Protocol Number: CV-NCOV-005

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

NCT Number: NCT04674189

Document Date: 22 December 2021

CLINICAL TRIAL PROTOCOL

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

Protocol Number:	CV-NCOV-005
EudraCT Number:	2020-004066-19
Investigational Product:	CV07050101 (referred to as CVnCoV)
Phase:	Phase 3
Sponsor:	CureVac AG Schumannstrasse 27 60325 Frankfurt Germany
Short Title:	Immunogenicity and Safety of CVnCoV in Adults
Protocol Version:	5.0
Protocol Date:	22 December 2021

PROTOCOL VERSION HISTORY:

Version 1.0 dated 19 November 2020

Version 2.0 dated 19 March 2021

Version 3.0 dated 23 July 2021

Version 4.0 dated 11 August 2021

PROTOCOL APPROVAL SIGNATURES

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

Protocol Number: CV-NCOV-005

This trial will be conducted with the highest respect for the individual subjects in compliance with the requirements of this clinical trial protocol (and amendments), and also in compliance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 (R2) Good Clinical Practice (GCP): Revised and consolidated guidelines [1].
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

Sponsor Signatory

[redacted]
CureVac AG

Medical Responsible Person

[redacted]
CureVac AG

Clinical Operations

[redacted]
CureVac AG

Statistician

[redacted]
CureVac AG

[redacted]

PROTOCOL APPROVAL SIGNATURES

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

Protocol Number: CV-NCOV-005

This trial will be conducted with the highest respect for the individual subjects in compliance with the requirements of this clinical trial protocol (and amendments), and also in compliance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 (R2) Good Clinical Practice (GCP): Revised and consolidated guidelines [1].
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

Sponsor Signatory

[redacted]

CureVac AG

Medical Responsible Person

[redacted]

CureVac AG

Clinical Operations

[redacted]

CureVac AG

[redacted]

Statistician

[redacted]

CureVac AG

[redacted]

INVESTIGATOR SIGNATURE PAGE

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

Protocol Number: CV-NCOV-005

Confidentiality and GCP Compliance Statement

I, the undersigned, have reviewed this protocol and all appendices, including Appendix 1 (Responsibilities of the Investigator) and Appendix 2 (Emergency Procedures), and I will conduct the trial as described in compliance with this protocol, Good Clinical Practice (GCP), and relevant International Council for Harmonisation (ICH) guidelines.

Once the protocol has been approved by the Independent Ethics Committee (IEC), I will not modify this protocol without obtaining prior approval of CureVac and of the IEC. I will submit the protocol modifications and/or any informed consent form modifications to CureVac and the IEC, and approval will be obtained before any modifications are implemented.

I understand that all information obtained during the conduct of the trial with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all electronic case report forms (eCRFs) and laboratory samples. Clinical information may be reviewed by CureVac or its representatives or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.

Information developed in this clinical trial may be disclosed by CureVac to other clinical Investigators, regulatory agencies, or other health authorities as required.

Investigator Signatory

[redacted]

SAE Hotline and Medical Monitor Contacts

SAE Hotline		
SAE reporting to PRA by **fax or email** within **24 hours** after discovery:		
Site Location	**Email (Primary Reporting Method)**	**Fax Number (Secondary Reporting Method)**
Europe	[redacted]	[redacted]
Safety Reporting after End of Trial	[redacted]	
Medical Monitor The Medical Monitor will provide 24/7 (24 hours per day and 7 days a week) on-call medical coverage to address trial-related questions from sites or Investigators, such as questions regarding eligibility requirements, the acceptability of concomitant medication or whether a subject should remain in the trial or needs to be discontinued.		
Name of Primary Contact:	[redacted]	
Address:	[redacted]	
Phone:	[redacted]	
Fax:	[redacted]	
Email:	[redacted]	

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

ADE	Antibody-dependent enhancement
AE	Adverse event
AESI	Adverse event of special interest
ARDS	Acute Respiratory Distress Syndrome
BoD	Burden of disease
CI	Confidence Interval
CMI	Cell-mediated immunity
CoV	Coronavirus
COVID-19	Coronavirus disease 2019
CPM	CovidPreventMainz
CRO	Contract research organization
CTL	Cytotoxic T lymphocyte
CVnCoV	Investigational SARS-CoV-2 mRNA vaccine
CyTOF	Cytometry by time-of-flight
DSMB	Data and Safety Monitoring Board
E	Envelope
EAS	Efficacy Analysis Set
eCRF	Electronic case report form
eDiary	Electronic Diary
ELISA	Enzyme-linked immunosorbent assay
ELISpot	Enzyme-linked immunospot
FDA	United States Food and Drug Administration
FIH	First-in-human
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMC	Geometric Mean Concentration
GMFC	Geometric mean of fold change
GMT	Geometric mean titer
HCW	Health Care Worker
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

IL	Interleukin
IM	Intramuscular(ly)
IMP	Investigational medicinal product
IRB	Institutional Review Board
IWRS	Interactive web response system
LL	Lower Limit
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
PPI	Per Protocol Immunogenicity
PT	Preferred Term
RBD	Receptor-binding domain
RNA	Ribonucleic acid
RR	Relative Risk
RT-PCR	Reverse transcription polymerase chain reaction
S	Spike
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	Safety Analysis Set
SASsol	Solicited adverse events Safety Analysis Set
SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse reaction
TLR	Toll-like receptor
VDE	Vaccine-dependent Disease Enhancement
VE	Vaccine efficacy
VNT	Viral neutralizing titer
WHO	World Health Organization

1 SYNOPSIS

Name of Investigational Vaccine:	CVnCoV
Sponsor:	CureVac AG
Coordinating Investigator:	[redacted]
Title of Trial:	COVID-19: A Phase 3, Randomized, Observer-Blinded, Placebo-Controlled Clinical Study Evaluating the Safety and Immunogenicity of Investigational SARS-CoV-2 mRNA Vaccine CVnCoV in Adult Health Care Workers in Mainz (Germany)
Rationale:	Coronaviruses are a large family of zoonotic ribonucleic acid (RNA) viruses causing respiratory disease, ranging from a common cold to severe diseases such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) in humans. In December 2019, an outbreak of respiratory disease caused by a novel coronavirus strain was reported in Wuhan City, Hubei Province, China. The novel coronavirus was named "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2), while the disease associated with it was referred to as COVID-19 (coronavirus disease 2019). The virus spread to different parts of China and an increasing number of countries worldwide and on 30 January 2020 the World Health Organization (WHO) announced the outbreak under International Health Regulations as a public health emergency of international concern (the WHO's highest level of alarm). On 12 March 2020, the WHO announced the outbreak as a pandemic. There are currently no specific treatments for COVID-19. Development of an effective COVID-19 vaccine represents the best hope to prevent further epidemics and outbreaks of the disease. CureVac AG is developing a novel SARS-CoV-2 vaccine referred to as CVnCoV. CVnCoV is a messenger RNA (mRNA)-based COVID-19 vaccine in which the mRNA is protected and delivered by encapsulation within lipid nanoparticles. The mRNA encodes the stabilized full-length spike (S) protein from the SARS-CoV-2 virus. Following intramuscular (IM) injection of CVnCoV, the S protein is translated from the mRNA stimulating an antigen-specific humoral and cellular immune response to the S protein. Importantly, functional viral neutralizing titers are induced following vaccination with CVnCoV. Phase 1 and 2a trial are being conducted to generate initial data on the safety, reactogenicity, and immunogenicity of 2 doses of CVnCoV, administered 28 days apart, to adults 18 years of age and older. In a subset of subjects, a booster dose at 2 or 6 months after the first dose will be investigated. The first-in-human (FIH) Phase 1 trial, CV-NCOV-001, is evaluating different dose levels of CVnCoV in seronegative and seropositive adults 18 to 60 years of age. Following review of the FIH data, a Phase 2a trial, CV-NCOV-002, was initiated and is evaluating CVnCoV at selected dose levels, including adults ≥ 61 years of age. Following the first part of Trial CV-NCOV-002, expansion cohorts of 220 subjects aged 18 to 60 years and 220 subjects aged ≥ 61 years are being enrolled and treated to generate additional safety and immunogenicity data. Dose level selection for subsequent trials will be informed by the safety and immunogenicity data from these 2 trials. The Trial CV-NCOV-004 is designed as a Phase 2b/3 pivotal efficacy and safety trial in adults 18 years of age and older. The trial will have a randomized, observer-blinded, placebo-controlled design. Subjects will be enrolled at multiple sites globally and will be randomized in a 1:1 ratio to

	receive a 2-dose schedule of either CVnCoV at a dose level of 12 µg mRNA or placebo {normal saline (0.9% NaCl)} as the control. The present trial CV-NCOV-005 is designed as a Phase 3 safety and immunogenicity trial in health care workers (HCWs), 18 years of age and older, in Mainz (Germany). The trial will be conducted as a randomized, observer-blinded, placebo-controlled trial. HCWs participating in a non-interventional cohort trial, COVID19-5-P-002 {or CovidPreventMainz (CPM)prevac}, currently being performed at the Mainz University will be asked to participate in trial CV-NCOV-005. Trial CV-NCOV-005 will also include other HCWs, and potentially students in clinical training. Subjects enrolled in CV-NCOV-005 will be randomized in a 1:1:1 ratio to receive a 2-dose schedule, 28 days apart, of either 1 of 2 lots of CVnCoV at a dose level of 12 µg mRNA or placebo {normal saline (0.9% NaCl) for injection} as the control. Primary objectives of CV-NCOV-005 trial are to generate additional safety and immunogenicity data, in the intended trial population of adults at the previously selected dose level. As a secondary objective, the efficacy of a 2-dose schedule of CVnCoV in the prevention of first episodes of virologically-confirmed cases of COVID-19 of any severity in SARS-CoV-2 naïve subjects will be assessed. The severity of COVID-19 cases occurring in the CVnCoV and placebo groups will also be described as a secondary objective. Lot-to-lot consistency of 2 lots of CVnCoV will also be assessed in this trial as a secondary objective. In an exploratory way, data regarding occurrence of COVID-19 cases and antibody testing to nucleocapsid (N) protein of SARS-CoV-2 obtained from subjects in the COVID19-5-P-002 trial not enrolling in CV-NCOV-005 will be pooled with data obtained from subjects in the placebo group in CV-NCOV-005 to provide additional controls in pooled efficacy analyses of both trials. Pooling of data from the 2 trials is justified given the similarity of the trial population for both trials at the Mainz site, the active surveillance and similar process for confirmation of COVID-19 cases, and for assessment of serostatus indicative of SARS-CoV-2 infection in both trials. Data from a 12-month follow-up period in trial COVID19-5-P-002, to be conducted in parallel with trial CV-NCOV-005 will be considered for the pooling. The results of the pooled analyses will be reported separately and a specific statistical analysis plan (SAP) will be done. This plan may be affected if another COVID-19 vaccine is approved and made available to the subjects during this trial. If an important percentage of subjects opt to receive that other vaccine, a re-randomization of additional subjects from the CPMprevac non-interventional trial into this trial will be considered. The first vaccine to prevent COVID-19 caused by SARS-CoV-2 was authorized by the European Medicines Agency on 21 December 2020. The first vaccinations began in Germany on 27 December 2020 and initially took place in a stepwise approach. Vaccines were initially available on a limited basis and were made available primarily to defined risk groups of the population. In Germany, extended availability of the authorized vaccines is effective since 07 June 2021, allowing all adult population (aged 18 or older) to access the vaccine. The trial CV-NCOV-005 protocol has been amended to address the available efficacy results of the study vaccine (CVnCoV). The CV-NCOV-005 trial will run in parallel with CV-NCOV-004, and will follow the design of that trial, including case collection and work-up, and antibody testing to N protein of SARS-CoV-2.

	The final analysis data from the HERALD study (CV-NCOV-004), conducted with the same study vaccine (CVnCoV) was made available on the 30th June 2021. The HERALD study results were statistically significant for the primary study objective. The final efficacy analysis showed an overall efficacy of 48.2% (LL (lower limit) 31,0%) for CVnCoV in the prevention of COVID-19 cases of any severity, reaching the predefined success criterion. Similar confirmatory results were observed in the prevention of moderate to severe COVID-19 cases, a key secondary efficacy objective, with an overall vaccine efficacy of 70.7% (LL 42.5%). Whereas, in the HERALD study, CVnCoV efficacy in the prevention of COVID-19 cases of any severity was confirmed in the 18 to 60 age group (VE 52.5%, LL 36.2%), data in study participants older than 60 years was not conclusive including due to the low number of cases (only 9% of all cases) and low number of participants under follow up in that age group. There was also no clear trend of efficacy in this age group. Similarly, vaccine efficacy in the prevention of moderate to severe disease was 77.2% (LL 51.8%) in participants 18 to 60 years old and no conclusive results were observed in participants older than 60 years. Since the efficacy results from the HERALD study for CVnCoV are available and all subjects in the CV-NCOV-005 study are currently eligible to receive an authorized vaccine, all subjects in this CV-NCOV-005 study will be unblinded. Each subject will be informed by the study physician of the available study results and whether he/she received the study vaccine (CVnCoV) or placebo in the study. The purpose of this measure is to provide the participants/subjects with sufficient information so that they can decide whether to take an authorized vaccine or not in a fully informed way. All subjects that received placebo in this study should follow the official recommendations regarding vaccination against SARS-CoV-2 outside of the study; no further follow up will be required and the subjects will leave the study. The subjects that received at least one dose of CVnCoV and already decided to take an authorized vaccine, will be asked to remain in the study to allow safety follow-up: Since for subjects older than 60 years, a favorable benefit-risk for CVnCoV could not be established based on the HERALD study results, subjects who received CVnCoV should follow the official recommendations regarding vaccination against SARS-CoV-2 outside of the study. Subjects 60 and younger willing to take the authorized vaccine should inform the site and are encouraged to speak with the study doctor/ investigator for further information on the CVnCoV final efficacy analysis results and how to access the authorized vaccine, out of the clinical study setting. All subjects receiving the authorized vaccine following at least one dose of CVnCoV should continue the safety follow-up in the study until the end of the trial (Schedule of Activities- Table 2). To date, no clinical trial has proactively investigated or been designed to evaluate the administration of authorized vaccines after vaccination with CVnCoV. A post-hoc analysis in June 2021 showed that 438 participants across CVnCoV studies were administered authorised COVID-19 vaccine through national vaccination programmes after having received one or two 12µg-doses of CVnCoV during clinical studies. The most frequent authorised

	vaccine administered after receiving CVnCoV was Comirnaty® (Pfizer-BioNTech); the second most frequently administered vaccine was Spikevax® (Moderna) followed by Vaxzevria® (AstraZeneca). Fewer participants received the Janssen COVID-19 Vaccine and finally the Sinopharm COVID-19 Vaccine. Although this set of data has important limitations, the assessment of the safety database for the 438 subjects who received an authorized vaccine after CVnCoV resulted in the following observations: • No cluster of adverse events (AEs) or events of concern have been observed after the administration of an authorized COVID-19 vaccine within a follow-up period between 1 and 18 weeks. • The most frequently reported AEs after administration of the authorized vaccine are related to local and systemic symptoms which are commonly reported after vaccination. Fatigue, headache, fever and body ache were the most frequently reported symptoms. Two serious adverse events were reported in one subject, in the CV-NCOV-005 study. This subject has a history of recurrent asthma exacerbation and has reported two serious AEs (both exacerbation of asthma) after receiving an authorized vaccine (Vaxzevria, AstraZeneca). This subject had also reported the same serious AE after receiving the first dose of CVnCoV.	
Trial Duration for Each Subject:	Each subject will participate in the trial for approximately 13 months.	**Phase:** 3
Primary Objectives:	**Primary Safety Objective** • To evaluate the safety (in all subjects) and reactogenicity (in a subset of subjects) of CVnCoV administered as a 2-dose schedule to adults 18 years of age or older. **Primary Immunogenicity Objective** • To assess antibody responses to the Receptor-binding domain (RBD) of S protein of SARS-CoV-2 after 1 and 2 doses of CVnCoV in adults 18 years of age or older included in a subset of subjects.	
Secondary Objectives:	**Secondary Efficacy Objectives** • To assess the efficacy of a 2-dose schedule of CVnCoV in the prevention of first episodes of virologically-confirmed symptomatic cases of COVID-19 of any severity in SARS-CoV-2 naïve subjects. • To describe the severity of first episodes of virologically-confirmed symptomatic cases of COVID-19 in SARS-CoV-2 naïve subjects, receiving a 2-dose schedule of CVnCoV compared to those administered placebo. • To assess the efficacy of a 2-dose schedule of CVnCoV in reducing the burden of disease (BoD) from COVID-19. **Secondary Immunogenicity Objectives** • To assess SARS-CoV-2 virus neutralizing antibody responses after 1 and 2 doses of CVnCoV in adults 18 years of age or older included in a subset of subjects. • To assess lot-to-lot consistency of 2 CVnCoV lots, as measured by antibody responses to the RBD of S protein of SARS-CoV-2, after 2 doses of CVnCoV, in adults 18 years of age or older included in a subset of subjects.	

Overall Design:	The trial will be conducted as a randomized, observer-blinded, placebo-controlled trial. Subjects will receive a 2-dose schedule, 28 days apart, of either 1 of 2 lots of CVnCoV, at a dose level of 12 µg mRNA, or placebo {normal saline (0.9% NaCl}) in a 1:1:1 ratio. Approximately 2,520 subjects (840 by randomization group), 18 years of age or older, previously enrolled in the non-interventional trial performed at the Mainz University, Germany (COVID19-5-P-002), other HCWs and potentially students in clinical training will be enrolled. The safety, reactogenicity, immunogenicity and efficacy of a 2-dose schedule of CVnCoV in HCW will be assessed descriptively. The primary safety objective is to expand the safety database that will demonstrate the safety profile of CVnCoV. The safety and reactogenicity of a 2-dose schedule of CVnCoV will be assessed in detail by measuring the frequency and severity of the following adverse events (AEs): solicited local and systemic AEs on the day of vaccination and for the following 7 days after each vaccination in a subset of subjects (Immunogenicity/Reactogenicity Subset); unsolicited AEs on the day of vaccination and for the following 28 days after each vaccination in a subset of subjects (Immunogenicity/Reactogenicity Subset); medically-attended AEs through 6 months after the second trial vaccination in all subjects; and AEs of special interest (AESIs) and serious adverse events (SAEs) through 1 year after the second trial vaccination in all subjects (see Appendix 9 and Appendix 10). A Data and Safety Monitoring Board (DSMB) will perform a review at regular meetings of the available safety data from CV-NCOV-004, CV-NCOV-005 and other trials with CVnCoV. The immunogenicity of CVnCoV after 1 and 2 doses will be evaluated in a subset of subjects (Immunogenicity/Reactogenicity Subset) by measuring binding antibodies to the SARS-CoV-2 RBD of S protein for the co-primary immunogenicity objective, and by measuring viral neutralizing antibodies for the secondary immunogenicity objective. It will be evaluated descriptively in a subset of subjects (Immunogenicity/Reactogenicity Subset) if antibody responses to the RBD of S protein of SARS-CoV-2 induced by 2 different lots of CVnCoV are equivalent when measured on Day 29 and 43. As a secondary efficacy objective, the efficacy of a 2-dose schedule of CVnCoV in the prevention of first episodes of virologically-confirmed cases of COVID-19 of any severity in SARS-CoV-2 naïve subjects will be assessed. The severity of COVID-19 cases occurring in the CVnCoV and placebo groups will also be described as a secondary objective. Subjects will undergo active surveillance for COVID-19 (see Appendix 6). During all site visits and phone calls, subjects will be reminded to contact the site if they have an acute illness with any symptoms clinically consistent with COVID-19 or if they tested positive for SARS-CoV-2 outside of the trial context. In addition, subjects will be messaged up to twice a week and will provide a yes or no response to having COVID-19 symptoms. Those who respond “yes” will be contacted by trial staff for a follow-up interview and assessment, if the investigator considers the symptoms could potentially indicate a COVID-19 case. If a subject is suspected of having COVID-19 illness, he/she will undergo testing for SARS-CoV-2 infection with samples collected at the site or at a home visit. If the subject is confirmed to have COVID-19, the subject will be followed until resolution of their disease. If the subject is hospitalized, the subject’s progress must continue to be followed by the Investigator and a discharge summary obtained at the end of the hospitalization. Information on clinical symptoms and signs, their duration and severity, and treatment and outcome of the COVID-19 episode will be documented by trial staff and recorded in the electronic case report form (eCRF). Upon resolution, subjects will continue to be followed through the

	trial end in the same manner as those who have not presented with COVID-19. A second or subsequent episode of COVID-19 in a subject with prior disease will be counted for the exploratory objective assessing the reoccurrence of COVID-19 in vaccinated subjects. For the analysis of efficacy, the case must meet the following criteria (moderate and severe COVID-19 disease is defined in Appendix 4 and Appendix 3, respectively): • Must be a virologically-confirmed case of COVID-19 defined as a positive SARS-CoV-2 specific reverse transcription polymerase chain reaction (RT-PCR) test in a person with clinically symptomatic COVID-19 (see Section 9.2). • Symptom onset must have occurred ≥ 15 days following the second trial vaccination. • The subject must not have a history of virologically-confirmed COVID-19 at enrollment (based on exclusion criterion 1) or have developed a case of virologically-confirmed COVID-19 before 15 days after the second trial vaccination {see Section 10.2.4, Efficacy Analysis Set (EAS) population for more details}. These efficacy cases might be confirmed by the Adjudication Committee. The DSMB will periodically monitor COVID-19 cases across CV-NCOV-004, CV-NCOV-005 and other trials with CVnCoV for signals of vaccine-dependent disease enhancement (VDE) with pre-specified criteria for halting based on these signals. An interim analysis is planned. The cut-off date for the interim analysis in CV-NCOV-005 will be based on the regulatory requirements to obtain early conditional approval in Europe. Trial CV-NCOV-005 will continue and remain fully blinded, except for the unblinded Submission Team, until CA and EC approval of study protocol version 3. Accrual of COVID-19 cases will continue.

Trial Visits/Contacts:	• **For subjects in the Immunogenicity/Reactogenicity Subset (see Table 1):**
	  • 7 protocol-scheduled site visits on Day 1, Day 29, Day 43, Day 57, Day 120, Day 211, and Day 393.
	  • 3 protocol-scheduled phone contacts (safety calls) on Day 2, Day 30 and Day 302.
	• **For all the other subjects and for subjects that, following unblinding, receive an authorized vaccine after having received at least one dose of CVnCoV (see Table 2):**
	  • 5 protocol-scheduled site visits on Day 1, Day 29, Day 43, Day 211 and Day 393.
	  • 3 protocol-scheduled phone contacts (safety calls) on Day 57, Day 120 and Day 302.
	• **For subjects who received placebo:**
	  • All subjects will be invited for an unscheduled End of Study-Visit in order to conduct a final safety assessment.

Collection of Blood Samples:	The maximum total volume of blood taken over the trial period from each subject is described below: • **For subjects in the Immunogenicity/Reactogenicity Subset** • Up to 318 mL taken over 56 weeks (Table 1).

	• **For all Other Subjects and for subjects that, following unblinding, receive an authorized vaccine after having received at least one dose of CVnCoV** • 18 mL taken over 56 weeks (Table 2).
Safety Assessments:	The safety, reactogenicity, and tolerability of a 2-dose schedule of CVnCoV will be assessed by measuring the frequency and severity of the following AEs as described below. **Safety assessments specific for subjects in the Immunogenicity/Reactogenicity Subset:** • Reactogenicity will be assessed daily on each vaccination day and the following 7 days by collection of solicited local AEs (injection site pain, redness, swelling, and itching) and solicited systemic AEs (fever, headache, fatigue, chills, myalgia, arthralgia, nausea/vomiting, and diarrhea) using electronic diaries (eDiaries). In addition, other indicators of safety will be collected (e.g., body temperature). • eDiaries will be used for collection of unsolicited AEs on each vaccination day and the following 28 days. **Safety assessments for all subjects:** • Medically-attended AEs will be collected through 6 months after the second trial vaccination. • AESIs will be collected through 1 year after the second trial vaccination. AESIs to be monitored include potential immune-mediated diseases (pIMDs), AESIs for SARS-CoV-2 vaccines, and non-serious intercurrent medical conditions that may affect the immune response to vaccination. • SAEs will be collected through 1 year after the second trial vaccination. • AEs leading to vaccine withdrawal or trial discontinuation will be collected through 1 year after the second trial vaccination.
Testing for COVID-19:	During the trial, subjects clinically suspected of having COVID-19 disease or with a positive result in a test for SARS-CoV-2 performed outside of the trial context will undergo testing for the SARS-CoV-2 virus as described below. Sample collection for the tests may be performed at the site or at a home visit by trial staff. Ideally, samples should be collected within 5 days of symptom onset or positive result. • The nasopharyngeal swab sample collected will be used to perform a SARS-CoV-2 specific RT-PCR test. The RT-PCR test result will be considered definitive. For positive RT-PCR tests, viral RNA of the SARS-CoV-2 might be sequenced to identify S protein variants. If the RT-PCR test is negative, but COVID-19 is still suspected based on the subject's exposure history and clinical presentation, another nasopharyngeal swab sample should be taken as soon as feasible for RT-PCR testing. The RT-PCR retest result will be considered definitive.
COVID-19 Case Detection and Case Definition for Efficacy Analysis:	**Case Detection:** • During all site visits and phone calls, subjects will be reminded to contact the site if they tested positive for SARS-CoV-2 outside of the trial context or have at least 1 of the following symptoms*:

	○ Fever or chills ○ Shortness of breath or difficulty breathing ○ New loss of taste or smell ○ Cough ○ Fatigue ○ Muscle or body aches ○ Headache ○ Sore throat ○ Congestion or runny nose ○ Nausea or vomiting ○ Diarrhea *FDA Guidance for Industry, Development and Licensure of Vaccines to Prevent COVID-19, June 2020. • In addition, subjects will be messaged up to twice a week to provide a yes or no response to having COVID-19 symptoms. Those who respond "yes" will be contacted by trial staff for follow-up information, if the investigator considers the symptoms could potentially indicate a COVID-19 case. • Based on a phone interview, if the subject is suspected of having COVID-19 illness or tested positive for SARS-CoV-2 outside of the trial context, he/she will undergo RT-PCR testing for SARS-CoV-2 infection as described above. If the subject is confirmed to have COVID-19, he/she will be followed until resolution of their disease, even if the initial presentation is considered as mild. Information on clinical signs/symptoms and duration, treatments and outcome of the disease will be documented by trial staff and recorded in the eCRF. **Definition of Virologically-Confirmed COVID-19 Case:** A virologically-confirmed case of COVID-19 is defined as a positive SARS-CoV-2 specific RT-PCR test in a person with clinically symptomatic disease consisting of 1 or more of the following symptoms (based on the same screening symptoms as above): ○ Fever or chills ○ Shortness of breath or difficulty breathing ○ New loss of taste or smell ○ Cough ○ Fatigue ○ Muscle or body aches ○ Headache ○ Sore throat ○ Congestion or runny nose ○ Nausea or vomiting ○ Diarrhea This definition is intended to capture all severities of virologically-confirmed clinically symptomatic cases of COVID-19. As such, different disease severities defined for COVID-19 (e.g., mild or severe disease) will be a subset of these cases. **Definition of Virologically-Confirmed COVID-19 Case for the Efficacy Analysis:** For the analysis of efficacy, the case must meet the following criteria: • Must be 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 as described above. • Symptom onset must have occurred ≥ 15 days following the second trial vaccination. • The subject must not have a history of virologically-confirmed COVID-19 illness at enrollment or have developed a case of virologically-confirmed COVID-19 before 15 days following the second trial vaccination. • The subject must have been SARS-CoV-2 naïve at baseline and Day 43 (defined as seronegative to N protein in the blood samples collected at baseline and Day 43). These efficacy cases might be confirmed by the Adjudication Committee.

Planned Number of Subjects:	HCWs participating in the observational COVID19-5-P-002 trial, other HCWs, and potentially students in clinical training will be enrolled. The total enrollment for the trial will be approximately 2,520 subjects (840 by randomization group).
Criteria for Inclusion and Exclusion:	**Inclusion criteria for all subjects:** Subjects will be enrolled in this trial only if they meet all of the following criteria: 1. Male or female subjects 18 years of age or older. 2. HCWs, employees or students in clinical training. 3. Provide written informed consent prior to initiation of any trial procedures. 4. Expected compliance with protocol procedures and availability for clinical follow-up through the last planned visit. 5. Females of non-childbearing potential defined as follows: surgically sterile (history of bilateral tubal ligation/occlusion, bilateral oophorectomy or hysterectomy) or postmenopausal {defined as amenorrhea for ≥ 12 consecutive months prior to screening (Day 1) without an alternative medical cause}. A follicle-stimulating hormone level may be measured at the discretion of the Investigator to confirm postmenopausal status. 6. Females of childbearing potential: negative urine pregnancy test (human chorionic gonadotropin) within 24 hours prior to each trial vaccination on Day 1 and Day 29. 7. Females 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 ligation; • Vasectomized partner or infertile partner; • Sexual abstinence {periodic abstinence (e.g., calendar, ovulation, symptothermal and post-ovulation methods) and withdrawal are not acceptable}. **Exclusion criteria for all subjects:** Subjects will not be enrolled in this trial if they meet **any** of the following criteria: 1. History of virologically-confirmed SARS-CoV-2 infection or SARS-CoV-2 positive serology. 2. For females: pregnancy or lactation. 3. Use of any investigational or non-registered product (vaccine or drug) within 28 days preceding the administration of the first trial vaccine or planned use during the trial. 4. Receipt of licensed vaccines within 28 days (for live vaccines) or 14 days (for inactivated vaccines) prior to the administration of the first trial vaccine.

	5. Prior administration of any investigational SARS-CoV-2 vaccine or another coronavirus (SARS-CoV, MERS-CoV) vaccine or planned use during the trial. 6. Any treatment with immunosuppressants or other immune-modifying drugs (including but not limited to corticosteroids, biologicals and methotrexate) for > 14 days total within 6 months preceding the administration of trial vaccine or planned use during the trial. For corticosteroid use, this means prednisone or equivalent, 0.5 mg/kg/day for 14 days or more. The use of inhaled, topical, or localized injections of corticosteroids (e.g., for joint pain/inflammation) is permitted. 7. Any medically diagnosed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination including known infection with human immunodeficiency virus; current diagnosis of or treatment for cancer including leukemia, lymphoma, Hodgkin disease, multiple myeloma or generalized malignancy; chronic renal failure or nephrotic syndrome; and receipt of an organ or bone marrow transplant. 8. Active or chronic disease of, or currently on treatment for, hepatitis B virus or hepatitis C virus. 9. History of angioedema (hereditary or idiopathic) or history of any anaphylactic reaction. 10. History of pIMD. 11. History of allergy to any component of CVnCoV vaccine. 12. Administration of immunoglobulins or any blood products within 3 months prior to the administration of trial vaccine or planned receipt during the trial. 13. Subjects with a significant acute or chronic medical or psychiatric illness that, in the opinion of the Investigator, precludes trial participation (e.g., may increase the risk of trial participation, render the subject unable to meet the requirements of the trial, or may interfere with the subject's trial evaluations). These include severe and/or uncontrolled cardiovascular disease, gastrointestinal disease, liver disease, renal disease, respiratory disease, endocrine disorder, and neurological and psychiatric illnesses. However, those with controlled and stable cases can be included in the trial. 14. Subjects with impaired coagulation or any bleeding disorder in whom an IM injection or a blood draw is contraindicated. 15. Foreseeable non-compliance with the trial procedures as judged by the Investigator.
Primary Endpoints:	**Primary Safety Endpoints** • Occurrence, intensity and relationship of medically-attended AEs collected through 6 months after the second trial vaccination in all subjects. • Occurrence, intensity and relationship of SAEs and AESIs collected through 1 year after the second trial vaccination in all subjects. • Occurrence of fatal SAEs through 1 year after the second trial vaccination in all subjects. • Occurrence of AEs leading to vaccine withdrawal or trial discontinuation through 1 year after the second trial vaccination in all subjects. • Occurrence, intensity and duration of each solicited local AE within 7 days after each trial vaccination in a subset of subjects. • Occurrence, intensity, duration of each solicited systemic AE within 7 days after each trial vaccination in a subset of subjects. • Occurrence, intensity and relationship of unsolicited AEs occurring within 28 days after each trial vaccination in a subset of subjects.

	Primary Immunogenicity Endpoint *SARS-CoV-2 RBD of S protein antibody responses in a subset of subjects* On Days 1, 29 and 43: • Serum antibodies to SARS-CoV-2 RBD of S protein. • Occurrence of seroconversion to SARS-CoV-2 RBD of S protein. • Seroconversion is defined as detectable SARS-CoV-2 RBD of S protein antibodies in the serum of subjects who tested seronegative at baseline.

Secondary Endpoints:	**Secondary Efficacy Endpoints**
	• Occurrence of first episodes of virologically-confirmed (RT-PCR) cases of COVID-19 of any severity meeting the case definition for the efficacy analysis.
	• Occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 meeting the case definition for the efficacy analysis by severity (mild, moderate, severe and moderate to severe COVID-19) as defined in Appendix 3 and Appendix 4.
	• BoD scores calculated based on first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity meeting the case definition for the efficacy analysis.
	  • BoD #1 – no disease (not infected or asymptomatic infection) = 0; mild or moderate disease = 1; severe disease = 2.
	  • BoD #2 – no disease (not infected or asymptomatic infection) = 0; disease without hospitalization = 1; disease with hospitalization = 2; death = 3
	Secondary Immunogenicity Endpoints
	SARS-CoV-2 virus neutralizing antibody responses in a subset of subjects
	On Days 1, 29 and 43:
	• Serum neutralizing antibodies to SARS-CoV-2 virus, as measured by a virus neutralizing assay.
	• Occurrence of seroconversion to SARS-CoV-2 virus, as measured by a virus neutralizing assay.
	  • Seroconversion is defined as detectable SARS-CoV-2 virus neutralizing antibodies in the serum of subjects who tested seronegative at baseline.
	Lot-to-lot consistency of 2 CVnCoV lots, as measured by SARS-CoV-2 RBD of S protein antibody responses in a subset of subjects
	On Day 43:
	• Serum antibodies to SARS-CoV-2 RBD of S protein.

Data and Safety Monitoring Board:	An independent DSMB will be convened to oversee the safety and efficacy of subjects participating in the trials CV-NCOV-004 and CV-NCOV-005, to assess the progress and conduct of the trials, to review the cumulative safety data from the trials, and to make recommendations to CureVac whether to continue, modify, or stop the trials. The DSMB will have regularly scheduled meetings to perform these responsibilities. During these meetings, the DSMB will be informed of the safety data being generated in other ongoing clinical trials of CVnCoV. In addition to safety data, the DSMB will be asked to review efficacy data at the interim analysis and at other time points during the trial for a continued assessment of the risk-benefit of the trial. As part of the risk-

	benefit analysis, the DSMB will periodically monitor COVID-19 cases for signals of VDE. The DSMB Charter will describe in detail the composition and objectives of the DSMB; the responsibilities of the DSMB, CureVac and the contract research organization; the schedule and conduct of the DSMB meetings; and the datasets to be reviewed.
Sample Size Justification:	HCWs participating to the observational COVID19-5-P-002 trial, other HCWs or students in clinical training will be enrolled. The anticipated sample size is 2,520 subjects. This number of subjects will give the trial more than 80% statistical power to detect AEs that may occur at about 1:1000 incidence.
Analysis Sets:	The main analysis populations are: **Safety Analysis Set** The Safety Analysis Set (SAS) will include all subjects randomized in the trial who received at least 1 dose of any lot of CVnCoV or placebo vaccine. The SAS will be the primary population for the safety endpoints collected on all subjects. Solicited and unsolicited AE endpoints will be analyzed on the SAS subjects who belong to the Immunogenicity/Reactogenicity subset. **Per Protocol Immunogenicity Subset** The Per Protocol Immunogenicity subset (PPI) will include all subjects who belong to the Immunogenicity/Reactogenicity Subset and who: • Received both doses as randomized and within the windows defined in the protocol. • Have no major protocol deviations expecting to impact the immunogenicity outcomes as specified in the SAP. • Have not received medical treatments (such as blood products, immunoglobulin therapy) that may interfere with 1 or both of the proposed immunogenicity measurements. • Have at least 1 blood sample collected starting at 14 days (Day 43) post-second vaccination available for analysis. The PPI will be the primary analysis population for SARS-CoV-2 RBD of S protein antibody responses and SARS-CoV-2 viral neutralizing antibody. Lot-to-lot consistency analysis will be performed on PPI subjects who: • Received 2 doses of CVnCoV coming from the same lot. • Have a negative SARS-CoV-2 RBD of S protein antibody titer at baseline. **Efficacy Analysis Set** The Efficacy Analysis Set (EAS) will include all subjects of the SAS who: • Received both trial doses (2 doses of CVnCoV or 2 doses of placebo) according to their randomization. • Had not developed a virologically-confirmed case of COVID-19 before trial entry (based on exclusion criteria 1) or before 15 days following the second vaccination. • Had not stopped the trial before 15 days following the second vaccination. • Were SARS-CoV-2 naïve at trial entry and at Day 43 visit (based on seronegativity to N protein). The EAS will be the primary analysis population for all efficacy endpoints.

Statistical Methodology:	**Missing data/discontinuation:** Concentration values of SARS-CoV-2 antibodies marked as below the lower limit of quantification (LLOQ) will be set to 0.5*LLOQ for the purpose of geometric mean concentration (GMC) computation. No imputation of missing values will be performed for any analysis (except the imputation for missing partial dates of AEs and concomitant medication). Currently no replacement of drop-out subjects is foreseen. This plan may be affected if another COVID-19 vaccine is approved and made available to the subjects during this trial. If an important percentage of subjects opt to receive that other vaccine, a re-randomization of additional subjects from the CPMprevac non-interventional trial into this trial will be considered.
Statistical Analyses:	**Analysis of Demographics and Other Baseline Characteristics:** Data will be summarized with respect to demographic and baseline characteristics, medical history, immune response measurements, and all safety measurements using descriptive statistics (quantitative data) and contingency tables (qualitative data) for each CVnCoV lot separately, for pooled CVnCoV lots, for placebo and overall. **Safety Analyses:** Safety endpoints will be described for each CVnCoV lot separately, for pooled lots, for placebo and overall. • **Solicited AEs:** The frequencies and percentages of subjects experiencing each solicited local and systemic AE within 7 days after each vaccination will be presented by intensity and overall. • **Unsolicited AEs:** Unsolicited AEs including SAEs and AESIs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) by System Organ Class (SOC) and Preferred Term (PT). The frequency and percentage of subjects reporting at least 1 AE and each unsolicited AE within 28 days after each vaccination and overall will be tabulated at the SOC and PT levels. Additional similar tabulations will be performed to evaluate severity and relationship to trial vaccine. **Immunogenicity Analysis:** Descriptive statistics for the immunogenicity endpoints will be provided for each CVnCoV lot separately (samples of 200 subjects analyzed), for pooled lots and for 50 subjects of the placebo group on Days 1, 29 and 43.. GMCs/Geometric mean titers (GMTs) with 95% confidence interval (CI) will be computed for SARS-CoV-2 RBD of S protein antibody levels and for neutralizing antibodies, overall and separately in subjects seronegative at baseline and in subjects seropositive at baseline. Geometric mean of fold change from baseline will be added for subjects seropositive at baseline. For each readout, seroconversion rates will also be summarized at each blood sampling time point in subjects who are SARS-CoV-2 seronegative at baseline. To assess lot-to-lot consistency descriptively, two-sided 95% CI of the ratio of GMCs of SARS-CoV-2 RBD of S protein antibodies between subjects receiving 2 different lots of CVnCoV will be computed for Day 43. **Efficacy Analyses:** The attack rates of first episodes of virologically-confirmed COVID-19 of any severity (according to case definition) in CVnCoV (pooled lots) and placebo groups will be computed as well as VE, defined as the percent reduction in the frequency of COVID-19 cases in vaccinated subjects compared with subjects who received placebo with its exact 95% CI as follows:

	VE = 1- RR = 1 - (ARV/ARP) = 1 - (p / r (1-p)) where ARV = attack rate in vaccinated groups (pooled lots) = nv/Nv = number of subjects reporting at least 1 COVID-19 episode in the CVnCoV groups / total follow-up time of evaluable subjects in the CVnCoV groups (number of person-month) ARP = attack rate in placebo group = np/Np = number of subjects reporting at least 1 COVID-19 episode in the placebo group / total follow-up time of evaluable subjects in the placebo group (number of person-month) RR = relative risk = ARV/ARP p = proportion of COVID-19 cases coming from the CVnCoV groups (pooled lots) among all cases = nv/(nv+np) r = ratio of total follow-up time of evaluable subjects in the CVnCoV groups (pooled lots) over total follow-up time of evaluable subjects in the placebo group = Nv/Np Similar analyses will be performed to describe the efficacy in the prevention of asymptomatic infections. The number and percentage of subjects reporting at least 1 mild, moderate, severe, and moderate to severe COVID-19 episode will be presented in each group. In order to consider incidence and severity of COVID-19 disease, a VE measure based on the BoD scores (VE_{BoD}) will be derived. VE_{BoD} is defined as the relative reduction in the BoD score in the CVnCoV groups compared to the placebo group and is calculated as 1 minus the relative risk. All efficacy endpoints will be analyzed without success criteria testing.

2 SCHEDULE OF ACTIVITIES

Subjects that received placebo in the trial following unblinding, will move from their initial schedule of activities (Table 1 or 2) to the End of Trial Visit (Table 2).

Subjects that, following unblinding, receive an authorized vaccine after having received at least one dose of CVnCoV will move to Table 2.

Table 1 Schedule of Trial Assessments and Procedures for Immunogenicity/Reactogenicity Subset

Immunogenicity/Reactogenicity Subset (n=1,260)

First 1,260 subjects enrolled	Vaccination Period						Follow-up Period			End of Trial
	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Clinic Visit		Clinic Visit		Phone Call	Clinic Visit
Clinic Visit Number	1[a]	-	2	-	3	4	5	6	-	7
Visit Window (days)	n/a	-0/+0	-3/+7	-0/+0	-3/+3	-3/+7	-7/+7	-7/+7	-7/+7	-0/+21
Trial Day	1	2	29	30	43	57	120	211	302	393
Vaccination Day (Reference for post-vaccination time points)	-	1	1	29	29+14	29+28	29+91	29+182	29+273	29+364
Visit Week (Wk) / Month (M)			Wk 4		Wk 6	Wk 8	M 4	M 7	M 10	M 13
Signed informed consent	X									
Inclusion/exclusion criteria	X									
Demographics	X									
Medical history	X									
Medication/vaccination history[b]	X									
Urine pregnancy test[c]	X		X							
Trial Vaccination										
Review criteria for delay or cancellation of trial vaccination[d]	X		X							

First 1,260 subjects enrolled	Vaccination Period						Follow-up Period			End of Trial
	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Clinic Visit		Clinic Visit		Phone Call	Clinic Visit
Clinic Visit Number	1[a]	-	2	-	3	4	5	6	-	7
Visit Window (days)	n/a	-0/+0	-3/+7	-0/+0	-3/+3	-3/+7	-7/+7	-7/+7	-7/+7	-0/+21
Trial Day	1	2	29	30	43	57	120	211	302	393
Vaccination Day (Reference for post-vaccination time points)	-	1	1	29	29+14	29+28	29+91	29+182	29+273	29+364
Visit Week (Wk) / Month (M)			Wk 4		Wk 6	Wk 8	M 4	M 7	M 10	M 13
Administration of CVnCoV or placebo (observer-blinded administration)	X		X							
Safety Monitoring										
Physical examination[e]	X									X
Symptom-directed physical examination[e]			X		X	X	X	X		
Vital signs[e,f]	X[f]		X[f]		X	X	X	X		X
eDiary collection of solicited local and systemic reaction data, and unsolicited AEs[g]	X	X	X	X	X	X				
Collection of following AEs through the eDiary[h]:										
• Medically-attended AEs	X	X	X	X	X	X	X	X		
• SAEs and AESIs	X	X	X	X	X	X	X	X	X	X
• AEs leading to vaccine withdrawal or trial discontinuation	X	X	X	X	X	X	X	X	X	X
• Concomitant medication/vaccination	X	X	X	X	X	X	X	X	X	X
COVID-19 Case Detection										
Case detection and collection of case information[i]	X	X	X	X	X	X	X	X	X	X
Antibody Testing[j]										
Binding ant body to RBD of S (sp ke) protein of SARS-CoV-2 (~6 mL blood)[k]	X[j]		X[j]		X	X	X	X		
SARS-CoV-2 viral neutralizing activity (~6 mL blood)[k]	X[j]		X[j]		X	X	X	X		
Binding ant body to the N (nucleocapsid) protein of SARS-CoV-2 (~6 mL blood)[k]	X[j]				X			X		

First 1,260 subjects enrolled	Vaccination Period						Follow-up Period			End of Trial
	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Clinic Visit		Clinic Visit		Phone Call	Clinic Visit
Clinic Visit Number	1[a]	-	2	-	3	4	5	6	-	7
Visit Window (days)	n/a	-0/+0	-3/+7	-0/+0	-3/+3	-3/+7	-7/+7	-7/+7	-7/+7	-0/+21
Trial Day	1	2	29	30	43	57	120	211	302	393
Vaccination Day (Reference for post-vaccination time points)	-	1	1	29	29+14	29+28	29+91	29+182	29+273	29+364
Visit Week (Wk) / Month (M)			Wk 4		Wk 6	Wk 8	M 4	M 7	M 10	M 13
Cell-mediated Immunity (CMI Subset n=120)										
In a subset of subjects: cell-mediated immunity (~38 mL blood)	X[j]		X[j]		X	X	X	X		
Maximum blood volume collected by visit (mL)[l]	56		50		56	50	50	56		
Trial End										X

AE: adverse event; AESI: adverse event of special interest; SAE: serious adverse event.

a. Procedures to establish subject eligibility may be performed within 21 days prior to trial vaccine administration, unless otherwise indicated. If all information to establish eligibility is available, these procedures can be done on the same day as trial vaccine administration. Eligibility criteria should be reviewed and confirmed prior to trial vaccine administration.

b. Medication/vaccination history taken within 6 months prior to enrollment should be recorded to establish eligibility.

c. A urine pregnancy test will be performed within 24h prior to vaccination before each trial vaccination on Day 1 and Day 29 for women of childbearing potential.

d. See Section 6.3 and Section 8.1 for an overview of the criteria leading to delay or cancellation of vaccine administration. In case of delay, the vaccination should take place within the allowed time windows, if feasible. The reasons for delay or cancellation should be documented in the subject chart.

e. Physical examination and vital signs must be performed/measured by a qualified healthcare professional. See Section 9.3.6 for an overview of the required assessments.

f. Vital signs will be measured pre- and post-vaccination prior to discharge. Subjects will be observed for at least 30 minutes following each vaccination. Vital signs must be within normal or clinically non-relevant abnormal ranges or have returned to pre-vaccination values for the subject to be discharged.

g. eDiary (electronic diary) for recording of post-vaccination solicited AEs will be provided to subjects as needed. Subjects should be trained on the use of the eDiary. Solicited local and systemic AEs occurring on the day of vaccination (Day 1 and Day 29) and for the following 7 days will be recorded by the subject in the eDiary. In addition, the eDiary will serve as a memory aid for the subject to report unsolicited AEs occurring on the day of vaccination (Day 1 and Day 29) and for the following 28 days. The data will be reviewed with the subject by trial staff at the site visits on Day 29, Day 43, and Day 57. During phone calls, the subject´s general well-being will be checked and the subject should be reminded to complete the safety information by eDiary. If the subject reports by phone any concerning local or systemic reactions, or other AEs (e.g., on Day 2 or Day 30), these should be followed-up either by a phone call(s) or by an unscheduled site visit, based on the judgment of the Investigator.

h. The eDiary will serve as a memory aid for the subject to report the following AEs during the safety follow-up. Subjects should be trained on the use of the eDiary. Medically-attended AEs will be collected through 6 months after the second trial vaccination. Medically-attended AEs are defined as AEs with medically-attended visits that are not routine visits for physical examination or vaccination, such as visits for hospitalization, an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason. SAEs, AESIs, and AEs leading to vaccine withdrawal or trial discontinuation will be collected through 1 year after the second trial vaccination. During all site visits and phone calls, trial staff will remind subjects to call the site immediately to report the following: if he/she experiences any concerning medical event; any medically-attended visits that are not routine visits for physical examination or vaccination, such as visits for hospitalization, an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason; or experience a serious medical event, have a change in overall health or be diagnosed with a new medical condition by a doctor. These should be reported regardless of the perceived relationship between the event and the trial vaccine.

i. During all site visits (except the End of Trial visit) and phone calls, trial staff will remind subjects to contact the site if they have any of the symptoms suggestive of COVID-19. In addition, subjects will be messaged up to twice a week basis to provide a yes or no response to having COVID-19 symptoms. Those who respond “yes” will be contacted by trial staff for follow-up information, if the investigator considers the symptoms could potentially indicate a COVID-19 case, and the process outlined in Section 9.2.1 should be followed. At the End of Trial visit, symptoms suggestive of COVID-19 or any confirmed COVID-19 case will be recorded.

j. Blood samples should be collected prior to trial vaccination on Day 1 and Day 29.

k. Binding antibodies to the RBD (receptor-binding domain) of the S (spike) protein and to the N (nucleocapsid) protein of SARS-CoV-2 will be measured by immunoassay. Viral neutralizing antibodies directed against SARS-CoV-2 will be measured by a functional activity assay. The N protein is not a component of the CVnCoV vaccine, but is being measured to determine serostatus of subjects to the SARS-CoV-2 virus (naïve or non-naïve to SARS-CoV-2); distinguish immune responses elicited by infection with SARS-CoV-2 from those induced by CVnCoV vaccination; and determine the occurrence of SARS-CoV-2 infection during the trial.

l. Blood will be collected for measurement of antibody responses on Days 1, 29, 43, 57, 120 and 211, and cell-mediated immunity on Days 1, 29, 43, 57, 120, and 211 for a total volume of up to 318 mL.

Table 2 Schedule of Trial Assessments and Procedures for All Other Subjects and for Subjects who, Following Unblinding, Receive an Authorized Vaccine After Having Received at least One Dose of CVnCoV

(n=1,260)

	Vaccination Period				Follow-up Period			End of Trial
	Clinic Visit			Phone Call	Phone Call	Clinic Visit	Phone Call[j]	Clinic Visit
Clinic Visit Number	1[a]	2	3	-	-	4	-	5
Visit Window (days)	n/a	-3/+7	-3/+3	-3/+7	-7/+7	-7/+7	-7/+7	-0/+21
Trial Day	1	29	43	57	120	211	302	393
Vaccination Day (Reference for post-vaccination time points)	-	1	29+14	29+28	29+91	29+182	29+273	29+364
Visit Week (Wk) / Month (M)		Wk 4	Wk 6	Wk 8	M 4	M 7	M 10	M 13
Signed informed consent	X							
Inclusion/exclusion criteria	X							
Demographics	X							
Medical history	X							
Medication/vaccination history[b]	X							
Urine pregnancy test[c]	X	X						
Trial Vaccination								
Review criteria for delay or cancellation of trial vaccination[d]	X	X						
Administration of CVnCoV or control vaccine (observer-blinded)	X	X						
Safety Monitoring								
Physical examination[e]	X							X
Symptom-directed physical examination[e]		X	X			X		
Vital signs[e,f]	X[f]	X[f]	X			X		X
Collection of following AEs through the eDiary[g]:								
• Medically-attended AEs	X	X	X	X	X	X		

	Vaccination Period				Follow-up Period			End of Trial
	Clinic Visit			Phone Call	Phone Call	Clinic Visit	Phone Call[j]	Clinic Visit
Clinic Visit Number	**1[a]**	**2**	**3**	**-**	**-**	**4**	**-**	**5**
Visit Window (days)	**n/a**	**-3/+7**	**-3/+3**	**-3/+7**	**-7/+7**	**-7/+7**	**-7/+7**	**-0/+21**
Trial Day	**1**	**29**	**43**	**57**	**120**	**211**	**302**	**393**
Vaccination Day (Reference for post-vaccination time points)	**-**	**1**	**29+14**	**29+28**	**29+91**	**29+182**	**29+273**	**29+364**
Visit Week (Wk) / Month (M)		**Wk 4**	**Wk 6**	**Wk 8**	**M 4**	**M 7**	**M 10**	**M 13**
• SAEs and AESIs	X	X	X	X	X	X	X	X
• AEs leading to vaccine withdrawal or trial discontinuation	X	X	X	X	X	X	X	X
Concomitant medication/vaccination	X	X	X	X	X	X	X	X
COVID-19 Case Detection								
Case detection and collection of case information[h]	X	X	X	X	X	X	X	X
Antibody Testing								
Binding antibody to the N (nucleocapsid) protein and of SARS-CoV-2[i] (~6mL blood)	X[i]		X			X		
Maximum blood volume collected by visit (mL)	6		6			6		
Trial End								**X**

AE: adverse event; AESI: adverse event of special interest; SAE: serious adverse event.

a. Procedures to establish subject eligibility may be performed within 21 days prior to trial vaccine administration, unless otherwise indicated. If all information to establish eligibility is available, these procedures can be done on the same day as trial vaccine administration. Eligibility criteria should be reviewed and confirmed prior to trial vaccine administration.

b. Medication/vaccination history taken within 6 months prior to enrollment should be recorded to establish eligibility.

c. A urine pregnancy test will be performed within 24h prior to vaccination before each trial vaccination on Day 1 and Day 29 for women of childbearing potential.

d. See Section 6.3 and Section 8.1 for an overview of the criteria leading to delay or cancellation of vaccine administration. In case of delay, the vaccination should take place within the allowed time windows, if feasible. The reasons for delay or cancellation should be documented in the subject chart.

e. Physical examination and vital signs must be performed/measured by a qualified healthcare professional. See Section 9.3.6 for an overview of the required assessments.

f. Vital signs will be measured pre- and post-vaccination prior to discharge. Subjects will be observed for at least 30 minutes following each vaccination. Vital signs must be within normal or clinically non-relevant abnormal ranges or have returned to pre-vaccination values for the subject to be discharged.

g. The eDiary will serve as a memory aid for the subject to report the following AEs during the safety follow-up. Subjects should be trained on the use of the eDiary. Medically-attended AEs will be collected through 6 months after the second trial vaccination. Medically-attended AEs are defined as adverse events with medically-attended visits that are not routine visits for physical examination or vaccination, such as visits for hospitalization, an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason. SAEs, AESIs, and AEs leading to vaccine withdrawal or trial discontinuation will be collected through 1 year after the second trial vaccination. During all site visits and phone calls, trial staff will remind subjects to call the site immediately to report the following: if he/she experiences any concerning medical event; any medically-attended visits that are not routine visits for physical examination or vaccination, such as visits for hospitalization, an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason; or experience a serious medical event, have a change in overall health or be diagnosed with a new medical condition by a doctor. These should be reported regardless of the perceived relationship between the event and the trial vaccine.

h. During all site visits (except the End of Trial visit) and phone calls, trial staff will remind subjects to contact the site if they have any of the symptoms suggestive of COVID-19. In addition, subjects will be messaged up to twice a week basis to provide a yes or no response to having COVID-19 symptoms. Those who respond “yes” will be contacted by trial staff for follow-up information, if the investigator considers the symptoms could potentially indicate a COVID-19 case, and the process outlined in Section 9.2.1 should be followed. At the End of Trial visit, symptoms suggestive of COVID-19 or any confirmed COVID-19 case will be recorded.

i. Binding antibodies to the N (nucleocapsid) protein of SARS-CoV-2 will be measured by immunoassay. The N protein is not a component of the CVnCoV vaccine, but is being measured to determine serostatus of subjects to the SARS-CoV-2 virus (naïve or non-naïve to SARS-CoV-2) and the occurrence of SARS-CoV-2 infection during the trial. The baseline blood sample should be collected prior to trial vaccination on Day 1.

j. After implementation of protocols version 3 and 4 no longer to be performed in placebo subjects.

3 INTRODUCTION

3.1 Background

3.1.1 Coronaviruses

Coronaviruses (CoVs) are enveloped, positive-sense, single-stranded ribonucleic acid (RNA) viruses that belong to the subfamily *Coronavirinae*, family *Coronavirdiae*, order *Nidovirales*. The virion has a nucleocapsid (N) composed of genomic RNA and phosphorylated N protein, which is buried inside phospholipid bilayers and covered by spike (S) proteins [2]. The membrane (M) protein (a type III transmembrane glycoprotein) and the envelope (E) protein are located among the S proteins in the virus envelope. CoVs were given their name based on a characteristic crown-like appearance.

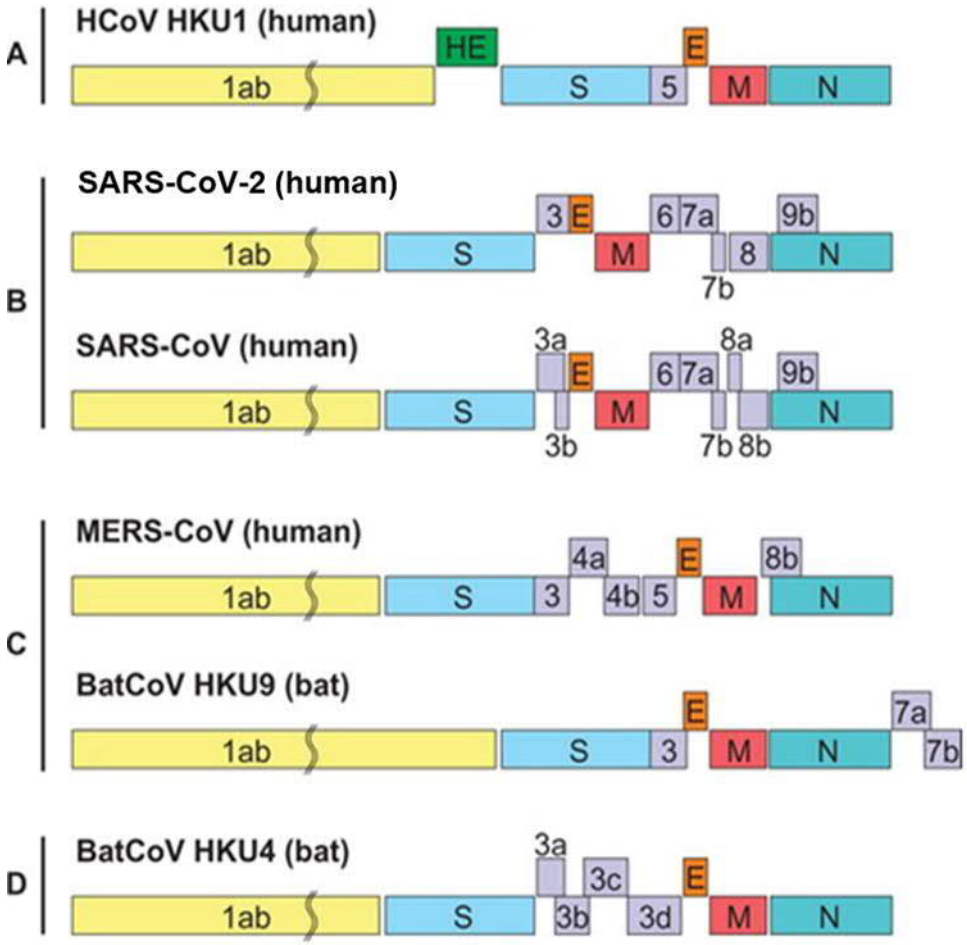
There are 4 genera of CoVs, namely, Alphacoronavirus (αCoV), Betacoronavirus (βCoV), Deltacoronavirus (δCoV) and Gammacoronavirus (γCoV) [3]. Evolutionary analyses have shown that bats and rodents are the gene sources of most αCoVs and βCoVs, while avian species are the gene sources of most δCoVs and γCoVs. CoVs have repeatedly crossed species barriers and some have emerged as important human pathogens, causing generally-mild acute respiratory illnesses known as the common cold [4].

Prior to December 2019, when clusters of pneumonia cases with unknown etiology were detected in Wuhan City, Hubei Province, China, only 2 additional strains of CoVs had caused outbreaks of severe acute respiratory disease in humans: the Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) and Middle East Respiratory Syndrome coronavirus (MERS-CoV). On 9 January 2020, a novel CoV, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was officially identified as the cause of an outbreak of viral pneumonia in Wuhan. In the following weeks, the virus spread rapidly within China and an increasing number of countries worldwide. On 30 January 2020 the World Health Organization (WHO) announced the outbreak under International Health Regulations as a public health emergency of international concern (the WHO's highest level of alarm) and on 12 March 2020, the WHO announced the outbreak as a pandemic.

SARS-CoV-2 falls into the genus βCoV, which includes CoVs discovered in humans, bats and other wild animals (SARS-CoV, bat SARS-like CoV, and others). Similar to other βCoVs, the SARS-CoV-2 genome contains 2 flanking untranslated regions and a single long open reading frame encoding a polyprotein [3]. The SARS-CoV-2 genome is arranged in the order of 5'-replicase (orf1/ab)-structural proteins [S-E-M-N]−3' and lacks the hemagglutinin-esterase gene which is characteristically found in lineage A βCoVs, as illustrated in Figure 1.

High sequence similarity (> 99%) has been reported following analysis of virus isolates from patients with SARS-CoV-2 infection [5-8].

Figure 1 Genome Organization of SARS-CoV-2 Compared with Other Betacoronaviruses



Source: Chan et al., 2020 [3]

The S gene of SARS-CoV-2 appears to be highly divergent to other CoVs, with less than 75% nucleotide sequence identity to all previously described SARS-CoVs, except a 93.1% nucleotide identity to RaTG13 [6]. The S genes of SARS-CoV-2 and RaTG13 S gene are longer than other SARS-CoVs. The major differences in SARS-CoV-2 are 3 short insertions in the N-terminal domain, and 4/5 key residues changes in the receptor-binding motif, in comparison with SARS-CoV. At the amino acid sequence level, the S glycoprotein of SARS-CoV-2 was found to have 76.3% identity and 87.3% similarity with the S glycoprotein of SARS-CoV [9].

The S2 subunit of SARS-CoV-2 was found to be highly conserved, sharing 99% sequence identity with those of the 2 bat SARS-like CoVs (SL-CoV ZXC21 and ZC45) and human SARS-CoV [3]. The S1 subunit of SARS-CoV-2 shares around 70% identity to that of the 2 bat SARS-like CoVs and human SARS-CoV. The domain of the receptor-binding domain (RBD) (excluding the external subdomain) is highly conserved, but the external subdomain of the SARS-CoV-2 RBD (which is responsible for the direct interaction with the host receptor) shares only 40% amino acid identity with other SARS-related CoVs.

To date, there is no information available on the immune responses to SARS-CoV-2. An immunoinformatics approach predicted 5 cytotoxic T lymphocyte (CTL) epitopes, 3 sequential B cell epitopes and 5 discontinuous B cell epitopes in the S glycoprotein [9]. Simulations suggested that the CTL epitopes bind the major histocompatibility complex class I peptide-binding grooves via multiple contacts, with continuous hydrogen bonds and salt bridge anchors, supporting their potential in generating immune responses. Of note, the simulations found only 1 overlapping CTL epitope between MERS-CoV and SARS-CoV-2 and no comparable epitopes with SARS-CoV.

3.1.2 COVID-19 Disease

SARS-CoV-2 is transmitted mainly through close contact and respiratory droplets. The mean incubation period is 4-6 days with about 95% of patients developing symptoms within 14 days after infection [10,11]. The most common symptoms of coronavirus disease 2019 (COVID-19) include fever, cough, dyspnea, and occasionally watery diarrhea. In an analysis of >1000 hospitalized patients from China, 44% initially presented with fever (although 89% developed fever at some point during hospitalization) and 68% with cough. Other symptoms included fatigue (23%), myalgia (15%) and gastrointestinal symptoms (8%) [11]. As with other systemic viral infections, a large spectrum of possible clinical manifestations are being reported in COVID-19 patients, including neurological symptoms and signs, cardiac disease, and cutaneous lesions [12-15]. Chemosensory dysfunction, such as anosmia and dysgeusia, are increasingly reported.

Data from more than 72,000 patients from China classified cases as mild (including mild pneumonia, 81%), severe (14%) or critical (5%) [16]. Severe and critical cases presented with severe pneumonia, septic shock and Acute Respiratory Distress Syndrome (ARDS). The critically ill patients requiring intensive care management present a large spectrum of complications in addition to ARDS, such as acute cardiac injury, acute renal injury, acro-ischemia, disseminated intravascular complications, bacterial or fungal superinfections [17,18].

In early stages of the outbreak, the reported case-fatality rate in China was 17% [19]. In admitted patients in Wuhan, mortality reached 25% in the middle of the epidemic. Similarly high death rates are recorded in those requiring intensive care: in a large retrospective cases series on COVID-19 confirmed patients admitted to intensive care units (Lombardy, Italy), mortality reached 26% [20]. The global mortality rate is estimated to be around 3% [21].

According to the 2020 World Health Statistics, the COVID-19 pandemic is causing significant loss of life, disrupting livelihoods, and threatening the recent advances in health and progress towards global sustainable development goals [22]. On 11 November 2020, according to WHO, 51 251 715 cases have been confirmed globally, including 1 270 930 deaths.

3.1.3 Development of CVnCoV

In spite of the severity of respiratory disease caused by emerging CoVs, there is currently no licensed vaccine available for prevention of CoV-associated disease. CureVac AG is developing a new SARS-CoV-2 messenger ribonucleic acid (mRNA) vaccine formulated with lipid nanoparticles (LNP), referred to as CVnCoV, for the prevention of COVID-19 disease when administered as a 2-dose primary vaccination schedule.

CVnCoV is an mRNA-based COVID-19 vaccine in which the mRNA is protected and delivered by encapsulation within LNPs. CVnCoV has been developed with CureVac's proprietary RNActive® technology platform, which uses chemically unmodified mRNA molecules as the basis for vaccination. The mRNA encodes the stabilized full-length S protein from the SARS-CoV-2 virus. Following intramuscular (IM) injection of CVnCoV, the S protein is translated from the mRNA stimulating an antigen-specific humoral and cellular immune response to the S protein. Importantly, functional viral neutralizing titers (VNTs) and T-cell mediated immunity are induced following vaccination with CVnCoV.

Phase 1 and 2a trials are generating initial data on the safety, reactogenicity and immunogenicity of CVnCoV administered to adults 18 years of age and older. Available data from these trials are provided in the Investigator's Brochure.

The HERALD Trial CV-NCOV-004 is designed as a Phase 2b/3 pivotal efficacy and safety trial in adults 18 years of age and older. The trial is conducted as a randomized, observer-blinded, placebo-controlled trial. Subjects were enrolled at multiple sites globally and were randomized in a 1:1 ratio to receive a 2-dose schedule of either CVnCoV at a dose level of 12 µg or placebo {normal saline (0.9% NaCl) for injection} as the control.

The objective of the Phase 2b part of the trial is to further characterize the safety, reactogenicity and immunogenicity of CVnCoV in the intended trial population of adults, 18 years of age and older, at the dose level selected for Phase 3 investigation. The design of Phase 2b is consistent with the Phase 3 efficacy part of the trial, allowing cases of COVID-19 that occur in Phase 2b to be pooled with those in Phase 3 for the primary analysis of vaccine efficacy (VE), thereby increasing the efficiency of the overall Phase 2b/3 trial. Combining COVID-19 cases in Phase 2b and 3 to expedite an efficacy outcome was considered to be justified in a pandemic setting. The detailed reactogenicity and immunogenicity data generated in Phase 2b will be the main dataset to be submitted in support of early conditional approval of CVnCoV.

The co-primary objectives of the combined Phase 2b/3 trial are to demonstrate the efficacy of a 2-dose schedule of CVnCoV in the prevention of COVID-19 cases of any severity or COVID-19 cases of moderate or higher severity. Due to the uncertain incidence rate of COVID-19 cases in a pandemic setting, the trial is conducted as a case-driven trial based on the any severity COVID-19 endpoint due to the higher number of cases required, which will include 2 interim analyses and a final analysis both triggered by achieving a predefined number of cases for each analysis. The safety objective of the trial is to generate a large-scale safety database that will demonstrate the safety of CVnCoV across the adult age groups of 18 to 60 and ≥ 61 years of age.

3.1.4 Trial Rationale

The present trial CV-NCOV-005 is designed as a Phase 3 safety and immunogenicity trial in health care workers (HCW), 18 years of age and older, in Mainz (Germany). The trial will be conducted as a randomized, observer-blinded, placebo-controlled trial. HCW participating in a non-interventional cohort trial, COVID19-5-P-002 {or CovidPreventMainz (CPM)prevac}, currently being performed at the Mainz University will be asked to participate in Trial CV-NCOV-005. Trial CV-NCOV-005 will also include other HCWs, and potentially students in clinical training.

Subjects enrolled in CV-NCOV-005 will be randomized in a 1:1:1 ratio to receive a 2-dose schedule, 28 days apart, of either 1 of 2 lots of CVnCoV at a dose level of 12 µg mRNA or placebo {normal saline (0.9% NaCl) for injection} as the control.

Primary objectives of the CV-NCOV-005 trial are to generate additional safety, and immunogenicity data, in the intended trial population of adults at the previously selected dose level. As a secondary objective, the efficacy of a 2-dose schedule of CVnCoV in the prevention of first episodes of virologically-confirmed cases of COVID-19 of any severity in SARS-CoV-2 naïve subjects will be assessed. The severity of COVID-19 cases occurring in the CVnCoV and placebo groups will be described as a secondary objective.

Lot-to-lot consistency of 2 lots of CVnCoV will also be assessed in this trial as a secondary objective.

Please refer to the Investigator's Brochure for details on the RNActive® technology, and information regarding the non-clinical and clinical trials of the investigational CVnCoV vaccine.

3.2 Risk/Benefit Assessment

3.2.1 Known Potential Risks

Non-clinical studies show that CVnCoV is well-tolerated in relevant animal species with no identified safety risks.

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

Furthermore, CureVac is consulting with external regulatory and scientific experts to help identify the best animal models to evaluate the theoretical risk of VDE. To that end, animal models that best recapitulate human disease have been chosen, inclusive of hamster and non-human primate challenge studies and are being evaluated, as recommended by Wang and colleagues [30]. These approaches are in line with those agreed upon for COVID-19 vaccine development by the International Coalition of Medicines Regulatory Authorities [31].

[redacted]

In addition, a list of AEs of special interest (AESIs) to be monitored following administration of investigational SARS-CoV-2 vaccines has been identified by the Brighton Collaboration Safety Platform for Emergency vACcines (SPEAC) Project. If any suspected AESI (pIMD or other AE specific to SARS-CoV-2 vaccines) should occur in a subject who received CVnCoV, a diagnostic workup should be performed by a specialist depending on the type of suspected reaction (e.g., endocrinologist for suspected autoimmune thyroiditis) and this condition will be monitored and documented throughout the trial.

CVnCoV has not been investigated in combination with other drugs or vaccines. Given the mechanism of action which relies on building up an adequate immune response, it is expected that immunosuppressive drugs like steroids may inhibit the desired pharmacological effect of the induction of a specific immune response against the SARS-CoV-2 RBD of S protein. Similarly, drugs that enhance the immune response like certain cytokines (IFN-α, IL-2) may increase the response to the vaccines which could theoretically result in increased efficacy, but also in an increased risk of toxicity.

Risks from phlebotomy are well known and minimal. Venipuncture is a routine procedure the medical community commonly uses to obtain blood samples. Immediate complications may include slight pain during puncture of the skin and, rarely, dizziness and syncope. Additionally, a hematoma may result from the venipuncture, but this has minimal risk. Infection of the skin/soft tissue at the puncture site, vein, or blood stream can occur, but are very rare with venous blood draws. Subject monitoring and aseptic techniques, such as using sterile disposable blood collection apparatuses and adhering to standard medical precautions, reduce any risk to a minimum. The amount of blood to be taken for sampling will not be harmful to the subject's health.

3.2.2 Known Potential Benefits

Subjects receiving the investigational CVnCoV vaccine may not directly benefit from this vaccination as it is not known if CVnCoV is effective in protecting against COVID-19 disease. Subjects receiving saline placebo will not directly benefit from trial vaccination.

Trial subjects will receive the following benefits:

- Subjects participating in this trial may benefit from having regular health checks as part of the trial procedures (e.g., physical examination, vital signs assessment). Where illnesses are newly diagnosed, a referral will be made for the subject to an appropriate health provider.
- If CVnCoV is found to be efficacious and meets regulatory approval, subjects in the placebo group may be offered CVnCoV as soon as feasible.
- If CVnCoV is found to be efficacious, then subjects will have made a significant public health contribution.

3.2.3 Assessment of Potential Risks and Benefits

To minimize the risk for subjects participating in this trial, an independent DSMB will oversee the safety of the participating subjects throughout the trial (see Section 9.3.8.1).

Potential important medical risks associated with CVnCoV, as specified in Section 3.2.1, can be managed should they occur.

Since the efficacy results from the HERALD study for CVnCoV are available and all subjects in the CV-NCOV-005 study are currently eligible to receive an authorized vaccine, all subjects in this CV-NCOV-005 study will be unblinded.

Each subject will be informed by the study physician of the available study results and whether he/she received the study vaccine (CVnCoV) or placebo in the study. The purpose of this measure is to provide the participants/subjects with sufficient information so that they can decide whether to take an authorized vaccine or not in a fully informed way.

4 TRIAL OBJECTIVES, ENDPOINTS, AND ESTIMANDS

4.1 Objectives

4.1.1 Primary Objectives

Primary Safety Objective

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

Primary Immunogenicity Objective

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

4.1.2 Secondary Objectives

Secondary Efficacy Objectives

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

Secondary Immunogenicity Objectives

- To assess SARS-CoV-2 virus neutralizing antibody responses after 1 and 2 doses of CVnCoV in adults 18 years of age or older included in a subset of subjects.
- To assess lot-to-lot consistency of 2 CVnCoV lots, as measured by antibody responses to the RBD of S protein of SARS-CoV-2, after 2 doses of CVnCoV, in adults 18 years of age or older included in a subset of subjects.

4.1.3 Exploratory Objectives

Exploratory Efficacy Objective

- To investigate in subjects with first episodes of virologically-confirmed COVID-19 during the trial:
    - The occurrence of second episodes of virologically-confirmed symptomatic cases of COVID-19 of any severity, in SARS-CoV-2 naïve adults receiving a 2-dose schedule of CVnCoV compared to those administered placebo.

4.2 Endpoints

4.2.1 Primary Endpoints

Primary Safety Endpoints

- Occurrence, intensity and relationship of medically-attended AEs collected through 6 months after the second trial vaccination in all subjects.
- Occurrence, intensity and relationship of SAEs and AESIs collected through 1 year after the second trial vaccination in all subjects.
- Occurrence of fatal SAEs through 1 year after the second trial vaccination in all subjects.
- Occurrence of AEs leading to vaccine withdrawal or trial discontinuation through 1 year after the second trial vaccination in all subjects.
- Occurrence, intensity and duration of each solicited local AE within 7 days after each trial vaccination in a subset of subjects.
- Occurrence, intensity, duration of each solicited systemic AE within 7 days after each trial vaccination in a subset of subjects.
- Occurrence, intensity and relationship of unsolicited AEs occurring within 28 days after each trial vaccination in a subset of subjects.

Primary Immunogenicity Endpoints

SARS-CoV-2 RBD of S protein antibody responses in a subset of subjects

On Days 1, 29 and 43 in 250 subjects (200 subjects having received CVnCoV; 50 subjects having received placebo):

- Serum antibodies to SARS-CoV-2 RBD of S protein.
- Occurrence of seroconversion to SARS-CoV-2 RBD of S protein.
    - Seroconversion is defined as detectable SARS-CoV-2 RBD of S protein antibodies in the serum of subjects who tested seronegative at baseline.

4.2.2 Secondary Endpoints

Secondary Efficacy Endpoints

- Occurrence of first episodes of virologically-confirmed {reverse transcription polymerase chain reaction (RT-PCR) positive} cases of COVID-19 of any severity meeting the case definition for the efficacy analysis.
- Occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 meeting the case definition for the efficacy analysis by severity (mild, moderate, severe and moderate to severe COVID-19) as defined in Appendix 3 and Appendix 4.
- BoD scores calculated based on first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity meeting the case definition for the efficacy analysis.
    - BoD #1 – no disease (not infected or asymptomatic infection) = 0; mild or moderate disease = 1; severe disease = 2.

- BoD #2 – no disease (not infected or asymptomatic infection) = 0; disease without hospitalization = 1; disease with hospitalization = 2; death = 3.

Secondary Immunogenicity Endpoints

SARS-CoV-2 virus neutralizing antibody responses in a subset of subjects

On Days 1, 29 and 43:

- Serum neutralizing antibodies to SARS-CoV-2 virus, as measured by a virus neutralizing assay.
- Occurrence of seroconversion to SARS-CoV-2 virus, as measured by a virus neutralizing assay.
    - Seroconversion is defined as detectable SARS-CoV-2 virus neutralizing antibodies in the serum of subjects who tested seronegative at baseline.

Lot-to-lot consistency of 2 CVnCoV lots, as measured by SARS-CoV-2 RBD of S protein antibody responses in a subset of subjects

On Day 43:

- Serum antibodies to SARS-CoV-2 RBD of S protein.

4.2.3 Exploratory Endpoints

Exploratory Efficacy Endpoint

The following endpoint will be analyzed in subjects who had a first episode of a virologically-confirmed (RT-PCR positive) case of COVID-19 of any severity meeting the case definition for the efficacy analysis:

- Occurrence of second episodes of virologically-confirmed (RT-PCR positive) symptomatic cases of COVID-19 of any severity.

4.3 Estimands

ENDPOINTS (subject level)	ESTIMANDS (population level)
Primary Safety	
• Occurrence, intensity and relationship of medically-attended AEs collected through 6 months after the second trial vaccination in all subjects. • Occurrence, intensity and relationship of SAEs and AESIs collected through 1 year after the second trial vaccination in all subjects. • Occurrence of fatal SAEs through 1 year after the second trial vaccination in all subjects. • Occurrence of AEs leading to vaccine withdrawal or trial discontinuation	In subjects who received at least 1 dose of CVnCoV or placebo vaccine, the number and percentage of subjects by group reporting at least 1 and of each type {by System Organ Class (SOC)/preferred term (PT)} of: • Medically-attended AE collected through 6 months after the second trial vaccination

through 1 year after the second trial vaccination in all subjects. • Occurrence, intensity and duration of each solicited local AE within 7 days after each trial vaccination in a subset of subjects. • Occurrence, intensity, duration and relationship of each solicited systemic AE within 7 days after each trial vaccination in a subset of subjects. • Occurrence, intensity and relationship of unsolicited AEs occurring within 28 days after each trial vaccination in a subset of subjects.	overall, by intensity and by causal relationship to trial vaccine. • SAE collected through 1 year after the second trial vaccination overall and by causal relationship to trial vaccine. • AESI collected through 1 year after the second trial vaccination overall, by intensity and by causal relationship to trial vaccine. • Fatal SAE collected through 1 year after the second trial vaccination. • At least 1 AE leading to vaccine withdrawal or trial discontinuation through 1 year after the second trial vaccination. In subjects who received at least 1 dose of CVnCoV or placebo vaccine, and belong to the Immunogenicity/Reactogenicity subset, the number and percentage of subjects by group reporting: • Each solicited local AE within 7 days after each trial vaccination by intensity and overall. • Each solicited systemic AE within 7 days after each trial vaccination by intensity, by relationship to trial vaccine and overall. • At least 1 unsolicited AE, at least 1 grade 3 unsolicited AE and each unsolicited AE by SOC/PT occurring within 28 days after each trial vaccination and overall by causal relationship to trial vaccine and overall. The mean duration in days by group with standard deviation of solicited AEs will be described.
Primary Immunogenicity	
SARS-CoV-2 RBD of S protein antibody responses On Days 1, 29 and 43: • Serum antibodies to SARS-CoV-2 RBD of S protein. • Occurrence of seroconversion to SARS-CoV-2 RBD of S protein • Seroconversion is defined as detectable SARS-CoV-2 RBD of S protein antibodies in the serum of subjects who tested seronegative at baseline.	In subjects belonging to the Immunogenicity/Reactogenicity subset and evaluable {complying with the definition of Per Protocol Immunogenicity Subset (PPI)}: On Days 1, 29 and43: • Geometric mean concentrations (GMCs) with 95% CI of SARS-CoV-2 RBD of S protein antibody responses by group and by baseline sero-status. On Days 29 and43 for subjects seropositive at baseline: • Geometric mean of Fold Change from baseline (GMFC) with 95% CI of SARS-CoV-2 RBD of S protein antibody responses by group. On Days 29 and 43 for subjects seronegative at baseline: • Number and percentage with exact 95%CI of subjects by group for whom a seroconversion

	is observed (detectable SARS-CoV-2 RBD of S protein antibodies in the serum).
Secondary Efficacy	
• Occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity meeting the case definition for the efficacy analysis.	In naïve evaluable subjects {complying with the definition of efficacy analysis set (EAS)} at least 15 days following second vaccination: • VE = 1- RR with exact 95% CI Where RR (relative risk) is the ratio of attack rates of COVID-19 cases per 100 person-month in the CVnCoV vaccine groups (pooled lots) over the placebo group
• Occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 meeting the case definition for the efficacy analysis by severity (mild, moderate, severe and moderate to severe COVID-19) as defined in Appendix 3 and Appendix 4.	In naïve evaluable subjects (complying with the definition of EAS) at least 15 days following second vaccination: • The number and percentage of subjects who developed a first episode of virologically-confirmed (RT-PCR positive) cases of COVID-19 meeting the case definition for the efficacy analysis, by severity (mild, moderate, severe and moderate to severe, as defined in Appendix 3 and Appendix 4).
• BoD scores calculated based on first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity meeting the case definition for the efficacy analysis. • BoD #1 – no disease (not infected or asymptomatic infection) = 0; mild or moderate disease = 1; severe disease = 2. • BoD #2 – no disease (not infected or asymptomatic infection) = 0; disease without hospitalization = 1; disease with hospitalization = 2; death = 3.	In naïve evaluable subjects (complying with the definition of EAS) at least 15 days following second trial vaccination: • VE_{BoD}= 1-RR with 95% CI Where RR is the ratio of the BoD score in the CVnCoV vaccine groups (pooled lots) divided by the BoD score in the placebo group

Secondary Immunogenicity	
SARS-CoV-2 virus neutralizing antibody responses in a subset of subjects On Days 1, 29 and43: • Serum neutralizing antibodies to SARS-CoV-2 virus, as measured by a virus neutralizing assay. • Occurrence of seroconversion to SARS-CoV-2 virus, as measured by a virus neutralizing assay. • Seroconversion is defined as detectable SARS-CoV-2 virus neutralizing antibodies in the serum of subjects who tested seronegative at baseline.	In subjects belonging to the Immunogenicity/Reactogenicity subset and evaluable (complying with the definition of the PPI): On Days 1, 29 and 43: • GMT with 95% CI of neutralizing antibodies to SARS-CoV-2 virus by group and by baseline sero-status On Days 29 and 43 for subjects seropositive at baseline: • GMFC with 95% CI of neutralizing antibodies to SARS-CoV-2 virus by group. On Days 29 and 43 for subjects seronegative at baseline: • Number and percentage with exact 95%CI of subjects by group for whom a seroconversion is observed (detectable neutralizing antibodies to SARS-CoV-2 virus in the serum).
Lot-to-lot consistency of 2 CVnCoV lots, as measured by SARS-CoV-2 RBD of S protein antibody responses in a subset of subjects On Day 43: • Serum antibodies to SARS-CoV-2 RBD of S protein.	In evaluable subjects of the Immunogenicity/Reactogenicity Subset, who belong to 1 of the CVnCoV vaccine groups, have a negative SARS-CoV-2 RBD of S protein antibody concentration at baseline: • Ratio of GMCs of SARS-CoV-2 RBD of S protein antibodies between subjects receiving 2 different lots of CVnCoV on Day 43
Exploratory Efficacy	
The following endpoint will be analyzed in subjects who had a first episode of a virologically-confirmed (RT-PCR positive) case of COVID-19 of any severity meeting the case definition for the efficacy analysis. • Occurrence of second episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity.	In naïve evaluable subjects (complying with the definition of EAS) who had a first episode of a virologically-confirmed (RT-PCR positive) case of COVID-19 of any severity meeting the case definition for the efficacy analysis, at least 15 days following second trial vaccination: • The number and percentage of subjects who developed a second episode of COVID-19.

5 TRIAL DESIGN

5.1 Overall Design

The trial will be conducted as a randomized, observer-blinded, placebo-controlled trial. Subjects will receive a 2-dose schedule, 28 days apart, of either 1 of 2 lots CVnCoV, at a dose level of 12 µg mRNA, or placebo {normal saline (0.9% NaCl}) in a 1:1:1 ratio. Approximately 2,520 subjects (840 by randomization group), 18 years of age or older, previously enrolled in the non-interventional trial performed at the Mainz University, Germany (COVID19-5-P-002), other HCWs and potentially students in clinical training will be enrolled.

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

The primary safety objective is to expand the safety database that will demonstrate the safety profile of CVnCoV. The safety and reactogenicity of a 2-dose schedule of CVnCoV will be assessed in detail by measuring the frequency and severity of the following AEs: solicited local and systemic AEs on the day of vaccination and for the following 7 days after each vaccination in a subset of subjects (Immunogenicity/Reactogenicity Subset); unsolicited AEs on the day of vaccination and for the following 28 days after each vaccination in a subset of subjects (Immunogenicity/Reactogenicity Subset); medically-attended AEs through 6 months after the second trial vaccination in all subjects; and AESIs and SAEs through 1 year after the second trial vaccination in all subjects (see Appendix 9 and Appendix 10).

A DSMB will perform a review at regular meetings of the available safety data of both Trials CV-NCOV-004 and CV-NCOV-005.

The immunogenicity of CVnCoV after 1 and 2 doses will be evaluated in a subset of subjects (Immunogenicity/Reactogenicity Subset) by measuring binding antibodies to the SARS-CoV-2 RBD of S protein for the primary immunogenicity objective, and by measuring viral neutralizing antibodies for the secondary immunogenicity objective. Antibody persistence will be evaluated.

It will be evaluated descriptively in a subset of subjects (Immunogenicity/Reactogenicity Subset) if antibody responses to the RBD of S protein of SARS-CoV-2 induced by 2 different lots of CVnCoV are equivalent when measured on Day 43.

As a secondary efficacy objective of the CV-NCOV-005 trial, the efficacy of a 2-dose schedule of CVnCoV in the prevention of first episodes of virologically-confirmed cases of COVID-19 of any severity in SARS-CoV-2 naïve subjects will be assessed. The severity of COVID-19 cases occurring in the CVnCoV and placebo groups will also be described as a secondary objective.

Subjects will undergo active surveillance for COVID-19 (see Appendix 6). During all site visits and phone calls, subjects will be reminded to contact the site if they have an acute illness with any symptoms clinically consistent with COVID-19 or if they tested positive for SARS-CoV-2 outside of the trial context. In addition, subjects will be messaged up to twice a week and will provide a yes or no response to having COVID-19 symptoms. Those who respond “yes” will be contacted by trial staff for a follow-up interview and assessment, if

the investigator considers the symptoms could potentially indicate a COVID-19 case. If a subject is suspected of having COVID-19 illness or if they tested positive for SARS-CoV-2 outside of the trial context, he/she will undergo testing for SARS-CoV-2 infection with samples collected at the site or at a home visit. All subjects with confirmed COVID-19 will be followed until resolution of their disease. If the virogically-confirmed COVID-19 case occurred after the first trial vaccination but prior to the second, this second vaccination can be administered once the subject is 2 weeks symptom-free, and provided the dose can be administered within the predefined visit window. If the subject is hospitalized, the subject's progress must continue to be followed by the Investigator and a discharge summary obtained at the end of the hospitalization. Information on clinical symptoms and signs, their duration and severity, and treatment and outcome of the COVID-19 episode will be documented by trial staff and recorded in the electronic case report form (eCRF). Upon resolution, subjects will continue to be followed through the trial end in the same manner as those who have not presented with COVID-19. A second or subsequent episode of COVID-19 in a subject with prior disease will be counted for the exploratory objective assessing the reoccurrence of COVID-19 in vaccinated subjects.

For the analysis of efficacy against COVID-19 disease, the case must meet the following criteria (mild, moderate and severe COVID-19 disease is defined in Appendix 3 and Appendix 4):

- Must be 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 (see Section 9.2).
- Symptom onset must have occurred ≥ 15 days following the second trial vaccination.
- The subject must not have a history of virologically-confirmed COVID-19 at enrollment (based on exclusion criterion 1) or have developed a case of virologically-confirmed COVID-19 before 15 days following the second trial vaccination (see Section 10.2.4, EAS population for more details).
- The subject must have been demonstrated to be SARS-CoV-2 naïve at baseline and at Day 43 (seronegative to N protein).

These efficacy cases might be confirmed by the Adjudication Committee.

The DSMB will periodically monitor COVID-19 cases across CV-NCOV-004 and CV-NCOV-005 for signals of VDE with pre-specified criteria for halting based on these signals.

An interim analysis is planned. The cut-off date for the interim analysis in CV-NCOV-005 will be based on the regulatory requirements to obtain early conditional approval in Europe. All subjects will be unblinded after the final analysis results of trial CV-NCOV-004. Subjects of the study CV-NCOV-005 who were assigned to CVnCoV will continue, until the end of the trial {when the last subject has completed the last visit on Day 393 (see Section 5.4)}. During this period, accrual of COVID-19 cases will continue. Subjects who were assigned to placebo will not continue after unblinding and will be invited to an End of Trial visit for a final safety examination.

5.2 Scientific Rationale for Trial Design

See also Sections 3.2 and 5.1.

The difference in appearance and presentation of the investigational CVnCoV vaccine and placebo requires the trial to be conducted in an observer-blinded manner, which is a commonly used and well-accepted method for trial blinding. The randomized, observer-blinded, and placebo-controlled design will reduce the risk of bias in the safety, immunogenicity and efficacy outcomes of the trial (see also Section 7.3).

A total of 3,500-4,000 subjects is aimed to participate in the observational trial COVID19-5-P-002 at the University of Mainz. HCWs participating to the observational trial COVID19-5-P-002 will be invited to participate in the CV-NCOV-005 trial. Pending the number of subjects continuing from the observational trial in the CV-NCOV-005 trial, additional HCWs, and potentially students in clinical training will be recruited for the present trial. Participants of COVID19-5-P-002 who do not join CV-NCOV-005 will continue participation in COVID19-5-P-002.

The primary safety objective is to generate a large-scale safety database that will demonstrate the safety of CVnCoV among HCWs. The safety and reactogenicity of a 2-dose schedule of CVnCoV will be assessed in detail by measuring the frequency and severity of the following AEs: solicited local and systemic reactions for 7 days after each vaccination; unsolicited AEs for 28 days after each vaccination; medically-attended AEs through 6 months after the second trial vaccination; and AESIs and SAEs through 1 year after the second trial vaccination. As such, each subject will participate in the trial for approximately 13 months for the safety follow-up.

The detailed reactogenicity and immunogenicity data generated in Phase 2b of Trial CV-NCOV-004 will be the main dataset to be submitted in support of early conditional approval of CVnCoV. The present trial will provide additional safety and immunogenicity data, in the intended trial population of adults at the selected dose level, to be available for the file to be submitted to obtain early conditional approval in the European Union.

As a secondary efficacy objective, the efficacy of a 2-dose schedule of CVnCoV in the prevention of first episodes of virologically-confirmed cases of COVID-19 of any severity in SARS-CoV-2 naïve subjects will be assessed.

For the analysis of efficacy against COVID-19 disease, COVID-19 case ascertainment begins at ≥ 15 days following the second vaccination of CVnCoV. This time point allows the immune response to mature and reach its full height following the second dose. As such, case ascertainment starting at this time point represents the evaluation of full VE of CVnCoV against COVID-19.

The trial will run in parallel with CV-NCOV-004, and will follow the design of the Phase 3 part of that trial, including case collection and work-up, so that an integrated analysis of VE taking potential trial heterogeneity into account can be conducted (see Section 3.1.4).

Individuals with history of virologically-confirmed COVID-19 illness will be excluded from participating in this trial, as well as subjects with history of asymptomatic virologically-confirmed SARS-CoV-2 infection or SARS-CoV-2 positive serology. SARS-CoV-2 serology will be known for all subjects enrolled in Trial CV-NCOV-005 from the trial COVID19-5-P-002, but not necessarily for other HCWs and medical students

enrolling in trial CV-NCOV-005. The CV-NCOV-005 trial will not screen these subjects for virologically-confirmed SARS-CoV-2 infection or SARS-CoV-2 positive serology. In addition, routine RT-PCR testing will not be performed at screening to exclude individuals with SARS-CoV-2 infection at the time of enrollment.

5.3 Justification for Dose

Selection of the 12 µg mRNA dose level of CVnCoV for Trial CV-NCOV-005 was based on the safety, tolerability and immunogenicity results from Trials CV-NCOV-001 and CV-NCOV-002.

Refer to the Investigator's Brochure for an overview of these data.

5.4 End of Trial Definition

A subject is considered to have completed the trial when he/she has completed all visits, and procedures and tests applicable for the group to which he/she was randomized to.

End of trial CV-NCOV-005 is defined as when the last subject who received CVnCoV has completed the last visit on Day 393 or prematurely discontinued the trial. Placebo subjects will discontinue the trial once study protocol version 3.0 and 4.0 are approved.

5.5 Stopping/Pausing Rules for Safety

5.5.1 Individual Subject Stopping Rules

The individual subject stopping rules are met in case any of the following events occur after the first trial vaccination:

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

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

5.5.2 Pausing of the Trial

The decision to pause the trial (i.e. temporary stopping of enrollment and vaccinations) due to a safety signal will be based on a recommendation from the DSMB in consultation with the Sponsor (see Section 9.3.8.1). The DSMB may recommend pausing the trial for a safety concern following a review of accumulating safety data presented at the regularly scheduled DSMB meetings or from an ongoing review of AEs, which include but are not limited to, suspected unexpected serious adverse reactions (SUSARs); all SAEs judged as related to trial vaccine; concerning SAEs (e.g., AESIs); and all life-threatening SAEs and deaths. These events will be monitored by the DSMB on a regular basis during the trial. The selected AEs and procedures for the safety review are described in detail in the DSMB Charter.

To ensure subject safety on an ongoing basis, a blinded listing of the AEs as described above will be routinely monitored by the Chair of the DSMB (or designee) at regular intervals. For each review, the Chair {or designee(s)} will determine whether any single event or group of events constitute a new safety signal. If not, the Chair will inform the

Trial Team that there are no safety concerns. Conversely, if there is a safety concern, the Chair may unblind the AE or AEs and, if necessary, convene an ad-hoc DSMB meeting for further assessment of the event(s).

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

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

6 TRIAL POPULATION

The criteria for enrollment are to be followed explicitly. If it is noted that a subject who does not meet 1 or more of the inclusion criteria and/or meets 1 or more of the exclusion criteria is inadvertently enrolled and dosed, the Sponsor must be contacted immediately.

In this trial, individuals with history of virologically-confirmed COVID-19 illness will be excluded from participating in this trial, as well as subjects with history of asymptomatic virologically-confirmed SARS-CoV-2 infection or SARS-CoV-2 positive serology. SARS-CoV-2 serology will be known for all subjects enrolled in trial CV-NCOV-005 from the trial COVID19-5-P-002, but not necessarily for other HCWs and medical students enrolling in trial CV-NCOV-005. The CV-NCOV-005 trial will not screen these subjects for virologically-confirmed SARS-CoV-2 infection or SARS-CoV-2 positive serology. In addition, routine RT-PCR testing will not be performed at screening to exclude individuals with SARS-CoV-2 infection at the time of enrollment.

Any country specific regulation(s) will be adhered to in addition.

6.1 Inclusion Criteria for All Subjects

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

1. Male or female subjects 18 years of age or older.
2. HCWs, employees or students in clinical training.
3. Provide written informed consent prior to initiation of any trial procedures.
4. Expected compliance with protocol procedures and availability for clinical follow-up through the last planned visit.
5. Females of non-childbearing potential defined as follows: surgically sterile (history of bilateral tubal ligation/occlusion, bilateral oophorectomy or hysterectomy) or postmenopausal {defined as amenorrhea for ≥ 12 consecutive months prior to screening (Day 1) without an alternative medical cause}. A follicle-stimulating hormone level may be measured at the discretion of the Investigator to confirm postmenopausal status.
6. Females of childbearing potential: negative urine pregnancy test (human chorionic gonadotropin) within 24 hours prior to each trial vaccination on Day 1 and Day 29.
7. Females 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 ligation;
- Vasectomized partner or infertile partner;
- Sexual abstinence {periodic abstinence (e.g., calendar, ovulation, symptothermal and post-ovulation methods) and withdrawal are not acceptable}.

Refer to the Clinical Trial Facilitation Group recommendations on contraception and pregnancy testing for further details [32].

6.2 Exclusion Criteria

Subjects will not be enrolled in this trial if they meet any of the following criteria:

1. History of virologically-confirmed SARS-CoV-2 infection or SARS-CoV-2 positive serology.
2. For females: pregnancy or lactation.
3. Use of any investigational or non-registered product (vaccine or drug) within 28 days preceding the administration of the first trial vaccine or planned use during the trial.
4. Receipt of licensed vaccines within 28 days (for live vaccines) or 14 days (for inactivated vaccines) prior to the administration of the first trial vaccine.
5. Prior administration of any investigational SARS-CoV-2 vaccine or another coronavirus (SARS-CoV, MERS-CoV) vaccine or planned use during the trial.
6. Any treatment with immunosuppressants or other immune-modifying drugs (including but not limited to corticosteroids, biologicals and methotrexate) for > 14 days total within 6 months preceding the administration of trial vaccine or planned use during the trial. For corticosteroid use, this means prednisone or equivalent, 0.5 mg/kg/day for 14 days or more. The use of inhaled, topical, or localized injections of corticosteroids (e.g., for joint pain/inflammation) is permitted.
7. Any medically diagnosed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination including known infection with human immunodeficiency virus; current diagnosis of or treatment for cancer including leukemia, lymphoma, Hodgkin disease, multiple myeloma or generalized malignancy; chronic renal failure or nephrotic syndrome; and receipt of an organ or bone marrow transplant.
8. Active or chronic disease of, or currently on treatment for, hepatitis B virus or hepatitis C virus.
9. History of angioedema (hereditary or idiopathic) or history of any anaphylactic reaction.
10. History of pIMD.
11. History of allergy to any component of CVnCoV vaccine.
12. Administration of immunoglobulins or any blood products within 3 months prior to the administration of trial vaccine or planned receipt during the trial.
13. Subjects with a significant acute or chronic medical or psychiatric illness that, in the opinion of the Investigator, precludes trial participation (e.g., may increase the risk of

trial participation, render the subject unable to meet the requirements of the trial, or may interfere with the subject's trial evaluations). These include severe and/or uncontrolled cardiovascular disease, gastrointestinal disease, liver disease, renal disease, respiratory disease, endocrine disorder, and neurological and psychiatric illnesses. However, those with controlled and stable cases can be included in the trial.

14. Subjects with impaired coagulation or any bleeding disorder in whom an IM injection or a blood draw is contraindicated.

15. Foreseeable non-compliance with the trial procedures as judged by the Investigator.

6.3 Vaccine Delay Recommendations

After enrollment, subjects may encounter clinical circumstances that could warrant a delay of trial vaccine administration as described below.

- Subjects with a clinically significant (≥ Grade 2) active infection or other acute disease (as assessed by the Investigator) or temperature ≥ 38.0°C (≥ 100.4°F), within 3 days of intended trial vaccination on Day 1 or Day 29. This includes symptoms that could represent COVID-19 illness.
  - Trial vaccination should be delayed until the active infection or other acute disease has recovered to ≤ Grade 1 or the subject's temperature has decreased to < 38.0°C (< 100.4°F). Following resolution of the illness, the subject may be rescheduled for trial vaccination based on the judgment of the Investigator.
  - Afebrile subjects with a minor illness may be vaccinated at the discretion of the Investigator.
- For subjects who develop virologically-confirmed COVID-19 after the first trial vaccination but prior to the second; this second vaccination can be administered once the subject is 2 weeks symptom-free, and provided the dose can be administered within the predefined visit window.
- Receipt of a licensed vaccine within 28 days (for live vaccines) or 14 days (for inactivated vaccines) prior to or after scheduled administration of trial vaccine. As these are recommended windows, rescheduling trial vaccination to be compliant with these windows should only be done if practical.

6.4 Failure to Meet Eligibility Criteria

The Investigator must account for all subjects who sign an informed consent. If the subject is found to be not eligible (i.e., did not meet all inclusion criteria or met 1 or more exclusion criteria), the Investigator should document this in the subject's source documents.

Re-screening, i.e., re-doing the full assessments for eligibility criteria as per Table 1 and Table 2 or re-doing 1 assessment, are allowed by the Investigator.

7 TRIAL VACCINE

7.1 Trial Vaccine Administration

7.1.1 Description of the Trial Vaccines

CVnCoV is an investigational LNP-formulated RNActive® SARS-CoV-2 vaccine. The IMP is composed of the active pharmaceutical ingredient, an mRNA that encodes the stabilized full-length S protein, and 4 lipid components: cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine, PEG-ylated lipid and a cationic lipid. It is supplied as a concentrate at 1 mg/mL of mRNA drug substance. Two different lots of the CVnCoV vaccine will be used.

The placebo vaccine will be sterile normal saline (0.9% NaCl) for injection.

7.1.2 Dosing and Administration

7.1.2.1 CVnCoV

Subjects randomized to CVnCoV will receive 2 injections of CVnCoV at a dose level of 12 µg mRNA, administered 28 days apart.

Administration of CVnCoV must be performed by IM injection in the deltoid area, preferably in the non-dominant arm. CVnCoV is intended strictly for IM injection and must not be injected subcutaneously, intradermally, or intravenously. The instructions for injection as described in the Pharmacy Manual must be followed.

7.1.2.2 Placebo Control (Normal Saline)

Subjects randomized to the control group of the trial will receive 2 doses of saline placebo {normal saline (0.9% NaCl) for injection}, administered 28 days apart.

Administration of saline placebo must be performed by IM injection in the deltoid area, preferably in the non-dominant arm. The instructions for injection described in the Pharmacy Manual must be followed.

7.1.2.3 Hypersensitivity Reactions to Vaccination

CVnCoV should not be administered to subjects with a known hypersensitivity to any of the components of the vaccine.

Since there is a theoretical risk of anaphylactic reactions, trial vaccine must only be administered if emergency equipment for the treatment of anaphylactic reactions (intravenous fluids, corticosteroids, H1 and H2 blocking agents, epinephrine, equipment for cardiopulmonary resuscitation) is readily available. **All subjects must remain under direct supervision of personnel trained in the treatment of these reactions for at least 30 minutes following administration of trial vaccine.**

If anaphylaxis or severe hypersensitivity reactions occur following trial vaccine administration, no further doses should be given (see Sections 5.5.1 and 8.1).

7.2 Preparation/Handling/Storage/Accountability

Refer to the Pharmacy Manual for detailed information on the preparation, handling, storage and blinding of CVnCoV and saline placebo.

7.2.1 CVnCoV Preparation

The concentrated CVnCoV must be diluted in the provided sterile normal saline (0.9% NaCl) diluent containing preservative to produce the dose solution for IM injection. This will be prepared by an unblinded qualified pharmacist/site personnel according to the Handling Manual for the IMP provided by CureVac AG. The unblinded pharmacist/site personnel will have no other trial function following vaccination and will maintain the treatment assignments in strict confidence.

7.2.2 CVnCoV Product Storage and Stability

Concentrated CVnCoV will be shipped to the site frozen at below -60°C.

Once at the site, concentrated CVnCoV should be stored frozen at below -60°C.

7.2.3 Placebo Control (Normal Saline)

The normal saline placebo control vaccine should be stored according to the Summary of Product Characteristics. Placebo will be prepared for injection by an unblinded pharmacist/site personnel.

7.2.4 Accountability

It is the responsibility of the Investigator to ensure that the current and accurate records of trial supplies received, stored, and dispensed at the site are maintained using appropriate forms according to applicable regulations and guidelines. The trial supplies must be stored under the recommended storage conditions, locked with restricted access (refer to the Pharmacy Manual). Authorized personnel must dispense the vaccine at the site and in accordance with the protocol and applicable regulations and guidelines.

IMP accountability and inventory logs must be kept up-to-date at the site with the following information:

- Dates and quantities of CVnCoV received from CureVac.
- Unique subject identifier.
- Date and quantity of trial vaccine dispensed to each subject.
- Initials of the person preparing the dose.
- Initials of the person administering the vaccine.

These logs must be readily available for inspections and are open to regulatory inspection at any time.

7.3 Randomization and Blinding

The trial will be randomized, observer-blinded, and placebo-controlled. The difference in appearance of the investigational CVnCoV vaccine and placebo required the trial to be conducted in an observer-blinded manner, which is a well-accepted method for blinding.

7.3.1 Randomization

Approximately 2,520 subjects 18 years of age or older will be enrolled at the site at Mainz University, Germany and will be randomized in a 1:1:1 ratio (840 by randomization group) to receive either 1 of 2 different lots of CVnCoV (CVn CoV Lot 1 group and CVnCoV Lot 2 group) or placebo (placebo group). The randomization will be performed centrally and stratified by age group (18 to 60 and ≥ 61 years of age). The randomization scheme will be generated and maintained by the Statistical and Data Management group at the contract research organization (CRO), PRA. Subjects will be enrolled into the trial online and randomized using an interactive web response system (IWRS). After demographic and eligibility criteria are entered into the system, subjects enrolled into the trial will be assigned their treatment assignment.

The first 1,260 subjects enrolled are planned to be included in the Immunogenicity/Reactogenicity Subset.

7.3.2 Blinding

Subjects will be randomized and vaccinated with CVnCoV or placebo in an observer-blinded manner (due to the difference in appearance and presentation of the investigational CVnCoV vaccine and placebo). The pharmacist/ personnel preparing the trial vaccine at the site will not be blinded to the identity of the trial vaccine being administered to the subject. However, the vaccinator, Investigator and all site personnel involved in the conduct of the trial (including follow-up of safety and COVID-19 case ascertainment) will be blinded to trial vaccine and subject treatment assignments. To maintain the blinding of the vaccinator, the unblinded pharmacist/site personnel will provide the dose of trial vaccine to the vaccinator prefilled in a syringe with a label covering the liquid contents so that it is not visible. All personnel at the CRO and Sponsor directly involved in the conduct of the trial will also be blinded. There will be certain individuals at the CRO and Sponsor whose function requires them to be unblinded during the trial {e.g., unblinded monitoring for trial vaccine accountability in the pharmacy; unblinded independent statistician assisting the DSMB; review of immunogenicity data (see next paragraph)}. These unblinded individuals will be identified and their responsibilities documented.

Because the immunogenicity results would unblind the subject's treatment assignment, the independent laboratory performing the assays will keep the results in strict confidence. An unblinded person, named at the start of the trial and independent of the conduct of the trial, will have the responsibility of reviewing the quality of the immunogenicity data as it is being generated. This person will maintain the results in strict confidence. To maintain the blind, the immunogenicity data will only be merged with the clinical database following unblinding of the trial.

It will be at the discretion of the DSMB members whether or not safety data reviewed at the DSMB meetings will be unblinded. If there are any safety concerns, the DSMB may request unblinding of an individual subject or a specific dataset at any time. In addition, the DSMB will periodically monitor COVID-19 cases by vaccine group for signals of VDE.

For the submission of documents for regulatory approval during the ongoing conduct of Trial CV-NCOV-004 and CV-NCOV-005 (e.g., if efficacy is demonstrated at 1 of the interim analyses), an unblinded Submission Team will be formed which will be completely

independent of the team conducting the trial. The Submission Team will comprise individuals from the Sponsor and CRO, and their roles and responsibilities on the unblinded team will be clearly defined.

7.3.3 Unblinding

7.3.3.1 Emergency Unblinding

Individual unblinding should only occur in emergency situations for reasons of subject safety when knowledge of the trial vaccine is essential for the clinical management or welfare of the subject. Unblinding in this situation will be based on the judgment of the Investigator, ideally in discussion with the Sponsor.

In general, the identity of the trial vaccine should not affect the clinical management of any SAE/AE. Whenever possible, the Investigator should attempt to contact the Sponsor before breaking the blind to discuss the need for emergency unblinding. Once agreed, code-breaking will be carried out via the IWRS.

When the blind is broken, the date, exact timing, and reason must be fully documented in the source documents. The Investigator should not inform other blinded trial staff of the identity of the IMP.

If the code has been broken and there are no medical reasons for discontinuation, the subject may continue in the trial. If the subject has received at least 1 dose of trial vaccine, it will be the judgment of the Investigator, in consultation with the Sponsor, whether the subject will be vaccinated with the second dose. If the subject is discontinued from the trial, every effort should be made to continue safety follow-up of the subject until the end of the trial.

7.3.3.2 Authorized/Licensed Vaccine

Unblinding is allowed in case a subject becomes eligible to receive an authorized/licensed vaccine.

Following the availability of the efficacy results from the HERALD study for CVnCoV and given that all subjects in this present study are currently eligible to receive an authorized vaccine, **all** subjects in this CV-NCOV-005 trial will be unblinded.

7.4 Vaccine Compliance

The Investigator must record all trial vaccinations administered in the subject's eCRF page.

7.5 Misuse and Overdose

Definition of misuse: Situations where the trial vaccine is intentionally and inappropriately used not in accordance with the protocol dosing instructions or authorized product information.

Definition of overdose: Administration of a quantity of the trial vaccine given per administration or cumulatively which is above the maximum recommended dose according to the protocol dosing instructions or authorized product information.

No toxic effects are expected from current clinical and non-clinical experience. Possible local reactions (pain) or systemic AEs (fever, headache, fatigue, chills, myalgia, arthralgia, nausea/vomiting and diarrhea) may be treated symptomatically with physical measures, paracetamol, or non-steroidal anti-inflammatory drugs.

7.6 Concomitant Therapy and Vaccines

Concomitant medication for underlying diseases and the underlying disease for which it is administered and vaccines must be recorded in the subject's eCRF.

For all subjects, concomitant therapies associated with an SAE or an AESI will be collected and recorded in the eCRF from the moment of informed consent was obtained through the end of the trial. Concomitant therapies associated with medically-attended AEs occurring from the moment of vaccination until 6 months after vaccination will also be collected and recorded in the eCRF.

For all subjects, concomitant therapies associated with COVID-19 will be captured in the eCRF for the duration of the trial.

For subjects in the immunogenicity / reactogenicity subset of the trial, concomitant therapies associated with unsolicited AEs occurring from the time of vaccination through 28 days after vaccination will be collected and recorded in the eCRF. Concomitant therapies associated with solicited AEs occurring from the time of vaccination through 7 days after vaccination will also be collected and recorded in the eCRF.

Throughout the entire trial, any medications/vaccines prohibited according to Section 7.6.2, including immunosuppressants or other immune-modifying drugs need to be documented, if taken by a subject.

7.6.1 Permitted Medications/Vaccines During the Trial

Subjects are permitted to use antipyretics and other pain medications to treat any ongoing condition(s) the subject may have. Antipyretics (e.g., paracetamol) or other pain medication may be used to treat any local and/or systemic reactions associated with trial vaccination. Paracetamol taken prophylactically for potential vaccine-associated reactions is also permitted in this trial. For example, if a subject experiences adverse reactions following the first trial vaccination, paracetamol may be taken prophylactically for these reactions for the second trial vaccination. In this case, paracetamol (up to 1 gram dose) may be taken after trial vaccination and at bedtime, and then in the morning and at bedtime during the next day. Alternatively, a 500 mg dose of paracetamol may be taken every 6 hours after trial vaccination for up to 36 hours. The dose and dosing schedule of paracetamol should be discussed with the Investigator.

Paracetamol administered as a treatment for vaccine-associated reactions or for prophylaxis, along with timing of administration with respect to trial vaccination must be documented in the eCRF.

Other than the prohibited medications and vaccines described in Section 6.2 and listed below in Section 7.6.2, medications that are required for the treatment of the subject's pre-existing medical conditions are permitted.

7.6.2 Prohibited Medications/Vaccines During the Trial

- Use of any investigational or non-registered product (vaccine or drug) is prohibited during the trial.
- Authorized SARS-CoV-2 vaccines are allowed. An interval of at least 21 days should be observed between the last dose of CVnCoV and the authorized vaccine.
- Other licensed vaccines should not be administered within 28 days (for live vaccines) or 14 days (for inactivated vaccines) of trial vaccine administration during the trial.
- Receipt of any other investigational SARS-CoV-2 vaccine or vaccines against other virus from the coronavirus family is prohibited during the trial.
- Any treatment with immunosuppressants or other immune-modifying drugs (including but not limited to corticosteroids, biologicals and methotrexate) is prohibited during the trial. For corticosteroid use, this means prednisone or equivalent, 0.5 mg/kg/day for 14 days or more. The use of inhaled, topical, or localized injections of corticosteroids (e.g., for joint pain/inflammation) is permitted.
- Administration of immunoglobulins or any blood products is prohibited during the trial.

7.7 Therapy Leading to Discontinuation

If a subject requires therapy listed as an exclusion criterion in Section 6.2 and which cannot be delayed, discontinuation would be considered to ensure integrity of the trial data, following individual case review. Every effort should be made to continue safety follow-up of the subject until the end of the trial.

7.8 Treatment After the End of Trial

No post-trial care will be provided.

8 DISCONTINUATION/WITHDRAWAL CRITERIA

Participation in the trial is strictly voluntary. A subject has the right to withdraw from the trial at any time and for any reason. The Investigator has the right to withdraw a subject from further trial vaccine administration and/or the trial if this is considered in the subject's best interest or as a result of a protocol deviation.

For discontinuations due to an AE, every effort should be made to document the outcome of the event.

Subjects who received at least 1 dose of CVnCoV will be encouraged to continue participation until the end of the trial for safety assessments.

8.1 Discontinuation of Trial Vaccine Administration

The primary reason for discontinuation of further administration of trial vaccine will be recorded in the subject's eCRF according to the following categories:

- Consent withdrawal by the subject.

  The reason for withdrawal, if provided, should be recorded in the eCRF.

  Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (i.e., withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category).

- The subject becomes eligible to receive an authorized/licensed SARS-CoV-2 vaccine, requests to be unblinded, and refrains from getting the second dose of trial vaccine.

- AE (including known side effects of the trial vaccine).

  If discontinuation is due to an AE possibly related to the trial vaccine or trial procedures, the subject must be followed-up by additional examinations according to the medical judgment of the Investigator until the condition is resolved or the Investigator deems further observations or examinations to be no longer medically indicated.

- Change in the subject's overall medical status prohibiting further participation.

- Pregnancy (see Section 9.3.4).

  Any subject who, despite the requirement for adequate contraception, becomes pregnant during the trial will not receive further trial vaccine doses. The site should maintain contact with the pregnant subject and complete a "Clinical Trial Pregnancy Form" as soon as possible. In addition, the subject should be followed-up until the birth of the child, or spontaneous or voluntary termination. When pregnancy outcome information becomes available, the information should be captured using the same form. The subject should be reported as an IMP discontinuation and the reason (i.e. pregnancy) should be given.

- Trial terminated by the Sponsor (in which case the minimum safety follow-up conducted at the end of trial visit on Day 393 would be performed in subjects who received CVnCoV).

- Major protocol deviation.
- Other.

Note: The specific reasons should be recorded in the “specify” field of the eCRF.

8.2 Withdrawal from the Trial

Subjects should be withdrawn from the trial in case any of the following situations occur:

- Continued participation jeopardizes the subject’s health, safety, or rights.
- The subject has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the subject’s health or the subject is unwilling to continue because of the AE. The reasons for not performing further safety or immunogenicity assessments should be documented.
- The subject did not return to the site and multiple attempts (a minimum of 3 attempts) to contact the subject were unsuccessful (lost to follow-up).
- The subject wishes to withdraw from the trial. The reason for withdrawal, if provided, should be recorded; this could include the availability of an approved COVID-19 vaccine.

All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (i.e., withdrawal due to an AE should not be recorded in the “voluntary withdrawal” category).

Any subject who prematurely terminates participation and who has received at least 1 trial vaccine dose will undergo the same procedures as for the end of trial visit, unless such procedures are considered to pose unacceptable risk to the subject.

After trial unblinding, i.e. after approval of study protocol version 3.0 and 4.0, all placebo subjects should be withdrawn at the earliest possible timepoint, if their originally planned End of Trial visit is later than February 2022 and will undergo the same procedures as for the End of Trial visit at their withdrawal visit. If a withdrawal visit cannot be scheduled for placebo subjects due to the pandemic setting, the end of trial assessment, i.e. collection of final safety data, can also be done by phone. In the e-CRF, the withdrawal reason for placebo subjects should be documented as “placebo subject withdrawn after trial unblinding”.

Discontinued or withdrawn subjects will not be replaced.

8.3 Trial Termination

The Sponsor reserves the right to terminate the trial at any time. Possible reasons for trial termination include the following:

- Outcome of the interim analysis may show high VE or futility.
- Safety reasons: the incidence of AEs in this or any other trial using a related vaccine indicates a potential health risk for the subjects.

- New scientific knowledge becomes known that makes the objectives of the trial no longer feasible/valid.
- The site is unlikely to be able to recruit sufficient subjects within the agreed time frame.
- The site does not respond to trial management requests.
- Repeated protocol deviations.
- Unsafe or unethical practices.
- Administrative decision.

Following a trial termination decision, the Investigator must contact all subjects within a time period set by the Sponsor. All trial materials must be collected and relevant documentation completed to the greatest extent possible.

The trial can also be terminated by the Regulatory Authority for any reason or if recommended by the DSMB, or at a site level by the Institutional Review Board or Independent Ethics Committee (IRB/IEC). The Sponsor may close the site prematurely for reasons such as poor protocol compliance or unsatisfactory recruitment of subjects.

8.4 Lost to Follow-Up

All efforts should be made to contact subjects who have not returned for the scheduled trial visit or who are unable to be contacted for a scheduled phone call. A minimum of 3 attempts should be made and documented. If a subject is lost to follow-up before resolution of related SAEs or AEs, the Sponsor may consider further attempts to contact the subject in order to collect follow-up safety information.

9 TRIAL ASSESSMENTS AND PROCEDURES

The trial assessments and procedures for trial CV-NCOV-005 are presented in Table 1, and Table 2. The trial assessments and procedures are discussed in this section.

For subjects who are unable to come to the site for protocol-specified site visits (e.g., due to the public health emergency related to COVID-19), safety assessments may be performed using alternative methods (e.g., phone contact, virtual visit, alternative location for assessment).

For further flexibility in trial conduct in the pandemic setting, home visits will be allowed to perform safety assessments and procedures including the collection of blood and nasopharyngeal swabs. If site visits, phone contacts or sample collection cannot be performed within the protocol-defined windows, in such unique circumstances as a public health emergency, it will be acceptable to perform these tasks outside of these windows. In the pandemic setting, the protocol-defined windows for site visits and phone contacts are provided for guidance and will not be considered deviations, if not strictly adhered to.

An electronic diary (eDiary) will be used during the trial for efficient collection of safety-related information. However, paper diaries may be substituted for some subjects during the trial.

9.1 Schedule of Trial Assessments and Procedures

By signing the informed consent form, subjects will be consenting to participate in trial CV-NCOV-005 for a total of approximately 13 months.

Refer to Table 1 (Immunogenicity/Reactogenicity Subset) and Table 2 (All Other Subjects and subjects that, following unblinding, receive an authorized vaccine after having received at least one dose of CVnCoV) for the Schedule of Trial Assessments and Procedures.

The trial assessments and procedures apply to all subjects, independent of their serology status at baseline.

During the conduct of the trial and interactions with subjects, any person with early warning signs of COVID-19 should be referred to emergency medical care immediately. These signs include, but are not limited to, the following: difficulty breathing, persistent pain or pressure in the chest, new confusion, inability to awake or stay awake, or bluish lips or face.

9.1.1 Immunogenicity/Reactogenicity Subset

The Immunogenicity/Reactogenicity Subset will include the first 1,260 subjects enrolled.

Subjects participating in the Immunogenicity/Reactogenicity Subset will be given a thermometer to measure body temperature orally and a measuring tape to determine the size of local injection site reactions. Subjects will be instructed on how to enter the solicited AEs daily for 7 days in the eDiary.

9.1.1.1 Clinic Visit 1: Day 1 - First Trial Vaccination

Note that procedures to establish subject eligibility, recording of demographic information and medical history may be performed within 21 days prior to trial vaccine administration, i.e., spread out over more than 1 day. However, if all information is available and assessments and procedures can be performed, eligibility can be established on the same day of trial vaccine administration. All eligibility criteria must be reviewed prior to trial vaccine administration on Day 1.

Pre-vaccination Procedures

- Obtain the signed informed consent form.
    - Signed informed consent must be obtained prior to the subject entering into the trial, and before any protocol-directed procedures are performed (see Section 12.4).
    - By signing the informed consent form, the subject voluntarily agrees to participate in the trial CV-NCOV-005.
- Review inclusion/exclusion criteria (see Section 6.1 and 6.2) and review prohibited medications listed as an exclusion criterion (see Section 6.2).
- Record demographic information.
- Record medical history.
- Record concomitant medications and vaccinations, including recurring medications for intermittent conditions, if taken within 6 months prior to enrollment in this trial.
- Perform a complete physical examination, including height and weight (see Section 9.3.6). If a complete physical examination was performed out of the scope of this trial within 21 days prior to trial vaccine administration, a symptom-directed physical examination should be performed on the day of vaccination prior to trial vaccine administration.
- Measure vital signs (body temperature, pulse, blood pressure; see Section 9.3.6).
- Perform urine pregnancy test in females of childbearing potential (Appendix 5).
- Collect pre-vaccination blood samples (see Table 1) for binding antibody testing to RBD of S protein of SARS-CoV-2 (~6 mL blood); SARS-CoV-2 viral neutralizing activity (~6 mL blood); and binding antibody testing to N protein of SARS-CoV-2 (~6 mL blood).
- Collect pre-vaccination blood samples for CMI (~38 mL blood) from subjects of the CMI Subset.
- Randomize the subject (see Section 7.3.1).

Vaccination Procedure

- Review criteria for delay or cancellation of vaccination. See Sections 6.3 and 8.1 for an overview of the criteria leading to delay or cancellation of vaccine administration.

In case of delay, the vaccination should take place within the allowed time windows. The reasons for delay or cancellation should be documented in the subject's chart.

- Administer the trial vaccine dose according to the subject's assignment.

Post-vaccination Procedures

- Observe the subject on site for at least 30 minutes following vaccination for safety monitoring. At the end of the observation period:
  - Measure vital signs (body temperature, pulse, blood pressure; see Section 9.3.6).
  - The subject may not be discharged until vital signs are within normal range or have returned to pre-vaccination levels.
  - Record the occurrence of any AEs following trial vaccination.
- Instructions for the subject:
  - Instruct the subject how to measure solicited AEs and how to complete the eDiary. The subject should record solicited local and systemic AEs occurring on the day of vaccination and the following 7 days, and unsolicited AEs (i.e., the occurrence of all other AEs) occurring on the day of vaccination and the following 28 days.
  - Remind the subject to call the site immediately to report the following:
    - If he/she experiences any concerning local or systemic reactions or other medical event.
    - Any medically-attended visits that are not routine visits for physical examination or vaccination, such as visits for hospitalization, an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason.
    - Experience a serious medical event, have a change in overall health or be diagnosed with a new medical condition by a doctor. These should be reported regardless of the perceived relationship between the event and the trial vaccine.
  - Remind the subject to contact the site immediately if he/she has any of the symptoms suggestive of COVID-19. In addition, subjects will be messaged up to twice a week to provide a yes or no response to having COVID-19 symptoms. Those who respond "yes" will be contacted by trial staff for follow-up information, if the investigator considers the symptoms could potentially indicate a COVID-19 case (see Section 9.2.1 and Section 9.5).
  - The subject should also be reminded to contact the site immediately if he/she had a positive SARS-CoV-2 test performed outside of the site, irrespective of whether they were symptomatic (COVID-19 illness) or asymptomatic at the time of the test.

    Note: Subjects without symptoms may have been tested for several reasons, for example, close exposure to a known person with SARS-CoV-2 infection or as part of their routine screening as a healthcare provider.

9.1.1.2 Phone Call: Day 2 (-0/+0 day)

The purpose of this phone contact is to inquire about the subject's general well-being and to assess safety 1 day after the first trial vaccination.

- During the phone call:
  - Review and record any newly reported safety data including solicited and unsolicited AEs, or other AEs (medically-attended AEs, SAEs).
  - Record concomitant medications and vaccinations, vaccinations according to instructions in Section 7.6.
  - If the subject reports any concerning local or systemic reactions, or other AEs (e.g., medically-attended AEs, SAEs), these should be followed-up either by a phone call(s) or by an unscheduled site visit based on the judgment of the Investigator.
- Instructions for the subject:
  - Remind the subject to continue recording solicited and unsolicited AEs (i.e., the occurrence of all other AEs) in the eDiary.
  - Remind the subject to call the site immediately to report the following:
    - If he/she experiences any concerning local or systemic reactions or other medical event.
    - Any medically-attended visits that are not routine visits for physical examination or vaccination, such as visits for hospitalization, an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason.
    - Experience a serious medical event, have a change in overall health or be diagnosed with a new medical condition by a doctor. These should be reported regardless of the perceived relationship between the event and the trial vaccine.
  - Remind the subject to contact the site immediately if he/she has any of the symptoms suggestive of COVID-19. In addition, subjects will be messaged up to twice a week to provide a yes or no response to having COVID-19 symptoms. Those who respond "yes" will be contacted by trial staff for follow-up information, if the investigator considers the symptoms could potentially indicate a COVID-19 case (see Section 9.2.1 and Section 9.5).
  - The subject should also be reminded to contact the site immediately if he/she had a positive SARS-CoV-2 test performed outside of the site, irrespective of whether they were symptomatic (COVID-19 illness) or asymptomatic at the time of the test.

9.1.1.3 Clinic Visit 2: Day 29 - Second Trial Vaccination (-3/+7 days)

<u>Pre-vaccination Procedures</u>

- Review and record any newly reported safety data including solicited and unsolicited AEs, or other AEs (medically-attended AEs, SAEs).

- Record concomitant medications and vaccinations, according to instructions in Section 7.6.
- Perform a symptom-directed physical examination (see Section 9.3.6).
- Measure vital signs (body temperature, pulse, blood pressure, see Section 9.3.6).
- Perform urine pregnancy test in females of childbearing potential (Appendix 5).
- Collect pre-vaccination blood samples (see Table 1) for binding antibody testing to RBD of S protein of SARS-CoV-2 (~6 mL blood) and SARS-CoV-2 viral neutralizing activity (~6 mL blood). No testing of antibody to N protein of SARS-CoV-2 will be performed at this time point.
- Collect pre-vaccination blood samples for CMI (~38 mL blood) from subjects of the CMI Subset.

Vaccination Procedure

- Review criteria for delay or cancellation of vaccination. See Sections 6.3 and 8.1 for an overview of the criteria leading to delay or cancellation of vaccine administration. In case of delay, the vaccination should take place within the allowed time windows. The reasons for delay or cancellation should be documented in the subject's chart.
- Administer the trial vaccine dose according to the subject's assignment.

Post-vaccination Procedures

- Observe the subject on site for at least 30 minutes following vaccination for safety monitoring. At the end of the observation period:
  - Measure vital signs (body temperature, pulse, blood pressure; see Section 9.3.6).
  - The subject may not be discharged until vital signs are within normal range or have returned to pre-vaccination levels.
  - Record the occurrence of any AEs following trial vaccination.
- Instructions for the subject:
  - Re-instruct the subject how to measure solicited AEs and how to complete the eDiary. The subject should record solicited local and systemic AEs occurring on the day of vaccination and the following 7 days, and unsolicited AEs (i.e., the occurrence of all other AEs) occurring on the day of vaccination and the following 28 days.
  - Remind the subject to call the site immediately to report the following:
    - If he/she experiences any concerning local or systemic reactions or other medical event.
    - Any medically-attended visits that are not routine visits for physical examination or vaccination, such as visits for hospitalization, an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason.

- Experience a serious medical event, have a change in overall health or be diagnosed with a new medical condition by a doctor. These should be reported regardless of the perceived relationship between the event and the trial vaccine.

- Remind the subject to contact the site immediately if he/she has any of the symptoms suggestive of COVID-19. In addition, subjects will be messaged up to twice a week to provide a yes or no response to having COVID-19 symptoms. Those who respond "yes" will be contacted by trial staff for follow-up information, if the investigator considers the symptoms could potentially indicate a COVID-19 case (see Section 9.2.1 and Section 9.5).

- The subject should also be reminded to contact the site immediately if he/she had a positive SARS-CoV-2 test performed outside of the site, irrespective of whether they were symptomatic (COVID-19 illness) or asymptomatic at the time of the test.

9.1.1.4 Phone Call: Day 30 (-0/+0 day)

The purpose of this phone contact is to inquire about the subject's general well-being and to assess safety 1 day after the second trial vaccination.

The assessments and procedures are identical to those performed during the phone call on Day 2.

9.1.1.5 Clinic Visit 3: Day 43 (-3/+3 days)

- Review and record any newly reported safety data including solicited and unsolicited AEs, or other AEs (medically-attended AEs, SAEs).
- Record concomitant medications and vaccinations, according to instructions in Section 7.6.
- Perform a symptom-directed physical examination (see Section 9.3.6).
- Measure vital signs (body temperature, pulse, blood pressure, see Section 9.3.6).
- Collect blood samples (see Table 1) for binding antibody testing to RBD of S protein of SARS-CoV-2 (~6 mL blood); SARS-CoV-2 viral neutralizing activity (~6 mL blood); and binding antibody testing to N protein of SARS-CoV-2 (~6 mL blood).
- Collect blood samples for CMI (~38 mL blood) from subjects of the CMI Subset.
- Instructions for the subject:
  - Inform the subject that recording of solicited local and systemic reactions in the eDiary is complete. Remind the subject to continue recording unsolicited AEs (all AEs).
  - Remind the subject to call the site immediately to report the following:
    - If he/she experiences any concerning medical event.
    - Any medically-attended visits that are not routine visits for physical examination or vaccination, such as visits for hospitalization, an emergency

room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason.

- Experience a serious medical event, have a change in overall health or be diagnosed with a new medical condition by a doctor. These should be reported, regardless of the perceived relationship between the event and the trial vaccine.

- Remind the subject to contact the site immediately if he/she has any of the symptoms suggestive of COVID-19. In addition, subjects will be messaged up to twice a week to provide a yes or no response to having COVID-19 symptoms. Those who respond “yes” will be contacted by trial staff for follow-up information, if the investigator considers the symptoms could potentially indicate a COVID-19 case (see Section 9.2.1 and Section 9.5).

- The subject should also be reminded to contact the site immediately if he/she had a positive SARS-CoV-2 test performed outside of the site, irrespective of whether they were symptomatic (COVID-19 illness) or asymptomatic at the time of the test.

9.1.1.6 Clinic Visit 4: Day 57 (-3/+7 days)

- Review and record any newly reported safety data including unsolicited AEs or other AEs (medically-attended AEs, SAEs).
- Record concomitant medications and vaccinations, according to instructions in Section 7.6.
- Perform a symptom-directed physical examination (see Section 9.3.6).
- Measure vital signs (body temperature, pulse, blood pressure, see Section 9.3.6).
- Collect a blood sample for immunogenicity assessment (see Table 1) for binding antibody testing to RBD of S protein of SARS-CoV-2 (~6 mL blood) and SARS-CoV-2 viral neutralizing activity (~6 mL blood). No testing of binding antibody to N protein of SARS-CoV-2 will be performed at this time point.
- Collect blood samples for CMI (~38 mL blood) from subjects of the CMI Subset.
- Instructions for the subject:
  - Inform the subject that reporting of unsolicited AEs is complete.
  - Remind the subject to call the site immediately to report the following:
    - If he/she experiences any concerning medical event.
    - Any medically-attended visits that are not routine visits for physical examination or vaccination, such as visits for hospitalization, an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason.
    - Experience a serious medical event, have a change in overall health or be diagnosed with a new medical condition by a doctor. These should be reported regardless of the perceived relationship between the event and the trial vaccine.

- Remind the subject to contact the site immediately if he/she has any of the symptoms suggestive of COVID-19. In addition, subjects will be messaged up to twice a week to provide a yes or no response to having COVID-19 symptoms. Those who respond “yes” will be contacted by trial staff for follow-up information, if the investigator considers the symptoms could potentially indicate a COVID-19 case (see Section 9.2.1 and Section 9.5).
- The subject should also be reminded to contact the site immediately if he/she had a positive SARS-CoV-2 test performed outside of the site, irrespective of whether they were symptomatic (COVID-19 illness) or asymptomatic at the time of the test.

9.1.1.7 Clinic Visit 5: Day 120 (-7/+7 days)

- Review and record any newly reported AEs since the site visit on Day 57 (medically-attended AEs, SAEs).
- Record concomitant medications and vaccinations, according to instructions in Section 7.6.
- Perform a symptom-directed physical examination (see Section 9.3.6).
- Measure vital signs (body temperature, pulse, blood pressure, see Section 9.3.6).
- Collect blood samples (see Table 1) for binding antibody testing to RBD of S protein of SARS-CoV-2 (~6 mL blood) and SARS-CoV-2 viral neutralizing activity (~6 mL blood). No testing of binding antibody to N protein of SARS-CoV-2 will be performed at this time point.
- Collect blood samples for CMI (~38 mL blood) from subjects of the CMI Subset.
- Instructions for the subject:
  - Remind the subject to call the site immediately to report the following:
    - If he/she experiences any concerning medical event.
    - Any medically-attended visits that are not routine visits for physical examination or vaccination, such as visits for hospitalization, an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason.
    - Experience a serious medical event, have a change in overall health or be diagnosed with a new medical condition by a doctor. These should be reported regardless of the perceived relationship between the event and the trial vaccine.
  - Remind the subject to contact the site immediately if he/she has any of the symptoms suggestive of COVID-19. In addition, subjects will be messaged up to twice a week to provide a yes or no response to having COVID-19 symptoms. Those who respond “yes” will be contacted by trial staff for follow-up information, if the investigator considers the symptoms could potentially indicate a COVID-19 case (see Section 9.2.1 and Section 9.5).

- The subject should also be reminded to contact the site immediately if he/she had a positive SARS-CoV-2 test performed outside of the site, irrespective of whether they were symptomatic (COVID-19 illness) or asymptomatic at the time of the test.

9.1.1.8 Clinic Visit 6: Day 211 (-7/+7 days)

The assessments and procedures are identical to those performed during Clinic Visit 5 on Day 120, except for the below.

- Collect blood samples (see Table 1) for binding antibody testing to RBD of S protein of SARS-CoV-2 (~6 mL blood); SARS-CoV-2 viral neutralizing activity (~6 mL blood); and binding antibody testing to N protein of SARS-CoV-2 (~6 mL blood).
- Collect blood samples for CMI (~38 mL blood) from subjects of the CMI Subset.

9.1.1.9 Phone Call: Day 302 (-7/+7 days)

The purpose of this phone contact is to inquire about the subject's general well-being and to assess safety since the site visit on Day 211.

- During the phone call:
  - Review and record any newly reported AEs since the site visit on Day 211 (SAEs).
  - Record concomitant medications and vaccinations, according to instructions in Section 7.6.
  - If the subject reports by phone any concerning AEs, these should be followed-up either by a phone call(s) or by an unscheduled site visit based on the judgment of the investigator.
- Instructions for the subject:
  - Remind the subject to call the site immediately to report the following:
    - If he/she experiences any concerning medical event.
    - Any medically-attended visits that are not routine visits for physical examination or vaccination, such as visits for hospitalization, an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason.
    - Experience a serious medical event, have a change in overall health or be diagnosed with a new medical condition by a doctor. These should be reported regardless of the perceived relationship between the event and the trial vaccine.
  - Remind the subject to contact the site immediately if he/she has any of the symptoms suggestive of COVID-19. In addition, subjects will be messaged up to twice a week to provide a yes or no response to having COVID-19 symptoms. Those who respond "yes" will be contacted by trial staff for follow-up information, if the investigator considers the symptoms could potentially indicate a COVID-19 case (see Section 9.2.1 and Section 9.5).

- The subject should also be reminded to contact the site immediately if he/she had a positive SARS-CoV-2 test performed outside of the site, irrespective of whether they were symptomatic (COVID-19 illness) or asymptomatic at the time of the test.

9.1.1.10 End of Trial Visit: Day 393 (-0/+21 days) in CVnCoV subjects; for placebo subjects the visit (or phone call) might take place earlier as they will be withdrawn after trial unblinding

For subjects who received CVnCoV, the end of trial visit will be performed on Day 393, 1 year after the last trial vaccine administration. For subjects who received placebo, the end of trial visit will be conducted after unblinding. If possible, this visit should also include subjects who prematurely discontinued vaccination during the trial. The following assessments should be performed:

- Review and record any newly reported AEs since the phone contact on Day 302 (SAEs).
- Record concomitant medications and vaccinations, according to instructions in Section 7.6.
- Record symptoms suggestive of COVID-19 or any confirmed COVID-19 case.
- Perform a complete physical examination, including height and weight (see Section 9.3.6).
- Measure vital signs (body temperature, pulse, blood pressure, see Section 9.3.6).

9.1.2 All Other Subjects and subjects that, following unblinding, receive an authorized vaccine after having received at least one dose of CVnCoV

Following enrollment of subjects into the Immunogenicity/Reactogenicity Subset (n=1,260), the remaining 1,260 subjects, 18 years of age and older, will be enrolled to this group.

Also, all subjects initially enrolled to the Immunogenicity/Reactogenicity Subset that receive an authorized vaccine following at least one dose of CVnCoV will be included in this group from the day when the authorized vaccine is administered (Schedule of Activities- Table 2).

9.1.2.1 Clinic Visit 1: Day 1 – First Trial Vaccination

Note that procedures to establish subject eligibility, recording of demographic information and medical history may be performed within 21 days prior to trial vaccine administration, i.e., spread out over more than 1 day. However, if all information is available and assessments and procedures can be performed, eligibility can be established on the same day of trial vaccine administration. All eligibility criteria must be reviewed prior to trial vaccine administration on Day 1.

<u>Pre-vaccination Procedures</u>

- Obtain the signed informed consent form.

- Signed informed consent must be obtained prior to the subject entering into the trial, and before any protocol-directed procedures are performed (see Section 12.4).
- By signing the informed consent form, the subject voluntarily agrees to participate in the trial CV-NCOV-005.

- Review inclusion/exclusion criteria (see Section 6.1 and 6.2) and review prohibited medications listed as an exclusion criterion (see Section 6.2).
- Record demographic information.
- Record medical history.
- Record concomitant medications and vaccinations, including recurring medications for intermittent conditions, if taken within 6 months prior to enrollment in this trial.
- Perform a complete physical examination, including height and weight (see Section 9.3.6). If a complete physical examination was performed out of the scope of this trial within 21 days prior to trial vaccine administration, a symptom-directed physical examination should be performed on the day of vaccination prior to trial vaccine administration.
- Measure vital signs (body temperature, pulse, blood pressure, see Section 9.3.6).
- Perform urine pregnancy test in females of childbearing potential (Appendix 5).
- Collect a pre-vaccination blood sample (see Table 2) for binding antibody testing to N protein of SARS-CoV-2 (~6 mL blood).
- Randomize the subject (see Section 7.3.1).

Vaccination Procedure

- Review criteria for delay or cancellation of vaccination. See Sections 6.3 and 8.1 for an overview of the criteria leading to delay or cancellation of vaccine administration. In case of delay, the vaccination should take place within the allowed time windows. The reasons for delay or cancellation should be documented in the subject chart.
- Administer the trial vaccine dose according to the subject's assignment.

Post-vaccination Procedures

- Observe the subject on site for at least 30 minutes following vaccination for safety monitoring. At the end of the observation period:
  - Measure vital signs (body temperature, pulse, blood pressure, see Section 9.3.6).
  - The subject may not be discharged until vital signs are within normal range or have returned to pre-vaccination levels.
  - Record the occurrence of any new AEs following trial vaccination.
- Instructions for the subject:
  - Remind the subject to call the site immediately to report the following:

- If he/she experiences any concerning local or systemic reactions or other medical event.
- Any medically-attended visits that are not routine visits for physical examination or vaccination, such as visits for hospitalization, an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason.
- Experience a serious medical event, have a change in overall health or be diagnosed with a new medical condition by a doctor. These should be reported regardless of the perceived relationship between the event and the trial vaccine.

- Remind the subject to contact the site immediately if he/she has any of the symptoms suggestive of COVID-19. In addition, subjects will be messaged up to twice a week to provide a yes or no response to having COVID-19 symptoms. Those who respond “yes” will be contacted by trial staff for follow-up information, if the investigator considers the symptoms could potentially indicate a COVID-19 case (see Section 9.2.1 and Section 9.5).
- The subject should also be reminded to contact the site immediately if he/she had a positive SARS-CoV-2 test performed outside of the site, irrespective of whether they were symptomatic (COVID-19 illness) or asymptomatic at the time of the test.

  Note: Subjects without symptoms may have been tested for several reasons, for example, close exposure to a known person with SARS-CoV-2 infection or as part of their routine screening as a healthcare provider).

9.1.2.2 Clinic Visit 2: Day 29 - Second Trial Vaccination (-3/+7 days)

Pre-vaccination Procedures

- Review and record any newly collected safety data including medically-attended AEs and SAEs.
- Record concomitant medications and vaccinations, according to instructions in Section 7.6.
- Perform a symptom-directed physical examination (see Section 9.3.6).
- Measure vital signs (body temperature, pulse, blood pressure, see Section 9.3.6).
- Perform urine pregnancy test in females of childbearing potential (Appendix 5).

Vaccination Procedure

- Review criteria for delay or cancellation of vaccination. See Sections 6.3 and 8.1 for an overview of the criteria leading to delay or cancellation of vaccine administration. In case of delay, the vaccination should take place within the allowed time windows. The reasons for delay or cancellation should be documented in the subject chart.
- Administer the trial vaccine dose according to the subject’s assignment.

Post-vaccination Procedures

- Observe the subject on site for at least 30 minutes following vaccination for safety monitoring. At the end of the observation period:
  - Measure vital signs (body temperature, pulse, blood pressure, see Section 9.3.6).
  - The subject may not be discharged until vital signs are within normal range or have returned to pre-vaccination levels.
  - Record the occurrence of any new AEs following trial vaccination.
- Instructions for the subject:
  - Remind the subject to call the site immediately to report the following:
    - If he/she experiences any concerning local or systemic reactions or other medical event.
    - Any medically-attended visits that are not routine visits for physical examination or vaccination, such as visits for hospitalization, an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason.
    - Experience a serious medical event, have a change in overall health or be diagnosed with a new medical condition by a doctor. These should be reported regardless of the perceived relationship between the event and the trial vaccine.
  - Remind the subject to contact the site immediately if he/she has any of the symptoms suggestive of COVID-19. In addition, subjects will be messaged up to twice a week to provide a yes or no response to having COVID-19 symptoms. Those who respond “yes” will be contacted by trial staff for follow-up information, if the investigator considers the symptoms could potentially indicate a COVID-19 case (see Section 9.2.1 and Section 9.5).
  - The subject should also be reminded to contact the site immediately if he/she had a positive SARS-CoV-2 test performed outside of the site, irrespective of whether they were symptomatic (COVID-19 illness) or asymptomatic at the time of the test.

9.1.2.3 Clinic Visit 3: Day 43 (-3/+3 days)

- Review and record any newly collected safety data including medically-attended AEs and SAEs.
- Record concomitant medications and vaccinations, vaccinations according to instructions in Section 7.6.
- Perform a symptom-directed physical examination (see Section 9.3.6).
- Measure vital signs (body temperature, pulse, blood pressure, see Section 9.3.6).
- Collect a blood sample (see Table 2) for binding antibody testing to N protein of SARS-CoV-2 (~6 mL blood).
- Instructions for the subject:

- Remind the subject to call the site immediately to report the following:
    - If he/she experiences any concerning local or systemic reactions or other medical event.
    - Any medically-attended visits that are not routine visits for physical examination or vaccination, such as visits for hospitalization, an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason.
    - Experience a serious medical event, have a change in overall health or be diagnosed with a new medical condition by a doctor. These should be reported regardless of the perceived relationship between the event and the trial vaccine.
- Remind the subject to contact the site immediately if he/she has any of the symptoms suggestive of COVID-19. In addition, subjects will be messaged up to twice a week to provide a yes or no response to having COVID-19 symptoms. Those who respond “yes” will be contacted by trial staff for follow-up information, if the investigator considers the symptoms could potentially indicate a COVID-19 case (see Section 9.2.1 and Section 9.5).
- The subject should also be reminded to contact the site immediately if he/she had a positive SARS-CoV-2 test performed outside of the site, irrespective of whether they were symptomatic (COVID-19 illness) or asymptomatic at the time of the test.

9.1.2.4 Phone Call: Day 57 (-3/+7 days) and Day 120 (-7/+7 days)

The purpose of these phone contacts is to inquire on the subject’s general well-being and to assess safety since the last phone contact or site visit.

- During the phone call:
    - Review and record any newly reported AEs since the site visit or phone call (medically-attended AEs, SAEs).
    - Record concomitant medications and vaccinations, according to instructions in Section 7.6.
    - If the subject reports by phone any concerning AEs, these should be followed-up either by a phone call(s) or by an unscheduled site visit based on the judgment of the investigator.
- Instructions for the subject:
    - Remind the subject to call the site immediately to report the following:
        - If he/she experiences any concerning medical event.
        - Any medically-attended visits that are not routine visits for physical examination or vaccination, such as visits for hospitalization, an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason.

- Experience a serious medical event, have a change in overall health or be diagnosed with a new medical condition by a doctor. These should be reported regardless of the perceived relationship between the event and the trial vaccine.

- Remind the subject to contact the site immediately if he/she has any of the symptoms suggestive of COVID-19. In addition, subjects will be messaged up to twice a week to provide a yes or no response to having COVID-19 symptoms. Those who respond "yes" will be contacted by trial staff for follow-up information, if the investigator considers the symptoms could potentially indicate a COVID-19 case (see Section 9.2.1 and Section 9.5).

- The subject should also be reminded to contact the site immediately if he/she had a positive SARS-CoV-2 test performed outside of the site, irrespective of whether they were symptomatic (COVID-19 illness) or asymptomatic at the time of the test.

9.1.2.5 Clinic Visit 4: Day 211 (-7/+7 days)

The assessments and procedures are identical to those performed during Clinic Visit 3 on Day 43.

9.1.2.6 Phone Call: Day 302 (-7/+7 days) – after approval of protocols version 3 and 4 no longer to be performed in placebo subjects

The purpose of this phone contact is to inquire on the subject's general well-being and to assess safety since the last site visit on Day 211.

- During the phone call:
  - Review and record any newly reported AEs since the site visit on Day 211 (SAEs).
  - Record concomitant medications and vaccinations, according to instructions in Section 7.6.
  - If the subject reports by phone any concerning AEs, these should be followed-up either by a phone call(s) or by an unscheduled site visit based on the judgment of the investigator.
- Instructions for the subject:
  - Remind the subject to call the site immediately to report the following:
    - If he/she experiences any concerning medical event.
    - Any medically-attended visits that are not routine visits for physical examination or vaccination, such as visits for hospitalization, an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason.
    - Experience a serious medical event, have a change in overall health or be diagnosed with a new medical condition by a doctor. These should be reported regardless of the perceived relationship between the event and the trial vaccine.

- Remind the subject to contact the site immediately if he/she has any of the symptoms suggestive of COVID-19. In addition, subjects will be messaged up to twice a week to provide a yes or no response to having COVID-19 symptoms. Those who respond “yes” will be contacted by trial staff for follow-up information, if the investigator considers the symptoms could potentially indicate a COVID-19 case (see Section 9.2.1 and Section 9.5).
- The subject should also be reminded to contact the site immediately if he/she had a positive SARS-CoV-2 test performed outside of the site, irrespective of whether they were symptomatic (COVID-19 illness) or asymptomatic at the time of the test.

9.1.2.7 End of Trial Clinic Visit: Day 393 (-0/+21 days) in CVnCoV subjects; for placebo subjects the visit (or phone call) might take place earlier as they will be withdrawn after trial unblinding

The end of trial visit will be performed on Day 393, 1 year after the last trial vaccine administration. If possible, this visit should include subjects who prematurely discontinued vaccination during the trial. The following assessments should be performed:

- Review and record any newly reported AEs since the phone contact on Day 302 (SAEs).
- Record concomitant medications and vaccinations, according to instructions in Section 7.6.
- Record symptoms suggestive of COVID-19 or any confirmed COVID-19 case.
- Perform a complete physical examination, including height and weight (see Section 9.3.6).
- Measure vital signs (body temperature, pulse, blood pressure, see Section 9.3.6).

9.2 Efficacy Assessments

9.2.1 COVID-19 Cases

Case detection will begin with the identification of subjects reporting at least 1 symptom from a standardized list of symptoms consistent with COVID-19 disease. Based on a phone interview with trial staff (see Appendix 6), subjects suspected of having COVID-19 disease will undergo testing for SARS-CoV-2 infection, consisting of a molecular-based RT-PCR test performed at the site. The testing strategy is described in Section 9.5 and Appendix 7. If the subject is confirmed to have COVID-19, subjects will be followed until resolution of their disease, even if the initial presentation is considered as mild. If the subject is hospitalized, the subject's progress must continue to be followed by the Investigator and a medical/discharge summary must be obtained at the end of the hospitalization.

9.2.1.1 Case Detection

9.2.1.1.1 Routine Surveillance for COVID-19

During all site visits and phone calls, subjects will be reminded to contact the site if they tested positive for SARS-CoV-2 outside of the trial context or if they have any of the following symptoms*:

- Fever or chills
- Shortness of breath or difficulty breathing
- New loss of taste or smell
- Cough
- Fatigue
- Muscle or body aches
- Headache
- Sore throat
- Congestion or runny nose
- Nausea or vomiting
- Diarrhea

* FDA Development and Licensure of Vaccines to Prevent COVID-19 guidance [33].

Subjects will also be messaged up to twice a week to provide a yes or no response to having COVID-19 symptoms. For both of the trial vaccinations, messaging will not begin until 4 days after vaccination to avoid confusing vaccine-associated reactions occurring during this time period (e.g., fever, chills, headache, fatigue, myalgia) with potential COVID-19 symptoms.

Those who report symptoms either at the site visit or by phone call, or respond "yes" to having symptoms by messaging will be contacted by trial staff for a follow-up phone interview. The trial staff will use a scripted interview (in which he/she has been trained on) to collect information about the subject's medical condition, which will be used to determine the probability of the subject having COVID-19. The interview script is provided in Appendix 6. If the subject is suspected of having COVID-19 illness, he/she will undergo testing for SARS-CoV-2 infection (see next section). If suspicion is low, then a subsequent phone call(s) will be performed to assess whether the subject's illness and symptoms have progressed and if the suspicion of COVID-19 has reached a sufficient level to test the subject. Based on clinical judgment, phone contact may be made as frequently as daily. All symptomatic subjects will be provided a thermometer and oxygen saturation monitor for home use. Trial staff will instruct subjects to take their oral body temperature and oxygen saturation levels at least 3 to 4 times per day, or whenever they feel symptomatic.

The testing strategy for SARS-CoV-2 infection is presented in Section 9.5 and Appendix 7. Testing will consist of a molecular-based RT-PCR test performed at the site. Depending on the Investigator and his/her facility and trial staff, nasopharyngeal swab samples for testing will be collected either at the site or at a home visit. The visit to the site or home visit by trial staff will be considered an "Illness Visit" and documented as such in the eCRF.

If the subject is virologically-confirmed to have COVID-19 by a positive RT-PCR test, subjects will be followed until resolution of their disease, even if the initial presentation is considered as mild. If the subject is hospitalized, the subject's progress must continue to be followed by the Investigator and a discharge summary must be obtained at the end of the hospitalization. Information on clinical symptoms and signs, their duration and severity, and treatment and outcome of the COVID-19 episode will be documented by trial staff and recorded in the eCRF.

For positive RT-PCR tests, viral RNA of the SARS-CoV-2 might be sequenced to identify S protein variants.

Upon resolution, subjects will continue to be followed in the same manner as those who have not presented with COVID-19 (i.e. they will return to routine case surveillance). A second episode of COVID-19 in a subject with prior disease will be included in the exploratory objective assessing the occurrence of second episodes of COVID-19 in vaccinated subjects.

If the subject is not virologically-confirmed by RT-PCR testing, he/she will return to routine surveillance for COVID-19 disease as a subject who is naïve to SARS-CoV-2 infection (unless determined otherwise by a seropositive test to the N protein).

9.2.1.1.2 Non-Routine Surveillance for COVID-19 (Positive Test Outside of the Site)

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

If the subject was symptomatic, trial staff will use the scripted interview to collect information about the subject's COVID-19 symptoms and medical condition (interview script in Appendix 6). The subject should be retested as soon as feasible to confirm the result. A nasopharyngeal swab sample should be taken for RT-PCR testing; the RT-PCR test result will be considered definitive as a virologically-confirmed case of COVID-19. If the subject is confirmed to have COVID-19, subjects will be followed until resolution of their disease, as described above for subjects who were detected by routine surveillance.

If the subject is not virologically-confirmed by RT-PCR testing, he/she will return to routine surveillance for COVID-19 disease as a subject who is naïve to SARS-CoV-2 infection (unless determined otherwise by a seropositive test to the N protein).

9.2.1.2 Definition of Virologically-Confirmed COVID-19 Case

A virologically-confirmed case of COVID-19 is defined as a positive SARS-CoV-2 specific RT-PCR test in a person with clinically symptomatic disease consisting of 1 or more of the following symptoms (based on the same screening symptoms as above):

- Fever or chills
- Shortness of breath or difficulty breathing
- New loss of taste or smell
- Cough
- Fatigue
- Muscle or body aches
- Headache
- Sore throat
- Congestion or runny nose
- Nausea or vomiting
- Diarrhea

This definition is intended to capture all severities of virologically-confirmed clinically symptomatic cases of COVID-19. As such, COVID-19 cases classified by severity (e.g., mild, moderate, or severe) will be a subset of these cases. See Appendix 3 and Appendix 4 for clinical definitions of severe and mild/moderate COVID-19, respectively.

9.2.1.3 COVID-19 Case Definition for the Efficacy Analysis

For the analysis of efficacy, the case must meet the following criteria:

- Must be 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, as defined above in Section 9.2.1.2.
- Symptom onset must have occurred ≥ 15 days following the second trial vaccination.
- The subject must not have a history of virologically-confirmed COVID-19 illness at enrollment or have developed a case of virologically-confirmed COVID-19 before 15 days following the second trial vaccination {see Section 10.2.4, (EAS) for more details}.
- The subject must have been SARS-CoV-2 naïve at baseline and Day 43 (defined as seronegative to N protein in the blood samples collected at baseline and Day 43).

These efficacy cases might be confirmed by the Adjudication Committee.

Day 43 is 14 days post-second dose which allows the immune response to CVnCoV to mature and reach its height following the second dose. As such, COVID-19 case ascertainment starting the next day at ≥ 15 days represents the evaluation of full VE of CVnCoV against COVID-19 disease.

9.2.1.4 Adjudication of COVID-19 Cases

An independent Committee of clinicians will be formed which might adjudicate COVID-19 cases. The Committee will be blinded to the treatment assignment of the subject. The cases might 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 with 1 or more of the symptoms listed above in Section 9.2.1.2.

- Was the RT-PCR test performed at the CureVac designated laboratory at the site?
- 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 asymptomatic? If asymptomatic, was the RT-PCR test positive ≥ 15 days following the second vaccination or before?
- Was it a mild, moderate, or severe case of COVID-19 based on the provided clinical definitions?
- Did the subject require supplemental oxygenation? What type of oxygen support did the subject receive?
- Was the subject hospitalized? Was the subject admitted to the intensive care unit?
- Did the subject die? Due to COVID-19 or other cause?

9.2.2 Asymptomatic Cases of SARS-CoV-2 Infection

There will be no active surveillance in this trial for asymptomatic SARS-CoV-2 infections. Subjects will be reminded to contact the site immediately if he/she had a positive SARS-CoV-2 test performed outside of the site, irrespective of whether they were symptomatic (COVID-19 illness) or asymptomatic at the time of the test. Subjects without symptoms may have been tested for several reasons, for example, close exposure to a known person with SARS-CoV-2 infection or as part of their routine screening as a healthcare provider.

If the subject was asymptomatic, trial staff will contact the subject immediately to collect information about the positive SARS-CoV-2 test the subject reported for information to be collected). The subject should be retested as soon as feasible to confirm the result. A nasopharyngeal swab sample should be taken for RT-PCR testing; a positive RT-PCR test result will be considered definitive as a virologically-confirmed case of SARS-CoV-2 infection.

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

If the subject is not virologically-confirmed by RT-PCR testing, he/she will return to routine surveillance for COVID-19 disease as a subject who is naïve to SARS-CoV-2 infection (unless determined otherwise by a seropositive test to the N protein).

9.3 Safety Assessments

The safety, reactogenicity, and tolerability of a 2-dose schedule of CVnCoV will be assessed as described below.

9.3.1 Safety Assessments Specific for Subjects in the Immunogenicity/Reactogenicity Subset

- Reactogenicity will be assessed daily on each vaccination day and the following 7 days by collection of solicited local AEs (injection site pain, redness, swelling, and itching) and systemic AEs (fever, headache, fatigue, chills, myalgia, arthralgia, nausea/vomiting, and diarrhea) using eDiaries. In addition, other indicators of safety will be collected (e.g., body temperature).
- The eDiary will also be used as a memory aid for the subject for the collection of unsolicited AEs on each vaccination day and the following 28 days.

9.3.2 Safety Assessments for All Subjects

- Medically-attended AEs will be collected through 6 months after the second trial vaccination.
- AESIs will be collected through 1 year after the second trial vaccination. AESIs to be monitored include pIMDs, AESIs for SARS-CoV-2 vaccines, and non-serious intercurrent medical conditions that may affect the immune response to vaccination (Appendix 9).
- SAEs will be collected through 1 year after the second trial vaccination.
- AEs leading to vaccine withdrawal or trial discontinuation will be collected through 1 year after the second trial vaccination.

{If the subject does not receive their second trial vaccination, the AE follow-up time (6 months or 1 year) will be determined based on the date scheduled for their second vaccination on Day 29}.

- The eDiary will be used as a memory aid for the subject for the collection of medically-attended AEs, AESIs, and SAEs.

9.3.3 Adverse Events

Definitions of AEs/SAEs, procedures for recording, evaluating, follow-up and reporting of AEs/SAEs/pregnancy/overdose, as well as assessments of intensity and causality of AEs, are provided in Appendix 10.

It is important to note that COVID-19 illness and its complications/sequelae are consistent with the efficacy endpoints of the trial and, as such, should not be recorded as AEs. These data will be captured on the relevant eCRF pages for cases of COVID-19 illness that occur in the trial, which are expected outcomes of the trial. Therefore, COVID-19 illness and its complications/sequelae will not be reported according to the standard expedited process for SAEs, even though the event may meet the criteria for an SAE. COVID-19 is to be reported as an AESI, according to Appendix 9.

9.3.3.1 Solicited Adverse Events

An eDiary will be distributed to all subjects in the Immunogenicity/Reactogenicity Subset for collection of solicited local AEs (injection-site pain, redness, swelling and itching) and solicited systemic AEs (fever, headache, fatigue, chills, myalgia, arthralgia,

nausea/vomiting and diarrhea) on the day of vaccination and the following 7 days. Subjects will be given a thermometer to measure body temperature orally and a measuring tape to determine the size of local injection-site reactions. Subjects will be instructed on how to enter the solicited AEs daily for 7 days in the eDiary.

Solicited AEs will be assessed on an intensity scale (Table 3 and Table 4). By definition, all local solicited AEs are considered related to trial vaccination. For solicited systemic AEs, the Investigator will assess the relationship between trial vaccine and occurrence of each AE and make an assessment of intensity for each AE.

If concerning to the subject or of prolonged duration, solicited Grade 3 AEs should be reported to the Investigator immediately. In case of related Grade 3 solicited AEs reported for more than 1 day on the eDiary, the subject will be questioned to establish the total duration of the AE as exactly as possible.

Table 3 Intensity Grading* for Solicited Local Adverse Events

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

*FDA toxicity grading scale [34].

Table 4 Intensity Grading* for Solicited Systemic Adverse Events

Adverse Event	Grade	Definition
Fever	0	< 38°C
	1	≥ 38.0 – 38.4°C
	2	≥ 38.5 – 38.9°C
	3	≥ 39°C
Headache	0	Absent
	1	Mild, no interference with normal activity
	2	Moderate, some interference with normal activity and/or repeated use of non-narcotic pain reliever > 24 hours
	3	Significant; any use of narcotic pain reliever and/or prevents daily activity
Fatigue	0	Absent
	1	Mild, no interference with normal activity
	2	Moderate, some interference with normal activity
	3	Significant, prevents normal activity
Chills	0	Absent
	1	Mild, no interference with normal activity
	2	Moderate, some interference with normal activity
	3	Significant, prevents normal activity
Myalgia	0	Absent
	1	Mild, no interference with normal activity
	2	Moderate, some interference with normal activity
	3	Significant, prevents normal activity
Arthralgia	0	Absent
	1	Mild, no interference with normal activity
	2	Moderate, some interference with normal activity
	3	Significant, prevents normal activity
Nausea/ Vomiting	0	Absent
	1	Mild, no interference with activity and/or 1 – 2 episodes/ 24 hours
	2	Moderate, some interference with activity and/or >2 episodes/ 24 hours
	3	Significant, prevents daily activity, requires outpatient IV hydration
Diarrhea	0	Absent
	1	2 – 3 loose stools over 24 hours
	2	4 – 5 stools over 24 hours
	3	6 or more watery stools over 24 hours or requires outpatient IV hydration

*FDA toxicity grading scale [34]; IV = Intravenous.

9.3.3.2 Unsolicited Adverse Events and Serious Adverse Events

Unsolicited AEs occurring on the day of vaccination and the following 28 days will be recorded by subjects included in the Immunogenicity/Reactogenicity Subset for each of the 2 trial vaccinations.

For all subjects, medically-attended AEs will be collected through 6 months after the second trial vaccination. AESIs will be collected through 1 year after the second trial vaccination (see Section 9.3.3.3). SAEs will be collected through 1 year after the second trial vaccination.

Medically-attended AEs are defined as AEs with medically-attended visits that are not routine visits for physical examination or vaccination, such as visits for hospitalization, an emergency room visit, or an otherwise unscheduled visit to or from medical personnel (medical doctor) for any reason.

The occurrence of AEs (serious and non-serious) will be assessed by non-directive questioning of the subject at each visit. AEs volunteered by the subject during or between visits as eDiary entries or detected through observation, physical examination, laboratory test, or other assessments during the entire trial, will be recorded in the eCRF if they fulfil the definitions as specified in section 9.3.2. Subjects should be instructed to report immediately any AEs with serious symptoms, subjective complaints or objective changes in their well-being to the Investigator or the site personnel, regardless of the perceived relationship between the event and the trial vaccine.

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

Non-serious intercurrent medical conditions that may affect the immune response to vaccination will also be collected throughout the trial.

9.3.3.3 Adverse Events of Special Interest

AESIs will be collected through 1 year after the second trial vaccination. The following events will be considered as AESI during this trial:

- AEs with a suspected immune-mediated etiology (pIMDs, see Appendix 8).
- Other AEs relevant to SARS-CoV-2 vaccine development or the target disease (see Appendix 9).
- Non-serious intercurrent medical conditions that may affect the immune response to vaccination will also be collected throughout the trial.

9.3.4 Pregnancies

Pregnancy is an exclusion criterion for enrollment in this trial, but subjects could potentially become pregnant during their active participation in this trial. Refer to Appendix 10 for details on the reporting and follow-up of pregnancies.

9.3.5 Safety Laboratory Assessments

(See Appendix 5)

A urine sample for pregnancy testing will be taken from women of childbearing potential on Day 1 prior to trial vaccination to establish eligibility. A urine pregnancy test will also be performed before the second trial vaccination on Day 29 to continue to determine eligibility.

9.3.6 Vital Signs and Physical Examination

At all trial visits (see Table 1 and Table 2), **vital signs** (body temperature, systolic/diastolic blood pressure and pulse) will be recorded in a standardized manner after the subject has rested in the sitting position for 5 minutes.

At the first trial visit on Day 1 and at the end of trial visit for all subjects in Trial CV-NCOV-005 (see Table 1 and Table 2), a complete **physical examination** will be performed, including examination of general appearance, eyes/ears/nose/throat, head/neck/thyroid, lymph node areas, cardiovascular system, lung/chest and abdomen, extremities and neurological examination, skin examination, measurement of weight and height. At all other trial visits, a symptom-directed physical examination will be performed at the discretion of the investigator and should include measurement of O_2 saturation.

9.3.7 Medical and Surgical History

All significant findings and pre-existing conditions present in a subject prior to enrollment must be reported on the relevant medical history/current medical conditions screen of the eCRF.

Information should be provided on medical and surgical history and concomitant medical conditions specifying those ongoing on Day 1.

9.3.8 Monitoring Committees

9.3.8.1 Data and Safety Monitoring Board (DSMB)

An independent DSMB will be convened to i) oversee the safety of subjects participating in this trial, CV-NCOV-005; ii) to assess the progress and conduct of the trial; iii) to review the cumulative safety data from the trial; iv) to perform an ongoing review of AEs of potential safety concern (see Section 5.5.2); and v) to make recommendations to the Sponsor whether to continue, modify, or pause the trial (see Section 5.5.2).

The DSMB will have regularly scheduled meetings to perform these responsibilities. During these meetings, the DSMB will also be informed of the safety data being generated in other ongoing clinical trials of CVnCoV. As described in Section 5.5.2, to further ensure subject safety on an ongoing basis, a listing of AEs of potential safety concern will be routinely monitored by the Chair of the DSMB (or designee) at regular intervals. As described in Section 7.3.2, the DSMB may request unblinding of an individual subject or a specific dataset at any time during the trial.

In addition to safety data, the DSMB will be asked to review efficacy data at the interim analysis or possibly at other time points during the trial for a continued assessment of the risk-benefit of the trial. As part of the risk-benefit analysis, the DSMB will periodically monitor COVID-19 cases for signals of VDE.

The DSMB Charter will describe in detail the composition and objectives of the DSMB; the responsibilities of the DSMB, CureVac, and CRO; the schedule and conduct of the DSMB meetings; and the datasets to be reviewed. The Charter will contain the SAP for the DSMB.

9.3.8.2 Adjudication Committee

An independent Committee of clinicians will be formed which might adjudicate COVID-19 cases for assessment of the secondary efficacy endpoint. The Committee will be blinded to the treatment assignment of the subject. The cases might be adjudicated by the members with respect to the questions presented in Section 9.2.1.4. The schedule of the meetings and approach to adjudication of cases will be defined in the Charter. The Committee Chair will attend the DSMB meetings as an ad-hoc member.

9.4 Immunogenicity Assessments

For subjects participating in the Immunogenicity/Reactogenicity Subset in Trial CV-NCOV-005, the timing of blood sample collection for immunogenicity assessments post-vaccination is provided in Table 1, indicating no further immunogenicity assessments after trial unblinding. Subjects in the Immunogenicity / Reactogenicity Subset who have received an authorized vaccine, will continue according to table 2 with no further immunogenicity assessments. After trial unblinding, placebo subjects will also continue according to table 2 with no further immunogenicity assessments.

For all subjects participating in the Trial CV-NCOV-005, the timing of blood sample collection for the determination of serology status to natural SARS-CoV-2 infection at baseline and during the trial is provided in Table 1 and Table 2.

Because the immunogenicity results would unblind the subject's treatment assignment, the laboratory performing the assays will keep the results in strict confidence. An unblinded person, named at the start of the trial and independent of the conduct of the trial, will periodically review the quality of the immunogenicity data. This person will maintain the results in strict confidence.

9.4.1 Antibody Responses to CVnCoV Vaccination (RBD of S Protein and Viral Neutralizing Antibodies)

Antibody responses to CVnCoV vaccination will only be evaluated for 250 subjects (200 verum subjects, i.e. 100 per lot / 50 placebo subjects) in the Immunogenicity/Reactogenicity Subset at the following time points. Baseline, Day 29 and Day 43.

The immune response induced by vaccination with CVnCoV will be evaluated by 2 assays:

- Binding antibodies to the SARS-CoV-2 RBD of the S protein measured in serum by immunoassay.

Viral neutralizing antibodies directed against SARS-CoV-2 measured in serum by a functional activity assay.

9.4.2 Antibody Responses to SARS-CoV-2 (N Protein)

Antibody responses to SARS-CoV-2 will be evaluated for all subjects by measuring the binding antibodies to the SARS-CoV-2 N protein (virus antigen not contained in the vaccine construct) at the time points specified in Table 1 and Table 2, and will be performed by immunoassay.

As a measure of prior infection with SARS-CoV-2, serological status to the N protein will be used for the following:

1. To determine, retrospectively, if subjects were naïve or non-naïve to SARS-CoV-2 infection at trial entry and on Day 43. For evaluation of the efficacy of a 2-dose schedule of CVnCoV in naïve subjects, subjects would have to be seronegative to the N protein at both time points.
2. To determine if vaccination with a 2-dose schedule of CVnCoV can reduce asymptomatic infection with SARS-CoV-2 by measuring seroconversion to the N

protein in seronegative subjects during the trial period. As described above, these subjects would have to be seronegative to the N protein at baseline and Day 43.

Measurements of the binding antibodies to the SARS-CoV-2 N protein will not be conducted for the timepoint Day 393.

N-antibody testing was foreseen in this trial in order to detect asymptomatic infections as a component of the analysis of vaccine efficacy. This analysis became obsolete due to inconclusive efficacy further to different approved vaccines administered at different timepoints in all treatment groups.

9.4.3 Cell-mediated Immunity

CMI was planned to be evaluated in the CMI Subset including 120 subjects of the Immunogenicity/Reactogenicity Subset: 40 subjects who receive lot 1, 40 subjects who receive lot 2 of CVnCoV; and 40 subjects who receive placebo.

This exploratory analysis was planned to understand the cellular component of the immune response to CVnCoV and association to antibody response and vaccine efficacy. Given the very low number of subjects (n=~10) in this trial potentially eligible for the analysis due to the fact that the majority of subjects received an authorized vaccine, these data would not add value to the result seen in previous trials or to further understanding of vaccine efficacy. Therefore this analysis is considered futile and not planned any longer.

9.5 Testing for SARS-CoV-2 Infection

9.5.1 Virological Confirmation of COVID-19 Disease

See Flow Diagrams in Appendix 6 and Appendix 7.

During the trial, subjects clinically suspected of having COVID-19 disease or with a positive result in a test for SARS-CoV-2 performed outside of the trial context will undergo testing for the SARS-CoV-2 virus as described below. Sample collection for the tests may be performed at the site or at a home visit by trial staff. Ideally, samples should be collected within 5 days of symptom onset or the positive result. The tests results will be documented on the appropriate eCRF page.

- The nasopharyngeal swab sample collected will be used to perform a SARS-CoV-2 specific RT-PCR test at the site. The RT-PCR test result will be considered definitive for SARS-CoV-2 infection. In the unlikely event that only 1 sample can be collected from the subject, the sample should be tested by RT-PCR. For positive RT-PCR tests performed, the same swab might be used to sequence the viral genome for the SARS-CoV-2 S protein to identify variants and mutations in this protein.
- If the RT-PCR test is negative, but COVID-19 is still suspected based on the subject's exposure history and clinical presentation, another nasopharyngeal swab sample should be taken as soon as feasible for RT-PCR testing. The RT-PCR retest result will be considered definitive for SARS-CoV-2 infection.

9.5.2 Confirmation of a Positive Test for SARS-CoV-2 Infection Performed Outside of the Site

See Section 9.2.1.1.2 and Section 9.2.2 for follow-up of subjects who report a positive test for SARS-CoV-2 infection performed outside of the site.

For subjects (symptomatic or asymptomatic) who report a positive test for SARS-CoV-2 infection which was performed outside of the site, regardless of the type of test, the subject should be retested as soon as feasible to confirm the result. A nasopharyngeal swab sample should be collected for RT-PCR testing at the site for confirmation. The retest result will be considered definitive.

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

10.1.1 Primary Safety Objective

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

With a total of 1,680 subjects receiving CVnCoV (840 for each lot), AEs with a true incidence of 1:1000 will likely be observed in this trial with a 81.4% probability of observing at least one. Additionally, observation of 0 AE in 1,680 subjects would be associated with a 95% confidence that the true incidence rate of this AE is below 1.8:1000.

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

Table 5 Probability of Observing at least one Adverse Event Given a True Incidence Rate

	Number of subjects receiving CVnCoV		
True AE incidence	All subjects Pooled lots (N=1,680)	Subset for solicited/unsolicited AE By lot (N=420)	Subset for solicited/unsolicited AE Pooled lots (N=840)
1:1000	81.4%	34.3%	56.8%
5:1000	100.0%	87.8%	98.5%
1:100	100.0%	98.5%	100.0%

AE: Adverse Event

10.1.2 Primary Immunogenicity Objective

The primary analysis for SARS-CoV-2 RBD of S protein antibody response performed on Days 1, 29 and 43 will be done for 250 subjects (200 on verum, i.e. 100 per lot and 50 on placebo) in the PPI.

.

10.2 Populations for Analyses

10.2.1 Safety Analysis Set

The Safety Analysis Set (SAS) will include all subjects randomized in the trial who received at least 1 dose of any lot of CVnCoV or placebo vaccine.

The SAS will be the primary population for safety endpoints collected on all subjects (i.e. medically-attended AEs, AESI, AEs leading to vaccine withdrawal or trial discontinuation and SAEs) and a supportive population for efficacy endpoints.

For safety analyses on the SAS, subjects will be analyzed in the group of treatment they actually received (as “treated”).

For efficacy analyses on the SAS, subjects will be analyzed in the group of treatment to which they were randomized (as “randomized”) to follow the “intent to treat” principle.

10.2.2 Safety Analysis Subsets

The Safety Analysis Subset (SAS 2) will include all subjects of the SAS who belong to the Immunogenicity/Reactogenicity Subset and will be used for unsolicited AEs analysis.

The SAS 2 for solicited AEs analysis (SASsol) population will include all subjects of the SAS who belong to the Immunogenicity/Reactogenicity Subset with at least 1 diary collection indicating the occurrence or lack of occurrence of solicited AEs and will be used for solicited AEs analysis.

In SAS 2 and SASsol, subjects will be analyzed in the group of treatment they actually received (as “treated”).

10.2.3 Per Protocol Immunogenicity Subset

The PPI will include 250 subjects who belong to the Immunogenicity/Reactogenicity Subset (200 verum subjects, i.e. 100 per lot and 50 placebo subjects) and who:

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

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

For assessment of seroconversion rates, the analyses will be restricted to PPI subjects who are naïve at baseline to SARS-CoV-2 RBD of S protein antibody or to SARS-CoV-2 viral neutralizing antibody depending on the endpoint analyzed.

The lot-to-lot consistency analysis on SARS-CoV-2 RBD of S protein antibody titers will be done on the PPI subjects who received 2 doses of CVnCoV vaccine coming from the same lot and who have a negative SARS-CoV-2 RBD of S protein antibody titer at baseline.

Subjects to be excluded from the PPI will be identified and reviewed at the Blinded Data Review Meeting held before unblinding of the trial. Major protocol deviations will be listed and summarized.

10.2.4 Efficacy Analysis Set

The EAS will include all subjects of the SAS who:

- Received both trial doses (2 doses of the same lot of CVnCoV or 2 doses of placebo) according to their randomization.
- Had not developed a virologically-confirmed case of COVID-19 before trial entry (based on exclusion criteria 1) or before 15 days following the second vaccination.
- Had not stopped the trial before 15 days following the second vaccination.
- Were SARS-CoV-2 naïve at trial entry and at Day 43 (i.e. at all the testing time points before 15 days after the second vaccination) based on seronegativity to N protein.

The EAS will be the primary analysis population for all efficacy endpoints.

The analysis of the efficacy endpoint related to seroconversion to the N protein of SARS-CoV-2 (asymptomatic infections) will be performed on the EAS population for whom at the Day 211 test result for N protein at ≥ 15 days post-second vaccination is available for analysis.

10.2.5 Summary of Analysis Sets

Table 6 below provides a summary of primary and supportive populations planned for analysis of each endpoint. Other analysis populations may be defined in the SAP.

Table 6 Primary and Supportive Populations for the Analysis of Each Endpoint

Endpoints	Primary Population	Supportive Population
Primary Safety Endpoints:		
• Solicited AEs	SASsol	-
• Unsolicited AEs	SAS 2	-
• SAEs, AESI, medically-attended AEs, AE leading to vaccine withdrawal	SAS	-
Primary Immunogenicity Endpoints:		
• SARS-CoV-2 RBD of S protein antibody titers	PPI	-
• Seroconversion to SARS-CoV-2 S protein antibody responses	PPI (RBD of S protein antibodies naïve subjects)	-
Secondary Efficacy Endpoints:		
• Any severity COVID-19	EAS	SAS
• Severity of COVID-19	EAS	SAS
• BoD scores	EAS	-
Secondary Immunogenicity Endpoints:		

• SARS-CoV-2 viral neutralizing antibody	PPI	-
• Seroconversion to SARS-CoV-2 viral neutralizing antibody	PPI (neutralizing antibodies naïve subjects)	-
• Lot-to-lot consistency on SARS-CoV-2 RBD of S protein antibody titers	PPI (CVnCoV subjects)	-
Exploratory Efficacy Endpoint:		
• Second episode of COVID-19	EAS	SAS

EAS: Efficacy Analysis Set; PPI: Per Protocol Immunogenicity set; SAS: Safety Analysis Set; SAS 2: Safety Analysis Subset; SASsol: SAS 2 for solicited adverse events analysis.

10.3 Statistical Analyses

10.3.1 General Considerations

Two analyses are planned: the interim (triggered by regulatory requirements to obtain early conditional approval in Europe, and the advancement of the accrual of a pre-defined number of COVID-19 cases in Trial CV-NCOV-004) and the final (on all data up to Day 393 visit). A SAP for both analyses will be prepared and finalized at the latest prior to database locks. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all trial objectives and the handling of missing data.

10.3.2 Demographic, Medical History, and Other Baseline aracteristics

Data will be summarized with respect to demographic and baseline characteristics (e.g., age, sex, height, weight) medical history, baseline immune status, and all safety measurements using descriptive statistics (quantitative data) and contingency tables (qualitative data) for pooled CVnCoV lots, for each CVnCoV lot separately, for placebo and overall.

10.3.3 Trial Vaccine Administration

The administrations of CVnCoV or placebo will be listed and the number of subjects actually receiving the vaccination doses will be summarized by group (each lot, pooled lot and placebo).

10.3.4 Concomitant Medication and Vaccinations

Concomitant medication/vaccination after the start of the trial will be listed and summarized by Anatomical Therapeutic Chemical term, overall and by group (each lot, pooled lot and placebo).

10.3.5 Safety Analysis

No formal statistical testing of safety data is planned.

Safety endpoints will be described for each CVnCoV lot separately, for pooled lots, for placebo and overall.

Solicited AEs: The frequencies and percentages of subjects experiencing each solicited local and systemic AE within 7 days after each vaccination will be presented by intensity and overall. For subjects with more than 1 episode of the same AE within 7 days after a vaccination, the maximum intensity will be used for tabulations. Similar tabulations will be performed for solicited systemic AEs by relationship to trial vaccination. Solicited local AEs will be by definition considered as related to the trial vaccine. Time to onset (in days) and duration (in days) will also be summarized for each solicited local and systemic AEs. Summary tables showing the occurrence of at least 1 local or systemic solicited AE within 7 days after each vaccination will also be presented.

Unsolicited AEs: Unsolicited AEs including SAEs and AESIs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) by SOC and PT.

The frequency and percentage of subjects reporting at least 1 unsolicited AE within the 28 days after each vaccination and overall will be tabulated globally and for each SOC and PT levels.

Similar tables will be provided for: related unsolicited AE, Grade 3 or higher unsolicited AE, medically-attended AEs that occur within 6 months after the second trial vaccination, SAE, related SAE, AESI, related AESI, AEs leading to withdrawal or trial discontinuation and SAE resulting in death through 1 year after the second trial vaccination.

When an AE occurs more than once for a subject within the 29 days post 1 vaccination, the maximal severity and strongest relationship to the vaccine group will be counted.

Only AE post first vaccination will be considered in the summary tables. AE starting prior to the first vaccination will only be listed.

Data listings of fatal and SAEs will be provided by subject.

Vital signs will be summarized by descriptive statistics at each visit including change from baseline and a listing will be provided.

10.3.6 Immunogenicity Analysis

No formal hypothesis on immunogenicity will be tested. Descriptive statistics for the immunogenicity endpoints will be provided for a subset of subjects for each CVnCoV lot separately (n = 100 per lot), for pooled lots and for a subset of subjects in the placebo group (n = 50) on Days 1, 29 and 43.

The following analyses will be done for SARS-CoV-2 RBD of the S protein antibody concentrations and for neutralizing antibodies titers :

- Geometric mean concentrations (GMC) / geometric mean titers (GMT) by group will be summarized with their 95% CI at blood sampling time points Day 1, Day 29 and Day 43 for 250 evaluable subjects and then separately in subjects seronegative at baseline and in subjects seropositive at baseline.
- The fold change from baseline will be computed for seropositive subjects at baseline and GMFC by group will be displayed with their 95% CI at the Day 29 and Day 43 blood sampling time point.
- The number and percentage of subjects SARS-CoV-2 seronegative at baseline for whom a seroconversion is observed will be summarized and presented at each blood

sampling time point after baseline until Day 43 with exact 95% CI. Seroconversion is defined as detectable antibodies in the serum {≥ lower limit of quantification (LLOQ)}.

Concentrations/titers marked as below the LLOQ will be arbitrary replaced by half of the LLOQ for GMC/GMT and GMFC computations purpose.

To assess lot-to-lot consistency, the two-sided 95% CI of the ratio of GMCs of SARS-CoV-2 RBD of S protein antibodies between subjects receiving 2 different lots of CVnCoV will be computed for Day 43.

Additional immunogenicity analyses including graphs will be described in SAP as applicable.

10.3.7 Efficacy Analyses

10.3.7.1 Secondary Efficacy Endpoint Analysis

Secondary Efficacy Analysis

The number of subjects reporting at least 1 episode of COVID-19 of any severity (meeting the case definition for the efficacy analysis), will be presented for pooled CVnCoV lots and placebo group with the attack rates.

The VE, defined as the percent reduction in the frequency of COVID-19 cases (according to the case definition) in vaccinated subjects (pooled lots) compared with subjects who received placebo, will be calculated as follows

VE = 1- RR = 1 - (ARV/ARP) = 1 - (p / r (1-p))

where

ARV = attack rate in vaccinated group (pooled lots) = nv/Nv = number of subjects reporting at least 1 COVID-19 episode in the CVnCoV groups / total follow-up time of evaluable subjects in the CVnCoV groups (number of person-month).

ARP = attack rate in placebo group = np/Np = number of subjects reporting at least 1 COVID-19 episode in the Placebo group / total follow-up time of evaluable subjects in the Placebo group (number of person-month).

RR = relative risk = ARV/ARP

p = proportion of COVID-19 cases (according to the case definition) coming from the CVnCoV groups among all cases = nv/(nv+np).

r = ratio of total follow-up time of evaluable subjects in the CVnCoV groups over total follow-up time of evaluable subjects in the placebo group = Nv/Np.

The VE will be presented with exact 95% CI computed using Clopper-Pearson method for interval around the proportion p.

The same analysis as described above will be done to describe the efficacy in the prevention or reduction of asymptomatic infection by SARS-CoV-2 as measured by seroconversion to the N protein of the virus.

The severity of COVID-19 cases will be described by presenting the number and percentage of subjects with mild, moderate, severe, and moderate to severe COVID-19 episode meeting the case definition in each group (pooled lots and placebo).

In order to consider incidence and severity of COVID-19 disease, a VE measure based on the BoD scores (VE_{BoD}) will be derived. VE_{BoD} is defined as the relative reduction in the BoD score in the CVnCoV groups compared to the placebo group and is calculated as 1 minus the relative risk (RR; the BoD score in the vaccinated groups divided by the BoD score in the placebo group).

$VE_{BoD} = 1- RR = 1 - (SV/SP)$

where

SV = mean BoD score in vaccinated group (pooled lots) / mean follow-up time (months) of evaluable subjects in the CVnCoV groups.

SP = mean BoD score in placebo group / mean follow-up time (months) of evaluable subjects in the Placebo group.

The 95% CI of the VE_{BoD} will be based on the normal distribution.

All efficacy endpoints will be analyzed descriptively without success criteria testing on the EAS.

A supportive analysis will be done on the SAS including all subjects whatever their serological status at baseline and considering all events occurring at any time after the first trial vaccination.

Sensitivity Analysis

As a sensitivity analysis, the time to first-occurrence of virologically-confirmed COVID-19 cases (according to the case definition) may be analyzed.

The Kaplan-Meier curves will display the estimated probabilities of not developing COVID-19 and log-rank test will be performed.

The time to first-occurrence of virologically-confirmed COVID-19 (date of symptoms onset) will start 15 days after the second vaccination.

Subjects who do not develop COVID-19 will be censored at the date of trial termination or cut-off date for analysis whichever comes first.

An additional sensitivity analysis may include a Cox proportional hazards regression model adjusted for relevant baseline covariates specified in the SAP.

More details on the analysis methods will be described in the SAP.

10.3.7.2 Exploratory Efficacy Endpoints Analyses

The number and percentage of subjects who developed a second episode of COVID-19 of any severity will be displayed by group (pooled lots and placebo) in naïve evaluable subjects (complying with the definition of EAS) having presented a first episode of COVID-19 meeting the case definition.

10.3.8 Interim Analysis

An interim analysis will be performed before the trial end based on the regulatory requirements to obtain early conditional approval in Europe, and the advancement of the accrual of a pre-defined number of COVID-19 cases in Trial CV-NCOV-004.

10.3.9 Missing Data

Analysis of vaccination variables 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 SARS-CoV-2 RBD of the S protein antibodies and neutralizing antibodies, concentration/titer values marked as below the LLOQ will be set to 0.5*LLOQ.

No imputation of missing values will be done for any analysis (except the imputation for missing partial dates of AEs and concomitant medication as specified in the SAP).

Currently no replacement of drop-out subjects is foreseen.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Electronic Case Report Forms

In this trial, all clinical data (including, but not limited to, AE/SAEs, concomitant medications/vaccines, medical history and physical assessments) will be entered onto eCRFs in a timely fashion by the Investigator and/or the Investigator's dedicated site staff. All data entered into the eCRF must be verifiable against source documents at the site. Any changes to the data entered into the electronic data capture system will be recorded in the audit trail.

The Investigator will maintain adequate and accurate records for each subject entered into the trial. Source documents such as hospital, clinic or office charts, laboratory reports, trial worksheets, and signed informed consent documents are to be included in the Investigator's files along with subject trial records.

The Sponsor or the CRO will check eCRF entries against source documents according to the guidelines of Good Clinical Practice (GCP). The consent form will include a statement by which subjects allow the Sponsor or designee, as well as authorized regulatory agencies, to have direct access to source data that support data of the eCRF (e.g., subject medical files, appointment books, original laboratory records, etc.). The Sponsor or designee, bound by secrecy, will not disclose subject identities or personal medical information.

11.2 Audit and Inspection

The site also may be subject to quality assurance audits by the Sponsor or designees. In this circumstance, the Sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the vaccine is stored and prepared, and any other facility used during the trial. In addition, there is the possibility that this trial may be inspected by regulatory agencies, including those of local or foreign governments. If the site is contacted for an inspection by a regulatory body, the Sponsor should be notified immediately. The Investigator and institution guarantee direct access for quality assurance auditors and inspectors to all trial documents and source data.

11.3 Monitoring

Data for each subject will be recorded in the subject's eCRF. Data collection must be completed for each subject who signs an informed consent form (ICF). For subjects who failed to meet the eligibility criteria, only demographic data and reason for failure will be documented.

In accordance with GCP, and regulatory requirements, the trial monitor will carry out source document verification at regular intervals to ensure that the data collected in the eCRF are accurate and reliable. The frequency of monitoring visits will be determined by the rate of subject recruitment. In case of travel restrictions and / or prolonged lockdowns due to the COVID-19 pandemic, remote source data verification may be performed.

The compliance with the protocol will be examined with regard to inclusion and exclusion criteria, therapies leading to elimination and timing and availability of planned assessments. Protocol deviations will be monitored on an ongoing basis during the trial and closed before database lock. Protocol deviations will be classified as minor, major, or critical deviations. The detailed definitions of important protocol deviations leading to elimination of subjects from analysis will be provided in the final version of the SAP and/or in the final signed minutes of the data review meeting.

The monitoring visits also provide the Sponsor with the opportunity to ensure the Investigators' obligations and all applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and regulatory requirements are being met.

The Investigators must permit the monitor, the IEC, the Sponsor's and CRO's auditors and representatives from regulatory authorities direct access to all trial-related documents and pertinent hospital or medical records for confirmation of data contained within the eCRF. Subject confidentiality will be protected at all times.

An electronic medical record may be the source document; however, the site must provide a standard operating procedure that details review and approval of data entries by the Principal Investigator(s) (audit trail). Furthermore, the electronic medical record must be compliant with the applicable regulations and with the expectations of each country.

11.4 Data Management and Coding

All data derived from the trial will remain the property of the Sponsor. The Sponsor assumes accountability for actions delegated to other individuals, e.g., the CRO. Data management of this trial will be performed by a CRO. The CRO's responsibilities will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical trial will be handled according to the data management plan and SAP or the relevant SOPs of the data management and biostatistics departments of the CRO.

Trial sites will enter data in the eCRF. Access to the eCRF will be strictly password protected and limited to personnel directly participating in the trial. All data entered into the eCRF must be verifiable against source documents at the site (see Section 11.3). This may include electronic source document verification. Data entered into the eCRF will be validated as defined in the data validation plan.

Medical coding will use MedDRA for concomitant diseases and AEs and WHO Drug Dictionary for medications.

Missing or inconsistent data will be queried to the Investigators for clarification. Subsequent modifications to the database will be documented.

12 ETHICS

12.1 Institutional Review Board/Independent Ethics Committee

Before initiation of the trial at the site, the protocol, the ICF, other written material given to the subjects and any other relevant trial documentation will be submitted to the appropriate IRB/IEC. Written approval of the trial and all relevant trial information must be obtained before the trial vaccine is released to the Investigators. Any necessary extensions or renewals of IRB/IEC approval must be obtained for changes to the trial such as modification of the protocol, the ICF, or other trial documentation. The written approval of the IRB/IEC together with the approved ICF must be filed in the trial files.

The Investigators will report promptly to the IRB/IEC any new information that may adversely affect the safety of the subjects or the conduct of the trial. The Investigators will submit written summaries of the trial status to the IRB/IEC as required. On completion of the trial, the IRB/IEC will be notified that the trial has ended.

12.2 Regulatory Authorities

The protocol, name, and site of the Investigators, the votes of the IRB(s)/IEC(s), as well as other relevant trial documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the trial. On completion of the trial, the regulatory authorities will be notified that the trial has ended. Individual subject medical information obtained as a result of this trial is considered confidential.

12.3 Ethical Conduct of the Trial

The Investigators and all parties involved in this trial should conduct the trial in adherence to the ethical principles based on the current version of the Declaration of Helsinki, GCP, ICH guidelines, and the applicable national and local laws and regulatory requirements.

GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trial activities that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of the subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki and that the trial data are credible.

The Investigators and all trial staff will conduct the trial in compliance with the IRB(s)/IEC(s) approved version of this protocol. The rights, safety and well-being of the subjects are the most important considerations and prevail over the interests of science and society. All personnel involved in the conduct of this trial must be qualified by education, training, and experience to perform their assigned responsibilities.

12.4 Informed Consent

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s) and must adhere to GCP.

The Investigators are responsible for ensuring that no subject undergoes any trial-related examination or activity before that subject has given written informed consent to participate in the trial.

The Investigator or designated personnel will inform the subject of the objectives, methods, anticipated benefits, and potential risks and inconveniences of the trial. The subject should be given every opportunity to ask for clarification of any points he does not understand and if necessary, ask for more information. At the end of the interview, the subject will be given ample time to consider the trial. Subjects will be required to sign and date the ICF. After signatures are obtained, the ICF will be kept and archived by the Investigator in the Investigator's trial file. A signed and dated copy of the subject ICF will be provided to the subject or his/her authorized representative.

It should be emphasized to the subject that the participation in the trial is voluntary and the subject may refuse to participate or discontinued from the trial at any time, without consequences for his/her further care or penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give or who withdraw written informed consent should not be included or continue in the trial.

If new information becomes available that may be relevant to the subject's willingness to continue participation in the trial, a new ICF will be approved by the IECs (and regulatory authorities if required). The trial subjects will be informed about this new information and re-consent will be obtained.

13 DATA HANDLING AND RECORD KEEPING

Essential documents are those documents that individually and collectively permit evaluation of the trial and quality of the data produced. After completion of the trial, all documents and data relating to the trial will be kept in an orderly manner by the Investigator in a secure trial file. This file will be available for audits by the Sponsor/CRO or inspections by the regulatory agencies. Essential documents should be retained for 15 years after end of the trial. It is the responsibility of the Sponsor to inform the site of when these documents no longer need to be retained. The Investigator must contact the Sponsor before destroying any trial-related documentation. In addition, all subject medical records and other source documentation will be kept for the maximum time required by the hospital, institution, or medical practice and in accordance with the national requirements. If an Investigator moves, withdraws from the trial, or retires, the responsibility for maintaining the records may be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed by the Sponsor.

In this trial processing of personal data will be carried out on behalf of Sponsor by CRO/the data processor, governed by a contract and strictly according and subject to the General Data Protection Regulation (GDPR) and any applicable data protection rules and regulations. The Sponsor and the CRO/data processor implement appropriate technical and organizational measures to ensure a level of security appropriate to the risk, taking into account the state of the art, the costs of implementation and the nature, scope, context and purposes of processing as well as the risk of varying likelihood and severity for the rights and freedoms of natural persons. Quality control will occur at each stage of data handling to ensure that all data are reliable and have been processed correctly. The Sponsor will ensure oversight of any trial-related duties and functions carried out on its behalf, including trial-related duties and functions that are subcontracted to another party by the CRO.

This trial will be registered on ClinicalTrials.gov in accordance with applicable laws or publication policy and may also be registered on other publicly accessible websites as necessary.

13.1 Data Protection

All information generated in this trial is considered highly confidential and must not be disclosed to any person or entity not directly involved with the trial unless prior written consent is gained from the Sponsor. However, authorized regulatory officials, IRB/IEC personnel, the Sponsor, and its authorized representatives are allowed full access to the records. All personal details will be treated as confidential by the investigator and staff at the CRO. Prior to the processing, the Sponsor performs an assessment of the impact of the envisaged processing operations on the protection of personal data (according to Article 35 of the GDPR).

Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred. All personal identifiers according to applicable regulations (e.g., name, phone number) must be redacted permanently by the site personnel and replaced with the subject's unique identification number in all records and data before transfer to the Sponsor (or designee).

The subject must be informed that his/her personal trial-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent. The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Subjects or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

13.2 Amendments to the Protocol

Amendments to this trial protocol may be made following the procedures specified by local laws and regulations. Substantial amendments to this trial protocol may be implemented only if the approval of the competent authorities and a favorable opinion of the IRB/IEC(s) have been obtained.

Substantial amendments to the conduct of the clinical trial may arise from changes to the protocol or from new information relating to the scientific documents in support of the trial. Amendments to the trial are regarded as “substantial” where they are likely to have a significant impact on:

The safety, physical health, and mental integrity of the subjects.

The scientific value of the trial.

The conduct or management of the trial.

The quality or safety of any medicinal product used in the trial.

If a new event occurs related to the conduct of the trial or the development of the IMP, which may affect the safety of the subjects, the Sponsor, and the Investigator will take appropriate safety measures to protect the subjects against any immediate hazard. The Sponsor will immediately inform the competent authorities and IRB(s)/IEC(s) of the new events and the measures taken.

13.3 Biological Samples and Record Retention

13.3.1 Biological Samples Retention and Destruction

Collected specimens (blood) will be processed, stored, and frozen appropriately for analysis. The Sponsor has put into place a system to protect subjects’ personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction. Excess biological specimens may be further tested with regard to investigation of the vaccine effect and respective required assay validation.

13.3.2 Retention of Trial Records

Records and source documents pertaining to the conduct of the trial and the distribution of the IMP (e.g., ICFs, laboratory slips, vaccination inventory records, and other pertinent information) must be retained by the Investigator for a period of at least 15 years.

13.4 Clinical Trial Report

The Sponsor is responsible for preparing and providing the appropriate regulatory authorities with the clinical trial report according to the applicable regulatory requirements. The Sponsor should ensure that this report meets the standards of the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3).

13.5 Publication Policy

Any publication or scientific communication related to this trial can only take place once the manuscript has been reviewed by the Sponsor and once a written agreement between the Sponsor and the Investigators has been reached. The Sponsor will comply with the requirements for publication of trial results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by mutual agreement. Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

14 REFERENCES

1. ICH Guidelines. Available at: http://www.ich.org/products/guidelines.html. Accessed 12 December 2017.
2. Li G, Fan Y, Lai Y, et al. Coronavirus Infections and Immune Responses. J Med Virol. 2020 Jan 25. https://onlinelibrary.wiley.com/doi/epdf/10.1002/jmv.25685
3. Chan JF, Kok KH, Zhu Z, et al. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. Emerg Microbes Infect. 2020 Dec;9(1):221-236.
4. Wu P, Hao X, Lau EHY, et al. Real-time tentative assessment of the epidemiological characteristics of novel coronavirus infections in Wuhan, China, as at 22 January 2020. Euro Surveill. 2020 Jan;25(3). https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.3.2000044#r11
5. Ren LL, Wang YM, Wu ZQ, et al. Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study. Chin Med J (Engl). 2020 Jan 30. https://www.ncbi.nlm.nih.gov/pubmed/32004165
6. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020 Feb 3. https://www.nature.com/articles/s41586-020-2012-7_reference.pdf
7. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020 Jan 30. pii: S0140-6736(20)30251-8. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30251-8/fulltext
8. Ceraolo C, Giorgi FM. Genomic variance of the 2019-nCoV coronavirus. J Med Virol. 2020 Feb 6. https://onlinelibrary.wiley.com/doi/epdf/10.1002/jmv.25700
9. Baruah V, Bose S. Immunoinformatics-aided identification of T cell and B cell epitopes in the surface glycoprotein of 2019-nCoV. J Med Virol. 2020 Feb 5. https://onlinelibrary.wiley.com/doi/epdf/10.1002/jmv.25698
10. Lauer SA, Grantz KH, Bi Q, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: Estimation and application. Ann Intern Med. 2020 Mar 10.
11. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of 2019 novel coronavirus infection in China. New England Journal of Medicine. 2020 Feb 28.
12. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol. 2020 Apr 10.
13. Wu Y, Xu X, Chen Z, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun. 2020 Mar 30.
14. Recalcati S. Cutaneous manifestations in COVID-19: a first perspective. Journal of the European Academy of Dermatology and Venereology. [cited 2020 Apr 16]. https://onlinelibrary.wiley.com/doi/abs/10.1111/jdv.16387
15. Atri D, Siddiqi HK, Lang J, et al. COVID-19 for the cardiologist: A current review of the virology, clinical epidemiology, cardiac and other clinical manifestations and potential therapeutic strategies. JACC Basic Transl Sci. 2020 Apr 10.

16. Team TNCPERE. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) — China, 2020. CCDCW. 2020 Feb 1;2:1–10.

17. Deng Y, Liu W, Liu K, et al. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 (COVID-19) in Wuhan, China: a retrospective study. Chin Med J. 2020 Mar 20.

18. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. The Lancet Respiratory Medicine. 2020 Feb 24. https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30079-5/abstract

19. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) [cited 2020 Mar 24]. https://www.who.int/publications-detail/report-of-the-who-china-joint-mission-on-coronavirus-disease-2019-(covid-19)

20. Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. JAMA. 2020 Apr 6. https://doi.org/10.1001/jama.2020.5394

21. WHO Director-General's opening remarks at the media briefing on COVID-19 - 3 March 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---3-march-2020

22. World Health Statistics 2020: Monitoring health for the SDGs, sustainable development goals. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.
https://apps.who.int/iris/bitstream/handle/10665/332070/9789240005105-eng.pdf?ua=1

23. Alberer M, Gnad-Vogt U, Hong HS, et al. Safety and immunogenicity of a mRNA Placebo vaccine in healthy adults: an open-label, non-randomised, prospective, first-in-human phase 1 clinical trial. Lancet. 2017;390(10101):1511-1520.

24. Kübler H, Scheel B, Gnad-Vogt U, et al. Self-adjuvanted mRNA vaccination in advanced prostate cancer patients: a first-in-man phase I/IIa study. Journal for Immunotherapy of Cancer. 2015;3:26. doi:10.1186/s40425-015-0068-y

25. Hong HS, Koch SD, Scheel B, et al. Distinct transcriptional changes in non-small cell lung cancer patients associated with multi-antigenic RNActive® CV9201 immunotherapy. Oncoimmunology. 2016;5(12):e1249560. doi:10.1080/2162402X.2016.1249560

26. Rausch S, Schwentner C, Stenzl A, Bedke J. mRNA vaccine CV9103 and CV9104 for the treatment of prostate cancer. Hum Vaccin Immunother. 2014;10(11):3146-52.

27. Pallesen J, Wang N, Corbett KS, et al. Immunogenicity and structures of a rationally designed prefusion MERS-CoV spike antigen. Proc Natl Acad Sci USA. 2017; 114(35):E7348-E7357.

28. Fotin-Mleczek M, Duchardt KM, Lorenz C, et al. Messenger RNA-based vaccines with dual activity induce balanced TLR-7 dependent adaptive immune responses and provide antitumor activity. J Immunother. 2011;34(1):1-15.

29. Graham B. S., et al. Rapid COVID-19 vaccine development; 2020; Science 10.1126/science.abb8923.
https://science.sciencemag.org/content/sci/early/2020/05/07/science.abb8923.full.pdf

30. Wang J and Zand MS. The potential for antibody-dependent enhancement of SARS-CoV-2 infection: Translational implications for vaccine development. Journal of Clinical and Translational Science. 2020;1-4.

31. Global regulatory workshop on COVID-19 vaccine development: Summary Report. International Coalition of Medicines Regulatory Authorities (ICMRA), 18 March 2020, https://www.pei.de/SharedDocs/Downloads/EN/newsroom-en/hp-news/icrma-report.pdf?__blob=publicationFile&v=2. Accessed 11 Jun 2020.

32. Clinical Trial Facilitation Group (CTFG) Recommendations related to contraception and pregnancy testing in clinical trials, September 2014. Available at: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

33. US Department of Health and Human Services. Food and Drug Administration (FDA). Guidance for Industry. Development and Licensure of Vaccines to Prevent COVID-19. 2020. [Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/development-and-licensure-vaccines-prevent-covid-19; Accessed October 2020].

34. 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].

35. Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika. 1983;70:659-63.

36. Verity R, Okell LC, Dorigatti I et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. Lancet Infect. Dis. 2020;20:669-77.

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

15 APPENDICES

Appendix 1 Responsibilities of the Investigator

Clinical research studies sponsored by the Sponsor are subject to ICH GCP and all the applicable local laws and regulations.

The Investigator agrees to assume the following responsibilities:

1. Conduct the trial in accordance with the protocol ICH-E6 (R2), and all the applicable local laws and regulations.
2. Personally conduct or supervise the staff who will assist with the protocol.
3. Ensure that trial-related procedures including trial specific (non-routine/non-standard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the trial are informed of these obligations.
5. Secure prior approval of the trial and any changes by an appropriate IEC and competent authority.
6. Ensure that the IEC will be responsible for initial review, continuing review, and approval of the protocol.
7. Ensure that requirements for informed consent, as outlined in ICH-E6 (R2) 4.8 and local regulations, are met.
8. Obtain valid informed consent from each subject and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the trial. If an informed consent form does not include such a subject authorization, then the Investigator must obtain a separate subject authorization form from each subject.
9. Prepare and maintain adequate case histories of all persons entered into the trial, including eCRFs, hospital records, laboratory results, etc., and maintain these data for a minimum of 2 years following notification by the Sponsor that all investigations have been discontinued or that the Regulatory Authority has approved the marketing application. The Investigator should contact and receive written approval from the Sponsor before disposing of any such documents.
10. Ensure that clinical data is entered into the eCRFs on the visit day during the staggered enrollment phase and within 5 days post-visit for all other visits.
11. Allow possible inspection and copying by the Regulatory Authority of GCP-specified source documents.
12. Maintain current records of the receipt, administration, and disposition of Sponsor-supplied vaccines, and return all unused Sponsor-supplied vaccines to the Sponsor.
13. In the event of an SAE, AESI or overdose notify the CRO within 24 hours via SAE/AESI/overdose/misuse report form signed by the Investigator.
14. Review and provide a signature as approval of the content of the clinical trial report.

Appendix 2 Emergency Procedures

During and after subjects' participation in this trial, the Investigator or institution should ensure that adequate medical care is provided to subjects who present with any AEs, including clinically significant laboratory values related to the administration of the trial vaccine. The Investigator or institution should inform subjects when medical care is needed for intercurrent illness(es) of which the Investigator becomes aware.

Emergency equipment for the immediate treatment of allergic/anaphylactic reactions (steroids, H1, H2 antihistaminergic agents, intravenous fluids, oxygen, epinephrine and equipment for cardiopulmonary resuscitation) must be available at all times for the treatment of these events, and trained personnel must be present at all times while subjects are being monitored after vaccination.

The site should have immediate access to equipment and appropriately qualified staff for resuscitating and stabilizing subjects in an acute emergency (such as cardiac emergencies, anaphylaxis, cytokine release syndrome, convulsions, hypotension), and ready availability of intensive care unit and other hospital facilities.

Appendix 3 Definition of Severe COVID-19 Disease

Severe COVID-19 cases are defined by any 1 of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 breaths per minute, heart rate ≥ 125 per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FIO2 < 300 mm Hg)
- SpO2 should be adjusted according to altitude.
- Respiratory failure (defined as needing high flow-oxygen, noninvasive ventilation, mechanical ventilation or ECMO)
- Evidence of shock (SBP < 90mm Hg, DBP < 60 mmHg, or requiring vasopressors)
- Significant renal, hepatic, or neurologic dysfunction
- Admission to ICU
- Death

FDA Development and Licensure of Vaccines to Prevent COVID-19 guidance [33].

Appendix 4 Definition of Moderate and Mild COVID-19 Disease

Moderate COVID-19 cases are defined by any 1 of the following:

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

Mild COVID-19 cases are defined by the following:

- Symptomatic AND
- No shortness of breath or difficulty breathing AND
- No hypoxemia (SpO2 saturation ≥ 95% on room air at sea level*) AND
  *SpO2 should be adjusted according to altitude
- Does not meet the case definition of moderate or severe COVID-19 disease

Appendix 5 Safety and SARS-CoV-2 Tests

The tests detailed in the tables below will be performed at a sponsor-designated laboratory. The Investigator must document his review of each laboratory report, by signing and dating the report.

Additional tests, including any safety laboratory assessments, may be performed at any time during the trial as deemed necessary by the Investigator or required by local regulations.

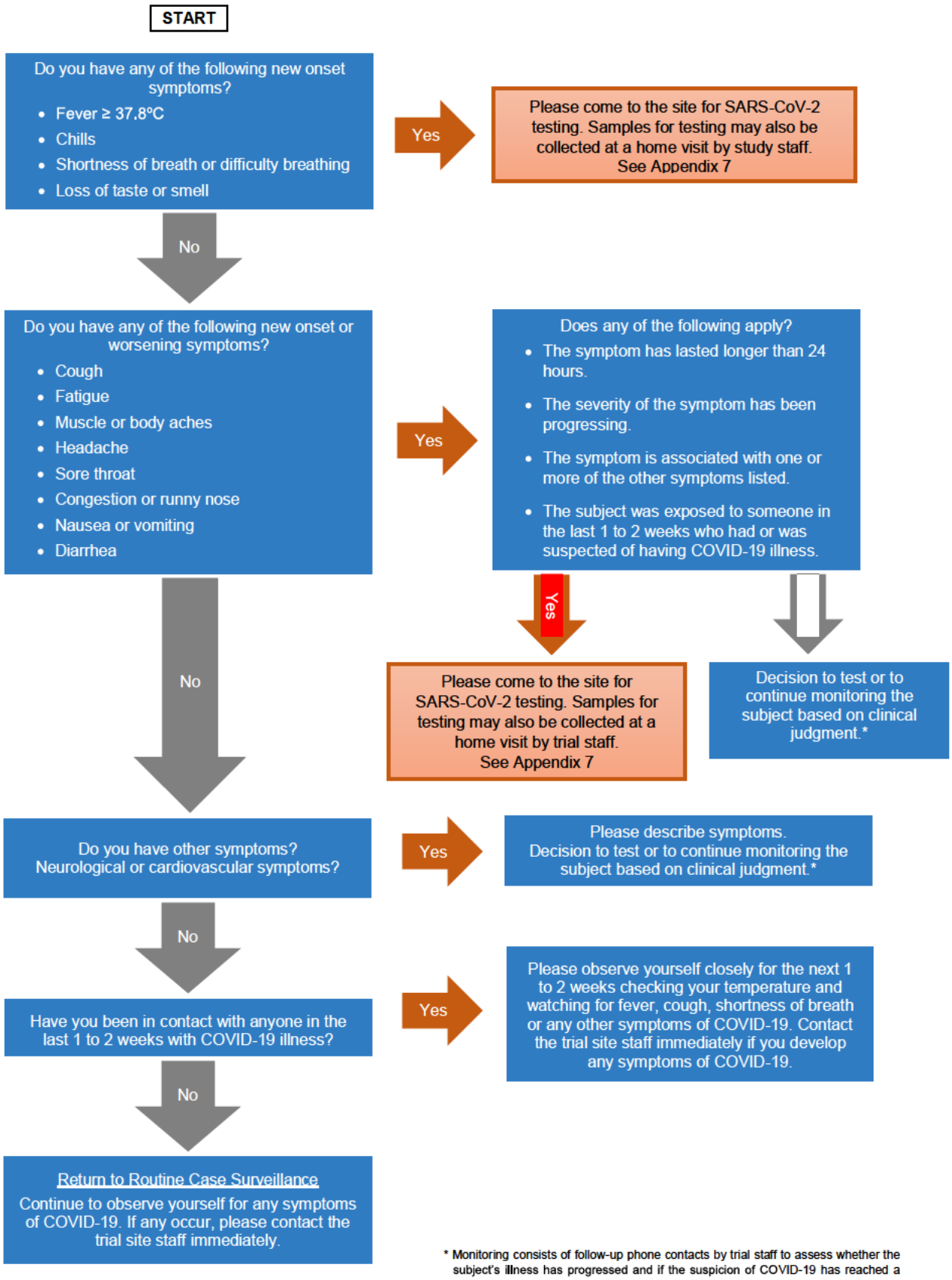
Protocol-Required Safety Laboratory Test

Laboratory Assessment	Parameters
Urine Pregnancy Test	Human chorionic gonadotropin

SARS-CoV-2 Molecular-Based Test

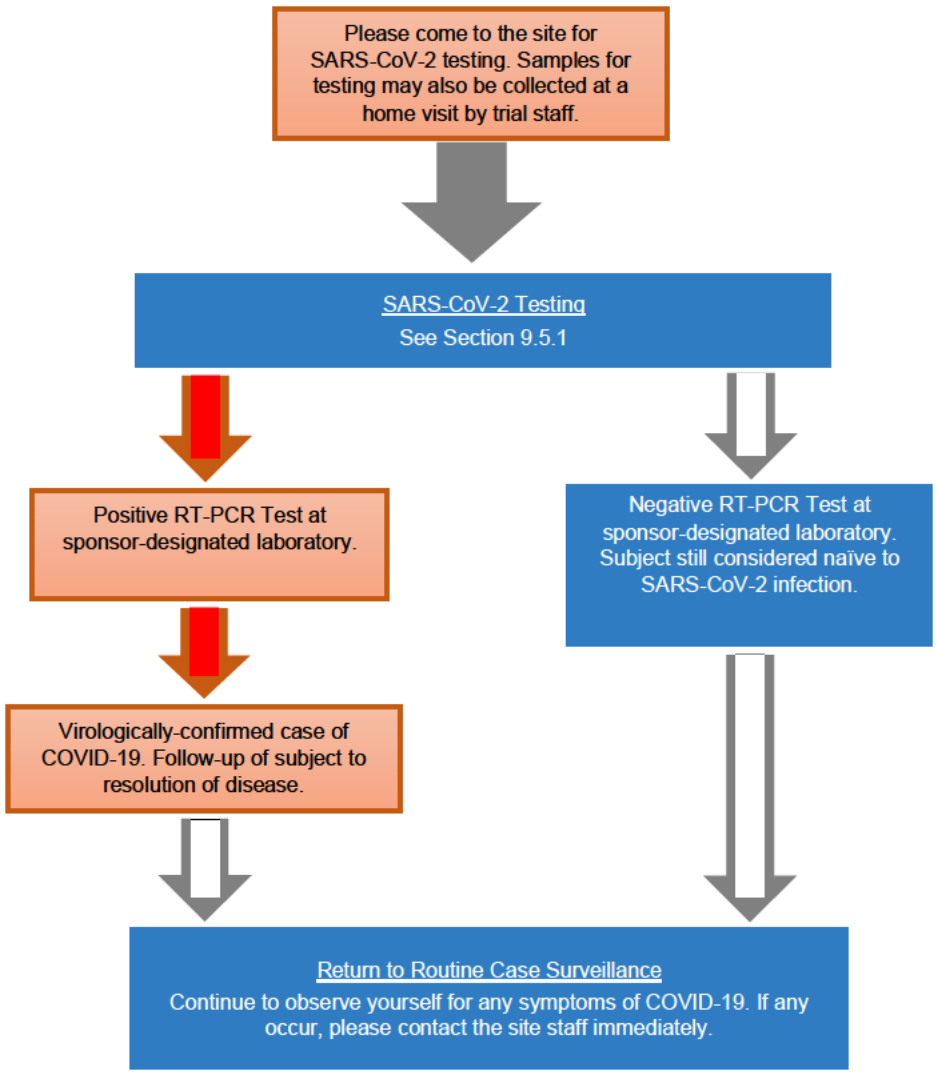
Laboratory Assessment	Parameters
SARS-CoV-2 Specific Reverse Transcriptase - Polymerase Chain Reaction (RT-PCR) Test	SARS-CoV-2 RNA in nasopharyngeal swab sample

Appendix 6 Flow Diagram for COVID-19 Case Interview



* Monitoring consists of follow-up phone contacts by trial staff to assess whether the subject's illness has progressed and if the suspicion of COVID-19 has reached a sufficient level to test the subject. Based on clinical judgment, phone contact may be made as frequently as daily.

Appendix 7 SARS-CoV-2 Testing Outcome



Appendix 8 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 9 Adverse Events of Special Interest (AESIs) 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 AR following immunization

Appendix 10 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of an Adverse Event (AE)

Definition of an AE:
An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. All AEs fall into 1 of 2 categories: “non-serious” or “serious”.
Examples of an AE include:
Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to a known concomitant disease). Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. New conditions detected or diagnosed after administration of the trial vaccine even though it may have been present before the start of the trial. Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. Signs, symptoms, or the clinical sequelae of a suspected overdose of either trial vaccine or a concomitant medication/vaccination. An adverse effect of the trial vaccine or concomitant medication/vaccination. An accident or injury.
Events NOT Meeting the AE Definition:
Medical or surgical procedures or other therapeutic interventions themselves are not AEs, but the condition for which the surgery/intervention is required is an AE and should be documented accordingly. Planned surgical measures and the condition(s) leading to these measures are not AEs, if the condition(s) was (were) known before the period of observation (see below) and did not worsen during trial. In the latter case the condition should be reported as medical history. Situations where an untoward medical occurrence did not occur (e.g., social and/or convenience admission to a hospital). Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the trial that do not worsen. Death is not considered an AE but an outcome.

Definition of an SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:
Results in death.
Is life-threatening. The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
Results in persistent disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect in the offspring of the subject.
Is an important medical event: Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Assessment of Intensity and Causality

Assessment of Intensity
The Investigator will make an assessment of intensity for each AE and SAE reported during the trial and assign it to 1 of the following categories. **Absent** (Grade 0): No AE. **Mild** (Grade 1): An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities. **Moderate** (Grade 2): An event that causes sufficient discomfort to interfere with normal everyday activities. **Severe** (Grade 3): An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

Assessment of Causality
The Investigator is obligated to assess the relationship between the trial vaccine and each occurrence of each AE/SAE. Causality will be determined as: **Related**: There is a reasonable causal relationship between the trial vaccine and the AE. **Unrelated**: There is no reasonable causal relationship between the trial vaccine and the AE. A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as underlying disease(s), concomitant therapy or vaccination, and other risk factors, as well as the temporal relationship of the event to the trial vaccine administration will be considered and investigated. The Investigator will also consult the Investigator's Brochure for CVnCoV in his/her assessment. For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the CRO. However, **it is very important that the Investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the CRO.** The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment. The causality assessment is 1 of the criteria used when determining regulatory reporting requirements. All local solicited symptoms are considered related to vaccination.

Recording of AEs and/or SAEs

AE and SAE Recording
The Investigator is responsible for recording all AEs/SAEs observed during the trial i.e. from the time the subject gives informed consent until the end of the trial visit or until the last follow-up visit, for the period described in Section 9.3.
When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
The Investigator will then record all relevant AE/SAE information in the eCRF.
SAEs need to be reported to the CRO within 24 hours (see section Reporting of SAEs).
It is **not** acceptable for the Investigator to send photocopies of the subject's medical records to the CRO in lieu of completion of the AE/SAE eCRF screen.
There may be instances when copies of medical records for certain cases are requested by the CRO. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the CRO.
The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
AESIs and cases of overdose must be documented and medically assessed by the Investigator and the outcome described on the SAE/AESI/overdose/misuse report form.
Pregnancy must be documented and medically assessed by the Investigator and the outcome described on the Pregnancy Report Form which is to be sent to the CRO.
Follow-up of AEs and SAEs
The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the CRO to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
If a subject dies during participation in the trial or during the follow-up period, the Investigator will provide the CRO with a copy of any post-mortem findings including histopathology.
New or updated information will be recorded in the originally completed eCRF.
The Investigator will submit any updated SAE data to the CRO within 24 hours of receipt of the information.

Reporting of AEs

AE Reporting
It is the responsibility of the Investigator to document all AEs that occur during the trial in the source documents. AEs will be elicited by asking the subject a non-leading question, for example, 'Have you experienced any new or changed symptoms since we last asked/since your last visit?'.
The Investigator must document all AEs that occur during the observation period set in this protocol and which fulfil the conditions as outlined in section 9.3.2. Safety Assessments for All Subjects on the screens provided in the eCRF.
The following approach will be taken for documentation:
All Adverse Events (whether serious or non-serious) which need to be reported according to section 9.3.2. must be documented on the "Adverse Event" screen of the eCRF. All AEs will be described using the sign, symptom, or medical diagnosis on the AE eCRF in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial expressions. Each AE will be defined as serious or non-serious according to the definitions in the section above. The Investigator will evaluate the severity of each AE and causal relationship of the event to the trial vaccine.

Reporting of SAEs

SAE Reporting
If the AE is **serious**, the Investigator must complete and sign, in addition to the "Adverse Event" screen in the eCRF, an "SAE/AESI/overdose/misuse report form" at the time the SAE is detected.
Email or facsimile transmission of the SAE/AESI/overdose/misuse paper report form is the preferred method to transmit this information to the CRO/medical monitor or the SAE coordinator.
This form must be marked as **"initial"** report and sent **immediately (i.e., within 24 hours upon becoming aware of the SAE)** to the CRO.
The Investigator will document the date when any employee/co-Investigator had first been aware of the report and fax or email all SAE reports (initial and follow-up reports) even if they are incomplete within 24 hours upon receipt to the safety department of the Sponsor or CRO.
In rare circumstances and in the absence of email or facsimile equipment, notification by phone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. Initial notification via phone does not replace the need for the Investigator to complete and sign the SAE report form within the designated reporting time frames.
The "**initial SAE report**" should be as complete as possible, including causality assessment, details of the current illness and (S)AE, the reason why the event was considered serious; date of onset and end date (if applicable); diagnostic procedures and treatment of the event; relevant medical history and concomitant medication and vaccinations; and action taken with the trial vaccine(s). The SAE report form **must be signed by the Investigator or his authorized designee(s)**.

Investigator must inform the CRO about AESIs and cases of overdose by applying the same timelines and rules of SAE reporting.
Determination of Expectedness, Reference Safety Information
Expectedness will be determined by the CRO according to the designated Reference Safety Information provided in the current Investigator's Brochure. Any updates or substantial amendments will be considered accordingly.
Observation Period
For the purpose of this trial, the period of observation for collection of AEs required to be reported in the CRF extends from the time the subject gives informed consent until the end of the trial, for the period described in Section 5.4 consisting of Trial CV-NCOV-005. All AEs that occur in the course of the clinical trial regardless of the causal relationship should be monitored and followed-up until the outcome is known or it is evident that no further information can be obtained. There must be documented reasonable attempts to obtain follow-up information and outcome. It is the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.
Post-Trial Events
If the Investigator becomes aware of any SAE that occurred after the end of the trial but is considered to be caused by the trial vaccine(s), this must be reported to the CRO. These SAEs will be processed by the CRO. Instructions for how to submit these SAEs will be provided in a handout in the Investigator Site File.

Reporting of Other Events

Reporting and Follow-up of Pregnancies
Pregnancy is an exclusion criterion for enrollment in this trial, but subjects could potentially become pregnant during their active participation in this trial. Any pregnancy in a subject having received a trial vaccine must be reported to the CRO within 24 hours of the site learning of its occurrence, using a pregnancy reporting form. If the subject becomes pregnant during the trial, she will not receive any further doses of any Sponsor-supplied trial vaccine. The pregnancy must be followed to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if the intended duration of safety follow-up for the trial has ended. The site should maintain contact with pregnant subjects to obtain pregnancy outcome information. Any complications during pregnancy (e.g., gestational diabetes or eclampsia) are to be considered as an AE; however, these complications could result in the event being an SAE. Spontaneous abortions, fetal death, stillbirth and congenital anomalies reported in the baby are always considered as SAEs. The pregnancy by itself will not be processed as an SAE. The Investigator will follow the subject until completion of the pregnancy and must assess the outcome in the shortest possible time but not more than

30 days within completion of the pregnancy. The Investigator should notify the CRO of the outcome of the pregnancy by submitting a Follow-up Pregnancy Report.

Reporting and Follow-up of SUSARs and Other Regulatory Reporting

Any SUSAR will be the subject of expedited reporting.

The Sponsor and/or the CRO shall ensure that all relevant information about a SUSAR that is fatal or life-threatening is reported to the relevant competent authorities and IEC(s) within 7 days after knowledge by the Sponsor of such a case and that relevant follow-up information is communicated within an additional 8 days.

The Sponsor will report all serious and unexpected AEs, which are judged by either the Investigator or the Sponsor as having a reasonable suspected causal relationship (suspected unexpected serious adverse reactions, SUSARs), to the competent authority, the concerned Independent Ethics Committee and Investigators according to applicable law.

Post-trial SUSARs that occur after the subject has completed the clinical trial must be reported by the Investigator to the Sponsor.

Reporting and Follow-up of Misuse and Overdose

Drug misuse and drug overdose should always be reported in the same format (i.e., on SAE form) and within the same timelines as a SAE, even if they may not result in an adverse outcome.

When an "overdose" or "drug misuse" of the trial vaccine occurs without an AE, the Investigator should also complete an "SAE/AESI/overdose/misuse report form" and send this to the Sponsor's safety contact.

It should be clearly stated that no AE was observed. If no SAE is associated, misuse/overdose will be assessed as non-serious.

In this case, there is no need to complete the "Averse Event" screen in the eCRF.

Product Quality Complaints

Pharmaceutical Technical Complaints associated with the trial vaccine must be reported to the Sponsor immediately (refer to the pharmacy manual for details).

The same reporting timelines as for SAEs apply.

Appendix 11 Protocol Amendment History

The trial was initiated using protocol version 1.0.

Protocol version 2.0: 19 March 2021

Section # and Name	Description of Important Change	Brief Rationale
Throughout	Changed “students in clinical years” for “students in clinical training”.	Clarification
Throughout	Subjects who report to have COVID-19 symptoms will only be followed-up if the Investigator considers the symptoms could potentially indicate a COVID-19 case.	Clarification
Throughout	Subjects who tested positive for SARS-CoV-2 outside of the trial context (RT-PCR) are to be considered for active surveillance for COVID-19 (see Appendix 6).	Completeness
Throughout	Unblinding will be allowed in the case a subject becomes eligible to receive an authorized/licensed vaccine.	Several vaccine candidates have been approved for emergency use since the original protocol
Synopsis	Inclusion of information on authorized vaccine availability.	Update
Synopsis and 6.2 Exclusion Criteria	History of pIMD separated from history of angioedema or anaphylactic reaction.	Clarification
Synopsis, 9.2.1.1.1 Routine Surveillance for COVID-19, and 9.5.1 Virological Confirmation of COVID-19 Disease	Instructions added to state that viral RNA of SARS-CoV-2 should be sequenced at a Sponsor-designated laboratory to identify S protein variants in subjects with positive RT-PCR tests.	To identify mutations in this protein

Section # and Name	Description of Important Change	Brief Rationale
5.1 Overall Design and 6.3 Vaccine Delay Recommendations	Guidance added that subjects may receive the second trial vaccine dose if they develop COVID-19 between the first and second doses (after being symptom-free for 2 weeks).	Clarification
9.3.3 Adverse Events	Inclusion of instructions that COVID-19 illness and its complications/sequelae are to be reported as an AESI, according to Appendix 9.	Clarification
9.3.6 Vital Signs and Physical Examination	Exclusion of the genitourinary system examination from the complete physical examination. Inclusion of O_2 saturation measurement at the discretion of the investigator.	Correction
Throughout	Minor editorial and document formatting revisions.	-

Protocol Version 3.0: 23 July 2021

Section # and Name	**Description of Important Change**	**Brief Rationale**
1 Synopsis, 2 Schedule of activities, 3.2.3 Assessment of potential risk and benefits, 4.2.3 Exploratory endpoints, 7.3.3.2 Authorized/ licensed vaccine, 7.6.2 Prohibited medications/ vaccines during the Trial, and 9.1 Schedule of Trial assessments and procedures	Introduced the summary of CVnCoV final efficacy analysis of the HERALD trial and, following that, the unblinding of all blinded subject and subsequent change on the schedules of activities to guarantee safety follow up of all the subjects exposed to CVnCoV and access to information on the HERALD final analysis results for all the subjects.	Update following availability of the final efficacy analysis results of the HERALD trial.

Protocol Version 4.0: 11 August 2021

Section # and Name	**Description of Important Change**	**Brief Rationale**
1 Synopsis and 3.2.3 Assessment of potential risk and benefits	Clarification that the Study Physician will be responsible for providing study results to subjects.	Clarification
9.4.3 Antibody Responses to CVnCoV Vaccination in Subjects Who Develop a Case of COVID-19	Subjects receiving authorized SARS-CoV-2 vaccines will not be included in the antibody response. See Table 2	Clarification
Throughout	Minor editorial and document formatting revisions.	-

Protocol Version 5.0: 22 December 2021

Section # and Name	**Description of Important Change**	**Brief Rationale**
Protocol Approval Signatures	New Medical Responsible Person [redacted]	Change of responsibility
SAE Hotline and Medical Monitor Contact	Added e-mail address for post-trial safety reporting	Change of safety reporting e-mail address after end of trial
Synopsis	Trial will remain blinded until approval of study protocol version 3.0.	Clarification
Synopisis / Schedule of Trial Assessments Table 1, 2 and 3 3.1.4 Trial Rationale 4.1.2 Secondary Endpoints 4.2 Endpoints 4.3 Estimands 5.1 Overall Design 5.2 Scientific Rationale for Trial Design 9.1.1.10; 9.1.2.7 End of Trial Visit 9.2.1.1.1 Routine Surveillance for COVID-19 9.4 Immunogenicity Assessments 10 Statistical Considerations	Assessment of cell mediated immune (CMI) response cancelled. Comparison of efficacy by pooling of results with study COVID19-5-P-002 cancelled. Limitation of immunogenicity analyses to 100 CVnCoV subjects per lot and 50 placebo subjects and to the following time points: Baseline, Day 29 and Day 43. Assessment of seroconversion to the N-protein of SARS-CoV-2 at Day 393 cancelled. Assessment of efficacy of CVnCoV in the prevention or reduction of asymptomatic infections cancelled.	Analyses no longer required.

	Measurement of antibody responses for all Covid-19 cases that occur in the trial cancelled. For positive RT-PCR tests, viral RNA of the SARS-CoV-2 sequencing to identify S protein variants no longer required.	
1. Synopsis 5.1 Overall Design 9.2.1.3 COVID-19 Case Definition for the Efficacy Analysis 9.2.1.4 Adjudication of COVID-19 Cases 9.3.8.2 Adjudication Committee	Efficacy cases must no longer be confirmed by adjudication	Confirmation no longer required
9.3.3.2 Safety Assessments for All Subjects Appendix 12 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	AE recording only to be done for criteria defined in section 9.3.2	Clarification
8 Discontinuation / Withdrawal Criteria	Withdrawal procedure for placebo subjects added	Clarification
11.3 Monitoring	Option for remote source data verification included	Implementation of Guidance on the Management of Clinical Trials during the Covid-19 (Coronavirus) Pandemic