Protocol Number: CV-NCOV-004

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

NCT Number: NCT04652102

Document Date: 25 November 2021

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CLINICAL TRIAL PROTOCOL

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

Protocol Number:	CV-NCOV-004
EudraCT Number:	2020-003998-22
Investigational Product:	CV07050101 (referred to as CVnCoV)
Trial Name:	HERALD
Phase:	Phase 2b/3
Sponsor:	CureVac AG Schumannstrasse 27 60325 Frankfurt Germany
Short Title:	Efficacy and Safety of CVnCoV in Adults
Protocol Version:	4.0
Protocol Date:	25 November 2021

PROTOCOL VERSION HISTORY:

Version 1.0 dated 11 November 2020

Version 2.0 dated 17 February 2021

Version 3.0 dated 29 March 2021

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PROTOCOL APPROVAL SIGNATURES

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

Protocol Number: CV-NCOV-004

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

[redacted]

Medical Responsible Person

[redacted]
CureVac AG

[redacted]

Clinical Operations

[redacted]
CureVac AG

[redacted]

Statistician

[redacted]
CureVac AG

[redacted]

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COORDINATING INVESTIGATOR SIGNATURE

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

Protocol Number: CV-NCOV-004

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 on Harmonisation (ICH) guidelines.

Coordinating Investigator

[redacted]

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INVESTIGATOR SIGNATURE PAGE

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

Protocol Number: CV-NCOV-004

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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

Name

Address

Signature

Date

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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]
Latin America	[redacted]	[redacted]
Medical Monitors The Medical Monitoring team 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. Medical Monitor Lead: [redacted]		
Medical Monitoring Support Center:		
Phone:	[redacted]	
	[redacted]	
Fax:	[redacted]	
	[redacted]	
Email:	[redacted]	

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TABLE OF CONTENTS

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LIST OF TABLES

LIST OF FIGURES

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LIST OF ABBREVIATIONS

ADE	Antibody-dependent enhancement
AE	Adverse event
AESI	Adverse event of special interest
ARDS	Acute respiratory distress syndrome
AV	Authorized/licensed vaccines for preventing COVID-19
BMI	Body mass index
BoD	Burden of disease
CI	Confidence interval
CMI	Cell-mediated immunity
CoV	Coronavirus
COVID-19	Coronavirus disease 2019
CRO	Contract research organization
CTL	Cytotoxic T lymphocyte
CVnCoV	Investigational SARS-CoV-2 mRNA vaccine
DSMB	Data and Safety Monitoring Board
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
E	Envelope
EAS	Efficacy Analysis Set
eCDC	European Centre for Disease Prevention and Control
eCRF	Electronic case report form
eDiary	Electronic Diary
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOT	End of Trial
FC	Fold change
FDA	United States Food and Drug Administration
FIH	First-in-human
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMFC	Geometric mean of the fold change
GMT	Geometric mean titer
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin

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HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFN	Interferon
IL	Interleukin
IM	Intramuscular(ly)
IMP	Investigational medicinal product
IRB	Institutional Review Board
IWRS	Interactive web response system
LLOQ	Lower limit of quantification
LNP	Lipid nanoparticles
M	Membrane
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
mRNA	Messenger ribonucleic acid
N	Nucleocapsid
PBMC	Peripheral blood mononuclear cell
pIMD	Potential immune-mediated disease
PPE	Per Protocol Efficacy
PPI	Per Protocol Immunogenicity
PT	Preferred Term
RBD	Receptor-binding domain
RNA	Ribonucleic acid
RT-PCR	Reverse transcription polymerase chain reaction
S	Spike
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	Safety Analysis Set
SAS 2	Safety Analysis Set
SASsol	Solicited adverse events Safety Analysis Set
SOC	System Organ Class

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SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
VDE	Vaccine-dependent Disease Enhancement
VE	Vaccine efficacy
VNT	Viral neutralizing titer
VOC	Variant of concern
WHO	World Health Organization

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PROTOCOL AMENDMENT RATIONALE

In view of the current availability of authorized/licensed vaccines for preventing COVID-19 (AVs) in the countries where the trial is being conducted, multiple unblinding requests have been granted to trial subjects seeking access to these AVs under their country's national vaccination programs, and as of 18 November 2021 nearly 80% of the trial subjects have been unblinded and approximately 49% have already received an AV.

CureVac has decided to focus its COVID-19 vaccine development towards the development of second-generation mRNA vaccine candidates in collaboration with GSK and to withdraw its first-generation COVID-19 vaccine candidate, CVnCoV, from the current approval process with the European Medicines Agency (EMA). As the number of COVID-19 cases needed for the determination of efficacy (case driven design) has been achieved in the current HERALD trial, completion of this trial will now focus on safety monitoring.

The purpose of this protocol amendment is:

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

The trial will, therefore, shift from a randomized observer-blinded to an open-label design.

After unblinding, subjects known to have received placebo do not require further safety monitoring and will be discontinued.

A simplification of the visit and calls schedule for the follow-up of the subjects is implemented in order to maintain subjects who received CVnCoV until the end of the trial. Subjects participating in the open-label phase of the trial will continue to be evaluated for symptomatic COVID-19 cases, but there will no longer be any inferential efficacy analysis (only a descriptive summary of cases).

A descriptive summary of the changes included in the current protocol amendment is provided in Appendix 11.

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1 SYNOPSIS

Name of Investigational Vaccine:	CVnCoV
Sponsor:	CureVac AG
Coordinating Investigator:	[redacted]
Title of Trial:	COVID-19: A Phase 2b/3, Randomized, Observer-Blinded, Placebo-Controlled, Multicenter Clinical Study Evaluating the Efficacy and Safety of Investigational SARS-CoV-2 mRNA Vaccine CVnCoV in Adults 18 Years of Age and Older
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. In view of the severity of respiratory disease caused by emerging coronaviruses, development of a vaccine has been undertaken by several pharmaceutical companies, and there are now vaccines available with emergency authorization/conditional marketing authorization for prevention of COVID-19 in several countries worldwide. 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 (LNPs). 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 (VNTs) are induced following vaccination with CVnCoV. Phase 1 and 2a trials 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 in 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 in preparation of Phase 2b/3 trials. Dose level selection for subsequent trials will be performed based on the safety and immunogenicity data from these 2 trials. In the FIH Phase 1 trial, a dose of 12 µg elicited the same immune response as that seen in patients who are recovering from having been infected with the real virus. Therefore, this dose was selected to be used in this trial.

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	The present 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 above described randomized, observer-blinded phase will be followed by an open-label phase. The open-label phase has been added to inform all subjects about the trial treatment they received and to allow follow-up of subjects who received at least 1 dose of CVnCoV, including those who decide(d) after unblinding to receive an authorized/licensed vaccine for preventing COVID-19 (AV) through their national vaccination program. Placebo subjects do not require further follow-up and will discontinue the trial.	
Trial Duration for Each Subject:	Approximately 13.5 months	**Phase:** 2b/3
Objectives for the Randomized Observe-Blinded Phase		
Primary Objectives:	**Primary Efficacy Objective** • To demonstrate the efficacy of a 2-dose schedule of CVnCoV in the prevention of first episodes of virologically-confirmed cases of COVID-19 of any severity in SARS-CoV-2 naïve subjects. **Primary Safety Objectives** • To evaluate the safety of CVnCoV administered as a 2-dose schedule to subjects 18 years of age and older. • To evaluate the reactogenicity of CVnCoV administered as a 2-dose schedule to subjects 18 years of age and older participating in Phase 2b of the trial.	
Secondary Objectives:	**Key Secondary Efficacy Objectives** • To demonstrate the efficacy of a 2-dose schedule of CVnCoV in the prevention of first episodes of virologically-confirmed moderate to severe cases of COVID-19 in SARS-CoV-2 naïve subjects. • To demonstrate the efficacy of a 2-dose schedule of CVnCoV in the prevention of first episodes of virologically-confirmed severe cases of COVID-19 in SARS-CoV-2 naïve subjects. • To demonstrate the efficacy of a 2-dose schedule of CVnCoV in the prevention of first episodes of virologically-confirmed cases of COVID-19 of any severity caused by “wild type” (i.e., WT/D614G lineages A.1/B.1 without the variant of concern [VOC] B.1.1.7 [Alpha], B.1.351 [Beta], B.1.429 [Epsilon]) and “UK” (B.1.1.7 [Alpha]) SARS-CoV-2 strains in SARS-CoV-2 naïve subjects. **Other Secondary Efficacy Objectives** *To evaluate in SARS-CoV-2 naïve subjects:* • The efficacy of a 2-dose schedule of CVnCoV in the prevention of first episodes of virologically-confirmed cases of COVID-19 of any severity in subjects ≥ 61 years of age. • The efficacy of a 2-dose schedule of CVnCoV in the prevention of first episodes of virologically-confirmed cases of SARS-CoV-2 infection, with or without symptoms. • The efficacy of a 2-dose schedule of CVnCoV in reducing the Burden of disease (BoD) from COVID-19.	

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	• The efficacy of CVnCoV after the first dose in the prevention of first episodes of virologically-confirmed cases of COVID-19 of any severity. **Secondary Immunogenicity Objectives** • 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 a subset of subjects participating in Phase 2b of the trial. • To assess SARS-CoV-2 viral neutralizing antibody responses after 1 and 2 doses of CVnCoV in a subset of subjects participating in Phase 2b of the trial.
Exploratory Objectives:	**Exploratory Efficacy Objectives** *To investigate in SARS-CoV-2 naïve subjects:* • The efficacy of a 2-dose schedule of CVnCoV in the prevention of first episodes of virologically-confirmed cases of COVID-19 of any severity caused by individual VOCs (see Section 9.2.1.6). • If cases of COVID-19 are milder in severity in subjects receiving a 2-dose schedule of CVnCoV compared to those administered placebo. • If the need for supplemental oxygenation due to COVID-19 is reduced in subjects receiving a 2-dose schedule of CVnCoV compared to those administered placebo. • If the need for mechanical ventilation due to COVID-19 is reduced in subjects receiving a 2-dose schedule of CVnCoV compared to those administered placebo. • If hospitalization due to COVID-19 is reduced in subjects receiving a 2-dose schedule of CVnCoV compared to those administered placebo. • If mortality due to COVID-19 is reduced in subjects receiving a 2-dose schedule of CVnCoV compared to those administered placebo. • If all-cause mortality is reduced in subjects receiving a 2-dose schedule of CVnCoV compared to those administered placebo. • To investigate the cell-mediated immune response of a 2-dose schedule of CVnCoV from approximately 200 subjects at selected site(s). *To investigate in SARS-CoV-2 naïve and non-naïve subjects:* • The efficacy of a 2-dose schedule of CVnCoV in the prevention of first episodes of virologically-confirmed cases of COVID-19 of any severity in all subjects, regardless of SARS-CoV-2 serological status at baseline. • The efficacy of CVnCoV after the first dose in the prevention of first episodes of virologically-confirmed cases of COVID-19 of any severity in all subjects, regardless of SARS-CoV-2 serological status at baseline. *To investigate in subjects with first episodes of virologically-confirmed COVID-19 during the trial:* • The occurrence of second episodes of COVID-19 in subjects receiving a 2-dose schedule of CVnCoV compared to those administered placebo. • To explore correlates of protective immunity induced by CVnCoV vaccination.
Objectives for the Open-label Phase:	• To evaluate safety in all subjects ≥ 18 years of age remaining in the trial after unblinding. *Open-label Exploratory Objective:* • To describe the number of first episodes of symptomatic virologically-confirmed cases of mild, moderate, and severe COVID-19 as assessed by the Investigator.
Overall Design:	Trial CV-NCOV-004 will start with an initial Phase 2b part followed by a large Phase 3 efficacy part. Both Phase 2b and Phase 3 parts will be randomized,

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	observer-blinded, and placebo-controlled. Adult subjects 18 years of age or older will be enrolled at multiple sites globally and will receive a 2-dose schedule of either CVnCoV at a dose level of 12 µg mRNA or placebo {normal saline (0.9% NaCl)} in a 1:1 ratio. Both Phase 2b and Phase 3 parts of the trial are consistent in design (e.g., for COVID-19 case ascertainment and case definition) so that cases of COVID-19 occurring in Phase 2b can be pooled with those in Phase 3 for the primary analysis of vaccine efficacy (VE). This randomized observer-blinded phase will be followed by a Phase 3 open-label phase. The trial will be unblinded on country/site level after receipt of Competent Authority/Ethics Committee approval of Protocol version 4.0. **Randomized Observer-blinded Phase 2b Design and Objectives** (See Table 1 and Table 2 for the Schedule of Trial Assessments and Procedures) The objective of Phase 2b is to further characterize the safety, reactogenicity, and immunogenicity of CVnCoV prior to initiating Phase 3. CVnCoV will be administered at the 12 µg dose level selected for Phase 3 investigation informed by the safety and immunogenicity data from the initial Phase 1 and 2a trials. Phase 2b will be conducted in 2 age groups of adults: 18 to 60 and ≥ 61 years of age, which represent the age range of the intended Phase 3 trial population. Approximately 4,000 subjects will be enrolled and randomized in a 1:1 ratio to receive 2 doses of either CVnCoV or placebo, administered 28 days apart. Of the 4,000 subjects enrolled, approximately 800 to 1,000 (20% to 25%) will be ≥ 61 years of age. Phase 2b will be performed in an observer-blinded manner to reduce any potential bias in the safety assessments. The sample size of 4,000 subjects is based on generating a robust and detailed dataset characterizing the safety, reactogenicity, and immunogenicity of CVnCoV prior to entering Phase 3. Furthermore, the data generated in Phase 2b will be the main dataset to be submitted in support of early conditional approval of CVnCoV. In Phase 2b, 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 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 AEs of special interest (AESIs) and serious adverse events (SAEs) through 1 year after the second trial vaccination. The immunogenicity of CVnCoV will be evaluated after 1 and 2 doses in a subset of subjects (first 600 subjects enrolled in each of the 2 age groups; a total of 1,200 subjects in the Immunogenicity Subset) by measuring binding antibodies to the SARS-CoV-2 RBD of S protein and viral neutralizing antibodies. Antibody persistence will also be evaluated in this trial. Cases of COVID-19 occurring in Phase 2b subjects will be collected and pooled with those occurring in Phase 3 and the total number of cases will be used for the primary analysis of efficacy. Surveillance for COVID-19 cases will be identical in Phase 2b and Phase 3. In addition, the independent Data and Safety Monitoring Board (DSMB) will periodically monitor COVID-19 cases for signals of Vaccine-dependent Disease Enhancement (VDE). Initiation of subject enrollment of the 2 target age groups into Phase 2b will be flexible. Depending on the timing of data from the Phase 1 and Phase 2a trials, enrollment of the 2 age groups into Phase 2b may be staggered, initially starting with subjects 18 to 60 years of age followed by subjects ≥ 61 years of age. As the older age group will comprise 20% to 25% of the total number of subjects in Phase 2b, the staggered start is not expected to impact overall enrollment of the Phase 2b cohort. An early safety review of the Phase 2b data will be performed by the DSMB. The safety review will be conducted when approximately 1,000 subjects have

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	been enrolled in Phase 2b (25% of subjects enrolled; 500 recipients of CVnCoV and 500 recipients of placebo) and have at least 1 week of safety follow-up after the first trial vaccination. If the safety profile is judged to be acceptable and there are no safety or tolerability concerns, it is anticipated that enrollment of subjects into Phase 3 can begin without interruption from Phase 2b. Another safety review by the DSMB will be conducted when approximately 1,000 Phase 2b subjects have received their second trial vaccination and have at least 1 week of safety follow-up. All available first dose safety data from the Phase 2b subjects will also be reviewed at this time. **Randomized Observer-blinded Phase 3 Design and Objectives** (See Table 3 for the Schedule of Trial Assessments and Procedures) The primary objective of the combined Phase 2b/3 is to demonstrate the efficacy of a 2-dose schedule of CVnCoV in the prevention of COVID-19 cases of any severity. Similar to Phase 2b, Phase 3 will be conducted as a randomized, observer-blinded, placebo-controlled trial. Approximately 32,500 subjects, 18 years of age or older, will be enrolled at multiple sites globally in Phase 3 and will receive a 2-dose schedule of either CVnCoV at the 12 µg dose level or placebo in a 1:1 ratio. Subjects will undergo active surveillance for COVID-19 (see Appendix 6A). 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. 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 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, 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, all subjects will be followed until resolution of their disease. Due to the uncertain incidence rate of COVID-19 cases in a pandemic setting, the trial will be conducted as a case-driven trial based on the any severity COVID-19 endpoint due to the higher number of cases required. The trial will include 2 interim analyses and a final analysis, each of which will be triggered by achieving a predefined number of cases meeting the primary efficacy case definition. As described above, cases of COVID-19 occurring in Phase 2b will be pooled with those in Phase 3 for the primary analysis of VE. As such, subjects participating in Phase 2b will contribute to the total sample size for the primary analysis of VE (N=36,500). With an equal follow-up time of evaluable subjects in the CVnCoV and placebo groups, efficacy would be demonstrated at the final analysis if 53 cases or less of 160 total cases of COVID-19 of any severity are in the CVnCoV group (estimated VE ≥ 50.5%). Two interim analyses for high efficacy or futility will be performed when 56/111 cases meeting the primary case definition of COVID-19 cases have been accrued and adjudicated (approximately 5/6.5 months after the first vaccination). If the follow-up time of evaluable subjects is equal in both groups, early high efficacy would be demonstrated if 9/32 cases or less of the 56/111 cases are in the CVnCoV group (estimated VE at interim ≥ 80.9/59.5%); conversely, futility would be reached if 25/40 cases or more are in the CVnCoV group (estimated VE at interim ≤ 19.4/43.7%). Similar to Phase 2b, subjects participating in Phase 3 will be evaluated for SARS-CoV-2 infection during the trial, as measured by the development of antibodies to the N protein of SARS-CoV-2 in seronegative subjects. The safety objective of Phase 3 is to generate a large-scale safety database that will demonstrate the safety of CVnCoV. All subjects participating in the Phase 2b and Phase 3 parts of the trial will have medically-attended AEs

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	collected for 6 months after the second vaccination; and AESIs (see Appendix 9 and Appendix 10) and SAEs collected until the End of Trial (EOT) visit. **Open-label Phase Design and Objectives** After unblinding, the trial will shift from a randomized observer-blinded to an open-label design, and the following cohorts will be defined: **Cohort A: CVnCoV-AV** (See Table 4 for the Schedule of Trial Assessments and Procedures): Subjects ≥ 18 years who received at least 1 dose of CVnCoV and choose to receive an AV are included in this cohort and will be recommended to procure AV as standard of care per their national vaccination program, if not already done. Subjects will be requested to remain in the trial for safety follow-up until the EOT (Day 393 of the original Phase 2b/3 schedule). Subjects who were individually unblinded and already received an AV before implementation of Protocol version 4.0 will also be included in this cohort. **Cohort B: CVnCoV only** (See Table 5 for the Schedule of Trial Assessments and Procedures): Subjects ≥ 18 years who received at least 1 dose of CVnCoV and choose to remain in the trial without receiving any AV will continue follow-up until EOT (Day 393 of the original Phase 2b/3 schedule). Subjects who were individually unblinded during the randomized observer-blinded phase and who received CVnCoV but did not receive an AV before implementation of Protocol version 4.0 and do not intend to receive an AV will also be included in this cohort. Subjects who initially intend to complete the trial without receiving an AV and later decide to receive an AV within the open-label phase will be switched to Cohort A. Placebo subjects do not require further follow-up and will discontinue the trial. The open-label phase will provide additional safety data, including data from subjects who receive an AV after CVnCoV. COVID-19 cases will continue to be documented, but there will no longer be any inferential efficacy analysis in the open-label phase (only descriptive summary of cases). Subjects will undergo passive surveillance for COVID-19 (see Appendix 6B). Trial unblinding and transition from the randomized observer-blinded phase to the open-label phase will be conducted on a country/site level, depending on full competent authority and Ethics Committee approval of Protocol version 4.0 per country/site.
Trial Visits/ Contacts:	**For subjects participating in Phase 2b Immunogenicity 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 subjects participating in Phase 2b non-immunogenicity (see Table 2):** ○ 6 protocol-scheduled site visits on Day 1, Day 29, Day 43, Day 120, Day 211, and Day 393. ○ 4 protocol-scheduled phone contacts (safety calls) on Day 2, Day 30, Day 57, and Day 302. **For subjects participating in the randomized observer-blinded Phase 3 (see Table 3):** ○ 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.

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	After trial unblinding: Subjects of the placebo treatment arm will be notified of the trial treatment they received by a Subject Information Letter and will be withdrawn after an EOT phone call. Subjects of the CVnCoV treatment arm will be notified of the trial treatment they received at the next planned trial visit/phone call. **For subjects participating in the Open-label Phase:** *Cohort A: CVnCoV-AV (Table 4) and Cohort B: CVnCoV only (Table 5):* ○ Phone calls or clinic visits will be performed after trial unblinding on Day 302 and Day 393/EOT of the original Phase 2b/3 schedule.
Collection of Blood Samples:	The maximum total volume of blood taken over the trial period from any subject is 304 mL.
Safety Assessments:	The safety and reactogenicity 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 Phase 2b:** • 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 in Phase 2b and Phase 3:** • Medically-attended AEs will be collected through 6 months after the second trial vaccination. • AESIs will be collected throughout the trial. 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 throughout the trial. • AEs leading to vaccine withdrawal or trial discontinuation will be collected throughout the trial. **Safety assessments for subjects in the Open-label Phase:** • AESIs will be collected until EOT (Day 393 of the original Phase 2b/3 schedule). AESIs to be monitored include pIMDs and AESIs for SARS--CoV-2 vaccines. • SAEs will be collected until EOT (Day 393 of the original Phase 2b/3 schedule). • AEs leading to trial discontinuation will be collected until EOT (Day 393 of the original Phase 2b/3 schedule).
Testing for COVID-19:	During the randomized observer-blinded phase of the trial, subjects clinically suspected of having COVID-19 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. • Subjects with a clinical suspicion of COVID-19 will undergo testing for SARS-CoV-2 infection using a rapid antigen test performed at the site

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	with the results provided to the subject. Nasopharyngeal swabs will be used to collect samples for the rapid antigen test. • Regardless of the result of the rapid antigen test, a nasopharyngeal swab sample collected at the same time will be sent to a central laboratory to perform a SARS-CoV-2 specific RT-PCR test. The RT-PCR test result will be considered definitive. o 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 and sent to the central laboratory for RT-PCR testing. The RT-PCR retest result will be considered definitive. • In the open-label phase, subjects should report diagnosis of symptomatic COVID-19 positive cases to the site. For countries/sites with limited access to COVID-19 testing, subjects with clinical symptoms still can call the sites and be invited for testing on site at the investigator discretion in the best interest of the subject. A nasopharyngeal swab sample will be collected and sent to a central laboratory to perform a SARS-CoV-2 specific RT-PCR test only if the result of the rapid antigen test is positive.
COVID-19 Case Detection and Case Definition for Primary Efficacy Analysis:	**Case Detection:** • **For the randomized observer-blinded phase:** During all site visits and phone calls, subjects will be reminded to contact the site if they have any 1 or more of the following symptoms*: o Fever or chills o Shortness of breath or difficulty breathing o New loss of taste or smell o Cough o Fatigue o Muscle or body aches o Headache o Sore throat o Congestion or runny nose o Nausea or vomiting o 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, using the definition applicable for the trial phase (randomized observer-blind versus open-label). • Based on a phone interview, if the subject is suspected of having COVID-19 illness, he/she will undergo RT-PCR testing for SARS-CoV-2 infection as described above. If the subject is confirmed to have COVID-19, all subjects 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 electronic case report form (eCRF). • **For the open-label phase:** In order to decrease the burden for the trial subjects during the open-label phase, when only subjects having received CVnCoV (followed or not by AV) are still under follow-up, a more

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	restrictive definition will be used for case detection. Subjects will be reminded to contact the site if they have any of the following symptoms: ○ Cough ○ Fever (≥ 37.8 ºC) ○ Shortness of breath ○ Sudden onset of anosmia, ageusia or dysgeusia (new loss of taste or smell). • During this phase of the trial, subjects are asked to report symptomatic COVID-19 positive cases (detected independent of the study procedures) to site, or can be tested as part of the study procedures if the subject has limited access to testing. **Definition of Virologically-Confirmed COVID-19 Case:** **For the randomized observer-blinded phase**, 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. **For the open-label phase**, 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. **Definition of Virologically-Confirmed COVID-19 Case for Primary Efficacy Analysis (Randomized Observer-blinded Phase only):** For the primary 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). (Primary efficacy cases must be confirmed by the Adjudication Committee.)
Planned Number of Subjects:	The total enrollment for the Phase 2b/3 trial will be approximately 36,500 subjects. The target enrollment for each phase of the trial is shown below: • 4,000 subjects enrolled in Phase 2b. • 32,500 subjects enrolled in Phase 3. Because this is a case-driven design, the final sample size will depend on the actual incidence rate of COVID-19 cases occurring during the trial. As such,

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	during the early stages of enrollment, an unblinded review of the incidence rate of cases will be performed by the DSMB. If the case accrual rate is lower or higher than expected, the DSMB may recommend an adjustment in sample size. If needed, another unblinded review by the DSMB may be performed later in the trial to further adjust the sample size.
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. Be willing and able to provide written informed consent prior to initiation of any trial procedures. 3. Expected compliance with protocol procedures and availability for clinical follow-up through the last planned visit. 4. 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 (FSH) level may be measured at the discretion of the Investigator to confirm postmenopausal status. 5. Females of childbearing potential: negative pregnancy test {human chorionic gonadotropin (hCG)} within 24 hours prior to each trial vaccination on Day 1 and Day 29. 6. 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 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 COVID-19 illness. 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 or any other vaccines) prior to the administration of the first trial vaccine.

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	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 anabolic steroids, 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 (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV); 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. History of angioedema (hereditary or idiopathic) or history of any anaphylactic reaction. 9. History of pIMD. 10. History of allergy to any component of CVnCoV vaccine. 11. Administration of immunoglobulins or any blood products within 3 months prior to the administration of trial vaccine or planned receipt during the trial. 12. 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. 13. Subjects with impaired coagulation or any bleeding disorder in whom an IM injection or a blood draw is contraindicated. 14. Foreseeable non-compliance with the trial procedures as judged by the Investigator. **Roll-over criteria for the open-label phase:** 1. Subjects must have received at least 1 dose of CVnCoV during the randomized observer-blinded phase. 2. Subjects must provide additional written informed consent to be eligible for the open-label phase. **Cohort A: CVnCoV-AV:** 3. Subjects of the CVnCoV treatment arm who received or will receive any AV as standard of care through their national vaccination program. **Cohort B: CVnCoV only:** 3. Subjects have not received any vaccination with any other investigational/authorized SARS-CoV-2 vaccine or another coronavirus (SARS-CoV, MERS-CoV) vaccine.

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Endpoints for the Randomized Observer-blinded Phase:	
Primary Endpoints:	**Primary Efficacy Endpoint** • Occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity meeting the case definition for the primary efficacy analysis. **Primary Safety Endpoints** All safety endpoints will be analyzed in all subjects, in subjects seronegative at baseline, and in subjects seropositive at baseline. • 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 throughout the trial in all subjects. • Occurrence of fatal SAEs throughout the trial in all subjects. • Occurrence, intensity, and duration of each solicited local AE within 7 days after each trial vaccination in Phase 2b subjects. • Occurrence, intensity, duration of each solicited systemic AE within 7 days after each trial vaccination in Phase 2b subjects. • Occurrence, intensity and relationship of unsolicited AEs occurring within 28 days after each trial vaccination in Phase 2b subjects. • Occurrence of AEs leading to vaccine withdrawal or trial discontinuation throughout the trial in all subjects.
Secondary Endpoints:	**Key Secondary Efficacy Endpoints** • Occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of moderate to severe COVID-19 meeting the case definition for the primary efficacy analysis (moderate and severe COVID-19 is defined in Appendix 3 and Appendix 4). • Occurrence of first episodes of virologically-confirmed (RT-PCR positive) severe cases of COVID-19 meeting the case definition for the primary efficacy analysis (severe COVID-19 defined in Appendix 3). • Occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity meeting the case definition due to infection with “wild type” (i.e., WT/D614G lineages A.1/B.1 without VOC B.1.1.7 [Alpha], B.1.351 [Beta], B.1.429 [Epsilon]) and “UK” (B.1.1.7 [Alpha]) SARS-CoV-2 strains in SARS-CoV-2 naïve subjects. **Other Secondary Efficacy Endpoints** • In subjects ≥ 61 years of age, occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity meeting the case definition for the primary efficacy analysis. • Occurrence of virologically-confirmed (RT-PCR positive) SARS-CoV-2 infection, with or without symptoms. *If subject was symptomatic, onset of symptoms must have occurred ≥ 15 days following the second trial vaccination; if subject was asymptomatic, the positive RT-PCR test must have occurred ≥ 15 days following the second trial vaccination.* • BoD scores calculated based on first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity meeting the case definition for the primary efficacy analysis.

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	○ BoD #1 – no disease (not infected or asymptomatic infection) = 0; mild or moderate disease = 1; severe disease = 2. ○ BoD #2 – no disease (not infected or asymptomatic infection) = 0; disease without hospitalization = 1; disease with hospitalization = 2; death = 3. • Occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity with symptom onset at any time after the first trial vaccination. **Secondary Immunogenicity Endpoints (Phase 2b Immunogenicity Subset)** *SARS-CoV-2 RBD of S protein antibody responses* On Days 1, 29, 43, 120, and 211: • Serum antibodies to SARS-CoV-2 RBD of S protein. • Occurrence of seroconversion to SARS-CoV-2 RBD of S protein. *Seroconversion is defined as detectable SARS-CoV-2 RBD of S protein antibodies in the serum of subjects who tested seronegative at baseline.* *SARS-CoV-2 viral neutralizing antibody responses* On Days 1, 29, 43, 120, and 211: • Serum neutralizing antibodies to SARS-CoV-2 virus, as measured by a viral neutralizing antibody assay. • Occurrence of seroconversion to SARS-CoV-2 virus, as measured by a viral neutralizing antibody assay. *Seroconversion is defined as detectable SARS-CoV-2 viral neutralizing antibodies in the serum of subjects who tested seronegative at baseline.*
Exploratory Endpoints:	**Exploratory Efficacy Endpoints** • Occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 caused by individual VOCs (see Section 9.2.1.6). • Severity assessment of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 meeting the case definition for the primary efficacy analysis (COVID-19 severity definitions provided in Appendix 3 and Appendix 4). The following endpoints will be analyzed as occurring ≥ 15 days following the second trial vaccination (full VE) and at any time after the first trial vaccination. *In SARS-CoV-2 naïve subjects:* • Occurrence of supplemental oxygenation due to COVID-19. • Occurrence of mechanical ventilation due to COVID-19. • Occurrence of hospitalization due to COVID-19. • Occurrence of death due to COVID-19. • Occurrence of death due to any cause. *In SARS-CoV-2 naïve and non-naïve subjects:* • In all subjects regardless of their baseline serostatus: occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity. 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 primary efficacy analysis. • Occurrence of second episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity.

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	Exploratory Immunogenicity Endpoints On Days 1, 29, 43, 120**, and 211** in peripheral blood mononuclear cells (PBMCs) from approximately 200*** subjects at selected site(s): • The frequency and functionality of SARS-CoV-2 RBD of S-specific T-cell response after antigen stimulation by intracellular cytokine staining (ICS) to investigate Th1 response and expression of Th2 markers. • The proportion of subjects with a detectable increase in SARS-CoV-2 RBD of S-specific T-cell response. *** Testing of samples collected on Day 120 and Day 211 will be done only in subjects categorized as T-cell responders on Day 29 and/or Day 43.* **** First testing of samples will be performed for a subset of these subjects and might be extended to 200 subjects if T-cell response is detectable.*
Endpoints for the Open-label phase:	• Occurrence, intensity, and relationship to CVnCoV of SAEs and AESIs collected throughout the trial until the EOT. • Occurrence of fatal SAEs throughout the trial until EOT. • Only for Cohort A: CVnCoV-AV: Occurrence of AEs leading to trial discontinuation after the first dose with an AV in the open-label phase until EOT. *Open-label Exploratory Endpoints:* • Occurrence of first episodes of symptomatic virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity as assessed by the Investigator. Any further modifications to endpoints in the open-label phase will be described in the statistical analysis plan (SAP).
Data and Safety Monitoring Board:	An independent DSMB will be convened to oversee the safety and efficacy of subjects participating in this trial, to assess the progress and conduct of the trial, to review the cumulative safety data from the trial, and to make recommendations to CureVac whether to continue, modify, or stop the trial. To ensure subject safety on an ongoing basis, a CureVac Safety Review Team reviews the safety data on a periodic basis. The outcome of these reviews and discussions are then shared with the DSMB Chair. In addition to safety data, the DSMB will be asked to review efficacy data at the interim analyses 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 will also be asked to perform an unblinded review(s) of the incidence rate of COVID-19 cases to recommend an adjustment(s) in sample size, if needed. 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 (CRO); the schedule and conduct of the DSMB meetings; and the datasets to be reviewed.
Sample Size Justification:	The total sample size of approximately 36,500 subjects for the combined Phase 2b/3 trial is based on formal statistical power calculations demonstrating the efficacy of CVnCoV. This trial is planned using a group sequential design with 2 interim analyses for high efficacy or futility using the O'Brien and Fleming error spending function for the primary endpoint of any COVID-19 cases. With an overall 2-sided alpha of 5%, 160 cases are needed at the final analysis for COVID-19 cases of any severity to reach 90% power to demonstrate that VE is above 30% (based on a margin of 30% for the lower bound of the confidence interval [CI] for VE), when considering the VE is 60%. The sample size is based on a test for one single proportion. Assuming an incidence rate of COVID-19 of 0.15% per month in placebo subjects; a VE of 60%; an enrollment period of 3 months; and a non-evaluable rate of 20%

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	during the trial which includes ~5% seropositivity of enrollees at baseline (i.e. non-naïve subjects), then 36,500 subjects randomized to receive either CVnCoV or placebo in a 1:1 ratio will achieve the 160 cases at approximately 9 months after the first vaccination. Because this is a case-driven trial design, the final sample size will depend on the actual incidence rate of COVID-19 cases occurring during the trial. As such, during the early stages of enrollment, an unblinded review of the incidence rate of cases will be performed by the DSMB. If the case accrual rate is lower or higher than expected, the DSMB may recommend an adjustment in sample size. If needed, another unblinded review by the DSMB may be performed later in the trial to further adjust the sample size. The sample size of ~4,000 subjects for Phase 2b is based on generating a robust and detailed dataset characterizing the safety, reactogenicity, and immunogenicity of CVnCoV prior to entering Phase 3 and for the early conditional approval submission.
Analysis Sets:	The main analysis populations are: **Safety Analysis Set (SAS)** The SAS will include all randomized subjects in Phase 2b or 3 who received at least 1 dose of CVnCoV or placebo. The SAS will be the primary population for the safety endpoints collected on all subjects and for the objectives evaluating efficacy after the first dose. **Efficacy Analysis Set (EAS)** The EAS will include all subjects randomized in Phase 2b and Phase 3 who: • Received both doses of trial vaccine according to the randomization (2 doses of CVnCoV or 2 doses of placebo). • Had not developed a virologically-confirmed case of COVID-19 before trial entry (based on Exclusion Criterion 1) or before 15 days following the second trial vaccination. • Had not stopped the trial before 15 days following the second trial vaccination. • Were SARS-CoV-2 naïve at baseline and Day 43 (based on seronegativity to N protein in the blood sample taken at baseline). The EAS will be the main analysis population for the primary efficacy endpoint and for the appropriate secondary efficacy endpoints. **Per Protocol Efficacy Set (PPE)** The PPE set will include EAS subjects who meet all eligibility criteria at trial entry and who have no major protocol deviations that would impact the efficacy outcomes as specified in the SAP. The PPE will be a supportive population for the primary and appropriate secondary efficacy endpoints. Additional populations that might be required for the analyses of the results from the open-label phase will be defined in an extended SAP.
Statistical Methodology:	**Missing Data/Discontinuation:** For SARS-CoV-2 RBD of S protein antibodies, concentration values marked as below the lower limit of quantification (LLOQ) will be set to 0.5*LLOQ for the purpose of geometric mean titer (GMT) 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.
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

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	contingency tables (qualitative data) overall, by vaccine group, and by age group and vaccine group. **Efficacy Analyses:** In the primary efficacy analysis, VE, defined as the percent reduction in the frequency of any COVID-19 cases (according to the primary case definitions) in vaccinated subjects compared with subjects who received placebo will be calculated with exact 95%* CI as follows: VE = 1- RR = 1 - (ARV/ARP) = 1 – {p / r (1-p)} where ARV = attack rate in vaccinated group = nv/Nv = number of subjects reporting at least 1 COVID-19 episode in the CVnCoV group / total follow-up time of evaluable subjects in the CVnCoV group (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 primary case definition) coming from the CVnCoV group among all cases = nv/(nv+np) r = ratio of total follow-up time of evaluable subjects in the CVnCoV group over total follow-up time of evaluable subjects in the placebo group = Nv/Np * Level of CI may be slightly adjusted due to the sequential design (see Section 10.3.8). The statistical hypothesis for the primary efficacy endpoint is: H_{0A}: VE ≤ 30% versus H_{1A}: VE > 30% A is related to COVID-19 cases of any severity The trial will be successful if the lower limit of the exact 2-sided 95% (to be slightly adjusted to consider the sequential design) CI of the VE endpoint of all COVID-19 cases of any severity is > 30% for H_{0A} or if the exact 2-sided 95% (to be slightly adjusted to consider the sequential design) CI of the VE endpoint of moderate to severe COVID-19 cases is > 20%. If the interim analyses and the final analysis are performed after 56/111 and 160 cases meeting the primary efficacy case definition have been reported, respectively, the 1-sided α-risk to consider at time of final analysis according to O'Brien-Fleming type error-spending-function will be 0.02281. Efficacy will be demonstrated at the final analysis if 53 cases or less of the total 160 are in the CVnCoV group and if the follow-up time of evaluable subjects is equal in both groups (Nv=Np). At the first interim analysis, early high efficacy would be demonstrated if 9 cases or less of the 56 cases are in the CVnCoV group (observed efficacy ≥ 80.9%); conversely, futility would be reached if 25 cases or more are in the CVnCoV group if Nv=Np. At the second interim analysis, early high efficacy will be demonstrated if 32 cases or less of the 111 cases are in the CVnCoV group (observed efficacy ≥ 59.5%); conversely, futility would be reached if 40 cases or more are in the CVnCoV group if Nv=Np. For the key secondary endpoints, no interim analysis is planned. However, descriptive statistic as VE and 95% CI will be presented. As a sensitivity analysis, the time to first-occurrence of virologically-confirmed COVID-19 cases (meeting the primary efficacy case definition) will also be analyzed. Kaplan-Meier curves will be displayed. Statistical testing of the 3 key secondary efficacy endpoints will be performed according to the conditional hierarchical testing procedure using the order

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	defined in the objectives and endpoints sections. Consequently: • Efficacy of CVnCoV in regard to moderate and severe cases will be demonstrated only if there is successful demonstration of the primary efficacy objective. • Efficacy of CVnCoV in regard to severe cases will be demonstrated only if there is successful demonstration of the primary efficacy objective and the key secondary objective on moderate and severe cases. • Efficacy of CVnCoV in regard to (RT-PCR positive) cases of "wild type" (i.e., WT/D614G lineages A.1/B.1 without VOC B.1.1.7 [Alpha], B.1.351 [Beta], B.1.429 [Epsilon]) and "UK" (B.1.1.7 [Alpha]) will be demonstrated only if there is successful demonstration of the primary efficacy objective and the key secondary objectives on moderate and severe cases and severe cases. Otherwise, these endpoints will be analyzed as secondary endpoints without success criteria testing. To assess the efficacy in the prevention of severe COVID-19 and asymptomatic infections, similar analyses to the primary efficacy endpoint will be performed. Efficacy will be demonstrated if the lower limit of the exact 2-sided 95% CI of the VE endpoint is > 10% for prevention of severe disease and > 0% for prevention of asymptomatic infections. **Interim Analysis:** Unblinded interim analyses for high efficacy, futility and for safety will be reviewed by the DSMB when 56/111 cases meeting the primary efficacy case definition have been reached. **The safety and immunogenicity analyses will be performed overall and, for specified subsets, by baseline serology status for SARS-CoV-2.** **Safety Analyses - 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. The results will be tabulated by vaccine group and age groups. 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. **Safety Analyses - 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 each unsolicited AE within the 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 by vaccine group and overall, and by vaccine group and age groups. GMT, Fold Change (FC) from baseline, Geometric mean of FC (GMFC) with their 95% 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. 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. **For the open-label phase,** safety analyses will be described by cohort. Details will be provided in an extended SAP.

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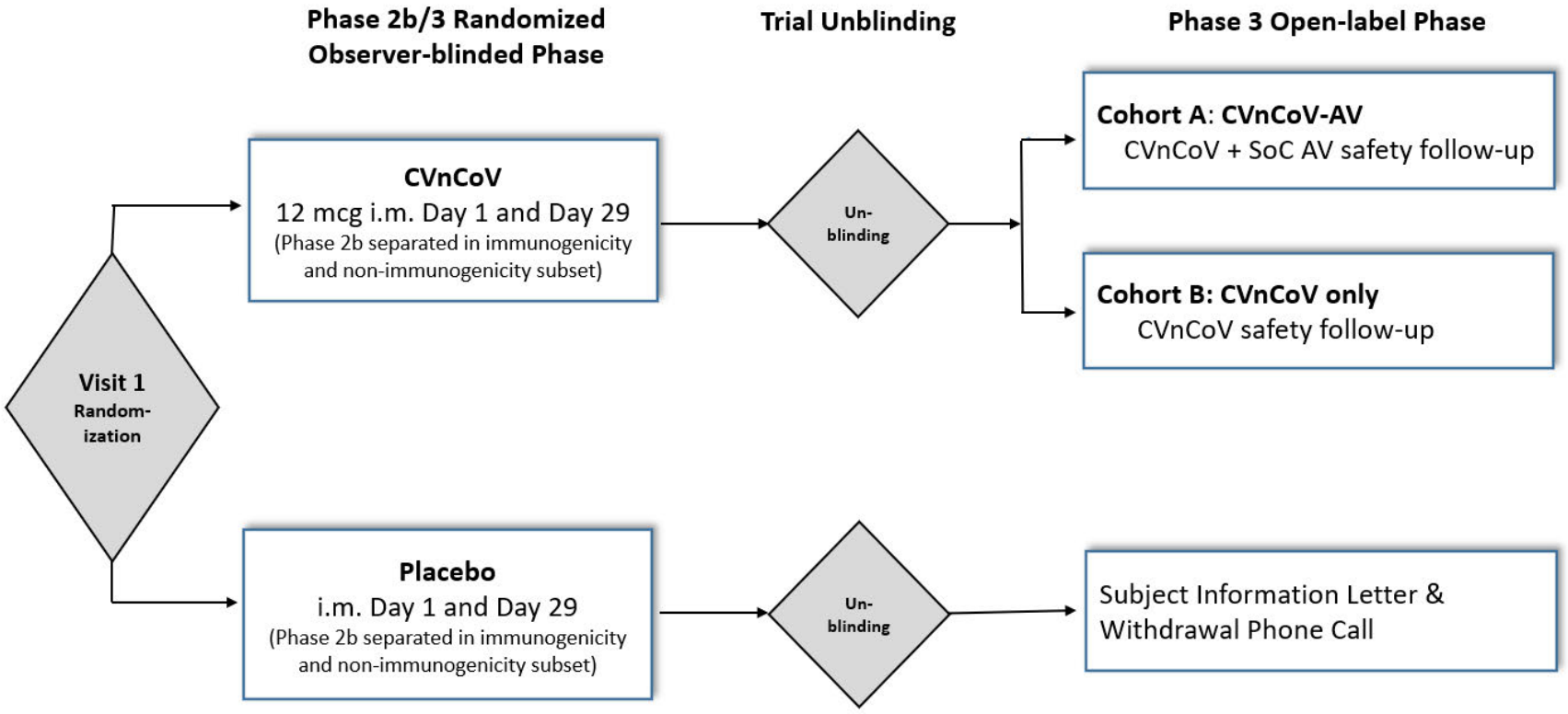
2 STUDY SCHEMATIC AND SCHEDULE OF ACTIVITIES

Figure 1 Overview of HERALD Trial CV-NCOV-004



AV: authorized/licensed vaccines for preventing COVID-19; i.m.: intramuscular; SoC: standard of care.

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Table 1 Schedule of Trial Assessments and Procedures for Phase 2b - Immunogenicity Subset

	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									
Smoking information	X									
Medical history	X									
Medication/vaccination history[b]	X									
Pregnancy test[c]	X		X							
Trial Vaccination										
Review criteria for delay or cancellation of trial vaccination[d]	X		X							
Randomization	X									
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:										
• Medically-attended AEs[h]	X	X	X	X	X	X	X	X		

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	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
• SAEs and AESIs[h]	X	X	X	X	X	X	X	X	X	X
• AEs leading to vaccine withdrawal or trial discontinuation[h]	X	X	X	X	X	X	X	X	X	X
Concomitant medication/vaccination[i]	X	X	X	X	X	X	X	X	X	X
COVID-19 Case Detection										
Case detection and collection of case information[j]	X	X	X	X	X	X	X	X	X	X
Antibody Testing[k] (n=1,200)										
Binding antibody to RBD of S (spike) protein of SARS-CoV-2 (~6 mL blood)[l]	X[k]		X[k]		X	X	X	X		
SARS-CoV-2 viral neutralizing activity (~6 mL blood)[l]	X[k]		X[k]		X	X	X	X		
Binding antibody to the N (nucleocapsid) protein of SARS-CoV-2 (~6 mL blood)[l]	X[k]				X			X		
Genomic Biomarkers (n=200 at selected sites)										
In subjects from selected site(s): genomic biomarkers (~6 mL whole blood)	X[k]		X[k]		X		X	X		
Cell-mediated Immunity (n=200 at selected sites)										
In subjects from selected site(s): cell-mediated immunity (~32 mL blood)	X[k]		X[k]		X		X	X		
Trial End										X

AE: adverse event; AESI: adverse event of special interest; eCRF: electronic case report form; n/a: not applicable; RBD: receptor-binding domain; 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.

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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 before each trial vaccination on Day 1 and Day 29 for women of childbearing potential. Where required by local laws and regulations, the pregnancy test will be performed in blood (3 mL).

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. 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. 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, AEs leading to vaccine withdrawal or trial discontinuation, and any non-serious intercurrent condition that may affect the immune response to vaccination 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.

   Medications associated with any solicited and unsolicited AE, medications for a medically-attended AE, AESI, or SAE, and any immune-suppressive/modulating medication will be documented in the eCRF for the time period specified in Table 6. In case any prohibited medication as defined in Section 7.6.2 was taken by the subject, this needs also be documented in the eCRF.

i. The eDiary will serve as a memory aid for the subjects to report additional concomitant medication or changes in concomitant medication and the corresponding symptoms. The Investigator needs to transcribe concomitant medication and symptoms if matching the criteria outlined in Table 6 and any new concomitant medication or changes in concomitant medication prescribed for any underlying disease present already at Visit 1.

j. During all site visits 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 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.

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

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l. 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.

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Table 2 Schedule of Trial Assessments and Procedures for Phase 2b - Non-Immunogenicity Subjects

	Vaccination Period						Follow-up Period			End of Trial
	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Clinic Visit		Phone Call	Clinic Visit
Clinic Visit Number	1[a]	-	2	-	3	-	4	5	-	6
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									
Smoking information	X									
Medical history	X									
Medication/vaccination history[b]	X									
Pregnancy test[c]	X		X							
Trial Vaccination										
Review criteria for delay or cancellation of trial vaccination[d]	X		X							
Randomization	X									
Administration of CVnCoV or placebo (observer-blinded)	X		X							
Safety Monitoring										
Physical examination[e]	X									X
Symptom-directed physical examination[e]			X		X		X	X		
Vital signs[e,f]	X[f]		X[f]		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:										
• Medically-attended AEs[h]	X	X	X	X	X	X	X	X		

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	Vaccination Period						Follow-up Period			End of Trial
	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Clinic Visit	Phone Call	Clinic Visit		Phone Call	Clinic Visit
Clinic Visit Number	1[a]	-	2	-	3	-	4	5	-	6
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
• SAEs and AESIs[h]	X	X	X	X	X	X	X	X	X	X
• AEs leading to vaccine withdrawal or trial discontinuation[h]	X	X	X	X	X	X	X	X	X	X
Concomitant medication/vaccination[i]	X	X	X	X	X	X	X	X	X	X
COVID-19 Case Detection										
Case detection and collection of case information[j]	X	X	X	X	X	X	X	X	X	X
Antibody Testing										
Binding antibody to the N (nucleocapsid) protein of SARS-CoV-2[k] (~6 mL blood)	X[k]				X			X		
Trial End										X

AE: adverse event; AESI: adverse event of special interest; eCRF: electronic case report form; n/a: not applicable; 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 before each trial vaccination on Day 1 and Day 29 for women of childbearing potential. Where required by local laws and regulations, the pregnancy test will be performed in blood (3 mL).

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.

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g. eDiary (electronic diary) for recording of post-vaccination solicited AEs will be provided to subjects as needed. 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. 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, AEs leading to vaccine withdrawal or trial discontinuation, and any non-serious intercurrent condition that may affect the immune response to vaccination 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.

   Medications associated with any solicited and unsolicited AE, medications for a medically-attended AE, AESI, or SAE, and any immune-suppressive/modulating medication will be documented in the eCRF for the time period specified in Table 6. In case any prohibited medication as defined in Section 7.6.2 was taken by the subject, this needs also be documented in the eCRF.

i. The eDiary will serve as a memory aid for the subjects to report additional concomitant medication or changes in concomitant medication and the corresponding symptoms. The Investigator needs to transcribe concomitant medication and symptoms if matching the criteria outlined in Table 6 and any new concomitant medication or changes in concomitant medication prescribed for any underlying disease present already at Visit 1.

j. During all site visits 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 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.

k. 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.

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

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Table 3 Schedule of Trial Assessments and Procedures for Phase 3

	Vaccination Period				Follow-up Period			End of Trial
	Clinic Visit			Phone Call	Phone Call	Clinic Visit	Phone Call	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							
Smoking information	X							
Medical history	X							
Medication/vaccination history[b]	X							
Pregnancy test[c]	X	X						
Trial Vaccination								
Review criteria for delay or cancellation of trial vaccination[d]	X	X						
Randomization	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:								
• Medically-attended AEs[g]	X	X	X	X	X	X		
• SAEs and AESIs[g]	X	X	X	X	X	X	X	X

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	Vaccination Period				Follow-up Period			End of Trial
	Clinic Visit			Phone Call	Phone Call	Clinic Visit	Phone Call	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
• AEs leading to vaccine withdrawal or trial discontinuation[g]	X	X	X	X	X	X	X	X
Concomitant medication/vaccination[h]	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
Antibody Testing								
Binding antibody to the N (nucleocapsid) protein of SARS-CoV-2[j] (~6 mL blood)	X[j]		X			X		
Trial End								X

AE: adverse event; AESI: adverse event of special interest; eCRF: electronic case report form; n/a: not applicable; 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 before each trial vaccination on Day 1 and Day 29 for women of childbearing potential. Where required by local laws and regulations, the pregnancy test will be performed in blood (3 mL).

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.

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g. 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, AEs leading to vaccine withdrawal or trial discontinuation, and any non-serious intercurrent condition that may affect the immune response to vaccination 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.

   Medications for a medically-attended AE, AESI, or SAE and any immune-suppressive/modulating medication will be documented in the eCRF for the time period specified in Table 6. In case any prohibited medication as defined in Section 7.6.2 was taken by the subject, this needs also be documented in the eCRF.

h. The eDiary will serve as a memory aid for the subjects to report additional concomitant medication or changes in concomitant medication and the corresponding symptoms. The Investigator needs to transcribe concomitant medication and symptoms if matching the criteria outlined in Table 6 and any new concomitant medication or changes in concomitant medication prescribed for any underlying disease present already at Visit 1.

i. During all site visits 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 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.

j. 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.

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Table 4 Schedule of Trial Assessments and Procedures for the Open-label Phase: Cohort A: CVnCoV-AV

	Follow-up Period	End of Trial
	Phone Call/Clinic Visit [a]	**Phone Call/Clinic Visit**
Clinic Visit Number	**OL-1**	**OL-2**
Visit Window (days)	**-3/+21**	**-0/+21**
Trial Day (Trial Day is referred to original Phase 2b/3 schedule)	**302**	**393**
Vaccination Day (Reference for CVnCoV post-vaccination time points)	**29+273**	**29+ 364**
Month (M)	**M 10**	**M 13**
Signed ICF [a]	X	(X)
Roll-over criteria for the open-label phase [b]	X	
Vaccination history [c]	X	
AV SoC vaccination		
Advise AV vaccination if subject did not already received [a]	X	
Safety Monitoring		
Collection of following AEs:		
• SAEs and AESIs [d]	X	X
• AEs leading to trial discontinuation [d]	X	X
Concomitant medication/vaccination (including COVID-19 AV vaccination) [e]	X	X
COVID-19 Case Reporting		
Case reporting and collection of case information [f]	X	X
Trial End		**X**

AE: adverse event; AESI: adverse event of special interest; AV: authorized/licensed vaccine for preventing COVID-19; COVID-19: coronavirus disease 2019; eCRF: electronic case report form: EOT: End of Trial; n/a: not applicable; ICF: informed consent form; OL : open-label; SAE: serious adverse event; SoC: standard of care

a. The open-label phase visits should be scheduled according to the originally scheduled visits/phone calls in the Phase 2b/3 schedule: Day 302 (-3/+21 days) and Day 393 (-0/+21 days). After trial unblinding, the Day 302 and Day 393 visits will be performed as phone calls, but a clinic visit may be performed if ICF signature cannot be done via e-mail, phone call, or mail.

   If the Day 302 phone call was already performed as part of the randomized observer-blinded phase before approval of Protocol version 4.0, the ICF will be signed at the Day 393/EOT phone call/visit.

   Subjects of the CVnCoV treatment arm who already received or plan to receive an AV are eligible for this cohort. The AV should be recorded in the eCRF.

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b. Roll-over criteria for the open-label phase should be reviewed and confirmed on Clinic Visit OL-1.

c. Vaccination history should be checked to establish eligibility. If the subject did not report any administration of a COVID-19 AV, he/she needs to be asked whether he/she received a COVID-19 AV already and, if confirmed, the AV needs to be documented in the eCRF.

d. SAEs, AESIs, and AEs leading to trial discontinuation will be collected until the EOT.

   During all site visits, trial staff will remind subjects to call the site immediately to report the following: if he/she experiences any concerning medical event; or experiences a serious medical event, has a change in overall health, or is 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.

   COVID-19 AV vaccination details (specific AV and vaccination dates) will be collected.

e. Medications for AESIs, or SAEs, and any immune-suppressive/modulating medications will be documented in the eCRF for the time period specified Table 6. Any prohibited medication (as defined in Section 7.6.2) taken by the subject also needs to be documented in the eCRF.

f. During all site visits/phone calls, trial staff will remind subjects to report any confirmed COVID-19 positive tests.

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Table 5 Schedule of Trial Assessments and Procedures for the Open-label Phase: Cohort B: CVnCoV only

	Follow-up Period	End of Trial
	Phone Call/Clinic Visit [a]	Phone Call/Clinic Visit
Clinic Visit Number	**OL-1**	**OL-2**
Visit Window (days)	**-3/+21**	**-0/+21**
Trial Day (Trial Day is referred to original Phase 2b/3 schedule)	**302**	**393**
Vaccination Day (Reference for CVnCoV post-vaccination time points)	**29+273**	**29+ 364**
Month (M)	**M 10**	**M 13**
Signed informed consent [a]	X	(X)
Roll-over criteria for the open-label phase [b]	X	
Vaccination history [c]	X	
Safety Monitoring		
Collection of following AEs:		
• SAEs and AESIs [d]	X	X
• AEs leading to trial discontinuation [d]	X	X
Concomitant medication/vaccination [e]	X	X
COVID-19 Case Reporting		
Case reporting and collection of case information [f]	X	X
Trial End		**X**

AE: adverse event; AESI: adverse event of special interest; COVID-19: Coronavirus disease-2019; eCRF: electronic case report form: EOT: End of Trial; n/a: not applicable; OL: open-label; SAE: serious adverse event

a. The open-label phase visits should be scheduled according to the originally scheduled visits/phone calls in the Phase 2b/3 schedule: Day 302 (-3/+21 days) and Day 393 (-0/+21 days). After trial unblinding, the Day 302 and Day 393 visits will be performed as phone calls, but a clinic visit may be performed if ICF signature cannot be done via e-mail, phone call, or mail.

   If the Day 302 phone call was already performed as part of the randomized observer-blinded phase before approval of Protocol version 4.0, the ICF will be signed at the Day 393/EOT phone call/visit.

b. Roll-over criteria for the open-label phase should be reviewed and confirmed on Clinic Visit OL-1.

c. Vaccination history should be checked to establish eligibility.

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d. SAEs, AESIs, and AEs leading to trial discontinuation will be collected until the EOT.

   During all site visits, trial staff will remind subjects to call the site immediately to report the following: if he/she experiences any concerning medical event; or experiences a serious medical event, has a change in overall health, or is 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.

e. Medications for AESIs, or SAEs, and any immune-suppressive/modulating medications will be documented in the eCRF for the time period specified Table 6. Any prohibited medication (as defined in Section 7.6.2) taken by the subject also needs to be documented in the eCRF.

f. During all site visits/phone calls, trial staff will remind subjects to report any confirmed COVID-19 positive tests.

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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 composed of genomic RNA and phosphorylated nucleocapsid (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 2.

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

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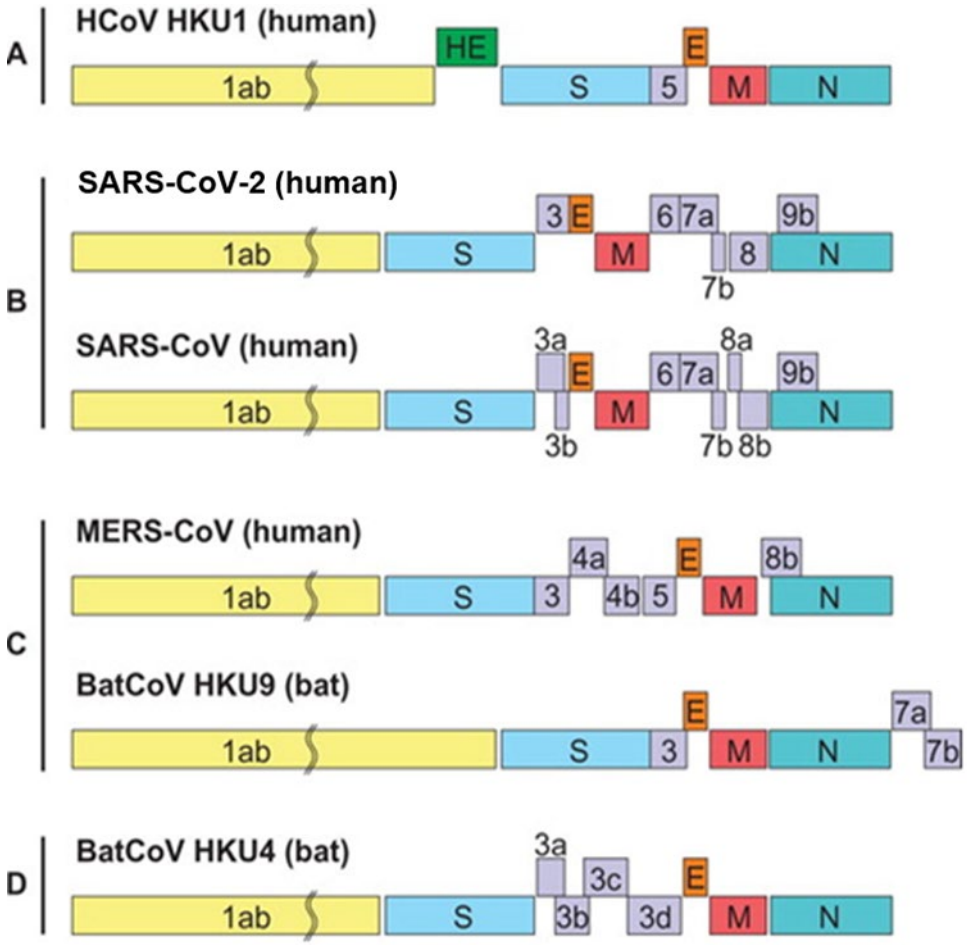
Figure 2 Genome Organization of SARS-CoV-2 Compared with Other Betacoronaviruses



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.

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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 one overlapping CTL epitope between MERS-CoV and SARS-CoV-2 and no comparable epitopes with SARS-CoV.

3.1.2 COVID-19

SARS-CoV-2 is transmitted mainly through close contact and inhalation of respiratory droplets and aerosol particles. 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 WHO, 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 08 November 2020, according to WHO, > 50 million cases have been confirmed globally, including 1.25 million deaths.

3.1.3 Development of CVnCoV

There is currently one fully licensed vaccine for prevention of CoV-associated disease on the market and those who received a conditional approval are not yet available for the majority of the society. CureVac AG is developing a new SARS-CoV-2 messenger ribonucleic acid (mRNA) vaccine formulated with lipid nanoparticles (LNP), referred to as

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CVnCoV, for the prevention of COVID-19 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.

3.1.4 HERALD Phase 2b/3 Results

The HERALD final efficacy analysis on 25,062 subjects meeting the inclusion criteria for the primary analysis, including 228 confirmed adjudicated COVID-19 cases, has demonstrated:

- An overall CVnCoV vaccine efficacy (VE) of 48% (p=0.01600, 95.826% CI 31.0-61.4%) for all age groups against COVID-19 of any severity, including single non-respiratory mild symptoms.
- Significant protection was also shown among subjects in the age group of 18 to 60 years, with an efficacy of 52.5% (95% CI 36.2-64.8%) against disease of any severity and across the 15 identified strains; protection against moderate to severe disease was 77% (95% CI 51.8-90.4%).
- In subjects over 60 years (21 cases, 9% of the analyzed COVID-19 cases), the available data did not allow a statistically significant determination of efficacy. Therefore, CureVac reassessed the benefit/risk by age group and advised the investigators to discuss administration of an AV to trial subjects ≥ 60 years.
- Overall, the data confirm the favorable safety profile of CVnCoV.

3.1.5 CVnCoV and Authorized/Licensed SARS-CoV-2 Vaccines

To date, no clinical trial has proactively investigated or been designed to evaluate the administration of authorized/licensed vaccines for preventing COVID-19 (AVs) after vaccination with CVnCoV.

A post-hoc analysis in September 2021, based on preliminary partially cleaned data, showed that > 11,200 subjects across CVnCoV trials were administered an AV through national vaccination programs after having received 1 or 2 doses of 12 to 20 µg CVnCoV. The most frequently administered vaccine after receiving CVnCoV was Comirnaty® (Pfizer-BioNTech). Although this set of data has certain limitations, the assessment of the safety database on those who received an AV after CVnCoV resulted in the following observations:

- In those having received at least 1 dose of CVnCoV, the follow-up time after receipt of AV amounts to 2535.1 person-years.

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- Most of the AEs following a commercial vaccine relate to the known reactogenicity profile of the commercial vaccines.
- No concerning clusters of AEs have been observed after the administration of an AV.
- There is no evidence that prior receipt of CVnCoV affects the likelihood of an SAE following any AV.

3.1.6 Trial Rationale

The present 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 will be conducted as a randomized, observer-blinded, placebo-controlled trial, followed by an open-label phase.

In the randomized observer-blinded Phase 2b/3 part of the trial, 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 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 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 primary objective of the combined Phase 2b/3 trial is to demonstrate the efficacy of a 2-dose schedule of CVnCoV in the prevention of COVID-19 cases of any severity. Due to the uncertain incidence rate of COVID-19 cases in a pandemic setting, the trial will be 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.

The open-label phase has been added to inform all subjects about the trial treatment they received and to allow follow-up of subjects who received at least 1 dose of CVnCoV, including those who decide(d) after unblinding to receive an authorized/licensed vaccine for preventing COVID-19 (AV) through their national vaccination program.

Placebo subjects do not require further follow-up and will discontinue the trial.

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.

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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.

As of October 2020, dose levels of 2, 4, 6, 8, 12, 16, and 20 µg have been administered to > 250 subjects in Trial CV-NCOV-001. The rate and severity of solicited AEs did not limit dose escalation or dose expansion in this trial. A total of 17 subjects did not receive the second dose administration at this time. Nine subjects were unable to attend the visit, 4 of them because of an unrelated concurrent AE. Four subjects discontinued participation in the trial before Day 29, and 4 subjects did not receive the second dose administration because of an AE following the first dose administration.

The majority of solicited AEs were Grade 1 or 2 in intensity and transient in nature, generally resolving to normal within 48 hours. Grade 3 solicited AEs were reported at all dose levels, consistently at a higher rate in the younger age category (18 to 40 years) as compared to the older age category (41 to 60 years). The most commonly reported investigational medicinal product (IMP)-related unsolicited AEs were:

- Dizziness/lightheadedness/vertigo: 19 subjects
- Hyper/hypo/paresthesia: 6 subjects
- Fatigue, sore throat, dysgeusia, palpitations: 13 subjects
- Abdominal pain, tachycardia, malaise, neck pain: 15 subjects
- Chest pain and circulatory problems: 3 subjects

Individual Grade 3 unsolicited AEs considered as IMP-related by the Investigator were reported for no more than 1 subject each, except for dizziness and fatigue, reported for 2 subjects each (fatigue both reported at the 2 µg dose level, and dizziness reported for 1 subject at 8 µg and 1 subject at 12 µg). Potential allergic reactions have been reported for 2 subjects: 1 potential allergic reaction presented as a case of Grade 1 macular rash that resolved spontaneously within a few hours and was not accompanied by additional systemic signs of allergic reaction; and 1 case of Grade 1 urticaria occurring approximately 25 hours after the first dose administration. The urticaria disappeared the next morning and was initially attributed to the use of sunscreen and/or paracetamol. After the second dose administration, the subject developed a rash 16 hours after vaccination and was accompanied by lip swelling, eyelid swelling and hoarseness. There was no shortness of

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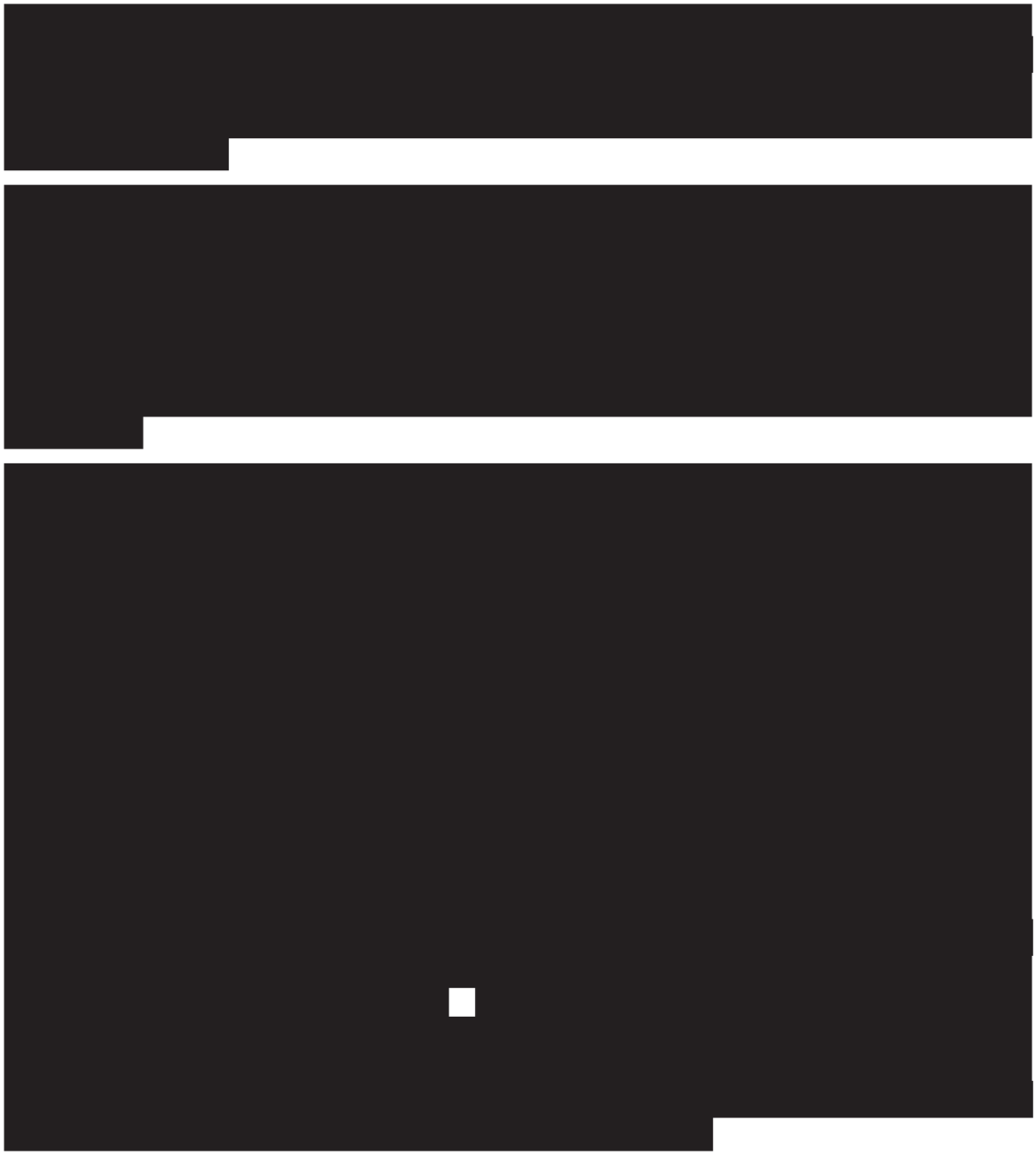
breath. The subject had palpitations overnight but did not have any episodes of feeling dizzy or lightheaded. Reported AEs were urticaria Grade 1, wheals, mucous membrane swelling, and palpitations Grade 2, and allergic reaction Grade 3. The symptoms resolved with betamethasone cream and cetirizine, with resolution after 2 days.

No related serious adverse event (SAEs) have been reported.



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

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COVID-19 vaccine development by the International Coalition of Medicines Regulatory Authorities [31].

[redacted]

In this Phase 2b/3 trial, cases of COVID-19 will be reviewed by an independent Data and Safety Monitoring Board (DSMB) for potential VDE. The DSMB will periodically review cases throughout the trial as defined by the DSMB Charter.

[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, but not COVID-19) 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.

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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.

Updated data from the currently ongoing CVnCoV trials are available in the Investigator's Brochure.

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. 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.

Updated information on CVnCoV vaccine is provided in Section 3.1.4.

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.

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4 TRIAL OBJECTIVES, ENDPOINTS, AND ESTIMANDS

4.1 Objectives

Objectives for the Randomized Observer-blinded Phase

4.1.1 Primary Objectives

Primary Efficacy Objective

- To demonstrate the efficacy of a 2-dose schedule of CVnCoV in the prevention of first episodes of virologically-confirmed cases of COVID-19 of any severity in SARS-CoV-2 naïve subjects.

Primary Safety Objectives

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

4.1.2 Secondary Objectives

Key Secondary Efficacy Objectives

- To demonstrate the efficacy of a 2-dose schedule of CVnCoV in the prevention of first episodes of virologically-confirmed moderate to severe cases of COVID-19 in SARS-CoV-2 naïve subjects.
- To demonstrate the efficacy of a 2-dose schedule of CVnCoV in the prevention of first episodes of virologically-confirmed severe cases of COVID-19 in SARS-CoV-2 naïve subjects.
- To demonstrate the efficacy of a 2-dose schedule of CVnCoV in the prevention of first episodes of virologically-confirmed cases of COVID-19 of any severity caused by “wild type” (i.e., WT/D614G lineages A.1/B.1 without the variant of concern [VOC] B.1.1.7 [Alpha], B.1.351 [Beta], B.1.429 [Epsilon]) and “UK” (B.1.1.7 [Alpha]) SARS-CoV-2 strains in SARS-CoV-2 naïve subjects.

Other Secondary Efficacy Objectives

To evaluate in SARS-CoV-2 naïve subjects:

- The efficacy of a 2-dose schedule of CVnCoV in the prevention of first episodes of virologically-confirmed cases of COVID-19 of any severity in subjects ≥ 61 years of age.
- The efficacy of a 2-dose schedule of CVnCoV in the prevention of first episodes of virologically-confirmed cases of SARS-CoV-2 infection, with or without symptoms.
- The efficacy of a 2-dose schedule of CVnCoV in reducing the Burden of disease (BoD) from COVID-19.

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- The efficacy of CVnCoV after the first dose in the prevention of first episodes of virologically-confirmed cases of COVID-19 of any severity.

Secondary Immunogenicity Objectives

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

4.1.3 Exploratory Objectives

Exploratory Efficacy Objectives

To investigate in SARS-CoV-2 naïve subjects:

- The efficacy of a 2-dose schedule of CVnCoV in the prevention of first episodes of virologically-confirmed cases of COVID-19 of any severity caused by individual VOCs (see Section 9.2.1.6).
- If cases of COVID-19 are milder in severity in subjects receiving a 2-dose schedule of CVnCoV compared to those administered placebo.
- If the need for supplemental oxygenation due to COVID-19 is reduced in subjects receiving a 2-dose schedule of CVnCoV compared to those administered placebo.
- If the need for mechanical ventilation due to COVID-19 is reduced in subjects receiving a 2-dose schedule of CVnCoV compared to those administered placebo.
- If hospitalization due to COVID-19 is reduced in subjects receiving a 2-dose schedule of CVnCoV compared to those administered placebo.
- If mortality due to COVID-19 is reduced in subjects receiving a 2-dose schedule of CVnCoV compared to those administered placebo.
- If all-cause mortality is reduced in subjects receiving a 2-dose schedule of CVnCoV compared to those administered placebo.
- To investigate the cell-mediated immune (CMI) response of a 2-dose schedule of CVnCoV from approximately 200 subjects at selected site(s).

To investigate in SARS-CoV-2 naïve and non-naïve subjects:

- The efficacy of a 2-dose schedule of CVnCoV in the prevention of first episodes of virologically-confirmed cases of COVID-19 of any severity in all subjects, regardless of SARS-CoV-2 serological status at baseline.
- The efficacy of CVnCoV after the first dose in the prevention of first episodes of virologically-confirmed cases of COVID-19 of any severity in all subjects, regardless of SARS-CoV-2 serological status at baseline.

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To investigate in subjects with first episodes of virologically-confirmed COVID-19 during the trial:

- The occurrence of second episodes of COVID-19 in subjects receiving a 2-dose schedule of CVnCoV compared to those administered placebo.
- To explore correlates of protective immunity induced by CVnCoV vaccination.

4.1.4 Objectives for the Open-label Phase

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

Open-label Exploratory Objective:

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

4.2 Endpoints

4.2.1 Primary Endpoints

Primary Efficacy Endpoint

- 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 primary efficacy analysis.

Primary Safety Endpoints

All safety endpoints will be analyzed in all subjects, in subjects seronegative at baseline, and in subjects seropositive at baseline.

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

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4.2.2 Secondary Endpoints

Key Secondary Efficacy Endpoints

- Occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of moderate to severe COVID-19 meeting the case definition for the primary efficacy analysis (moderate and severe COVID-19 defined in Appendix 3 and Appendix 4).
- Occurrence of first episodes of virologically-confirmed (RT-PCR positive) severe cases of COVID-19 meeting the case definition for the primary efficacy analysis (severe COVID-19 defined in Appendix 3).
- Occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity meeting the case definition due to infection with “wild type” (i.e., WT/D614G lineages A.1/B.1 without VOC B.1.1.7 [Alpha], B.1.351 [Beta], B.1.429 [Epsilon]) and “UK” (B.1.1.7 [Alpha]) SARS-CoV-2 strains in SARS-CoV-2 naïve subjects.

Other Secondary Efficacy Endpoints

- In subjects ≥ 61 years of age, occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity meeting the case definition for the primary efficacy analysis.
- Occurrence of virologically-confirmed (RT-PCR positive) SARS-CoV-2 infection, with or without symptoms.

  If subject was symptomatic, onset of symptoms must have occurred ≥ 15 days following the second trial vaccination; if subject was asymptomatic, the positive RT-PCR test must have occurred ≥ 15 days following the second trial vaccination.
- BoD scores calculated based on first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity meeting the case definition for the primary efficacy analysis.
  - BoD #1 – no disease (not infected or asymptomatic infection) = 0; mild or moderate disease = 1; severe disease = 2.
  - BoD #2 – no disease (not infected or asymptomatic infection) = 0; disease without hospitalization = 1; disease with hospitalization = 2; death = 3.
- Occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity with symptom onset at any time after the first trial vaccination.

Secondary Immunogenicity Endpoints (Phase 2b Immunogenicity Subset)

SARS-CoV-2 RBD of S protein antibody responses

On Days 1, 29, 43, 120, and 211:

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

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

SARS-CoV-2 viral neutralizing antibody responses

On Days 1, 29, 43, 120, and 211:

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

  Seroconversion is defined as detectable SARS-CoV-2 viral neutralizing antibodies in the serum of subjects who tested seronegative at baseline.

4.2.3 Exploratory Endpoints

Exploratory Efficacy Endpoints

- Occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 caused by individual VOCs (see Section 9.2.1.6).
- Severity assessment of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 meeting the case definition for the primary efficacy analysis (COVID-19 severity definitions provided in Appendix 3 and Appendix 4).

The following endpoints will be analyzed as occurring ≥ 15 days following the second trial vaccination (full VE) and at any time after the first trial vaccination.

In SARS-CoV-2 naïve subjects:

- Occurrence of supplemental oxygenation due to COVID-19.
- Occurrence of mechanical ventilation due to COVID-19.
- Occurrence of hospitalization due to COVID-19.
- Occurrence of death due to COVID-19.
- Occurrence of death due to any cause.

In SARS-CoV-2 naïve and non-naïve subjects:

- In all subjects regardless of their baseline serostatus, occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity.

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 primary efficacy analysis.

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

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Exploratory Immunogenicity Endpoints

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

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

  *** Thereby, testing of samples collected on Day 120 and Day 211 will be done only in subjects categorized as T-cell responders on Day 29 and/or Day 43.*

  **** First testing of samples will be performed for a subset of these subjects and might be extended to 200 subjects if T-cell response is detectable.*

4.2.4 Open-label Endpoints

- Occurrence, intensity, and relationship to CVnCoV of SAEs and AESIs collected throughout the trial until the end of trial (EOT).
- Occurrence of fatal SAEs throughout the trial until EOT.
- Only for Cohort A: CVnCoV-AV: Occurrence of AEs leading to AV withdrawal or trial discontinuation after the first dose with an AV in the open-label phase until EOT.

Open-label Exploratory Endpoint

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

Any further modifications to endpoints in the open-label phase will be described in the statistical analysis plan (SAP).

4.3 Estimands

Primary Efficacy (randomized observer-blinded phase only)	
ENDPOINTS (subject level)	**ESTIMANDS (population level)**
• Occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity meeting the case definition for the primary efficacy analysis.	In naïve evaluable subjects (complying with the definition of Efficacy Analysis Set [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 group over the placebo group.

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<table>
<tr><th colspan="2">Primary Safety (randomized observer-blinded phase only)</th></tr>
<tr><th>ENDPOINTS (subject level)</th><th>ESTIMANDS (population level)</th></tr>
<tr><td>• Occurrence, intensity, and relationship of medically-attended AEs collected through 6 months after the second trial vaccination in all subjects.
• Occurrence, intensity, and relationship of SAEs and AESIs collected through EOT visit in all subjects.
• Occurrence of fatal SAEs through EOT visit in all subjects.</td><td>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 at each type (by SOC/PT) of:
• Medically-attended AE in the 6 months after the last vaccination overall, by intensity and by causal relationship to trial vaccine.
• SAE in the year after the last vaccination overall and by causal relationship to trial vaccine.
• AESI in the year after the last vaccination overall, by intensity and by causal relationship to trial vaccine.
• Fatal SAE in the year after the last vaccination.</td></tr>
<tr><td>• Occurrence, intensity, and duration of each solicited local AE within 7 days after each trial vaccination in Phase 2b subjects.
• Occurrence, intensity, duration of each solicited systemic AE within 7 days after each trial vaccination in Phase 2b subjects.
• Occurrence, intensity, and relationship of unsolicited AEs occurring within 28 days after each trial vaccination in Phase 2b subjects.
• Occurrence of AEs leading to vaccine withdrawal or trial discontinuation through EOT visit in all subjects.</td><td>In Phase 2b subjects who received at least 1 dose of CVnCoV or placebo vaccine:
The number and percentage of subjects by group reporting:
• Each solicited local AE within 7 days (after each trial vaccination by intensity and overall)
• Each solicited systemic AE within 7 days after each trial vaccination by intensity, by relationship to trial vaccine and overall.
• At least 1 unsolicited AEs, at least 1 Grade 3 unsolicited AEs and each unsolicited AEs by SOC/PT occurring within 28 days after each trial vaccination and overall by causal relationship to trial vaccine and overall
• At least 1 AE leading to vaccine withdrawal or trial discontinuation in the year after the last trial vaccination
The mean duration in days by group with standard deviation of solicited AEs (within the solicited period, total duration).</td></tr>
</table>

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Key Secondary Efficacy (randomized observer-blinded phase only)	
ENDPOINTS (subject level)	**ESTIMANDS (population level)**
• Occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of moderate to severe COVID-19 meeting the case definition for the primary efficacy analysis.	In naïve evaluable subjects (complying with the definition of 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 group over the placebo group.
• Occurrence of first episodes of virologically-confirmed (RT-PCR positive) severe cases of COVID-19 meeting the case definition for the primary efficacy analysis.	In naïve evaluable subjects (complying with the definition of EAS) at least 15 days following second vaccination: VE = 1- RR with exact 95% CI Where RR is the ratio of attack rates of severe COVID-19 cases per 100 person-month in the CVnCoV vaccine group over the placebo group.
• Occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of “wild type” and “Alpha” SARS-CoV-2 strains in SARS-CoV-2 naïve subjects.	In naïve evaluable subjects (complying with the definition of EAS) at least 15 days following second vaccination: VE = 1- RR with exact 95% CI Where RR is the ratio of attack rates of COVID-19 cases per 100 person-month in the CVnCoV vaccine group over the placebo group.

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Other Secondary Efficacy (randomized observer-blinded phase only)	
ENDPOINTS (subject level)	**ESTIMANDS (population level)**
• In subjects ≥ 61 years of age, occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity meeting the case definition for the primary efficacy analysis.	In naïve evaluable subjects ≥ 61 years of age at randomization (complying with the definition of 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 group over the placebo group.
• Occurrence of virologically-confirmed (RT-PCR positive) SARS-CoV-2 infection, with or without symptoms. If subject was symptomatic, onset of symptoms must have occurred ≥ 15 days following the second trial vaccination; if subject was asymptomatic, the positive RT-PCR test must have occurred ≥ 15 days following the second trial vaccination.	In naïve evaluable subjects (complying with the definition of EAS) at least 15 days following second trial vaccination: VE = 1- RR with exact 95% CI Where RR is the ratio of attack rates of virologically-confirmed (RT-PCR positive) SARS-CoV-2 infection per 100 person-month in the CVnCoV vaccine group over the placebo group.
• BoD scores calculated based on first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity meeting the case definition for the primary efficacy analysis. o BoD #1 – no disease (not infected or asymptomatic infection) = 0; mild or moderate disease = 1; severe disease = 2. o 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- SV/SP with exact 95% CI Where SV denotes the ratio of mean BoD score in the CVnCoV group and the mean follow-up time (years) in the CVnCoV group and SP denotes the ratio of mean BoD score in the placebo group and the mean follow-up time (years) in the placebo group.
• Occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity with symptom onset at any time after the first trial vaccination.	In naïve subjects who received at least 1 dose of CVnCoV or placebo vaccine at any time after the first vaccination: VE = 1- RR with exact 95% CI Where RR is the ratio of attack rates of COVID-19 cases per 100 person-month in the CVnCoV vaccine group over the placebo group.

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Secondary Immunogenicity (randomized observer-blinded phase only)	
ENDPOINTS (subject level)	**ESTIMANDS (population level)**
On Days 1, 29, 43, 120, and 211: • Serum antibodies to SARS-CoV-2 RBD of S protein. • Occurrence of seroconversion to SARS-CoV-2 RBD of S protein. Seroconversion is defined as detectable SARS-CoV-2 RBD of S protein antibodies in the serum of subjects who tested seronegative at baseline.	On Days 1, 29, 43, 120, and 211: • Geometric mean of titers (GMT) with 95% CI of SARS-CoV-2 RBD of S protein antibody responses by group and by baseline sero-status and group. On Days 29, 43, 120, and 211 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, 43, 120, and 211 for subjects seronegative at baseline: • Number and percentage with exact 95% CI of subjects by group for who a seroconversion is observed (detectable SARS-CoV-2 RBD of S protein antibodies in the serum).
SARS-CoV-2 viral neutralizing antibody responses On Days 1, 29, 43, 120, and 211: • Serum viral neutralizing antibodies to SARS-CoV-2 virus. • Occurrence of seroconversion to SARS-CoV-2 virus. Seroconversion is defined as detectable SARS-CoV-2 viral neutralizing antibodies in the serum of subjects who tested seronegative at baseline.	On Days 1, 29, 43, 120, and 211: • GMT with 95% CI of neutralizing antibodies to SARS-CoV-2 virus by group and by baseline serostatus and group. On Days 29, 43, 120, and 211 for subjects seropositive at baseline: • GMFC with 95% CI of neutralizing antibodies to SARS-CoV-2 virus by group. On Days 29, 43, 120, and 211 for subjects seronegative at baseline: • Number and percentage with exact 95% CI of subjects by group for who a seroconversion is observed (detectable neutralizing antibodies to SARS-CoV-2 virus in the serum).

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Exploratory Efficacy (randomized observer-blinded phase only)	
ENDPOINTS (subject level)	**ESTIMANDS (population level)**
• Occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 caused by any other identified variants.	In naïve evaluable subjects (complying with the definition of EAS) at least 15 days following second trial vaccination: VE = 1- RR with exact 95% CI Where RR (relative risk) is the ratio of attack rates of virologically-confirmed (RT-PCR positive) SARS-CoV-2 infection per 100 person-month in the CVnCoV vaccine group over the placebo group.
• Severity assessment of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 meeting the case definition for the primary efficacy analysis	In naïve evaluable subjects (complying with the definition of 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 primary efficacy analysis: • The proportions of mild, moderate, and severe COVID-19 cases among all cases by severity group.
The following endpoints will be analyzed as occurring ≥ 15 days following the second trial vaccination (full VE) and at any time after the first trial vaccination. • Occurrence of supplemental oxygenation due to COVID-19. • Occurrence of mechanical ventilation due to COVID-19. • Occurrence of hospitalization due to COVID-19. • Occurrence of death due to COVID-19. • Occurrence of death due to any cause.	In naïve evaluable subjects (complying with the definition of EAS) at least 15 days following second vaccination AND in subjects who received at least 1 dose of CVnCoV or placebo vaccine at any time after the first trial vaccination: Number and percentages by group of subjects who: • Need for supplemental oxygenation due to COVID-19. • Need for mechanical ventilation due to COVID-19. • Hospitalized due to COVID-19. • Deceased due to COVID-19. • Deceased due to any cause.

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• In all subjects regardless of their baseline serostatus, occurrence of first episodes of virologically-confirmed (RT-PCR positive) cases of COVID-19 of any severity.	In subjects who received at least 1 dose of CVnCoV or placebo vaccine, at any time after the first trial vaccination: VE = 1- RR with exact 95% CI Where RR is the ratio of attack rates of COVID-19 cases per 100 person-month in the CVnCoV vaccine group over the placebo group.
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 primary 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 primary efficacy analysis, at least 15 days following second vaccination: • The number and percentage of subjects who developed a second episode of COVID-19.

Exploratory Immunogenicity (randomized observer-blinded phase only)	
ENDPOINTS (subject level)	**ESTIMANDS (population level)**
On Days 1, 29, 43, 120**, and 211** in peripheral blood mononuclear cells (PBMCs) from up to 200*** subjects at selected site(s): • The frequency and functionality of SARS-CoV-2 RBD of S-specific T-cell response after antigen stimulation by intracellular cytokine staining (ICS) to investigate Th1 response and expression of Th2 markers. • The proportion of subjects with a detectable increase in SARS-CoV-2 RBD of S-specific T-cell response. *** Thereby, testing of samples collected on Day 120 and Day 211 will be done only in subjects categorized as T-cell responders on Day 29 and/or Day 43.* **** First testing of samples will be performed for a subset of these subjects and might be extended to 200 subjects if T-cell response is detectable.*	In subjects belonging to the Immunogenicity/Reactogenicity subset and selected to take part in the CMI subset: • The number and percentage of subjects for whom a SARS-CoV-2 RBD of S-specific T-cell response is observed The number and percentage of subjects with a detectable increase in SARS-CoV-2 RBD of S-specific T-cell response.

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Open-label Safety Cohort A: CVnCoV-AV	
ENDPOINTS (subject level)	**ESTIMANDS (population level)**
• Occurrence, intensity and relationship of SAEs and AESIs collected throughout the trial until the EOT. • Occurrence of fatal SAEs throughout the trial until the EOT. • Occurrence of AEs leading to trial discontinuation.	In subjects who received at least 1 dose of CVnCoV and participate in the open-label phase of the trial: • SAE after the first dose with an AV in the open-label phase until the EOT. • AESI after the first dose with an AV in the open-label phase until the EOT. • Fatal SAE in the open-label phase through EOT. • At least 1 AE leading to trial discontinuation.

Estimands corresponding to occurrence of virologically-confirmed (RT-PCR positive) cases of COVID-19 will be described in the SAP.

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5 TRIAL DESIGN

5.1 Overall Design

Trial CV-NCOV-004 will start with an initial Phase 2b part followed by a large Phase 3 efficacy part. Both Phase 2b and Phase 3 parts will be randomized, observer-blinded, and placebo-controlled. Adult subjects 18 years of age or older will be enrolled at multiple sites globally and will receive a 2-dose schedule of either CVnCoV at a dose level of 12 µg mRNA or placebo {normal saline (0.9% NaCl)} in a 1:1 ratio. Both Phase 2b and Phase 3 parts of the trial are consistent in design (e.g., for COVID-19 case ascertainment and case definition) so that cases of COVID-19 occurring in Phase 2b can be pooled with those in Phase 3 for the primary analysis of VE.

This randomized observer-blinded phase will be followed by a Phase 3 open-label phase. The trial will be unblinded on country/site level after receipt of Competent Authority/Ethics Committee approval of Protocol version 4.0 (see Figure 1). Subjects who received at least 1 dose of CVnCoV may opt to remain in the trial to be followed-up as initially planned, or they may opt/may have opted to receive an AV through their national vaccination program after unblinding. Subjects who received placebo will be withdrawn after trial unblinding.

5.1.1 Randomized Observer-blinded Phase 2b Design and Objectives

(See Table 1 and Table 2 for the Schedule of Trial Assessments and Procedures).

The objective of Phase 2b is to further characterize the safety, reactogenicity, and immunogenicity of CVnCoV prior to initiating Phase 3. CVnCoV will be administered at the 12 µg dose level selected for Phase 3 investigation informed by the safety and immunogenicity data from the initial Phase 1 and 2a trials. Phase 2b will be conducted in 2 age groups of adults: 18 to 60 and ≥ 61 years of age, which represent the age range of the intended Phase 3 trial population.

Approximately 4,000 subjects will be enrolled and randomized in a 1:1 ratio to receive 2 doses of either CVnCoV at a dose level of 12 µg mRNA or placebo, administered 28 days apart. Of the 4,000 subjects enrolled, approximately 800 to 1,000 (20% to 25%) will be ≥ 61 years of age. Phase 2b will be performed in an observer-blinded manner to reduce any potential bias in the safety assessments. The sample size of 4,000 subjects is based on generating a robust and detailed dataset characterizing the safety, reactogenicity, and immunogenicity of CVnCoV prior to entering Phase 3. Furthermore, the data generated in Phase 2b will be the main dataset to be submitted in support of early conditional approval of CVnCoV.

In Phase 2b, 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. The immunogenicity of CVnCoV will be evaluated after 1 and 2 doses in a subset of subjects (first 600 subjects enrolled in each of the 2 age groups; a total of 1,200 subjects in the Immunogenicity Subset) by measuring binding antibodies to the SARS-CoV-2 RBD of S protein and viral neutralizing antibodies. Antibody persistence will also be evaluated in this trial.

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Cases of COVID-19 occurring in Phase 2b subjects will be collected and pooled with those occurring in Phase 3 and the total number of cases will be used for the primary analysis of efficacy. In addition, the DSMB will periodically monitor COVID-19 cases for signals of VDE.

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

An early safety review of the Phase 2b data will be performed by the DSMB (see Section 9.3.8.1). The safety review will be conducted when approximately 1,000 subjects have been enrolled in Phase 2b (25% of subjects enrolled; 500 recipients of CVnCoV and 500 recipients of placebo) and have at least 1 week of safety follow-up after the first trial vaccination. If the safety profile is judged to be acceptable and there are no safety or tolerability concerns, it is anticipated that enrollment of subjects into Phase 3 can begin without interruption from Phase 2b. Another safety review by the DSMB will be conducted when approximately 1,000 Phase 2b subjects have received their second trial vaccination and have at least 1 week of safety follow-up. All available first dose safety data from the Phase 2b subjects will also be reviewed at this time.

5.1.2 Randomized Observer-blinded Phase 3 Design and Objectives

(See Table 3 for Schedule of Assessments and Procedures)

The primary objective of the combined Phase 2b/3 trial is to demonstrate the efficacy of a 2-dose schedule of CVnCoV in the prevention of COVID-19 cases of any severity. Similar to Phase 2b, Phase 3 will be conducted as a randomized, observer-blinded, placebo-controlled trial. Approximately 32,500 subjects, 18 years of age or older, will be enrolled at multiple sites globally in Phase 3 and will receive a 2-dose schedule of either CVnCoV at the 12 µg dose level or placebo in a 1:1 ratio. Similar to Phase 2b, enrollment will target subjects ≥ 61 years of age to be approximately 20% to 25% of the Phase 3 trial population (6,500 to 8,125 subjects). The total enrollment of the combined Phase 2b and Phase 3 parts of the trial will be 36,500 subjects.

Subjects will undergo active surveillance for COVID-19 (see Appendix 6A). 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. 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, all subjects 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

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will continue to be followed through the trial end in the same manner as those who have not presented with COVID-19. A second episode of COVID-19 in a subject with prior disease will not be counted as a primary efficacy case, but will be counted for the exploratory objective assessing the reoccurrence of COVID-19 in vaccinated subjects.

Due to the uncertain incidence rate of COVID-19 cases in a pandemic setting, the trial will be conducted as a case-driven trial based on the any severity COVID-19 endpoint, which will include 2 interim analyses and a final analysis both triggered by achieving a predefined number of cases for each analysis. As described above, cases of COVID-19 occurring in Phase 2b will be pooled with those in Phase 3 for the primary analysis of VE. As such, subjects participating in Phase 2b will contribute to the total sample size for the primary analysis of VE (N=36,500).

For the primary analysis of efficacy, the case must meet the following criteria (moderate and severe COVID-19 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 10.2.3, Efficacy Analysis Set (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).

Primary efficacy cases must be confirmed by the Adjudication Committee.

This trial will utilize a group sequential design with 2 interim analyses for high efficacy or futility using the O'Brien and Fleming error spending function for the primary endpoint of virologically-confirmed COVID-19 cases of any severity. With an overall 2-sided alpha of 5% and a total of 160 COVID-19 cases of any severity meeting the primary efficacy case definition at the final analysis, the trial will have an overall power of 90% to demonstrate a VE greater than 30% (based on a margin of 30% for the lower bound of the 95% confidence interval [CI] for VE) when considering VE is 60%. Two interim analyses of high efficacy or futility will be performed once 56/111 cases meeting the primary case definition have been accrued and adjudicated (35/69% of final case number). These points were chosen based on 2 criteria: i) the robustness of 56/111 cases to support the decision of high efficacy or futility and ii) if high efficacy, this would shorten the duration of the trial and potentially allow the vaccine to be available earlier.

Assuming an incidence rate of COVID-19 of 0.15% per month (1.5 cases/1000/month) in placebo subjects; a VE of 60%; and a non-evaluable rate of 20% during the trial which includes ~5% seropositivity of enrollees at baseline (i.e. non-naïve subjects), follow-up of 36,500 subjects enrolled over 3 months (18,250 per vaccine group) will accrue the target 160 COVID-19 cases of any severity approximately 9 months after the first vaccination.

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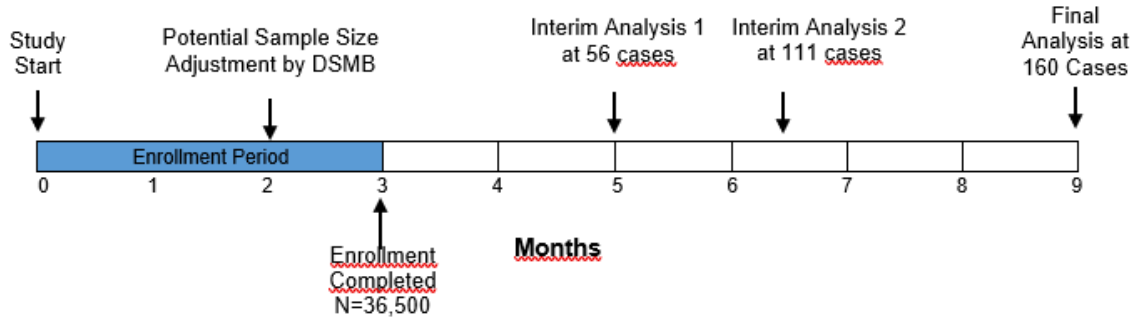
During the early stages of enrollment, an unblinded review of the incidence rate of cases will be performed by the DSMB. If the case accrual rate is lower or higher than expected, the DSMB may recommend an adjustment in sample size. If needed, another unblinded review by the DSMB may be performed later in the trial to further adjust the sample size. The trial events are shown in the timeline below (Figure 3).

Figure 3 Trial Timeline – HERALD Trial CV-NCOV-004



With an equal follow-up time of evaluable subjects in the CVnCoV and placebo groups, efficacy would be demonstrated at the final analysis if 53 cases or less of 160 total cases of COVID-19 are in the CVnCoV group (estimated VE ≥ 50.5%). Two interim analyses for high efficacy or futility will be performed when 56/111 cases meeting the primary case definition have been accrued and adjudicated (approximately 5/6.5 months after trial start). If the follow-up time of evaluable subjects is equal in both groups, early high efficacy would be demonstrated if 9/32 cases or less of the 56/111 cases are in the CVnCoV group (estimated VE at interim ≥ 80.9/59.5%); conversely, futility would be reached if 25/40 cases or more are in the CVnCoV group (estimated VE at interim ≤ 19.4/43.7%). The assessment of the interim analyses will be performed by the DSMB and the outcome will be communicated without unblinding the Trial Team or the Sponsor.

Similar to Phase 2b, subjects participating in Phase 3 will be evaluated for SARS-CoV-2 infection during the trial, as measured by the development of antibodies to the N protein of SARS-CoV-2 in seronegative subjects.

The safety objective of Phase 3 is to generate a large-scale safety database that will demonstrate the safety of CVnCoV. All subjects participating in the Phase 2b and Phase 3 parts of the trial will have medically-attended AEs collected for 6 months after the second vaccination; and AESIs (see Appendix 9 and Appendix 10) and SAEs collected until the EOT visit.

5.1.3 Open-label Phase Design and Objectives

After unblinding, the trial will shift from a randomized observer-blinded to an open-label design, and the following cohorts will be defined:

Cohort A: CVnCoV-AV (See Table 4 for the Schedule of Trial Assessments and Procedures): Subjects ≥ 18 years who received at least 1 dose of CVnCoV and choose to receive an AV are included in this cohort and will be recommended to procure AV as standard of care per their national vaccination program, if not already done. Subjects will be requested to remain in the trial for safety follow-up until the EOT (Day 393 of the original

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Phase 2b/3 schedule). Subjects who were individually unblinded and already received an AV before implementation of Protocol version 4.0 will also be included in this cohort.

Cohort B: CVnCoV only (See Table 5 for the Schedule of Trial Assessments and Procedures): Subjects ≥ 18 years who received at least 1 dose of CVnCoV and choose to remain in the trial without receiving any AV will continue follow-up until EOT (Day 393 of the original Phase 2b/3 schedule). Subjects who were individually unblinded during the randomized observer-blinded phase and who received CVnCoV but did not receive an AV before implementation of Protocol version 4.0 and do not intend to receive an AV will also be included in this cohort. Subjects who initially intend to complete the trial without receiving an AV and later decide to receive an AV within the open-label phase will be switched to Cohort A.

Placebo subjects do not require further follow-up and will discontinue the trial (see Section 9.1.4.2).

The open-label phase will provide additional safety data, including data from subjects who receive an AV after CVnCoV. COVID-19 cases will continue to be documented, but there will no longer be any inferential efficacy analysis in the open-label phase (only descriptive summary of cases). Subjects will undergo passive surveillance for COVID-19 (see Appendix 6B).

Trial unblinding and transition from the randomized observer-blinded to the open-label phase will be conducted on a country/site level, depending on full Competent Authority and Ethics Committee approval of Protocol version 4.0 per country/site.

5.2 Scientific Rationale for Trial Design

See also Sections 3.2 and 5.1.

HERALD Trial CV-NCOV-004 will be conducted in the following parts: an initial Phase 2b trial followed by a large Phase 3 efficacy trial, followed by an open-label phase.

Randomized Observer-blinded Phase

Both Phase 2 and Phase 3 parts of the trial are consistent in design, so that cases of COVID-19 occurring in Phase 2 can be pooled with those in Phase 3 for the primary analysis of VE. Combining COVID-19 cases in Phase 2 and 3 to expedite an efficacy outcome was considered warranted in a pandemic setting.

Both Phase 2b and Phase 3 will be randomized, observer-blinded, and placebo-controlled. 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 and efficacy outcomes of the trial (see also Section 7.3).

As the elderly are affected most by SARS-CoV-2 and have a high risk for severe disease and mortality, it is critical to investigate CVnCoV in this population and therefore subjects ≥ 61 years of age will be included in the randomized observer-blinded Phase 2b/3.

The sample size of 4,000 subjects in Phase 2b is based on generating a robust and detailed dataset characterizing the safety, reactogenicity, and immunogenicity of CVnCoV

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prior to entering Phase 3. Furthermore, the data generated in Phase 2b will be the main dataset to be submitted in support of early conditional approval of CVnCoV.

The total sample size of 36,500 subjects for the combined Phase 2b/3 trial is based on demonstrating VE above 30% (based on a margin of 30% for the lower bound of the 95% CI for VE) when considering VE is 60%. With a 2-sided alpha of 5% and a total of 160 COVID-19 cases, the trial will have a 90% power to demonstrate a VE above 30%. Assuming an incidence rate of COVID-19 of 0.15% per month in control subjects; and a non-evaluable rate of 20% during the trial which includes 5% seropositivity of enrollees at baseline (i.e. non-naïve subjects), follow-up of 36,500 subjects enrolled over 3 months (18,250 per vaccine group) will accrue the target 160 COVID-19 cases approximately 9 months after the first vaccination.

For the primary analysis of efficacy, 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 safety objective of Phase 3 is to generate a large-scale safety database that will demonstrate the safety of CVnCoV. All subjects participating in the Phase 2b and observer-blinded Phase 3 parts of the trial will have medically-attended AEs collected for 6 months after the second vaccination; and AESIs and SAEs collected for 1 year after the second vaccination. As such, each subject will participate in the trial for approximately 13.5 months for the safety follow-up.

Individuals with history of virologically-confirmed COVID-19 illness will be excluded from participating in this trial. However, this trial will not screen for or exclude subjects with history or laboratory evidence of prior SARS-CoV-2 infection, many of which might have been asymptomatic. Because pre-vaccination screening for prior infection is unlikely to occur in practice, it is important to understand vaccine safety and COVID-19 outcomes in in individuals with prior infection with SARS-CoV-2 virus.

CMI will be evaluated in approximately 200 subjects: 100 who receive CVnCoV and 100 who receive placebo. The goals of this are to identify immunological biomarkers to identify vaccine responders and people having a better immune response to CVnCoV, to better understand the biology of the immune response to CVnCoV, and to investigate the duration of the immune response to CVnCoV. Analysis of immunologically relevant genomic biomarkers will be limited to DNA sequencing of the subject's T-cell receptor and human leukocyte antigen type. The purpose is not to test for any genetic disorders or to identify predisposition to any disease.

Open-label Phase

In view of the current availability of AVs in the countries where the trial is being conducted, multiple unblinding requests have been granted to trial subjects seeking access to these AVs under their country's national vaccination programs, and as of 18 November 2021 nearly 80% of the trial subjects have been unblinded and approximately 49% have already received an AV. After approval of Protocol version 4.0, all trial subjects will be unblinded and the trial will shift to an open-label design as described in Section 5.1.3. The open-label

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phase will provide additional safety data, including data from subjects who receive an AV after CVnCoV.

5.3 Justification for Dose

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

In Trial CV-NCOV-001, a dose of 12 µg elicited the same immune response as that seen in patients who are recovering from having been infected with the real virus.

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. After trial unblinding, a placebo subject is considered to have completed the trial when he/she has completed the EOT phone call.

End of Trial is defined as when the last subject has completed the last visit on Day 393 or prematurely discontinued the trial, for both the randomized observer-blinded Phase 2b/3 and the open-label phase.

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 AEs 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 CureVac Safety Review Team reviews the safety data on a periodic basis. The outcome of these reviews and discussions are then shared with the DSMB Chair.

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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. 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.

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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 a history of virologically-confirmed COVID-19 illness will be excluded from the trial. However, this trial will not screen for or exclude individuals with a history or laboratory evidence of prior SARS-CoV-2 infection. 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. Be willing and able to provide written informed consent prior to initiation of any trial procedures.
3. Expected compliance with protocol procedures and availability for clinical follow-up through the last planned visit.
4. 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 (FSH) level may be measured at the discretion of the Investigator to confirm postmenopausal status.
5. Females of childbearing potential: negative pregnancy test {human chorionic gonadotropin {hCG)} within 24 hours prior to each trial vaccination on Day 1 and Day 29.
6. 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;

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- 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 for All Subjects

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

1. History of virologically-confirmed COVID-19 illness.
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 or any other 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 anabolic steroids, 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 (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV); 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. History of angioedema (hereditary or idiopathic) or history of any anaphylactic reaction.
9. History of pIMD.
10. History of allergy to any component of CVnCoV vaccine.
11. Administration of immunoglobulins or any blood products within 3 months prior to the administration of trial vaccine or planned receipt during the trial.
12. 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

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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.

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

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

6.3 Roll-over Criteria for the Open-label Phase

1. Subjects must have received at least 1 dose of CVnCoV during the randomized observer-blinded phase.

2. Subjects must provide additional written informed consent to be eligible for the open-label phase.

6.3.1 Cohort A: CVnCoV-AV

3. Subjects of the CVnCoV treatment arm who received or will receive any AV as standard of care through their national vaccination program.

6.3.2 Cohort B: CVnCoV only

3. Subjects have not received any vaccination with any other investigational/authorized SARS-CoV-2 vaccine or another coronavirus (SARS-CoV, MERS-CoV) vaccine.

6.4 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 and COVID-19 is either not clinically suspected and/or SARS-CoV-2 testing is negative) or temperature ≥ 38.0°C (≥ 100.4°F), within 3 days of intended trial vaccination on Day 1 or Day 29.
    - 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.

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- Receipt of a licensed non-COVID-19 vaccine within 28 days (for live vaccines) or 14 days (for inactivated or any other vaccines) prior to or after scheduled administration of trial vaccine or AV. As these are recommended windows, rescheduling trial vaccination to be compliant with these windows should only be done if practical.

6.5 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 assessment as per Table 1, Table 2, and Table 3, or re-doing one assessment is allowed based on the judgment of the Investigator.

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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 (DSPC), PEG-ylated lipid and a cationic lipid. It is supplied as a concentrate at 1 mg/mL of mRNA drug substance.

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 arm 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 Authorized Vaccines

Countries participating in the HERALD trial currently have access to an AV such as Comirnaty® (Pfizer-BioNTech), Spikevax® (Moderna), Janssen COVID-19 Vaccine® (Janssen), Vaxzevria® (AstraZeneca), Convidecia® (Cansino), Sinopharm COVID-19 vaccine, CoronaVac® (Sinovac), and Gam-COVID-Vac® (Sputnik V).

Trial subjects have or will have access soon to an approved or authorized vaccination through their national vaccination programs. The type of vaccine and range of age for vaccination is decided by national vaccination programs, outside of the clinical trial procedures.

After trial unblinding, investigators will provide subjects with information about the treatment they have received and currently available AVs at country level to allow subjects to make an informed decision.

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7.1.2.4 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 unblinded pharmacists or physicians or any other qualified persons according to local law. These pharmacists/qualified persons will have no other trial function following preparation of the blinded syringes for 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/qualified 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 trial 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 trial site with the following information:

- Dates and quantities of CVnCoV received from CureVac.

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- 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

Both Phase 2b and Phase 3 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 (Randomized Observer-blinded Phase only)

Subjects 18 years of age or older will be enrolled at multiple sites globally and will be randomized in a 1:1 ratio to receive either CVnCoV or placebo. The randomization will be performed centrally and stratified by country and age group (18 to 60 and ≥ 61 years of age). The randomization scheme will be generated and maintained by an Independent Statistical 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, each subject enrolled into the trial will be assigned their treatment assignment.

7.3.2 Blinding (Randomized Observer-blinded Phase only)

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/qualified site personnel who prepared the injection 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 pharmacist/qualified site personnel who prepared the injection 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

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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. At the interim analyses, the DSMB will review COVID-19 cases by vaccine group for efficacy or futility, and will communicate the outcome to the Sponsor in a blinded manner.

For the submission of documents for regulatory approval during the ongoing conduct of Trial CV-NCOV-004 (e.g., if efficacy is demonstrated at one 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 (randomized observer-blinded phase only)

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 Trial Unblinding

Since the efficacy results from the HERALD trial are available and subjects in this trial are currently allowed to receive an AV, all subjects in this trial will be unblinded. Unblinding will be performed by country/site depending on full Competent Authority and Ethics Committee approval of Protocol version 4.0 per country/site.

The CRO will provide the sites with the subject numbers potentially eligible for each cohort. Each subject will be informed by the Investigator of the available results and whether he/she received CVnCoV or placebo in the trial (see Section 9.1.4).

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Subjects who received at least 1 dose of CVnCoV will be asked to remain in the trial to allow safety follow-up. Subjects who received placebo will be withdrawn after trial unblinding.

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 (in the randomized observer-blinded phase) 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 Phase 2b part, 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

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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.

AVs are allowed during the open-label Phase (Cohort A: CVnCoV-AV). AVs will be procured and provided to the subject as standard of care per the subject's national vaccination program, outside of the clinical trial procedures. Receipt of any other investigational SARS-CoV-2 vaccine or other coronavirus vaccine (e.g., SARS-CoV, MERS-CoV, etc) is prohibited during the trial.

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. Treatment with an investigational COVID-19 drug will be allowed in case of diagnosed COVID-19, and this will be recorded as concomitant medication.
- Licensed vaccines (other than that for COVID-19) should not be administered within 28 days (for live vaccines) or 14 days (for inactivated or any other vaccines) of trial vaccine administration during the trial.
- Receipt of any other investigational SARS-CoV-2 vaccine or other coronavirus vaccine (e.g., SARS-CoV, MERS-CoV, etc) is prohibited during the trial. AVs are allowed if the subject is eligible according to the national vaccination program.
- 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.

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7.8 Treatment After the End of Trial

No post-trial care will be provided.

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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 trial vaccine 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 (before trial unblinding).

- 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 EOT visit on Day 393 would be performed).

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- Major protocol deviation.
- Other.

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

For subjects who develop virologically-confirmed COVID-19 after the first trial vaccination but prior to the second during the randomized observer-blinded phase; 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.

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.
- After trial unblinding, placebo subjects will be withdrawn from the trial.

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 in the randomized observer-blinded phase and who has received at least 1 trial vaccine dose will undergo the same procedures as for the EOT visit, unless such procedures are considered to pose unacceptable risk to the subject.

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.

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- 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 Independent Ethics Committee or Institutional Review Board (IEC/IRB). The Sponsor may close an individual 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.

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9 TRIAL ASSESSMENTS AND PROCEDURES

The trial assessments and procedures for this trial are presented in Table 1, Table 2, Table 3, Table 4, and Table 5. 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 any bio-samples. 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.

After trial unblinding, no blood samples will be collected; home visits will no longer be performed, and clinic visits may be replaced with phone calls if suitable to reduce contacts in the pandemic setting.

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

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

The maximum total volume of blood taken over the trial period from any subject is 304 mL.

9.1 Schedule of Trial Assessments and Procedures

Refer to Table 1 (Immunogenicity Subjects) and Table 2 (Non-Immunogenicity Subjects) for the Schedule of Trial Assessments and Procedures for Phase 2b, Table 3 for the Schedule of Trial Assessments and Procedures for the randomized observer-blinded Phase 3, Table 4 for the Schedule of Trial Assessments and Procedures for the open-label phase Cohort A, and Table 5 for the Schedule of Trial Assessments and Procedures for the open-label phase Cohort B.

The trial assessments and procedures apply to all subjects, independent if they had known SARS-CoV-2 positive serology before the trial or independent of the serology status at baseline as per retrospective analysis.

Subjects participating in Phase 2b will be given a thermometer to measure body temperature orally and a measuring tape to determine the size of local injection site reactions.

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Subjects will be instructed on how to enter the solicited AEs daily for 7 days in the eDiary. Subjects should be reminded to use the provided Mobile Health Platform for the eDiary as applicable during the randomized observer-blinded phase of the trial.

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 Phase 2b: Immunogenicity Subset

The Immunogenicity Subset of Phase 2b will include the first 600 subjects enrolled into each of the 2 age groups, 18-60 and ≥ 61 years of age, into Phase 2b. As such, the target total enrollment will be approximately 1,200 subjects.

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 signed informed consent form (ICF).
  - 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).
- Review inclusion/exclusion criteria (see Section 6.1 and 6.2) and review prohibited medications listed as an exclusion criterion (see Section 6.2).
- Randomize the subject in IWRS after confirmation of eligibility.
- Record demographic and smoking information.
- Record medical history.
- Record concomitant medications and vaccinations according to instructions in Section 7.6, 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 the complete physical examination to establish eligibility was performed 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).

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- Perform 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 genomic biomarkers (~6 mL blood) from subjects at selected site(s).
- Collect pre-vaccination blood samples for CMI (~32 mL blood) from subjects at selected site(s).

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.

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.

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- 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, 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.

- Complete the source documents and eCRF for this visit.

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 (e.g., medically-attended AEs, SAEs).
  - Record concomitant medications and 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.

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- 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, whether they were symptomatic (COVID-19 illness) or asymptomatic at the time of the test.

- Complete the source documents and eCRF for this phone call.

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

Pre-vaccination Procedures

- Review and record any newly reported safety data including solicited and unsolicited AEs, or other AEs (e.g., medically-attended AEs, SAEs).
- Record concomitant medications and vaccinations according to instructions in Section 7.6.
- Perform a symptom-directed physical examination (at the discretion of the Investigator; see Section 9.3.6).
- Measure vital signs (body temperature, pulse, blood pressure, see Section 9.3.6).
- Perform 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 genomic biomarkers (~6 mL blood) from subjects at selected site(s).
- Collect pre-vaccination blood samples for CMI (~32 mL blood) from subjects at selected site(s).

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.

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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, whether they were symptomatic (COVID-19 illness) or asymptomatic at the time of the test.
- Complete the source documents and eCRF for this visit.

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.

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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 (e.g., medically-attended AEs, SAEs).
- Record concomitant medications and vaccinations according to instructions in Section 7.6.
- Perform a symptom-directed physical examination (at the discretion of the Investigator; 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 genomic biomarkers (~6 mL blood) from subjects at selected site(s).
- Collect blood samples for CMI (~32 mL blood) from subjects at selected site(s).
- 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, whether they were symptomatic (COVID-19 illness) or asymptomatic at the time of the test.
- Complete the source documents and eCRF for this visit.

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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 (e.g., medically-attended AEs, SAEs).
- Record concomitant medications and vaccinations according to instructions in Section 7.6.
- Perform a symptom-directed physical examination (at the discretion of the Investigator; 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).
- 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, whether they were symptomatic (COVID-19 illness) or asymptomatic at the time of the test.
- Complete the source documents and eCRF for this visit.

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 (e.g., medically-attended AEs, SAEs).

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- Record concomitant medications and vaccinations according to instructions in Section 7.6.
- Perform a symptom-directed physical examination (at the discretion of the Investigator; 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 pre-vaccination blood samples for genomic biomarkers (~6 mL blood) from subjects at selected site(s).
- Collect pre-vaccination blood samples for CMI (~32 mL blood) from subjects at selected site(s).
- 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, whether they were symptomatic (COVID-19 illness) or asymptomatic at the time of the test.
- Complete the source documents and eCRF for this visit.

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);

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and binding antibody testing to N (nucleocapsid) protein of SARS-CoV-2 (~6 mL blood).

- Collect blood samples for genomic biomarkers (~6 mL blood) from subjects at selected site(s).

Collect blood samples for CMI (~32 mL blood) from subjects at selected site(s).

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 (e.g., 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, whether they were symptomatic (COVID-19 illness) or asymptomatic at the time of the test.
- Complete the source documents and eCRF for this phone call.

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9.1.1.10 End of Trial Visit: Day 393 (-0/+21 days)

The EOT 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 (e.g., SAEs).
- Record concomitant medications and vaccinations according to instructions in Section 7.6.
- 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).
- Compete the eCRF for this visit.

Inform the subjects that they have completed the trial and can now delete the eDiary app.

9.1.2 Phase 2b: Non-Immunogenicity Subjects

Following enrollment of subjects into the Immunogenicity Subset of Phase 2b (n=1,200), the remaining 2,800 subjects, 18 years of age and older, will be enrolled into Phase 2b.

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.

Pre-vaccination Procedures

- Obtain the signed ICF.
  - 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).
- Review inclusion/exclusion criteria (see Section 6.1 and 6.2) and review prohibited medications listed as an exclusion criterion (see Section 6.2).
- Randomize the subject in IWRS after confirmation of eligibility.
- Record demographic and smoking information.
- Record medical history.
- Record concomitant medication and vaccination according to instructions in Section 7.6, including recurring medication for intermittent conditions, if taken within 6 months prior to enrollment in this trial.

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- Perform a complete physical examination, including height and weight (see Section 9.3.6). If the complete physical examination to establish eligibility was performed 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 pregnancy test in females of childbearing potential (Appendix 5).
- Collect pre-vaccination blood sample (see Table 2) for binding antibody testing to N protein of SARS-CoV-2 (~6 mL blood).

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.

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.

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- 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, 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.

- Complete the source documents and eCRF for this visit.

9.1.2.2 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 (e.g., medically-attended AEs, SAEs).
  - Record concomitant medications and 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.

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- 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, whether they were symptomatic (COVID-19 illness) or asymptomatic at the time of the test.

- Complete the source documents and eCRF for this phone call.

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

Pre-vaccination Procedures

- Review and record any newly reported safety data including solicited and unsolicited AEs, or other AEs (e.g., medically-attended AEs, SAEs).
- Record concomitant medications and vaccinations according to instructions in Section 7.6.
- Perform a symptom-directed physical examination (at the discretion of the Investigator; see Section 9.3.6).
- Measure vital signs (body temperature, pulse, blood pressure, see Section 9.3.6).
- Perform 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.

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

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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, whether they were symptomatic (COVID-19 illness) or asymptomatic at the time of the test.

- Complete the source documents and eCRF for this visit.

9.1.2.4 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.

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

- Review and record any newly reported safety data including solicited and unsolicited AEs, or other AEs (e.g., medically-attended AEs, SAEs).
- Record concomitant medications and vaccinations according to instructions in Section 7.6.
- Perform a symptom-directed physical examination (at the discretion of the Investigator; see Section 9.3.6).
- Measure vital signs (body temperature, pulse, blood pressure, see Section 9.3.6).

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- Collect blood sample (see Table 2) for binding antibody testing to N protein of SARS-CoV-2 (~6 mL blood).
- 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, whether they were symptomatic (COVID-19 illness) or asymptomatic at the time of the test.
- Complete the source documents and eCRF for this visit.

9.1.2.6 Phone Call: Day 57 (-3/+7)

The purpose of this phone contact is to inquire about the subject’s general well-being and to assess safety since site visit on Day 43.

- During the phone call:
  - Review and record any newly reported safety data including unsolicited AEs or other AEs (e.g., medically-attended AEs, SAEs).
  - Record concomitant medications and 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.

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- 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, whether they were symptomatic (COVID-19 illness) or asymptomatic at the time of the test.
- Complete the source documents and eCRF for this phone call.

9.1.2.7 Clinic Visit 4: Day 120 (-7/+7)

- Review and record any newly reported AEs since the phone call on Day 57 (e.g., medically-attended AEs, SAEs).
- Record concomitant medications and vaccinations according to instructions in Section 7.6.
- Perform a symptom-directed physical examination (at the discretion of the Investigator; see Section 9.3.6).
- Measure vital signs (body temperature, pulse, blood pressure, see Section 9.3.6).
- 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.

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- 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, whether they were symptomatic (COVID-19 illness) or asymptomatic at the time of the test.

- Complete the source documents and eCRF for this visit.

9.1.2.8 Clinic Visit 5: Day 211 (-7/+7)

The assessments and procedures are identical to those performed during Clinic Visit 4 on Day 120, except for the below.

Collect a blood sample (see Table 2) for binding antibody testing to N protein of SARS-CoV-2 (~6 mL blood).

9.1.2.9 Phone Call: Day 302 (-7/+7)

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 (e.g., 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.

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  - 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, whether they were symptomatic (COVID-19 illness) or asymptomatic at the time of the test.

- Complete the source documents and eCRF for this phone call.

9.1.2.10 End of Trial Clinic Visit: Day 393 (-0/+21 days)

The EOT 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 (e.g., SAEs).
- Record concomitant medications and vaccinations according to instructions in Section 7.6.
- 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).
- Complete the source documents and eCRF for this visit.

Inform the subjects that they have completed the trial and can now delete the eDiary app.

9.1.3 Randomized Observer-blinded Phase 3 Subjects

Approximately 32,500 subjects, 18 years of age and older, will be enrolled into Phase 3.

9.1.3.1 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 ICF.

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- 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).

- Review inclusion/exclusion criteria (see Section 6.1 and 6.2) and review prohibited medications listed as an exclusion criterion (see Section 6.2).
- Randomize the subject in IWRS after confirmation of eligibility.
- Record demographic and smoking information.
- Record medical history.
- Record concomitant medications and vaccinations according to instructions in Section 7.6, 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 the complete physical examination to establish eligibility was performed 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 pregnancy test in females of childbearing potential (Appendix 5).
- Collect a pre-vaccination blood sample (see Table 3) for binding antibody testing to N protein of SARS-CoV-2 (~6 mL blood).

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.

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 any adverse reaction which constitutes an AESI, medically-attended AE, or an SAE.
- Instructions for the subject:
  - Remind the subject to call the site immediately to report the following:

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- 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, 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).

- Complete the source documents and eCRF for this visit.

9.1.3.2 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 (at the discretion of the Investigator; see Section 9.3.6).
- Measure vital signs (body temperature, pulse, blood pressure, see Section 9.3.6).
- Perform 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.

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- Administer the trial vaccine.

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 any adverse reaction which constitutes an AESI, medically-attended AE, or an SAE.
- 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, whether they were symptomatic (COVID-19 illness) or asymptomatic at the time of the test.
- Complete the source documents and eCRF for this visit.

9.1.3.3 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 according to instructions in Section 7.6.
- Perform a symptom-directed physical examination (at the discretion of the Investigator; see Section 9.3.6).

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- Measure vital signs (body temperature, pulse, blood pressure, see Section 9.3.6).
- Collect a blood sample (see Table 3) 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, whether they were symptomatic (COVID-19 illness) or asymptomatic at the time of the test.
- Complete the source documents and eCRF for this visit.

9.1.3.4 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 (e.g., 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:

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- 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, whether they were symptomatic (COVID-19 illness) or asymptomatic at the time of the test.

- Complete the source documents and eCRF for this phone call.

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

The assessments and procedures are identical to those performed during the clinical visit on Day 43.

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

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.

The assessments and procedures are identical to those performed during the phone calls on Day 57 and Day 120, except for medically-attended AEs, which are only collected through 6 months after the second dose.

9.1.3.7 End of Trial Clinic Visit: Day 393 (-0/+21 days)

The EOT 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 (e.g., SAEs).
- Record concomitant medications and vaccinations according to instructions in Section 7.6.
- Perform a complete physical examination, including height and weight (see Section 9.3.6).

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- Measure vital signs (body temperature, pulse, blood pressure, see Section 9.3.6).
- Complete the source documents and eCRF for this visit.

Inform the subjects that they have completed the trial and can now delete the eDiary app.

9.1.4 Open-label Phase

The open-label phase will start immediately after regulatory and ethical approval was obtained for Protocol version 4.0 on country/site level. Sites will be provided with a list of treatment assignments for subjects who are still blinded at the timepoint of trial unblinding.

The eDiary app will no longer be used during the open-label phase.

9.1.4.1 Subjects who Received CVnCoV: Cohorts A and B

Subjects in the CVnCoV treatment arm who did not yet receive an AV will have to decide whether they will opt to receive an AV in addition to CVnCoV. Subjects of the CVnCoV treatment arm will be included in Cohort A if they received an AV after individual unblinding or will receive an AV after trial unblinding. Subjects will be included in Cohort B if they have not received and do not receive any AV until the EOT.

Subjects who initially intend to complete the trial without receiving an AV and later decide to receive an AV within the open-label phase will be switched to Cohort A.

All subjects who received CVnCoV and continue in the open-label phase will sign a new ICF after trial unblinding.

The open-label phase visits should be scheduled according to the originally scheduled visits/phone calls in the Phase 2b/3 schedule: Day 302 (-3/+21 days) and Day 393 (-0/+21 days). After trial unblinding, the Day 302 and Day 393 visits will be performed as phone calls, but a clinic visit may be performed if ICF signature cannot be done via e-mail, phone call, or mail.

9.1.4.1.1 Phone Call/Clinic Visit OL-1: Day 302 of the Original Phase 2b/3 Schedule (-3/+21 days)

During this visit, a new ICF will be obtained. If the Day 302 phone call was already performed as part of the randomized observer-blinded phase before approval of Protocol version 4.0, the ICF will be signed at the Day 393/EOT phone call/clinic visit.

Subjects in the CVnCoV treatment arm who already received or plan to receive an AV are eligible for Cohort A. The AV should be recorded in the eCRF.

The following assessments should be performed:

- Obtain the signed ICF: A new signed informed consent must be obtained after trial unblinding (see Section 12.4).
- For Cohort A: Confirm choice for AV.
- Review roll-over criteria for the open-label phase (see Section 6.3).
- Record concomitant medications and vaccinations (including COVID-19 AV vaccination) since last visit or phone call, according to instructions in Section 7.6.

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- Review and record any newly reported AEs since the last site visit or phone call (e.g., SAEs, AESIs, AEs leading to trial discontinuation).
- If the subject reports 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 subjects:
  - Remind the subject to call the site immediately to report the following:
    - If he/she experiences any concerning medical event.
    - 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 report any confirmed COVID-19 positive test, or in case sites continue to perform the test, remind the subject to call the Investigator in case of new symptoms according to the more restrictive definition used for the open-label phase (see Section 9.2.1.3.1).
- Complete the source documents and eCRF for this visit.

9.1.4.1.2 End of Trial Phone Call/Clinic Visit OL-2: Day 393 of the Original Phase 2b/3 Schedule (-0/+21 days)

The EOT phone call/clinic visit will be performed on Day 393, approximately 1 year after the last CVnCoV administration.

The following assessments should be performed:

- If the Day 302 phone call was already performed as part of the randomized observer-blinded phase before approval of Protocol version 4.0, the ICF will be signed at the Day 393/EOT phone call/clinic visit.
- Review and record any newly reported AEs since the last site visit or phone call (e.g., SAEs, AESIs).
- Record concomitant medications and vaccinations (including COVID-19 AV vaccination for Cohort A) according to instructions in Section 7.6.
- Complete the source documents and eCRF for this visit.

Inform the subjects that they have completed the trial.

9.1.4.2 Placebo Subjects

Subjects of the placebo treatment arm will be notified of the trial treatment they received by a Subject Information Letter and they will be withdrawn after an EOT phone call. In case the subject needs to attend the site around the time of unblinding, a visit may be performed instead of the phone call.

Before the EOT phone call, the subject's medical records and eCRF need to be reviewed to identify any potential ongoing SAE or AESI.

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At the EOT phone call, any follow-up information on SAEs and AESIs needs to be documented. Subjects further need to be asked for any new SAE or AESI since the last trial contact and if any, those need to be documented.

The subject should be informed that the e-diary app can now be deleted and that no further tracking for COVID-19 is possible within the trial after the subject was withdrawn.

The EOT phone call will be documented in the subject's medical records, and the End-of-Trial form in the eCRF will be completed.

9.2 Efficacy Assessments

9.2.1 COVID-19 Cases

9.2.1.1 COVID-19 Cases in the Randomized Observer-blinded Phase

COVID-19 case ascertainment will occur in identical manner in both the Phase 2b and Phase 3 parts of the trial. Case detection will begin with the identification of subjects reporting at least 1 symptom from a standardized list of symptoms consistent with COVID-19. Based on a phone interview with trial staff (see Appendix 6A), subjects suspected of having COVID-19 will undergo testing for SARS-CoV-2 infection, consisting of a rapid antigen test performed locally by the trial staff and a molecular-based RT-PCR test performed at a designated central laboratory. The 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.

The following definitions will apply:

- Any SARS-CoV-2 infection: a SARS-CoV-2 infection detected by either RT-PCR or seroconversion to the N protein in a seronegative subject.
- Subject without evidence of prior SARS-CoV-2 infection: subject is seronegative to the S and N proteins by immunoassay.
- Subject with evidence of prior SARS-CoV-2 infection: subject is seropositive to the S and/or N proteins by immunoassay.
- Subject with high risk of severe COVID-19: subject's with the following conditions are at increased risk of severe COVID-19:
  - Cancer
  - Chronic kidney disease
  - Chronic obstructive pulmonary disease
  - Heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies
  - Immunocompromised state (weakened immune system) from solid organ transplant

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- Obesity (body mass index [BMI] ≥ 30 kg/m^2 but < 40 kg/m^2)
- Severe obesity (BMI ≥ 40 kg/m^2)
- Pregnancy
- Sickle cell disease
- Smoking
- Type 2 diabetes mellitus

9.2.1.2 COVID-19 Cases in the Open-label Phase

COVID-19 case ascertainment stopped on 18 June 2021 (cut-off date for the final efficacy analysis) and will not occur during the open-label phase.

During the open-label phase, subjects will undergo passive surveillance for COVID-19 (see Appendix 6B). If beneficial for the subject, rapid testing and RT-PCR test may be performed based on European Centre for Disease Prevention and Control (eCDC) case definition (see Section 9.2.1.3.1) at the investigator discretion. The testing strategy is described in Section 9.5 and Appendix 7.

9.2.1.3 Case Detection

9.2.1.3.1 Routine Surveillance for COVID-19

Randomized observer-blinded phase:

During all site visits and phone calls, subjects will be reminded to contact the site 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 if the Investigator considers the symptoms could potentially indicate a COVID-19 case. 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 6A. 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

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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 2 tests: a rapid antigen test performed locally by the trial staff and a molecular-based RT-PCR test performed at a designated central laboratory. 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.

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 not be counted as a primary efficacy case, but 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 as a subject who is naïve to SARS-CoV-2 infection (unless determined otherwise by a seropositive test to the N protein).

Open-label phase:

In order to decrease the burden for the trial subjects during the open-label phase, when only subjects having received CVnCoV (followed or not by AV) are still under follow-up, a more restrictive definition will be used for case detection. Subjects will be reminded to contact the site if they have any of the of the following symptoms:

- cough
- fever (≥ 37.8 ºC)
- shortness of breath
- sudden onset of anosmia, ageusia or dysgeusia (new loss of taste or smell).

During this phase of the trial, subjects are asked to report symptomatic COVID-19 positive cases (detected independent of the study procedures) to site, or can be tested as part of the study procedures if the subject has limited access to testing.

Subjects who report symptoms consistent with the eCDC criteria either at the site visit or by phone call will be contacted by trial staff for a follow-up phone interview if the Investigator considers the symptoms could potentially indicate a COVID-19 case, using the definition applicable for the OL phase. The trial staff will use a scripted interview (in which he/she has been trained on) to collect information about the subject's medical

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condition, which will be used to determine the probability of the subject having COVID-19. The interview script is provided in Appendix 6B. If the subject is suspected of having COVID-19, he/she will undergo testing for symptomatic COVID-19 (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.

The testing strategy for symptomatic COVID-19 is presented in Section 9.5 and Appendix 7. Testing will consist of 2 tests: a rapid antigen test performed locally by the trial staff and a molecular-based RT-PCR test performed at a designated central laboratory. 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 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.

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).

If the subject is not virologically-confirmed by RT-PCR testing, he/she will return to routine surveillance for COVID-19.

9.2.1.3.2 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, and they were symptomatic (COVID-19 illness) at the time of the test.

If 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 within 2 weeks to confirm the result. A nasopharyngeal swab sample should be sent to the Sponsor-designated central laboratory 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 as a subject who is naïve to SARS-CoV-2 infection (unless determined otherwise by a seropositive test to the N protein).

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9.2.1.4 Definition of Virologically-confirmed COVID-19 Case

For the randomized observer-blinded phase, 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 or severe) will be a subset of these cases. See Appendix 3 and Appendix 4 for clinical definitions of severe and mild COVID-19, respectively.
For the open-label phase, 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.

9.2.1.5 COVID-19 Case Definition for Primary Efficacy Analysis (Randomized Observer-blinded Phase only)

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

- Must be a virologically-confirmed case of COVID-19 (of any severity) defined as a positive SARS-CoV-2 specific RT-PCR test in a person with clinically symptomatic COVID-19, as defined above in Section 9.2.1.4.
- 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 10.2.3, Efficacy Analysis Set [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).

The primary efficacy cases must 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.

9.2.1.6 SARS-CoV-2 Genome Lineage Characterization (Randomized Observer-blinded Phase only)

The characterization of SARS-CoV-2 variants in this trial will be implemented by viral whole genome sequencing of nasopharyngeal swab samples of subjects followed by

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comparison with previously sequenced and typified genomes. Analysis will follow the methodology to assign names to lineages of SARS-CoV-2 using a dynamic nomenclature [34], using the software pangolin (V2) (https://cov-lineages.org/). The assignment algorithm uses machine learning, which offers a classification tree that has been trained using over approximately 60,000 SARS-CoV-2 sequences retrieved from GISAID, machine learning reconstruction and manual curation for all the lineages. Each base per genome was one-hot encoded, which makes every position informative for further prediction. Those models are available under cov-lineages/pangoLEARN at github (https://github.com/cov-lineages/pangoLEARN/tree/master/pangoLEARN).

The characterization will be done centrally. The following phylogenetic clustering will be applied:

1. “Wild type” virus: WT/D614G, lineages A.1/B.1 without the VOCs (i.e., without B.1.1.7 [Alpha], B.1.351 [Beta], B.1.429 [Epsilon])
2. “UK” VOC: B.1.1.7 (Alpha)
3. All other variants of concern.

In this trial, the primary efficacy endpoint will be based on all strains, the “wild type” virus and all SARS-CoV-2 variants (as defined under numbers 1, 2, and 3 above); the key secondary efficacy endpoint will be based on the “wild type” virus and the UK variant B.1.1.7 (Alpha) (as defined under numbers 1 and 2 above); and the exploratory efficacy endpoint will be based on disease caused by individual variants of concern (as defined under numbers 2 and 3 above).

9.2.1.7 Adjudication of COVID-19 Cases (Randomized Observer-blinded Phase only)

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

- Is the case a virologically-confirmed case of COVID-19 defined as a positive SARS-CoV-2 specific RT-PCR test in a person with clinically symptomatic COVID-19 with 1 or more of the symptoms listed above in Section 9.2.1.4.
    - Was the RT-PCR test performed at the CureVac designated central laboratory?
- Was the symptom onset of the case ≥ 15 days following the second vaccination? Or did it occur before 15 days following the second trial vaccination?
- Was the subject naïve or non-naïve to SARS-CoV-2 at baseline and Day 43? (defined as being seronegative or seropositive to the SARS-CoV-2 N protein).
- Was the subject 18 to 60 years of age or ≥ 61 years of age?
- Was the subject asymptomatic? If asymptomatic, was the RT-PCR test positive ≥ 15 days following the second vaccination or before?
- Was it a mild or severe case of COVID-19 based on the provided clinical definitions?

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- 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 (Randomized Observer-blinded Phase only)

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, 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. The subject should be retested as soon as feasible to confirm the result. A nasopharyngeal swab sample should be sent to the Sponsor-designated central laboratory 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 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

9.3.1 Safety Assessments for Subjects in the Randomized Observer-blinded Phase

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

9.3.1.1 Safety Assessments Specific for Subjects in Phase 2b

- 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.

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9.3.1.2 Safety Assessments for All Subjects in Phase 2b and Phase 3

- Medically-attended AEs will be collected through 6 months after the second trial vaccination.
- AESIs will be collected throughout the trial. 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.
- SAEs will be collected throughout the trial.
- AEs leading to vaccine withdrawal or trial discontinuation will be collected throughout the trial.

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

9.3.2 Safety Assessments for Subjects in the Open-label Phase

- AESIs will be collected until EOT (Day 393 of the original Phase 2b/3 schedule). AESIs to be monitored include pIMDs and AESIs for SARS-CoV-2 vaccines.
- SAEs will be collected until EOT (Day 393 of the original Phase 2b/3 schedule).
- AEs leading to trial discontinuation will be collected until EOT (Day 393 of the original Phase 2b/3 schedule).

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.

In Phase 2b, any AEs occurring during the 30-minute observation period after vaccination will be recorded in the eCRF. In Phase 3, only those AEs occurring during the 30-minute observation period after vaccination which constitute an AESI, medically-attended AE, or an SAE will be recorded in the eCRF.

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. Only for any complications and sequelae of COVID-19 illness not mentioned on the COVID-19 summary form in the eCRF, an AE form needs to be completed. For consistency, the reporting procedure for COVID-19 cases in the open-label phase will remain as in the randomized observer-blinded phase despite the efficacy analysis is already completed. COVID-19 illness and its complications/sequelae as well as all symptoms listed in Section 9.2.1.4 will not be reported according to the standard expedited process for SAEs, even though the event may meet the criteria for an SAE. However please note that all fatal cases resulting from COVID-19 and its complications/sequelae and from all other events will be reported as SAEs and need to be reported to the CRO within 24 hours (see section Reporting of SAEs in Appendix 10).

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The reporting period for each type of AE and corresponding concomitant medication use is shown in Table 6.

Table 6 Reporting Period by Type of Adverse Event

AE Type	Days 1 to 8	Days 29 to 36	Days 1 to 57	Day 1 to Month 6 [a]	Day 1 to EOT
Solicited AEs (Phase 2b)	X	X			
Unsolicited AEs (Phase 2b)			X		
Medically-attended AEs				X	
SAE/AESI/COVID-19 fatal cases					X
Any vaccination other than CVnCoV					X
Any immune-suppressive/ modulating medication or other prohibited medication					X
Non-serious intercurrent medical conditions that may affect the immune response to vaccination					X

AE; adverse event; AESI: AE of special interest; AV: Authorized/licensed vaccines for preventing COVID-19; EOT: End of Trial; SAE: serious AE.

9.3.3.1 Solicited Adverse Events

An eDiary will be distributed to all subjects in Phase 2b 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 of absent, mild, moderate and severe (Table 7 and Table 8). 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.

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Table 7 Intensity Grading* for Solicited Local Adverse Events

Adverse Event	Grade/Intensity	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 [35].

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Table 8 Intensity Grading* for Solicited Systemic Adverse Events

Adverse Event	Grade/Intensity	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 [35]; 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 Phase 2b subjects for each of the 2 trial vaccinations.

For all subjects in Phase 2b and Phase 3, medically-attended AEs will be collected through 6 months after the second trial vaccination or until the EOT if that occurs earlier than

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6 months after the second trial vaccination. SAEs and AESIs will be collected throughout the trial (see Table 6).

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. Clinic visits for COVID-19 testing resulting in negative test results are not considered as medically-attended visits, if there is no confirmed diagnosis and no prescribed concomitant medication.

The occurrence of AEs (serious and non-serious) will be assessed by non-directive questioning of the subject at each visit during the reporting periods specified in Table 6. 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 as well as the intensity (see Appendix 10).

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 throughout the trial.

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

- AEs with a suspected immune-medicated etiology (pIMDs, see Appendix 8).
- Other AEs relevant to SARS-CoV-2 vaccine development or the target disease (see Appendix 9).

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 (or blood, where required according to local laws and regulations) for pregnancy testing will be taken from women of childbearing potential on Day 1 prior to trial vaccination to establish eligibility. A urine (or blood, where required according to local laws and regulations) 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 for Phase 2b (see Table 1 and Table 2) and Phase 3 (see Table 3), **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.

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At the first trial visit on Day 1 and EOT visit on Day 393 (see Table 1, Table 2, and Table 3), 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, abdomen, extremities and neurological examination, skin examination, and 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, HERALD: CV-NCOV-004; 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).

To ensure subject safety on an ongoing basis, a CureVac Safety Review Team reviews the safety data on a periodic basis. The outcome of these reviews and discussions are then shared with the DSMB Chair.

In addition to safety data, the DSMB will be asked to review efficacy data at the interim analyses 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 will also be asked to perform an unblinded review(s) of the incidence rate of COVID-19 cases to recommend an adjustment(s) in sample size, if needed.

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 to adjudicate COVID-19 cases for assessment of the primary endpoint. The Committee will be blinded to the treatment assignment of the subject. The cases will be adjudicated by the members with respect to the questions presented in Section 9.2.1.7. 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.

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9.4 Immunogenicity Assessments (Randomized Observer-blinded Phase only)

For Phase 2b subjects in the Immunogenicity Subset, the timing of blood sample collection for immunogenicity assessments post-vaccination is provided in Table 1.

For all subjects, 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, Table 2, and Table 3.

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.

No samples will be obtained at Day 393 after trial unblinding. The Day 57 immunogenicity samples in the Phase 2b Immunogenicity Subset will not be analyzed, as Day 57 data would not add any relevant scientific value to the already available data.

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 in the Phase 2b part of the trial and only for subjects in the Immunogenicity Subset at the time points specified in Table 1.

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 in all parts of the trial and 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, Table 2, and Table 3, 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.
    a. 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 baseline and Day 43.
    b. For evaluation of the efficacy after the first dose of CVnCoV in naïve subjects, subjects would have to be seronegative to the N protein at baseline only.

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2. To determine if vaccination with a 2-dose schedule of CVnCoV can reduce infection with SARS-CoV-2 by measuring seroconversion to the N protein in seronegative subjects during the trial period. As described above in 1a, these subjects would have to be seronegative to the N protein at baseline and Day 43.

9.4.3 Antibody Responses to CVnCoV Vaccination in Subjects Who Develop a Case of COVID-19

For all cases of COVID-19 as per primary adjudication definition that occur in the randomized observer-blinded phase, the antibody response to trial vaccination will be determined in the subject's blood samples collected on Day 1 (pre-vaccination baseline), Day 43, and Day 211 of the trial if available. These assays will only need to be performed for subjects in the Phase 2b part who are not in the Immunogenicity Subset and for Phase 3 subjects. Subjects in the Phase 2b Immunogenicity Subset will already have these performed as part of the cohort. These results will be used to explore correlates of protective immunity induced by CVnCoV vaccination.

9.4.4 Cell-mediated Immunity

CMI will be evaluated in approximately 200 subjects: 100 who receive CVnCoV and 100 who receive placebo (first testing of samples will be performed for a subset of these subjects and might be extended to 200 subjects if T-cell response is detectable).

The frequency and functionality of SARS-CoV-2 RBD of S-specific T-cell response after antigen stimulation will be determined in PBMC in comparison to baseline. For example, ICS to investigate Th1 response and production of Th2 markers will be used to investigate whether vaccination induces a Th1 shift from the baseline. Further high profiling T-cell immune responses may be investigated with other technologies such as ELISpot or CyTOF, analysis of genomic biomarkers or any other established assays. CMI assessment will be performed on Day 1 (baseline), Day 29, Day 43, Day 120 and Day 211. Note that testing on Day 120 and Day 211 will only be performed on subjects who are determined as T-cell responders on Day 29 and/or Day 43.

9.5 Testing for SARS-CoV-2 Infection

9.5.1 Virological Confirmation of COVID-19

See Flow Diagrams in Appendix 6 (A and B) and Appendix 7.

9.5.1.1 Randomized Observer-blinded Phase

During the randomized observer-blinded phase of the trial, subjects clinically suspected of having COVID-19 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. The test results will be documented on the appropriate eCRF page.

- Subjects with a clinical suspicion of COVID-19 will undergo testing for SARS-CoV-2 infection using a rapid antigen test performed at the site with the results provided to the subject. Nasopharyngeal swabs will be used to collect samples for the rapid antigen test.

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- Regardless of the result of the rapid antigen test, a nasopharyngeal swab sample collected at the same time will be sent to a central laboratory to perform a SARS-CoV-2 specific RT-PCR test. 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 at the central laboratory.
    - 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 and sent to the central laboratory for RT-PCR testing. The RT-PCR retest result will be considered definitive for SARS-CoV-2 infection.

  Subjects who are negative for all testing will be considered naïve to SARS-CoV-2 infection. In the unlikely case that a subject tests positive by the rapid antigen test but negative by RT-PCR, the subject will still be considered naïve without a positive virological confirmation by RT-PCR (unless determined otherwise by a seropositive test to the N protein).

9.5.1.2 Open-label Phase

In the open-label phase, subjects should report diagnosis of symptomatic COVID-19 positive cases to the site. For countries/sites with limited access to COVID-19 testing, subjects with clinical symptoms still can call the sites and be invited for testing on site at the investigator discretion in the best interest of the subject. A nasopharyngeal swab sample will be collected and sent to a central laboratory to perform a SARS-CoV-2 specific RT PCR test only if the result of the rapid antigen test is positive.

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

See Section 9.2.1.3.2 and Section 9.2.2 for follow-up of symptomatic subjects who report a positive test for SARS-CoV-2 infection performed outside of the site.

For symptomatic subjects according to the eCDC criteria 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 within 2 weeks to confirm the result. A nasopharyngeal swab sample should be sent to the central laboratory for RT-PCR testing for confirmation. The retest result at the central laboratory will be considered definitive.

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10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

10.1.1 Primary Efficacy Objective

This is an event-driven trial. Sample size and power considerations are based on the primary objective for demonstrating efficacy of CVnCoV in the prevention of virologically-confirmed cases of COVID-19 of any severity meeting the primary case definition. A group sequential design with 2 interim analyses for cases of COVID-19 of any severity demonstrating a high level of efficacy or reaching futility is planned using O'Brien and Fleming type error-spending-function [36] and the sample size is based on the test for one single proportion (i.e. the proportion of cases in the CVnCoV group, among all cases). The group sequential design is based on the any severity COVID-19 endpoint, due to the higher case number required to meet this endpoint.

With an overall 2-sided alpha of 5%, a total of 160 COVID-19 cases of any severity (meeting the primary efficacy case definition for COVID-19 of any severity) are needed at final analysis, to have a power of 90% to demonstrate the VE is above 30% based on the lower bound of the CI for VE, when considering the VE under the alternative hypothesis is 60% (i.e. equivalently to demonstrate the proportion of cases in the CVnCoV group is below 0.4118, based on the upper bound of the CI for proportion when considering the proportion under the alternative hypothesis is equal to 0.2857).

The 2 interim analyses for high efficacy or futility of the primary objective of COVID-19 cases of any severity will be performed once 56/111 cases have been accrued and adjudicated (approximately 30/60% of cases).

Assuming an incidence rate of COVID-19 of 0.15% per month in placebo subjects, an overall non-evaluable rate of 20% (corresponding to subjects excluded from the EAS and drop-outs) and a VE of 60%, 36,500 subjects enrolled over approximately 3 months (18,250 per vaccine group) will accrue 160 COVID-19 cases of any severity at approximately 9 months after the first vaccination. A lower incidence rate, a longer enrollment duration, or a higher non-evaluable rate or VE will delay the acquisition of the 160 cases and the time of final analysis. Subjects will be randomized to receive either CVnCoV or placebo in a 1:1 ratio, stratified by country and age group (18 to 60 and ≥ 61 years of age).

10.1.2 Key Secondary Efficacy Objectives

For the key secondary efficacy objective evaluating the prevention of virologically-confirmed moderate to severe cases of COVID-19, a lower number of cases will be collected at the time of final analysis compared to the primary endpoint. If 1/3 of COVID-19 cases of any severity are moderate to severe, then 53 moderate to severe cases can be expected when the total number of COVID-19 cases is 160. The trial will then have 91.5% power to obtain a lower limit of the 95% CI of the VE above 20% when assuming the true VE is 70%.

For the key secondary efficacy objective evaluating the prevention of virologically-confirmed severe cases of COVID-19, a lower number of cases will be collected at the time of final analysis compared to the primary endpoint. Based on an

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analysis of a large database by Verity et al. [37], approximately 20% of COVID-19 cases can be clinically defined as severe or critical, the latter requiring intensive care.

For the key secondary efficacy objective evaluating the prevention of virologically-confirmed moderate to severe cases of COVID-19, a lower number of cases will be collected at the time of final analysis compared to the primary endpoint. If 50% of COVID-19 cases of any type are “wild type” (i.e., WT/D614G lineages A.1/B.1 without VOC B.1.1.7 [Alpha], B.1.351 [Beta], B.1.429 [Epsilon]) and “UK” (B.1.1.7 [Alpha]), then 80 such cases can be expected when the total number of COVID-19 cases is 160. The trial will then have 90.7% power to obtain a lower limit of the 95% CI of the VE above 30% when assuming the true VE is 70%.

With 32 cases of severe COVID-19 (20% of 160 cases), the trial will have 81.5% power to obtain a lower limit of the 95% CI of the VE above 10% when assuming the true VE is 70%. The power increases to 91% if the true VE against severe cases is 75%. With complete follow-up of all evaluable subjects for 1 year in this trial, it is expected that the additional number of COVID-19 cases accrued post-second vaccination would permit a more robust evaluation of CVnCoV efficacy against severe disease. This analysis will be presented in the SAP.

10.2 Populations for Analyses

In the Safety Analysis Set (SAS), Safety Analysis Set 2 (SAS 2), and the Solicited AEs Safety Analysis Set (SASsol), subjects will be analyzed in the group they actually received (as “treated”).

Following the “intent to treat” principle in the Efficacy sets and Per-Protocol Sets, subjects will be analyzed in the group to which they were randomized (as “randomized”).

Additional populations that might be required for the analyses of the results from the open-label phase are of exploratory nature and will be defined in an extended SAP.

An authorized/licensed SARS-CoV-2 vaccine has become available during the trial and subjects can request to be unblinded. The censoring rules to avoid any bias for such subjects will be described in the SAP (randomized observer-blinded phase only).

10.2.1 Safety Analysis Set (SAS)

The SAS will include all subjects randomized in Phase 2b or 3 who received at least 1 dose of CVnCoV or placebo.

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

10.2.2 Safety Analysis Sets 2 (SAS 2, SASsol)

As solicited and unsolicited AEs are collected only for Phase 2b subjects, these analyses will then be restricted to the Phase 2b subjects.

The SAS 2 population will include all Phase 2b subjects of the SAS and will be used for unsolicited AEs analysis.

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The SASsol population will include all Phase 2b subjects of the SAS with at least 1 diary collection indicating the occurrence or lack of occurrence of solicited AEs and will be used for solicited AEs analysis.

10.2.3 Efficacy Analysis Set (EAS)

The EAS will include all subjects randomized in Phase 2b or Phase 3 who:

- Received both doses of trial vaccine according to their randomization (2 doses of CVnCoV or 2 doses of placebo).
- Had not developed a virologically-confirmed case of COVID-19 before trial entry (based on Exclusion Criterion 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 baseline and Day 43 (based on seronegativity to N protein in the blood sample taken at baseline).

The EAS will be the primary analysis population for all efficacy endpoints (except for the key secondary efficacy endpoint related to seroconversion and for the efficacy endpoints evaluating efficacy starting after the first dose).

10.2.4 Per Protocol Efficacy Set (PPE)

The PPE set will include EAS subjects who meet all eligibility criteria at trial entry and who have no major protocol deviations that would impact the efficacy outcomes as specified in the SAP.

The PPE will be a supportive population for efficacy endpoints (except for the efficacy secondary endpoint evaluating efficacy starting after the first dose).

10.2.5 Per Protocol Immunogenicity Set (PPI)

The PPI set will include all Phase 2b subjects who belong to the Immunogenicity Subset (IS) (i.e. ~first 600 subjects enrolled into each of the 2 age groups in Phase 2b [18-60 and ≥ 61 years of age]) 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 one 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.

Subjects to be excluded from the PPE/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.

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Table 9 provides a summary of primary and supportive populations planned for analysis of each endpoint. Other analysis populations may be defined in the SAP.

Table 9 Primary and Supportive Populations for the Analysis of Each Endpoint

Endpoints	Primary Population	Supportive Population
Primary Efficacy Endpoint	**EAS**	**PPE**
Primary Safety Endpoints		
• SAEs, AESI, medically-attended AEs	**SAS**	-
• Solicited AEs	**SASsol**	-
• Unsolicited AEs	**SAS 2**	-
• AE leading to vaccine withdrawal	**SAS**	-
Secondary Efficacy Endpoints:		
• Moderate to Severe COVID-19	**EAS**	**PPE**
• Severe COVID-19	**EAS**	**PPE**
• eWild type" (i.e., WT/D614G lineages A.1/B.1 without VOC B.1.1.7 [Alpha], B.1.351 [Beta], B.1.429 [Epsilon]) and "UK" (B.1.1.7 [Alpha]) SARS-CoV-2 strains	**EAS**	**PPE**
• COVID-19 in ≥ 61 years of age	**EAS (≥ 61 years of age subjects)**	**PPE (≥ 61 years of age subjects)**
• All SARS-CoV-2 infection (RT-PCR positive)	**EAS**	**PPE**
• COVID-19 after first dose	**SAS (naïve subjects)**	-
Secondary Immunogenicity Endpoints:		
• SARS-CoV-2 RBD of spike (S) protein antibody responses	**PPI**	-
• SARS-CoV-2 viral neutralizing antibody	**PPI**	-
Exploratory Efficacy Endpoints:		
• Severity of COVID-19	**EAS**	-
• Any strain COVID-19	**EAS**	
• Supplemental oxygenation, hospitalization, mechanical ventilation, death	**EAS**	**SAS**
• COVID-19 after first dose	**SAS**	-

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Endpoints	Primary Population	Supportive Population
• Second episode of COVID-19	**EAS**	-
Exploratory Immunogenicity Endpoints:		
• RBD of S-specific T-cell response after antigen stimulation by intracellular cytokine staining (ICS) to investigate Th1 response and expression of Th2	**PPI**	-
• The proportion of subjects with a detectable increase in SARS-CoV-2 RBD of S-specific T-cell response	**PPI**	-

Additional populations that might be required for the analyses of the results from the open-label phase are of exploratory nature and will be defined in the SAP.

10.3 Statistical Analyses

10.3.1 General Considerations

Four analyses are planned: 2 interim analyses (when 56/111 cases are reached); the final analysis (when 160 cases are reached); and at the EOT. An SAP for the interim and final 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.

For the open-label phase, analyses will be described by cohort. Details will be provided in an extended SAP.

10.3.2 Demographic, Medical History, and Other Baseline Characteristics

Data will be summarized with respect to demographic and baseline characteristics (e.g., age, gender, height, weight), medical history, baseline immune status, and all safety measurements using descriptive statistics (quantitative data) and contingency tables (qualitative data) overall, by vaccine group, and by age group and vaccine group.

10.3.3 Trial Vaccine Administration

The administrations of CVnCoV or control will be listed and the number of subjects actually receiving the vaccination doses will be summarized by vaccine group.

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 vaccine group.

10.3.5 Efficacy Analyses

10.3.5.1 Primary Efficacy Endpoint Analysis

Primary Efficacy Analysis

In primary efficacy analysis, the VE, defined as the percent reduction in the frequency of any COVID-19 cases (according to primary case definitions) in vaccinated subjects

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compared with subjects who received placebo will be calculated with exact 95%* CI as follows:

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

where

ARV = attack rate in vaccinated group = nv/Nv = number of subjects reporting at least 1 COVID-19 episode in the CVnCoV group / total follow-up time of evaluable subjects in the CVnCoV group (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 primary case definition) coming from the CVnCoV group among all cases = nv/(nv+np).

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

*Level of CI may be slightly adjusted due to the sequential design (see Section 10.3.8).

The statistical hypotheses for the primary efficacy endpoint is:

H_{0A}: VE ≤ 30% versus H_{1A}: VE > 30%

A is related to COVID-19 cases of any severity

The trial will be successful if either the lower limit of the exact 2-sided 95% (to be slightly adjusted to consider the sequential design) CI of VE endpoint is > 30% for all COVID-19 cases of any severity or if the lower limit of the exact 2-sided 95% CI of VE endpoint is > 20% for severe to moderate COVID-19 cases.

If the 2 interim analyses and the final analysis for COVID-19 cases of any severity are performed after 56/111 and 160 cases have been reported, respectively, the 1-sided α-risk to consider at the time of final analysis according to O'Brien-Fleming type error spending function will be 0.02281 and efficacy will be demonstrated at the final analysis if 53 cases or less over 160 are in the CVnCoV group (observed VE ≥ 50.5%). To note, the rule in terms of split of cases to demonstrate efficacy can slightly differ if r ≠ 1 (total follow-up time different in both groups).

Sensitivity Analysis

As a key sensitivity analysis, the time to first-occurrence of virologically-confirmed COVID-19 cases (according to primary case definitions) will 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 following the second vaccination.

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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.

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

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

10.3.5.2 Secondary Efficacy Endpoints Analyses

Statistical testing of the 3 key secondary efficacy endpoints will be performed according to the conditional hierarchical testing procedure using the order defined in the objective/endpoints sections. Consequently:

- Efficacy of CVnCoV in regard to moderate and severe cases will be demonstrated only if there is successful demonstration of the primary efficacy objective.
- Efficacy of CVnCoV in regard to severe cases will be demonstrated only if there is successful demonstration of the primary efficacy objective and the key secondary objective on moderate and severe cases.
- Efficacy of CVnCoV in regard to (RT-PCR positive) cases of “wild type” (i.e., WT/D614G lineages A.1/B.1 without VOC B.1.1.7 [Alpha], B.1.351 [Beta], B.1.429 [Epsilon]) and “UK” (B.1.1.7 [Alpha]) will be demonstrated only if there is successful demonstration of the primary efficacy objective and the key secondary objective on moderate and severe cases and severe cases.

Otherwise, these endpoints will be analyzed as exploratory endpoints without success criteria testing.

To assess the efficacy in the prevention of “wild type” (i.e., WT/D614G lineages A.1/B.1 without VOC B.1.1.7 [Alpha], B.1.351 [Beta], B.1.429 [Epsilon]) and “UK” (B.1.1.7 [Alpha]) cases, moderate to severe, severe disease and asymptomatic infections, similar analyses to those performed on the primary efficacy endpoint will be performed. The efficacy will be demonstrated if the lower limit of the exact 2-sided 95% CI of VE is above 30% for “wild type” (i.e., WT/D614G lineages A.1/B.1 without VOC B.1.1.7 [Alpha], B.1.351 [Beta], B.1.429 [Epsilon]) and “UK” (B.1.1.7 [Alpha]) cases, 20% for moderate to severe disease, 10% for severe disease and above 0% for asymptomatic infections.

Other secondary efficacy endpoints will be analyzed similarly to the primary efficacy endpoint but no formal testing will be performed for those endpoints. For efficacy after the first dose, the time to first-occurrence of virologically-confirmed COVID-19 (date of symptom onset) will start after the first vaccination. The BoD will be analyzed using 2 different scoring systems. Both BoD scoring systems place more weight on efficacy against severe COVID-19 or severe disease as reflected by hospitalization or death. In addition, VE and associated CI will be calculated for each of the BoD categories.

10.3.5.3 Exploratory Efficacy Endpoints Analyses

The proportions of COVID-19 cases of any severity caused by identified SARS-CoV-2 VOCs and mild, moderate, and severe COVID-19 cases (according to primary case definition) among all cases will be summarized by group.

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Description of frequencies and percentages will be provided by group for subjects who:

- Need supplemental oxygenation due to COVID-19.
- Need mechanical ventilation due to COVID-19.
- Are hospitalized due to COVID-19.
- Died due to COVID-19.
- Died due to any cause.

This will be done for events occurring ≥ 15 days following the second trial vaccination (full VE) and then for events occurring at any time after the first trial vaccination.

The VE in the prevention of first episodes of virologically-confirmed cases of COVID-19 of any severity will be reassessed on all subjects whatever their serological status at baseline for cases occurring ≥ 15 days following the second trial vaccination and then for all cases occurring after the first dose.

Finally, the number and percentage of subjects who developed a second episode of COVID-19 will be displayed by group.

10.3.6 Secondary and Exploratory Immunogenicity Analysis

No formal hypothesis on immunogenicity will be tested. Descriptive statistics for the immunogenicity endpoints will be provided for each vaccine group and overall, and by vaccine group and age groups. Data will be presented after each vaccine dose.

The following analyses will be performed for antibody levels to the SARS-CoV-2 RBD of S protein and for neutralizing antibodies overall and separately in subjects seronegative at baseline and in subjects seropositive at baseline:

- Geometric mean titers (GMTs) will be summarized with their 95% CI at each blood sampling time point.
- The Fold Change (FC) from baseline will be computed for each subject and Geometric mean of FC (GMFC) will be displayed with their 95% CI at each blood sampling time point after baseline.

Non-detectable antibodies will be arbitrary replaced by half of the detection cut-off for GMT and GMFC computations purpose.

For each readout, 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 with exact 95% CI. Seroconversion is defined as detectable antibodies in the serum.

Percentages of subjects seroconverting for SARS-CoV-2 RBD of S protein antibodies and SARS-CoV-2 neutralizing antibodies will be summarized. The frequency of immune cell populations induced by the vaccine will be summarized. Further characterization of the T-cell immune response may be done with other technologies like ELISpot, CyTOF and/or analysis of genomic biomarkers.

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

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10.3.7 Safety Analysis

No formal statistical testing of safety data is planned.

The descriptive safety analyses will be performed overall by vaccine group, by age group and vaccine group, and by serostatus and vaccine group.

For the open-label phase, applicable descriptive analyses will also be performed by cohort.

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 System Organ Class (SOC) and Preferred Term (PT).

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

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

When an AE occurs more than once for a subject within the 28 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 be recorded as medical history.

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.

10.3.8 Interim Analysis

Two interim analyses will be performed for this trial by an unblinded independent statistician and reviewed by the DSMB when 56/111 cases of COVID-19 of any severity (meeting the primary efficacy case definition) are observed. This analysis will aim to assess early high efficacy or futility on the primary efficacy endpoint and will be done on the EAS population only. The safety data that is available at this time point will also be described.

For the analysis of early demonstration of high efficacy or futility, cumulative O'Brien-Fleming type error spending function [36] is used to provide statistical stopping

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rules for high efficacy (α-boundaries) and futility (β-boundaries) for the interim analysis, based on the information accumulated until that specific interim stage.

At the interim stage, if the p-value for the test of the primary objective is lower than the α-boundary, a high level of efficacy for CVnCoV will be declared. Conversely, demonstration of futility will occur if the p-value is higher than the β-boundary.

The interim analyses are planned to occur when 56/111 cases of COVID-19 of any severity have been observed. Table 10 below shows the boundaries for demonstrating high efficacy or futility, calculated on a 1-sided p-value scale using the cumulative error spending function. At the time of the interim analysis only descriptive statistics such as the point estimate of VE and respective 95% CI for key secondary objectives will be displayed, no formal testing will be done to protect the overall type one error at the final analyses of 160 cases.

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Table 10 Two Stage Group Sequential Design with Interim Analyses at 56 and 111 Cases and Final Analysis at 160 Cases

	Interim Analysis 1	Interim Analysis 2	Final Analysis
Number of Cases	56	111	160
Efficacy α-Boundary on p-value scale (1-sided)	0.00015	0.00707	0.02281
Futility β-Boundary on p-value scale (1-sided)	0.66345	0.12356	NA
Efficacy success criteria*	Success if ≤ 9 cases in CVnCoV group over 56 cases (observed VE ≥ 80.9%)	Success if ≤ 32 cases in CVnCoV group over 111 cases (observed VE ≥ 59.5%)	Success if ≤ 53 cases in CVnCoV group over 160 cases (observed VE ≥ 50.5%)
Futility*	Futility if ≥ 25 cases in CVnCoV group over 56 cases (observed VE ≤ 19.4%)	Futility if ≥ 40 cases in CVnCoV group over 111 cases (observed VE ≤ 43.7%)	NA

*Rules in terms of split of cases to demonstrate efficacy/futility can slightly differ if the total number of evaluable subjects is unequal in both groups ($r \neq 1$).

If the interim analysis is performed exactly after 56/111 cases have been reported, a 1-sided p-value lower than 0.00015/0.00707 (i.e. lower limit of the 2-sided 99.99/99.3% CI > 30%) will lead to the conclusion of high efficacy, while a 1-sided p-value higher than 0.66345/0.12356 will result in the demonstration of futility. Otherwise, the final analysis will be performed at 160 cases. Similarly, if the number of evaluable subjects is equal in both groups, it means that the trial will conclude early high efficacy if 9/32 cases or less over 56/111 are coming from the CVnCoV group, while futility of the trial will be demonstrated if 25/40 cases or more are coming from the CVnCoV group.

Of note, the actual boundaries used for decision making would depend on the exact number of cases occurring and reported at each analysis (interim and final).

The boundaries will be applied in a nonbinding way as there are many other factors that would be part of the decision-making process.

10.3.9 Missing Data and Discontinuation

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 S protein antibodies, concentration values marked as below the lower limit of quantification (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.

Reasons for discontinuation from the trial vaccine and trial will be listed and summarized.

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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 (according to instructions in Section 7.6), medical history and physical assessments) will be entered into eCRFs in a timely fashion by the Investigator and/or the Investigator's dedicated site staff, except for the laboratory data, which are transmitted to the Sponsor or designee directly. All data entered into the eCRF must be verifiable against source documents at the trial site, except eDiary entries of solicited AEs, which are automatically integrated into the eCRF. 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 trial 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 trial 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. 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 if allowed by country regulations and within the limits established (refer to the Monitoring Plan for details).

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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 important or non-important. 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 trial site must provide a standard operating procedure (SOP) 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 trial site, except for solicited AEs recorded in the eDiary (see Section 11.3). The subject's eDiary entries of solicited AEs after vaccination will be considered source data and will be integrated automatically in the eCRF. 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.

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12 ETHICS

12.1 Institutional Review Board/Independent Ethics Committee

Before initiation of the trial at the trial 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 trial 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.

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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 discontinue 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.

An additional signed ICF will be obtained after unblinding from subjects who continue in the open-label phase.

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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 trial 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 the 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).

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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.

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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.

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15 APPENDICES

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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 ICF 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 ICF 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 (Coordinating Investigator only).

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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 trial 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.

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Appendix 3 Definition of Severe COVID-19

Severe COVID-19 cases are defined by any one 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].

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Appendix 4 Definition of Moderate and Mild COVID-19

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

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

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

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Appendix 5 Safety and SARS-CoV-2 Tests

The tests detailed in the tables below will either be performed locally at the site or at a Sponsor-designated central 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 Performed at the Study Site

Laboratory Assessment	Parameters
Pregnancy Test (urine or blood)	Human chorionic gonadotropin

SARS-CoV-2 Rapid Antigen Test Performed at the Study Site

Assessment	Parameters
Abbott Panbio™ COVID-19 Ag Rapid Test	SARS-CoV-2 antigen in nasopharyngeal swab sample

SARS-CoV-2 Molecular-Based Test Performed at the Central Laboratory

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

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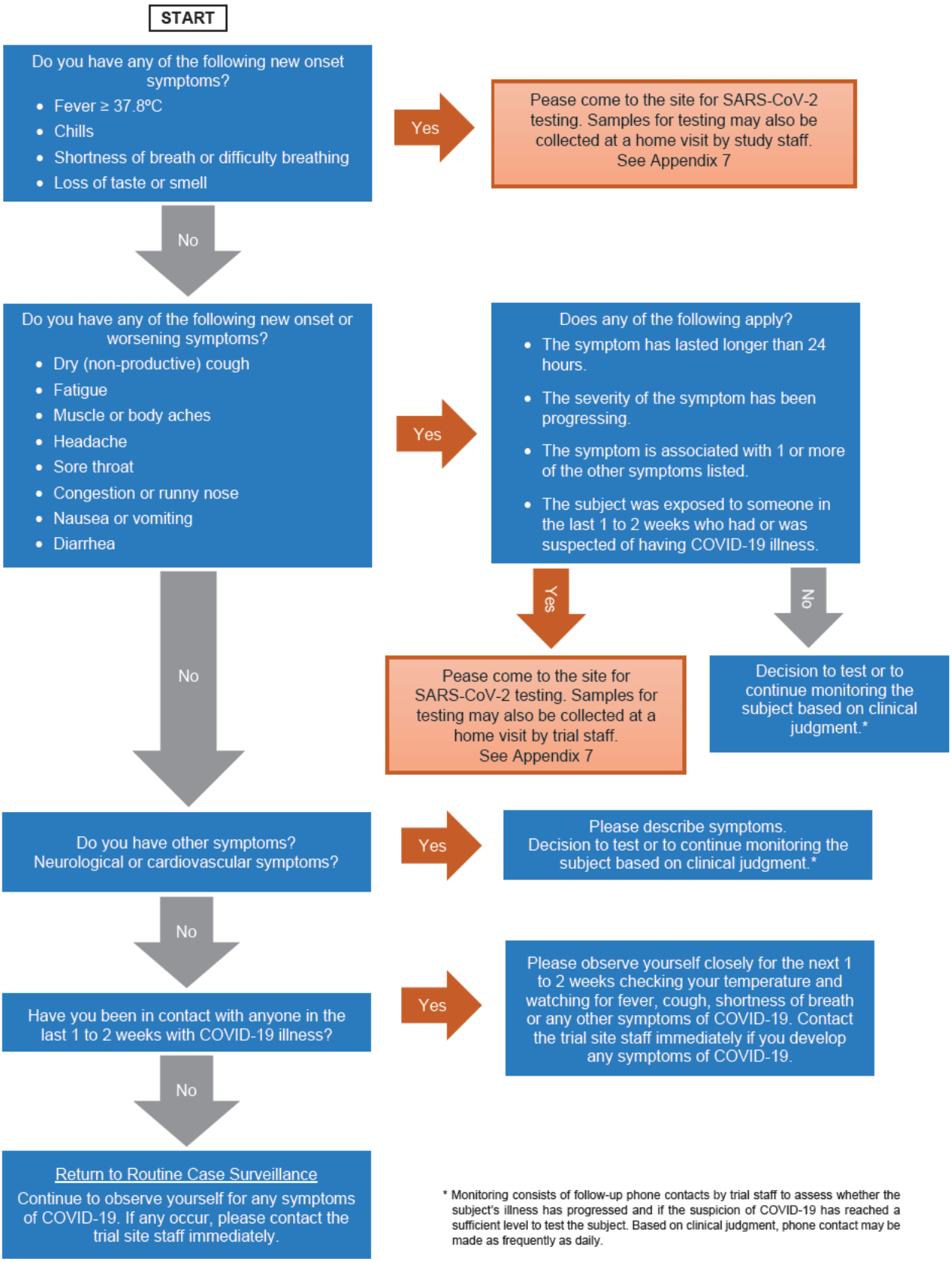
Appendix 6 Flow Diagram for COVID-19 Case Interview

6A: Randomized Observer-blinded Phase



* 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.

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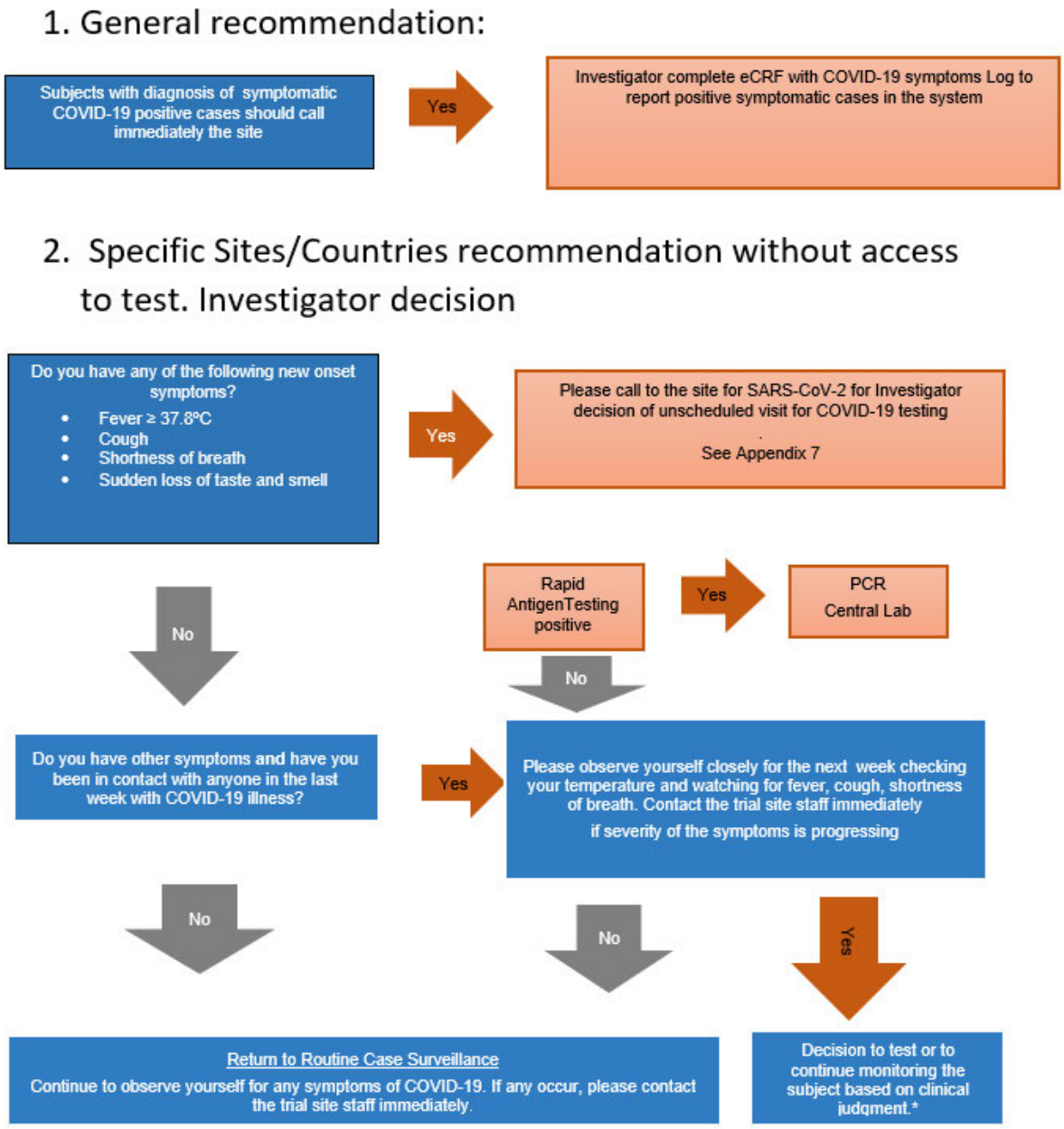
6B: Open-label Phase



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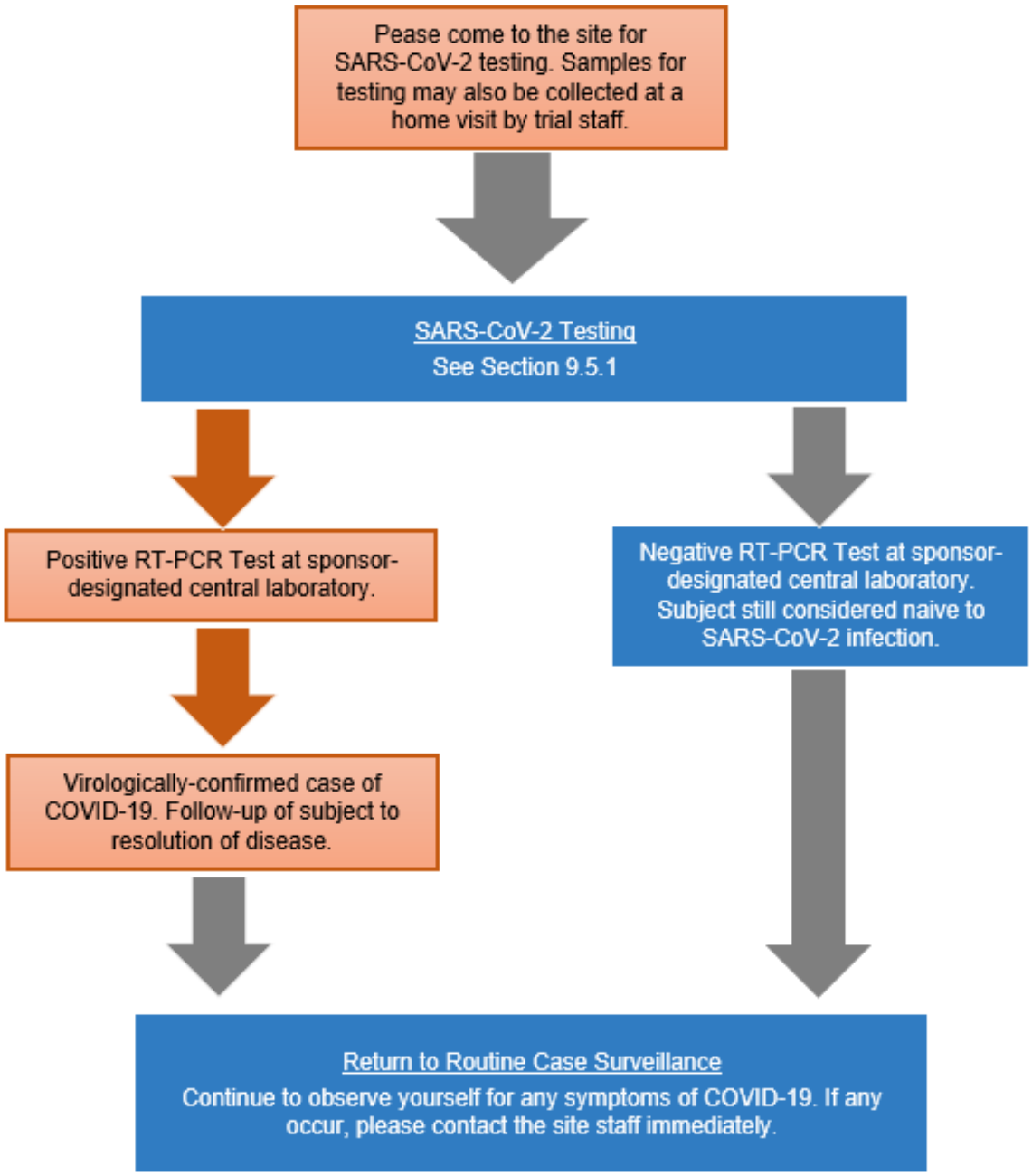
Appendix 7 SARS-CoV-2 Testing Outcome



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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 Thyroiditis (including autoimmune [Hashimoto's disease] and subacute 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

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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

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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 (MIS) and adults

Respiratory disorders:
- o Acute Respiratory Distress Syndrome

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
- o Acute pancreatitis

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

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

It is important to note that COVID-19 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 that occur in the trial, which are expected outcomes of the trial. Therefore, COVID-19 and its complications/sequelae as well as all symptoms listed in Section 9.2.1.4 will not be reported according to the standard expedited process for SAEs, even though the event may meet the criteria for an SAE. However please note that all fatal cases resulting from COVID-19 and its complications/sequelae and from all other events will be reported as SAEs and need to be reported to the CRO within 24 hours (see section Reporting of SAEs). An AE form should be completed for any symptoms not listed in Section 9.2.1.4.

Definition of an Adverse Event (AE)

Definition of an AE:
An AE is any untoward medical occurrence in a 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 temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product. All AEs fall into one 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 study 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 the study vaccine or a concomitant medication/vaccination. • An adverse effect of the study 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.

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- 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.
- All non-fatal cases resulting from COVID-19 and its complications/sequelae (these events are reported in the eCRF on the COVID-19 Summary form).

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

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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 one 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 unsolicited AE and SAE reported during the trial and assign it to one 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 study vaccine and each occurrence of each unsolicited AE/SAE. Causality will be determined as:

Related: There is a reasonable causal relationship between the study vaccine and the AE.

Unrelated: There is no reasonable causal relationship between the study 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 study 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**

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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 one 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 Table 6.
- 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.
- 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 (except for COVID-19, which should not be recorded as an AE in this trial).
- 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 Unsolicited 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.

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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

Unsolicited 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, described in Section 9.3, that occur during the reporting period set in this protocol (Table 6) 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 (not COVID-19) 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 study 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

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and treatment of the event; relevant medical history and concomitant medication and vaccinations; and action taken with the study 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.

Reporting 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. The reporting period of medically-attended AEs, AESIs, SAEs, and intercurrent medical conditions is defined in Table 6.

All AEs that occur in the course of the clinical trial regardless of the causal relationship should be monitored and followed-up as described in Section 9.3 and Table 6 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 study 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 study 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 study 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 trial site should maintain contact with pregnant subjects to obtain pregnancy outcome information.

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The pregnancy information in the female partners of male participants will not be collected for this trial.

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.

If pregnancy is reported while on anti-conceptional method/hormonal contraceptives (oral, injectable, hormonal intrauterine device, etc.), and if contraception failure is confirmed, 'Pregnancy on contraceptive' should be reported as an SAE (Important Medical Event) using a SAE report form. However, if the contraceptive use was not followed as recommended per the respective product label of the contraceptive (including patient compliance), only 'pregnancy' should be reported to the CRO using a pregnancy report form.

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 study 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.

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Product Quality Complaints
Pharmaceutical Technical Complaints associated with the study vaccine must be reported to the Sponsor immediately (refer to the pharmacy manual for details). The same reporting timelines as for SAEs apply.

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Appendix 11 Protocol Amendment History

The trial was initiated using protocol version 1.0.

Protocol version 4.0: 25 November 2021

This amendment was considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

None of the below changes affect the safety and well-being of subjects; the benefit-risk ratio remains favorable.

Section # and Name	Description of Important Change	Brief Rationale
Throughout	The trial will be unblinded and an open-label phase will be added for follow-up of subjects who received CVnCoV.	*In view of the current availability of authorized/licensed vaccines for preventing COVID-19 (AVs) in the countries where the trial is being conducted, multiple unblinding requests have been granted to trial subjects seeking access to these AVs under their country's national vaccination programs, and as of 18 November 2021 nearly 80% of the trial subjects have been unblinded and approximately 49% have already received an AV. This has led to the decision to unblind all subjects in the HERALD trial and continue safety follow-up of those who received CVnCoV, including those who received or will receive AV after CVnCoV.
Throughout	Two cohorts have been defined for the open-label phase: - Cohort A for subjects who received at least 1 dose of CVnCoV and received/will receive an AV after unblinding. - Cohort B for subjects who received at least 1 dose of CVnCoV and continue follow-up as initially planned, without receiving further COVID-19 vaccination. Subjects who received placebo do not require follow-up after unblinding and will discontinue the trial.	
Throughout	Wording has been added to paragraphs and headings, or subheadings, to specify whether the paragraphs/sections are applicable to the randomized observer-blinded phase, open-label phase, or entire trial.	Clarification.

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Section # and Name	Description of Important Change	Brief Rationale
Throughout	Addition of WHO classification names to the SARS-CoV-2 strains.	Update.
Protocol approval signature page	Name of Medical Responsible Person has been modified	Administrative change.
Coordinating Investigator signature	Addition of a specific signature page for the Coordinating Investigator	Administrative change.
SAE Hotline and Medical Monitor contacts	Display of Medical Monitors contact details has been modified	To clarify that the contact details are for the Medical Monitoring Support Center
Synopsis, 3.1.6 Trial Rationale, 5.2 Scientific Rationale for Trial Design	Wording addition in the trial rationale regarding the open-label phase	As above* described.
Synopsis, 4.1.4 Open-label Objectives, 4.2.4 Open-label Endpoints	Addition of objectives and endpoints for the open-label phase.	As above* described.
Synopsis, 4.1.2 Secondary Objectives, 4.2.2 Secondary Endpoints, 4.3 Estimands, 5.1.1 Randomized Observer blinded Phase 2b Design and Objectives, 10.2.4 Efficacy Analysis Set for Seroconversion (EASS), 10.3.5.2 Secondary Efficacy Endpoints Analyses	Removal of key secondary objective and endpoint regarding seroconversion to the N protein of the virus.	The result of this analysis is not relevant in the current situation for CVnCoV and with many subjects having received an AV (as above* described).
Synopsis, 5.1 Overall Design, 5.1.3 Open-label Design and Objectives	Modification of wording and addition of new section in the trial design regarding the open-label phase.	As above* described.

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Section # and Name	Description of Important Change	Brief Rationale
Synopsis, 2 Study schematic and Schedule of Activities, 9.1 Schedule of Trial Assessments and Procedures	Addition/modification of trial visits for the open-label phase, addition of Schedules of Assessments for the open-label phase (Tables 4 and 5).	As above* described.
Synopsis, 4.2.1 Primary Endpoints, 4.3 Estimands, 5.1.2 Randomized Observer-blinded Phase 3 Design and Objectives, 9.3.1.2 Safety Assessments for All Subjects in Phase 2b and Phase 3, 9.3.2 Safety Assessments for Subjects in the Open-label Phase, 9.3.3.2 Unsolicited Adverse Events and Serious Adverse Events, 9.3.3.3 Adverse Events of Special Interest	Clarification of the follow-up period for the randomized observer-blinded phase of AESIs, SAEs, and AEs leading to withdrawal or discontinuation throughout the trial (until EOT) and addition of safety assessments for the open-label phase.	As above* described.
Synopsis, 9.2.1.2.1 Routine Surveillance for COVID-19, 9.5.1 Virological Confirmation of COVID-19, Appendix 6	Deletion of bullet about virus sequencing for positive RT-PCR tests. Description of COVID-19 testing during the open-label phase, with addition of Appendix 6B.	Sequencing will not be performed. As above* described.
Synopsis, 9.2.1.2. COVID-19 Cases in the Open-label Phase, 9.2.1.3 Case Detection, 9.2.1.4 Definition of Virologically-confirmed COVID-19 Case	COVID-19 case definition for the open-label phase has been added according to the eCDC criteria.	As above* described.
Synopsis, 6.3 Roll-over Criteria for the Open-label Phase	Roll-over criteria for the open-label phase are defined.	As above* described.

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Section # and Name	Description of Important Change	Brief Rationale
Synopsis, Tables 1 to 3, 4.2.2 Secondary Endpoints (Randomized Observer-blinded Phase only),4.3 Estimands,) Trial Assessments and Procedures, 9.4 Immunogenicity Assessment (Randomized Observer-blinded Phase only), 9.4.3 Antibody Responses to CVnCoV Vaccination in Subjects Who Develop a Case of COVID-19	No samples will be obtained at Day 393 after trial unblinding. The Day 57 immunogenicity samples will not be analyzed.	Day 393 sampling has been removed for the open-label phase after unblinding. Day 57 data would not add any relevant scientific value to the already available data.
Synopsis, 4.2.3 Exploratory Endpoints (Randomized Observer-blinded Phase only), 4.3 Estimands, 9.4.4 Cell-mediated Immunity	Wording added to clarify that for exploratory immunogenicity endpoints, first testing of samples will be performed for a subset of these subjects and might be extended to 200 subjects if T-cell response is detectable.	Clarification.
Synopsis, 5.5.2 Pausing of the Trial, 9.3.8.1 Data Safety Monitoring Board	Modification of the frequency of Safety Review Team reviews to “a periodic basis.”	In case the weekly review may not be maintained during the open-label phase.
Synopsis, 10 Statistical considerations	Wording added regarding statistical analysis for the open-label phase, to be performed by cohort and to be defined in an extended SAP.	As above* described.
3.1.2 COVID-19	Addition of aerosol particles (inhalation) as SARS-CoV-2 method of transmission.	Update.
3.1.3 Development of CVnCoV	Wording modified to indicate that currently there is one licensed vaccine.	Update.

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Section # and Name	Description of Important Change	Brief Rationale
3.1.4 HERALD Phase 2b/3 Results, 3.1.5 CVnCoV and Authorized/ Licensed Sars.CoV.2 Vaccines	New sections with results from the HERALD trial and data about administering an AV after CVnCoV.	Update.
3.2.1 Known Potential Risks	Addition of reference to the Investigator Brochure for updated safety and immunogenicity data from currently ongoing CVnCoV trials.	Update.
4.3 Estimands	Corrections made in the estimands table according to SAP, and addition of estimands for the open-label endpoints.	Correction and as above* described.
5.4 End of Trial Definition	Wording addition to account for placebo subjects who withdraw after unblinding.	As above* described.
7.1.2.3 Authorized Vaccines	New section/wording addition to describe current availability of AVs and access for trial subjects.	As above* described.
7.3.3.2 Trial Unblinding	New section to describe trial unblinding.	As above* described.
7.6.1 Permitted Medications/ Vaccines During the Trial, 7.6.2 Prohibited Medications/ Vaccines During the Trial, 8.1 Discontinuation of Trial Vaccine Administration	Wording addition to clarify allowance of AVs after unblinding.	As above* described.
8.2 Withdrawal from the Trial	Wording addition to indicate that after unblinding, placebo subjects will be withdrawn from the trial.	As above* described.
9 Trial Assessments and Procedures	Wording addition to allow visits to be replaced with phone calls if suitable for the subject.	As above* described.

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Section # and Name	Description of Important Change	Brief Rationale
9.1.1.10, 9.1.2.10, 9.1.3.7. End Of trial Clinic Visit: Day 393	Deletion of wording about Day 393 samples and about participation in the 1-year Extension Study.	As above* described.
9.1.4 Open-label phase	New section to describe procedures during the open-label phase.	As above* described.
9.2.1.3.2 Non-Routine Surveillance for COVID-19 (Positive Test Outside of the Site), 9.5.2 Confirmation of a Positive Test for SARS-CoV-2 Infection Performed Outside of the Site	Change of timing for confirmation retest to 2 weeks.	Time window added to avoid retest occurring after end of trial.
9.3.3 Adverse Events	Explanation added for reporting of COVID-19 complications/sequelae.	Clarification and as above* described.
9.3.3.3 Adverse Events of Special Interest	Deletion of sentence about intercurrent medical conditions.	These are not adverse events of special interest and the sentence is already in previous section.
11.3 Monitoring	Wording added about remote source data verification on this trial.	This is occurring due to the pandemic and should be noted in the protocol.
12.4 Informed Consent	Wording added to indicate that subjects continuing in the open-label phase will sign a new ICF after unblinding.	As above* described.
Appendix 6 Flow Diagram for COVID-19 Case Interview	Addition of flowchart for the open-label phase.	As above* described.
Appendix 8 Potential Immune-Mediated Diseases	Lists of potential immune-mediate diseases has been updated.	Safety review meeting decision.

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Section # and Name	Description of Important Change	Brief Rationale
Appendix 9 Adverse Events of Special Interest (AESIs) for SARS -CoV-2 Vaccines	Lists of AESIs has been updated.	Safety review meeting decision.
Appendix 10 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow up, and Reporting	Wording added regarding events that do not meet the AE definition and aspects of pregnancy reporting.	Clarification.

Protocol version 3.0: 29 March 2021

This amendment was considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

None of the below changes affect the safety and well-being of subjects; the benefit-risk ratio remains favorable.

Section # and Name	Description of Important Change	Brief Rationale
Throughout	The co-primary objective (and corresponding endpoint) regarding the efficacy of CVnCoV in the prevention of moderate to severe COVID-19 was changed to a secondary objective. Subsequently, the corresponding statistical calculations were also updated.	It is now generally accepted that a vaccine that protects against disease of any severity, will also (or even better) protect against more severe disease, therefore reducing the need to maintain this as a primary endpoint and thereby preserving the alpha.
Throughout	Addition of a key secondary efficacy objective (and corresponding endpoint) to demonstrate the efficacy of CVnCoV in the prevention of COVID-19 caused by the “wild type” (i.e., WT/D614G lineages A.1/B.1 without VOC B.1.1.7, B.1.351, B.1.429) and “UK” (B.1.1.7) strain.	Various strains have been identified since the original protocol and the efficacy to each individual strain should also be evaluated.

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Section # and Name	Description of Important Change	Brief Rationale
Throughout	Addition of an exploratory objective (and corresponding endpoint) to demonstrate the efficacy on any other strains.	Various strains have been identified since the original protocol and the efficacy to each individual strain should also be evaluated.
Throughout	Decrease in the number of subjects needed for exploratory immunogenicity from 400 to 200.	These assessments will only be performed in 200 subjects in the Immunogenicity Subset from selected sites in Europe.
Synopsis and 6.2 Exclusion Criteria	Addition of anabolic steroid use.	Clarification
Synopsis and 9.1 Trial Assessments and Procedures	Increase of 38 mL in maximum blood volume.	Addition of a genomic biomarker (6 mL) and CMI (32 mL) sample on Day 120 for subjects in the Immunogenicity Subset.
Tables 1, 2, and 3	Addition of footnotes regarding concomitant medication.	Clarification
Tables 2 and 3 and 9.1 Schedule of Trial Assessments and Procedures	Removal of cell-mediated immune response and genomic biomarkers sampling.	These assessments will only be performed in 200 subjects in the Immunogenicity Subset from selected sites in Europe.
9.2.1.4 SARS-CoV-2 Genome Lineage Characterization	New section to detail the different strains that will be investigated in this trial.	To pre-specify the phylogenetic clustering that will be used.
9.3.3 Adverse Events and Appendix 10	Addition of instruction that any COVID-19 cases leading to death should be reported as SAEs and in accordance with SAE reporting procedures.	Clarification
Throughout	Minor editorial and document formatting revisions.	-

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Protocol version 2.0: 17 February 2021

This amendment was considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

None of the below changes affect the safety and well-being of subjects; the benefit-risk ratio remains favorable.

Section # and Name	**Description of Important Change**	**Brief Rationale**
Throughout	The 1-year Extension study was removed from this protocol.	It is now considered a separate trial, CV-NCOV-004Ext
Throughout	Subjects who report to have COVID-19 symptoms will only be followed up if the Investigator considers the symptoms to be related to COVID-19.	Clarification
Throughout	Guidance added for subjects who request to be unblinded due to being eligible to receive an authorized/licensed vaccine.	Several vaccine candidates have been approved for emergency use since the original protocol
Throughout	Text regarding sample size adapted to apply also if the case accrual rate is higher than expected; in which case the DSMB may recommend a decrease in sample size.	Clarification
Throughout	Instructions added not to record COVID-19 as an AE.	Clarification
Throughout	More text added to record all AEs only during the defined reporting period for the specific type of AE.	Clarification
Synopsis	Name of coordinating investigator was added.	Informational

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Section # and Name	Description of Important Change	Brief Rationale
Synopsis, Tables 1, 2, and 3, and 9 Trial Assessments and Procedures	Maximum blood volume updated based on changes in assessments; removed from the schedule of activities tables and added to Section 9.	Editorial
Synopsis and 4.1.1 Primary Objectives	The secondary objective regarding reactogenicity for the Phase 2b part was changed to a primary objective.	Based on feedback from Regulatory Authorities
Synopsis and 4.2.1 Primary Endpoints	Secondary safety endpoints moved to primary.	To correspond with the objectives
Synopsis and 6.1 Inclusion Criteria	All pregnancy tests to be done in serum (instead of urine) where required by local laws.	To adhere to local laws and regulations
Synopsis and 9.5.1 Virological Confirmation of COVID-19 Disease	Instructions added that gene sequencing should be performed for the S protein in subjects with positive RT-PCR tests performed at the central laboratory.	To identify mutations in this protein
Tables 1, 2, and 3	Blood volume for pregnancy tests added and clarification that all pregnancy tests should be performed in blood (and not urine) if required by local laws and regulations.	To adhere to local laws and regulations
Tables 2 and 3	CMI and genomic biomarkers added as an assessment in any part of the trial.	Subjects in these subsets do not necessarily have to be part of the Immunogenicity Subset
Tables 1, 2, and 3 and 7.6 Concomitant Therapy and Vaccines	Instructions added to record concomitant medications used to treat AEs during the same period as the reporting period for the type of AE.	Clarification

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Section # and Name	Description of Important Change	Brief Rationale
5.2 Scientific Rationale for Trial Design and 5.2 Justification for Dose	Justification for dose and CMI assessments added.	Based on feedback from Regulatory Authorities
6.3 Vaccine Delay Recommendations and 8.1 Discontinuation of Trial Vaccine Administration	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
9.1 Schedule of Trial Assessments and Procedures	Minor changes made throughout the section.	Clarification
9.2.1 COVID-19 Cases	Definitions for SARS-CoV-2 infection (overall and in seronegative and seropositive subjects) and subjects with a high risk of severe COVID-19 added.	Clarification
11.3 Monitoring	Instruction that data should be collected for all subjects who sign an ICF removed.	Data from screening failures are not entered in the electronic data capture system
Appendix 9	COVID-19 removed as an AESI.	Correction
Appendix 10	Minor changes made for consistency with the body of the protocol.	Clarification
Throughout	Minor editorial and document formatting revisions.	-