccine, all subjects in this trial will be unblinded following protocol version 3.0. Hence, all subjects will be unblinded prior end of the trial, and their data will be censored in all analyses. The below rules are still applicable as subjects could request unblinding or became eligible to receive a licensed/authorized vaccine prior to the protocol V3.0.

The following censoring rules will be applied to these subjects to avoid any study bias.

- Subjects who are unblinded will be censored for the safety endpoints at the first day after unblinding. Any related follow-up data that is collected from censoring time point forward will be included in the listings output.
- Subjects who are unblinded but decide not to receive the alternate licensed/authorized vaccine and to stay in the study will be analyzed for immunogenicity as planned.
- Subjects who are unblinded, but decide to receive the alternate licensed/authorized vaccine, will have their immunogenicity data censored at the first day after receiving the alternate licensed/authorized vaccine. However, any related follow-up data that is collected from this time point forward will be included in the listings output.
- Subjects who received an alternate licensed/authorized vaccine without or before being unblinded will be censored for safety and immunogenicity at the first day after receiving the alternate licensed/authorized vaccine. As described above, data collected from the censoring timepoint forward will be included in the listings output.

This is summarized in Table 7.

Table 7 Censoring Rules for for Subjects Unblinded Prior to Protocol Version 3.0

Analysis	Treatment Received in CV-NCOV-002	Alternate Licensed/Authorized Vaccine Received?	Censoring Rule
Safety	CVnCoV	No	Censored at the first day after unblinding
		Yes	
	Active Control	No	
		Yes	
Immunogenicity	CVnCoV	No	Analyzed as planned
		Yes	Censored at the first day after receiving the alternate licensed/authorized vaccine.
	Active Control	No	Analyzed as planned
		Yes	Censored at the first day after receiving the alternate licensed/authorized licensed vaccine

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 will count 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 alternate licensed/authorized vaccine:

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

As these imputations of incomplete 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 study conduct.

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

10.9 Adjudication of COVID-19 Cases

An independent committee of clinicians will be formed to adjudicate COVID-19 cases. The committee will be blinded to the treatment assignment of the subject. The cases will be adjudicated by the members with respect to the following questions consistent with the endpoints of the trial.

- 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?
- 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).
- Was the subject 18 to 60 years of age or ≥ 61 years of age?
- Was it a mild, moderate, or severe case of COVID-19 based on the information available on the AESI form (investigator judgement)?
- Was the subject hospitalized? Was the subject admitted to the intensive care unit?
- Did the subject die? Due to COVID-19 or other cause?

These data will be listed only.

11.0 Interim Analyses, DSMB and iSRC

11.1 Interim Analyses

Three interim analysis were performed, 7 days after the second dose, 6 weeks after dose 2 and for the booster dose until day 208. The analyses will be based on a data snapshot. As this trial is of exploratory nature and no inferential statistics are planned, no adjustment for multiple testing will be done. Depending on the evolving state of the current pandemic and the public health need, an early analysis may be performed, and a study report based on interim data may be written to engage with collaborators and/or regulators.

11.2 Safety Monitoring Committees

If any SAE considered as related to the trial vaccine according to the Investigator occurs at any time during the trial, all vaccinations will be put on hold. The DSMB will perform a comprehensive review of all relevant safety and reactogenicity data before making a decision to stop, continue, or modify vaccination (including evaluating lower doses).

The DSMB may recommend additional measures including modification or halt of the trial.

Group 2 (subjects >60 years, 6 µg) will be initiated in 4 sentinel subjects. These subjects should be vaccinated at least 60 minutes apart. Safety and reactogenicity data reported during an observation period of at least 24 hours after vaccination will be collected and reviewed by an iSRC. In this review, the iSRC will review all available safety data, but focus specifically on Grade 3 adverse reactions (defined as solicited systemic, solicited local, or unsolicited Grade 3 AEs considered as related to the trial vaccine). Based on this review, the iSRC will decide on continuation of enrollment of subjects at this dose level. In a next step, 8 additional sentinel subjects will be enrolled. Safety and reactogenicity data reported during an observation period of at least 24 hours after vaccination will be collected and reviewed by the iSRC. In this review, the iSRC will review all available safety data, but focus specifically on Grade 3 adverse reactions. The same procedure will be followed for Group 4 (subjects >60 years, 12 µg) and the iSRC will decide on continuation of enrollment of subjects at this dose level after review of the first 12 sentinel subjects.

12.0 Statistical Methods

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 study will be displayed in data listings, unless otherwise specified. Data listings will be sorted by dose level 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.

Expansion for subjects 18 to 60 years of age may start once the final dose for subjects in this age category has been selected based on the data from Trial CV-NCOV-001. Expansion for subjects >60 years of age may start once the final dose for these subjects has been selected based on data from this trial. Subjects enrolled in the expansion cohorts will be handled in the same manner as subjects in the first phase of the study.

The analysis will be presented in the following manner if not otherwise stated:

- Age; Overall age, age 18-60 and age >60 (61 years or older),
- Dose; any, dose 1, dose 2, booster doses at day 57 and day 180
- CVnCoV, active control (hepatitis A vaccine, or pneumococcal vaccine), and total.

Subjects in the expansion cohorts will be presented together with subjects from the initial phase of the trial.

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, the 2-dose vaccination regimen and booster at either day 57 or day 180, completed study, and reason for discontinuing further vaccination and study 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 any inclusion/exclusion criteria will be listed only.

12.2 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 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 will be reviewed prior to each formal analysis (i.e. interim analyses of final analyses) and if applicable important deviations leading to elimination of subjects from analysis sets will be identified. If applicable detailed definitions will be provided in the final signed minutes of the data review meetings prior to each formal analysis and prior to database lock. Important subject-level protocol deviation will be summarized and listed.

12.3 Demographic and Baseline Characteristics

Demographic characteristics to be summarized based on the safety set will include gender, ethnicity, race, age at informed consent (years), age group (18 - 60 years, >60 years, 18-50 years, >50 years), baseline immune status measured retrospectively, height (cm), weight (kg), BMI (kg/m^2) and childbearing potential.

Subjects who are unblinded or censored due to requesting to be unblinded for receiving a licensed/authorized COVID-19 vaccine will be presented in a separate summary table.

12.4 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) using version 24.0 or higher. Medical history will be listed only using the safety set.

12.5 Trial Vaccine Exposure

The administrations of CVnCoV or the active control will be listed. The number and percentage of subjects who received at least one vaccination and the individual vaccinations on day 1 (dose 1), 29 (dose 2), day 57 (booster dose) and day 180 (booster dose) including the reasons for not receiving a dose (where available) will be summarized using the safety set.

12.6 Prior and Concomitant Medications and Vaccinations

Prior and concomitant medication will be summarized with number and percentage according to WHODRUG (Version March 2020 Global B3 or higher), by Anatomical Therapeutic Chemical (ATC) using the safety set. ATC level 1 and preferred name will be displayed in the tables and listings. Concomitant vaccinations will be identified via ATC. Medications with ATC level 2 code J07 are considered to be vaccinations. Concomitant medications and concomitant vaccinations will be listed as well.

12.7 Adjudication of COVID-19 Cases

This data will be listed only.

12.8 Adverse Events

The primary, secondary and exploratory endpoints will be analyzed overall, as well as in subjects retrospectively SARS-CoV-2 seronegative at baseline, and in subjects retrospectively SARS-CoV-2 seropositive at baseline as per the definition given in section 10.6.3.

Unsolicited AEs, including SAEs, and AESIs and solicited AE integrated to or recorded on the CRF will be coded using MedDRA Version 24.0 or higher, by SOC and PT.

If not stated otherwise, all summaries of unsolicited AEs will also include relevant 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, dose 2 and booster at day 57 and day 180. Any dose is defined as a subject who received at least one dose of either CVnCoV or active control.

In general, percentages will be based on the number of subjects in the respective analysis set. In summary tables for AEs after the second or booster vaccination, percentages will be based on the number of subjects in the respective analysis set who received the second, or booster vaccination as applicable.

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

12.8.1 Analysis of Unsolicited 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), presenting the number and percentage of subjects with

- 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)

The overall summary will also be presented by sex (female/male) for any dose regardless of retrospective serology status at baseline.

The following summaries of 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 unsolicited AEs by maximum severity (mild / moderate / severe)
- Occurrence of related unsolicited AEs by maximum severity (mild / moderate / severe)
- Occurrence of SAEs (includes solicited AEs)
- Occurrence of related SAEs (includes solicited AEs)
- 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 intercurrent medical conditions affecting immune response (includes solicited AEs)
- Occurrence of AESIs (includes solicited AEs)
- Occurrence of related AESIs (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 vaccine withdrawal (includes solicited AEs)
- Occurrence of AEs leading to withdrawal from trial (includes solicited AEs)
- Occurrence of AEs related to SMQs as defined in Section 10.5.9 (includes solicited AEs)

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

Further AE listings supporting the AE tables described above will include both relevant solicited and unsolicited AEs. Solicited AEs occurring on the day of vaccination and the following 7 days and unsolicited AEs will be listed together.

12.8.2 Analysis 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:

- Summary of solicited AEs, local AEs and systemic AEs, overall and by maximum grade
    - will also be presented by sex (female/male) for any dose, dose 1, dose 2 and booster dose regardless of retrospective serology status at baseline.
- Occurrence of local AEs, overall and by maximum grade
- Occurrence of systemic AEs, overall and by maximum grade
- Occurrence of related systemic AEs, overall and by maximum grade (mild / moderate / severe)
- 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
- 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, 0.5) prior distribution for each dose level and dose will be calculated and summarized.
- Individual solicited local and systemic adverse events will be displayed in by-subject figures
- Individual grade 3 solicited local and systemic adverse events will be presented in a figure.

12.9 Immunogenicity Analysis

12.9.1 Primary Immunogenicity Analyses

The primary immunogenicity will be analyzed for day 29 and 43. The primary humoral response endpoints will be analyzed with the immunogenicity set population for all available time points. All tables will be presented overall and by retrospective serology status (seropositive and seronegative) at baseline (see section 10.6.3). The primary immunogenicity endpoint will be analyzed with the immunogenicity set (see section 9.5.2). Once a subject (eligible for a booster dose) received the booster dose, the subject's measurement will be censored at the day after receiving the dose. Subjects receiving a booster dose will be analyzed separately.

The following two types of analyses will be performed:

- Estimate and 95%-credibility (using the prior beta(1.9, 0.1) intervals and proportion and 95%-confidence intervals (exact Clopper-Pearson) of subjects seroconverting with a 2-fold (definition for for subjects seropositive at baseline) 4-fold increase, and any increase for subjects seronegative at baseline for SARS-CoV-2 spike (RBD) protein antibodies, as measured by ELISA, and serum SARS-CoV-2 neutralizing antibodies.

Geometric mean (GM), geometric standard deviation (GSD), 95%-confidence intervals and fold change of serum SARS-CoV-2 spike (RBD) protein antibodies, as measured by ELISA, and serum SARS-CoV-2 neutralizing antibodies.

Analysis for subjects eligible (and receiving) booster dose at day 57 or day 180 will be presented separately.

In addition, the following figures will be presented for serum SARS-CoV-2 spike (RBD) protein antibodies, as measured by ELISA, and serum SARS-CoV-2 neutralizing antibodies. All figures will be presented overall and by retrospective serology status (seropositive and seronegative) at baseline, except for subjects receiving a booster dose at day 57 or day 180 and are seropositive at baseline. For these no figures will be presented. All figures will be presented by overall age, age groups and dose level:

- Individual line plots.
- Line plots of fold change from baseline.
- Line plots of mean fold change from baseline (with 95% confidence intervals).
- Line plots of geometric mean titers (with 95% confidence intervals).
- Line plot of geometric mean fold change from baseline.

Box plot of geometric mean, minimum, Q1, median, Q3 and maximum. All immunogenicity data will be listed.

12.9.2 Secondary Immunogenicity Analyses

The secondary humoral immune analyses will be repeated (based on the primary immunogenicity analyses) for subjects receiving the booster dose only for Day 57, Day 180, Day 208, and Day 393 (Months 6, 7, and 13). The secondary humoral response endpoints will be analyzed with the immunogenicity set.

12.9.3 Sensitivity Immunogenicity Analyses

A sensitivity analysis will be performed for the primary and secondary humoral immune response endpoints.

Applicable for sensitivity analysis for 1) 2-dose regime and 2) in addition for subjects eligible for a booster dose and receiving booster dose at day 57 or day 180. As per the immunogenicity set in section 9.5.2 with the additions:

- Subjects receiving dose 1 and dose 2 (for the separate booster sensitivity dose analysis the subjects must have received the booster dose at day 57 or day 180).
- Subjects must have no protocol deviation with impact on the immunogenicity measurement.
- Subjects in the 2-dose regime: The baseline blood sample for immunogenicity assessment and one sample at least 14 days after receiving the second dose.
- Subjects eligible and receiving a booster dose: The baseline blood sample for immunogenicity assessment and one sample at least 14 days after receiving the booster dose are available for analysis.
- Subjects must not be exposed to SARS-CoV-2 before the trial or during the trial before the endpoint evaluation.

For the tables the N will however be based on the immunogenicity set as per definition in section 9.5.2. The seroconversion rates are based on the n at relevant time point.

12.9.4 Exploratory Immunogenicity

Cell-mediated immune (CMI) response

On Day 1, Day 29, and Day 43 in peripheral blood mononuclear cells (PBMCs) in a subset of subjects:

The frequency and functionality of SARS-CoV-2 spike-specific T-cell response after antigen stimulation.

The CMI data will be listed only.

Innate immune response
On Day 1 and Day 2 in a subset of subjects:

Serum cytokine concentrations will presented as descriptive summary with change from baseline. The following concentrations will be included: APRIL/TNFSF13, BAFF/TNFSF13B, CCL4/MIP-1β, CD40L, FasL, CXCL11 /I-TAC, ICAM-1, IFN-β, IL-13, IL-17A , IL-5, IP-10/CXCL10, MCP-1/CCL2, MCP-4/CCL13, MDC/CCL22, MICA, CXCL9/MIG, MIP-1α/CCL3, SCF, CD62L/L-selectin, INF-γ, IL-1α, IL-6, IL-10, CXCL13, INFα, IL-2, IL-4, IL-12p70, and TNFα.

12.9.5 Additional Exploratory Analysis

Evaluation of infection:

Number and percentages of subjects with virologically-confirmed SARS-CoV-2 infection as measured by reverse transcription polymerase chain reaction (RT-PCR) at clinically determined time points throughout the trial. This analysis will be performed on the safety set.

Number and percentages of subjects with asymptomatic SARS-CoV-2 infection as measured by serology and RT-PCR test at predefined time points.

- The definition of SARS-CoV-2 infection as measured by serology and RT-PCR results before and during the trial is outlined in sections 10.6.3.
- Subjects with a COVID-19 disease symptoms are excluded. Exclusion is based on COVID-19 cases classified as AESI. Adjudicated cases are also excluded.

This analysis will be performed on the immunogenicity set.

12.10 Other Safety Analyses

12.10.1 Laboratory Data

Blood samples for determination of hematology, clinical biochemistry and coagulation will be analyzed on Day 1, 2, 29, 85, 180 and 208. 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 study.

Laboratory data will be graded according with the United States Food and Drug Administration (FDA) toxicity grading scale [1].

12.10.1.1 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 and by group. 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.

12.10.1.2 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 and by group. 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.

12.10.1.3 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 and by arm. 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.

12.10.1.4 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.

12.10.2 Vital Signs

Vital signs will be summarized descriptively at each study time point they are collected, including screening. Change from baseline values will be summarized for the post-vaccination time point. 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).

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

12.10.3.1 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.

12.10.3.2 Electrocardiogram

ECG interpretation (abnormal, normal, unevaluable and unknown) and clinically significance will be collected on Day 1 for all subjects. Additionally, ECGs should be performed as clinically indicated. ECG results will be listed only.

13.0 References

1. 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/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf; 'Accessed at: March 2019].

14.0 Glossary of Abbreviations

List of abbreviations

ADE	Antibody-dependent enhancement
AE	Adverse event
AESI	Adverse event of special interest
ANA	Antinuclear antibody
ARDS	Acute respiratory distress syndrome
BMI	Body mass index
CCL	Chemokine ligand
CEPI	Coalition for Epidemic Preparedness Innovations
CI	Confidence interval
CMI	Cell-mediated immunity
CoV	Coronavirus
CRO	Contract research organization
CVnCoV	Investigational SARS-CoV-2 mRNA vaccine
DDS	Dose-determining set
DSMB	Data and safety monitoring board
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
E	Envelope
ECG	Electrocardiogram
eCRF	Electronic case report form
ELISA	Enzyme-linked immunosorbent assay
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMT	Geometric mean titer
hCG	Human chorionic gonadotropin
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICS	Intracellular cytokine staining
IEC	Independent Ethics Committee
IFN	Interferon
Ig	Immunoglobulin

IL	Interleukin
IM	Intramuscularly
IMP	Investigational medicinal product
IP-10	IFN-γ-induced protein 10
IRB	Institutional Review Board
iSRC	Internal safety review committee
IVRS	Interactive voice response system
LLOQ	Lower limit of quantification
LNP	Lipid nanoparticles
M	Membrane
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
mRNA	Messenger ribonucleic acid
N	Nucleocapsid
PBMC	Peripheral blood mononuclear cell
pIMD	Potential immune-mediated disease
PT	Preferred Term
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
SOC	System Organ Class
TSH	Thyroid-stimulating hormone
VDE	Vaccine-dependent disease enhancement
WHO	World Health Organization

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
- o Autoimmune 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

Appendix 3 Inclusion/Exclusion Criteria

Inclusion Criteria

Subjects will be enrolled in this trial only if they meet **all** of the following criteria:

1. Healthy male and female subjects ≥18 years of age.

   A healthy subject is defined as an individual who is in good general health, according to the Investigator's assessment. Chronic health conditions are acceptable if the condition is considered well controlled with treatment according to the discretion of the Investigator.
2. Expected to be compliant with protocol procedures and available for clinical follow-up through the last planned visit.
3. Physical examination without clinically significant findings according to the Investigator's assessment.
4. Body mass index (BMI) ≥18.0 and ≤32.0 kg/m^2.
5. Female subjects of childbearing potential: at the time of enrollment, negative human chorionic gonadotropin (hCG) pregnancy test (serum) for women presumed to be of childbearing potential on the day of enrollment. On Day 1 (pre-vaccination): negative urine pregnancy test (required if serum pregnancy test was performed more than 3 days before).
6. Female subjects of childbearing potential must use highly effective methods of birth control from 2 weeks before the first administration of the trial vaccine until 3 months following the last administration. The following methods of birth control are considered highly effective when used consistently and correctly:

   - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal);
   - Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable);
   - Intrauterine devices;
   - Intrauterine hormone-releasing systems;
   - Bilateral tubal occlusion;
   - Vasectomized partner;
   - Sexual abstinence (periodic abstinence [e.g., calendar, ovulation, symptothermal and post-ovulation methods] and withdrawal are not acceptable).

   Male subjects should be instructed not to get their partners pregnant during the study.

Exclusion Criteria

Subjects will not be enrolled in this trial if they meet **any** of the exclusion criteria.

1. Use of any investigational or non-registered product (vaccine or drug) other than the trial vaccine within 28 days preceding the administration of the trial vaccine, or planned use during the trial period.

2. Receipt of any other vaccines within 28 days prior to enrollment in this trial or planned receipt of any vaccine within 28 days of trial vaccine administration (primary dose or booster dose).
3. Receipt of any investigational SARS-CoV-2 or other coronavirus vaccine prior to the administration of the trial vaccine.
4. Any treatment with immunosuppressants or other immune-modifying drugs (including, but not limited to, corticosteroids, biologicals, and methotrexate) within 6 months prior to the administration of the trial vaccine or planned use during the trial, with the exception of topically-applied, inhaled, or intranasal steroids.
5. Use of hormonal therapy for gender reassignment.
6. Any medically diagnosed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination, including known human immunodeficiency virus infection, hepatitis B virus infection, and hepatitis C virus infection.
7. History of immune-mediated or autoimmune disease.
8. History of angioedema (known C1 inhibitor deficiency).
9. History of anaphylaxis or allergy to any component of CVnCoV or aminoglycoside antibiotics.
10. History of or current alcohol and/or drug abuse.
11. Subjects who are active smokers, were active smokers within the last year (including any vaping in the last year), or have a total smoking history ≥10 pack years. A pack year is calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked.
12. History of virologically-confirmed SARS, MERS, or COVID-19 disease or known exposure (without any personal protective equipment) to an individual with confirmed COVID-19 disease or SARS-CoV-2 infection within the past 2 weeks.
13. Administration of immunoglobulins and/or any blood products within the 3 months preceding the administration of any dose of the trial vaccine.
14. Presence or evidence of significant uncontrolled acute or chronic medical or psychiatric illness. Significant medical or psychiatric illnesses include but are not limited to:
    - Uncontrolled respiratory disease (e.g., chronic obstructive pulmonary disease, asthma), including use of the following asthma medications: intravenous corticosteroids, leukotriene modifiers, biologics.
    - Uncontrolled cardiovascular disease (e.g., congestive heart failure, cardiomyopathy, ischemic heart disease, history of stroke, peripheral artery disease, pulmonary embolism).
    - History of myocarditis or pericarditis as an adult.
    - Diabetes mellitus (insulin-dependent).
    - Uncontrolled neurological disorders or Guillain-Barré syndrome or history of seizure, except for febrile seizures during childhood.
    - Current or past malignancy, unless completely resolved without sequelae for >5 years.
15. Foreseeable non-compliance with protocol, as judged by the Investigator.

16. For female subjects: pregnancy or lactation.
17. Subjects with impaired coagulation or any bleeding disorder in whom an intramuscular injection or a blood draw is contraindicated. This includes subjects on treatment with anticoagulants (e.g., vitamin K antagonists, novel oral anticoagulants, and heparin). Use of platelet aggregation inhibitors is not exclusionary.
18. Subjects employed by the Sponsor, Investigator, or trial site, or relatives of research staff working on this trial.
19. Subjects considered at the Investigator's discretion to be at increased risk of exposure to COVID-19 disease.

Appendix 4 MedDRA Terms for CMQs

MeddRA Version 24.0

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