Protocol Number: CV-NCOV-002

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

NCT Number: NCT04515147

Document Date: 03 December 2021

CLINICAL TRIAL PROTOCOL

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

Protocol Number:	CV-NCOV-002
Investigational product:	CV07050101 (referred to as CVnCoV)
Phase:	Phase 2a
Sponsor:	CureVac AG Schumannstrasse 27 60325 Frankfurt Germany
Short Title:	Safety, reactogenicity and immunogenicity of CVnCoV in adults
Protocol Version:	3.0
Protocol Date:	03 December 2021

PROTOCOL VERSION HISTORY:

Version 1.0 dated 23 July 2020

Version 2.0 dated 20 October 2020

PROTOCOL APPROVAL SIGNATURES

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

Protocol Number: CV-NCOV-002

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

Signature

Date

Medical Responsible Person

[redacted]

CureVac AG

Signature

Date

Vice President Clinical Operations

[redacted]

CureVac AG

Signature

Date

Statistician

[redacted]

CureVac AG

Signature

Date

INVESTIGATOR SIGNATURE PAGE

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

Protocol Number: CV-NCOV-002

Confidentiality and GCP Compliance Statement

I, the undersigned, have reviewed this protocol, including appendices and I will conduct the trial as described in compliance with this protocol, GCP, and relevant ICH guidelines.

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

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

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

Investigator Signatory

Name

Address

Signature

Date

SAE hotline and medical monitor contacts

SAE Hotline	
SAE reporting to PRA Health Sciences by **fax or email** within **24 hours** after discovery:	
SAE Fax-no.:	[redacted]
Email:	[redacted]
Medical Monitor The Medical Monitor will provide 24/7 (24 hours per day and 7 days a week) on-call medical coverage to address trial-related questions from sites or Investigators, such as questions regarding eligibility requirements, the acceptability of concomitant medication or whether a subject should remain in the trial or needs to be discontinued.	
Name of Primary Contact:	[redacted]
Address:	[redacted]
Phone:	[redacted]
Fax:	[redacted]
Email:	[redacted]

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

ADE	Antibody-dependent enhancement
AE	Adverse event
AESI	Adverse event of special interest
ANA	Antinuclear antibody
ARDS	Acute respiratory distress syndrome
BMI	Body mass index
CCL	Chemokine ligand
CEPI	Coalition for Epidemic Preparedness Innovations
CI	Confidence interval
CMI	Cell-mediated immunity
CoV	Coronavirus
CRO	Contract research organization
CVnCoV	Investigational SARS-CoV-2 mRNA vaccine
DDS	Dose-determining set
DSMB	Data and safety monitoring board
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
E	Envelope
ECG	Electrocardiogram
eCRF	Electronic case report form
ELISA	Enzyme-linked immunosorbent assay
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMT	Geometric mean titer
hCG	Human chorionic gonadotropin
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICS	Intracellular cytokine staining
IEC	Independent Ethics Committee
IFN	Interferon
Ig	Immunoglobulin
IL	Interleukin
IM	Intramuscularly
IMP	Investigational medicinal product
IP-10	IFN-γ-induced protein 10

IRB	Institutional Review Board
iSRC	Internal safety review committee
IVRS	Interactive voice response system
LLOQ	Lower limit of quantification
LNP	Lipid nanoparticles
M	Membrane
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
mRNA	Messenger ribonucleic acid
N	Nucleocapsid
PBMC	Peripheral blood mononuclear cell
pIMD	Potential immune-mediated disease
PT	Preferred Term
RBD	Receptor-binding domain
RNA	Ribonucleic acid
RT-PCR	Reverse transcription polymerase chain reaction
S	Spike
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SOC	System Organ Class
TSH	Thyroid-stimulating hormone
VDE	Vaccine-dependent disease enhancement
WHO	World Health Organization

1 SYNOPSIS

Name of Investigational Vaccine:	CVnCoV	
Sponsor:	CureVac AG	
Coordinating Investigator:	[redacted]	
Title of Trial:	COVID-19: A Phase 2a, partially observer-blind, multicenter, controlled, dose-confirmation clinical trial to evaluate the safety, reactogenicity and immunogenicity of the investigational SARS-CoV-2 mRNA vaccine CVnCoV in adults >60 years of age and 18 to 60 years of age	
Rationale:	Coronaviruses are a large family of zoonotic 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 is referred to as COVID-19. The virus spread to different parts of China and then globally, and on 12 March 2020 the World Health Organization (WHO) announced that the outbreak was characterized as a pandemic. In spite of the severity of respiratory disease caused by emerging coronaviruses, there is currently no licensed vaccine available for prevention of coronavirus-associated disease. In partnership with the Coalition for Epidemic Preparedness Innovations (CEPI), CureVac AG is developing a new SARS-CoV-2 (messenger ribonucleic acid [mRNA]) vaccine formulated with lipid nanoparticles (referred to as CVnCoV). The safety and immunogenicity of this vaccine was evaluated for the first time in humans in the dose-finding trial CV-NCOV-001. At this time, 6 dose levels (2, 4, 6, 8, 12, and 16 µg) have been tested in healthy adults 18 to 60 years of age. This second trial was conducted to confirm the safety and immunogenicity of CVnCoV at different dose levels in adults >60 years (i.e., 61 years or older) when administered according to a 0 (Day 1), 1-month (Day 29) primary vaccination schedule. The dose levels to be administered in this trial will be selected based on data from the CV-NCOV-001 trial. For this elderly population, higher dose levels than the dose levels investigated for adults 18 to 60 years of age will be considered to address potentially reduced immunogenicity in the context of immunosenescence. In addition, the safety and immunogenicity of a booster dose of CVnCoV administered at approximately 2 months (Day 57) or 6 months (Day 180) after the first dose will be evaluated in a subgroup of subjects. In order to bridge to the population evaluated in Trial CV-NCOV-001, adults 18 to 60 years will also be enrolled in this trial. Throughout the trial, cases of COVID-19 disease will be identified and documented for later potential pooling of cases across trials in the clinical development program, such as the CV-NCOV-004 and the CV-NCOV-005 trials.	
Trial Duration for Each Subject:	Approximately 13 months for each subject	**Phase:** 2a
Objectives:	***Primary*** • To evaluate the safety and reactogenicity profile after 1 and 2 dose administrations of CVnCoV at different dose levels. • To evaluate the humoral immune response after 1 and 2 dose administrations of CVnCoV.	

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

Overall Design:	This is a Phase 2a, partially blind, active-controlled, dose-confirmation trial to assess the safety and immunogenicity of provisionally selected CVnCoV dose levels of 6 and 12 µg in an older adult population. The design of the trial will allow an increase or decrease in dose based on data from Trial CV-NCOV-001 and the initial phase of this trial. An overview of the planned number of subjects to be enrolled per trial group and the vaccination schedule is provided in Synopsis Table 1.
	Subjects will be recruited independent of their SARS-CoV-2 serology status. Their serostatus will be determined retrospectively by a blood sample drawn at baseline and analyzed to allow post hoc stratified analyses of subjects who are SARS-CoV-2 seronegative or seropositive at baseline.
	Initial Phase
	Subjects will be enrolled in 3 cohorts divided into 6 groups:
	• 6 µg dose level cohorts
	  ○ Group 1 (observer-blind): CVnCoV 6 µg on Day 1 and 6 µg on Day 29 (in subjects 18 to 60 years of age)
	  ○ Group 2 (observer-blind): CVnCoV 6 µg on Day 1 and 6 µg on Day 29 (in subjects >60 years of age [i.e., 61 years or older])
	• 12 µg dose level cohorts
	  ○ Group 3 (observer-blind): CVnCoV 12 µg on Day 1 and 12 µg on Day 29 (in subjects 18 to 60 years of age)
	  ○ Group 4 (observer-blind): CVnCoV 12 µg on Day 1 and 12 µg on Day 29 (in subjects >60 years of age [i.e., 61 years or older])
	• Active control cohort
	  ○ Group 5 (observer-blind): licensed hepatitis A vaccine on Day 1 and on Day 29 (in subjects 18 to 60 years of age)
	  ○ Group 6 (observer-blind): licensed pneumococcal vaccine on Day 1 and on Day 29 (in subjects >60 years of age [i.e., 61 years or older])
	A subgroup of subjects in Group 3 will receive a booster dose of CVnCoV on Day 180 and a subgroup of subjects in Group 4 will receive a booster dose of CVnCoV on Day 57 or Day 180, each in an open-label manner.
	The 6 µg and 12 µg groups will be enrolled sequentially, i.e., enrollment in the 12 µg groups will only be initiated once Groups 1 and 2 have been fully enrolled.
	Group 2 (subjects >60 years, 6 µg) will be initiated in 4 sentinel subjects. These subjects should be vaccinated at least 60 minutes apart. Safety and reactogenicity data reported during an observation period of at least 24 hours after vaccination will be collected and reviewed by an internal safety review committee (iSRC). In this review, the iSRC will review all available safety data, but focus specifically on Grade 3 adverse reactions. Based on this review, the iSRC will decide on continuation of enrollment of subjects at this dose level. In a next step, 8 additional sentinel subjects will be enrolled. Safety and reactogenicity data reported during an observation period of at least 24 hours after vaccination will be collected and reviewed by the iSRC.

	In this review, the iSRC will review all available safety data, but focus specifically on Grade 3 adverse reactions. The same procedure will be followed for Group 4 (subjects >60 years, 12 µg) and the iSRC will decide on continuation of enrollment of subjects at this dose level after review of the first 12 sentinel subjects. Subjects in the initial phase will be randomized according to a 10:1 ratio to receive CVnCoV or the active control in an observer-blinded manner. **Expansion Cohorts** Following the initial phase, a separate expansion cohort of 220 subjects aged 18 to 60 years and 220 subjects aged >60 years (i.e., 61 years or older) will be enrolled to be vaccinated on Days 1 and 29. Expansion for subjects 18 to 60 years of age may start once the final dose for subjects in this age category has been selected based on the data from Trial CV-NCOV-001. Expansion for subjects >60 years of age may start once the final dose for these subjects has been selected based on data from this trial. Subjects in the expansion cohorts will be randomized according to a 10:1 ratio to receive either the selected dose of CVnCoV or the active control in an observer-blinded manner. **Change in Dose Level** Other possible dose levels to be administered in this trial will continuously be assessed based on the ongoing Trial CV-NCOV-001 in adults aged 18 to 60 years. If the dose level of 12 µg is considered too reactogenic for adults aged 18 to 60 years in the CV-NCOV-001 trial, the dose level in this trial would be reduced from 12 µg to 8 µg. In case additional dose levels are investigated in this trial, such a dose level will be initiated in additional sentinel subjects in the same manner as described above. In case of any dose increases, the next dose level will only be given to subjects once initial data from the previous dose level have been reviewed by the iSRC. In case the starting dose level is not well tolerated, a decrease in the dose level may occur and the lower dose levels will be assessed in the same manner as described above.

Synopsis Table 1 Trial Groups and Vaccination Schedule

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

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

Trial Visits/ Contacts:	6 to 9 protocol-scheduled visits on Day 1, Day 2, Day 29, Day 43, Day 57 (only for subjects receiving the booster dose on Day 57), Day 85 (only for subjects receiving the booster dose on Day 57), Day 180, Day 208 (only for subjects receiving the booster dose on Day 180), and Day 393 (only for subjects receiving the booster dose on Day 180) Protocol-scheduled phone contacts on Day 15, Day 30, Day 57 (not required for subjects receiving the booster dose on Day 57), Day 58 (only for subjects receiving the booster dose on Day 57), Day 181 (only for subjects receiving the booster dose on Day 180), and Day 393 (only for subjects who did not receive a booster on Day 180) 2 protocol-scheduled prompts on Day 120 and Day 270
Collection of Blood Samples:	The maximum total volume of blood taken over the trial period from any subject will be approximately 279 mL (or 435 mL for subjects in who cell-mediated immunity and cytokines will be assessed) (Table 1).
Safety Assessments:	Reactogenicity will be assessed daily on each vaccination day and the following 7 days via collection of solicited local adverse events (AEs; injection site pain, redness, swelling, and itching) and systemic AEs (fever, headache, fatigue, chills, myalgia, arthralgia, nausea/vomiting, and diarrhea) using diary cards (electronic or paper). In addition, other indicators of safety will be collected (e.g., body temperature). Diaries will also be used for collection of unsolicited AEs on each vaccination day and the following 28 days. In addition, subjects will receive a prompt (by e.g., a phone call or text message) to verify whether the subjects had any health concerns since the last visit. Subjects with any Grade 3 solicited or unsolicited AEs reported electronically by the subject will be contacted by the Investigator, and subjects who did not enter any diary information will be prompted and then contacted in case of non-response within 24 hours. Unscheduled visits will be performed when deemed necessary for safety assessments or to ensure data integrity. SAEs, adverse events of special interest (AESIs), and AEs leading to vaccine withdrawal or trial discontinuation will be collected throughout the trial. Non-serious intercurrent medical conditions that may affect the immune response to vaccination will also be collected throughout the trial. AESIs to be monitored throughout the trial include potential immune-mediated diseases (pIMDs) and COVID-19 disease. In case of confirmed COVID-19 disease, a disease-specific diary will be completed by the subject and/or the treating health care provider.
Laboratory Testing for COVID-19 Disease:	As a baseline assessment, a reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 will be performed in all subjects. Testing will be done for SARS-CoV-2 spike protein to evaluate vaccine-induced immune responses as well as for SARS-CoV-2 N-antigen (not contained in the vaccine construct) to evaluate immune responses induced by natural infection. This will allow to retrospectively define the subject's serology status, including the baseline status for the by-group/cohort analysis. Subjects will be prompted once or twice per week to report if the subjects have any of the following symptoms: cough, shortness of breath, difficulty breathing, fever ≥37.8°C, fatigue, myalgia, chills, wheezing, nasal congestion, runny nose, sore throat, headache, diarrhea, or new olfactory

	and taste disorders. A COVID-19 symptoms log listing these symptoms will be provided to subjects with RT-PCR-confirmed COVID-19 disease. If any of these symptoms are observed, the Investigator will collect appropriate samples as soon as feasible and locally perform RT-PCR and/or serological assays as locally available to evaluate for infection with SARS-CoV-2. If a serological assay is performed, this should look at antibodies against N protein antigen, but not to antibodies against Spike viral antigen, as this is part of the vaccine. These assays will be repeated 7 to 14 days after the initial assessment. Any subject with clinical suspicion of SARS-CoV-2 infection will undergo appropriate testing and referral within the local healthcare system as appropriate. Subjects with a confirmed acute SARS-CoV-2 infection during the trial should not receive any additional vaccine dose, but will be closely monitored for disease patterns and severity. In order to assess severity of disease, subjects will document disease progression on a symptom log and Investigators will document additional clinical parameters based on hospital records, if applicable.
Planned Number of Subjects:	Approximately 660 subjects will be enrolled. 223 subjects during the initial phase of the trial: • 23 subjects in the CVnCoV 6 µg cohort (Groups 1 and 2): 11 subjects 18 to 60 years and 12 subjects >60 years (i.e., 61 years or older) • Approximately 180 subjects in the CVnCoV 12 µg cohort (Groups 3 and 4): approximately 90 subjects 18 to 60 years and approximately 90 subjects >60 years (i.e., 61 years or older) • Approximately 20 subjects in the active control cohort (Groups 5 and 6): approximately 10 subjects 18 to 60 years and approximately 10 subjects >60 years (i.e., 61 years or older) 440 subjects during the expansion phase of the trial: • Approximately 220 subjects 18 to 60 years: 200 will receive CVnCoV and 20 will receive active control • Approximately 220 subjects >60 years (i.e., 61 years or older): 200 will receive CVnCoV and 20 will receive active control
Criteria for Inclusion and Exclusion:	**Inclusion criteria:** Subjects will be enrolled in this trial only if they meet **all** of the following criteria: 1. Healthy male and female subjects ≥18 years of age. A healthy subject is defined as an individual who is in good general health, according to the Investigator's assessment. Chronic health conditions are acceptable if the condition is considered well controlled with treatment according to the discretion of the Investigator. 2. Expected to be compliant with protocol procedures and available for clinical follow-up through the last planned visit. 3. Subjects who are able to understand and willing to provide informed consent. 4. Physical examination without clinically significant findings according to the Investigator's assessment. 5. Body mass index (BMI) ≥18.0 and ≤32.0 kg/m^2. 6. Female subjects of childbearing potential: at the time of enrollment, negative human chorionic gonadotropin (hCG) pregnancy test

	(serum) for female subjects presumed to be of childbearing potential on the day of enrollment. On Day 1 (pre-vaccination): negative urine pregnancy test (required if serum pregnancy test was performed more than 3 days before). 7. Female subjects of childbearing potential must use highly effective methods of birth control from 2 weeks before the first administration of the trial vaccine until 3 months following the last administration. The following methods of birth control are considered highly effective when used consistently and correctly: o Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal); o Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable); o Intrauterine devices; o Intrauterine hormone-releasing systems; o Bilateral tubal occlusion; o Vasectomized partner; o Sexual abstinence (periodic abstinence [e.g., calendar, ovulation, symptothermal and post-ovulation methods] and withdrawal are not acceptable). Male subjects should be instructed not to get their partners pregnant until 3 months after the last administration. **Exclusion criteria:** Subjects will not be enrolled in this trial if they meet **any** of the exclusion criteria. 1. Use of any investigational or non-registered product (vaccine or drug) other than the trial vaccine within 28 days preceding the administration of the trial vaccine, or planned use during the trial period. 2. Receipt of any other vaccines within 28 days prior to enrollment in this trial or planned receipt of any vaccine within 28 days of trial vaccine administration (primary dose or booster dose). 3. Receipt of any investigational or licensed/authorized SARS-CoV-2 or other coronavirus vaccine prior to the administration of the trial vaccine. 4. Any treatment with immunosuppressants or other immune-modifying drugs (including, but not limited to, corticosteroids, biologicals, and methotrexate) within 6 months prior to the administration of the trial vaccine or planned use during the trial, with the exception of topically-applied, inhaled, or intranasal steroids. 5. Use of hormonal therapy for gender reassignment. 6. Any medically diagnosed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination, including known human immunodeficiency virus infection, hepatitis B virus infection, and hepatitis C virus infection. 7. History of immune-mediated or autoimmune disease. 8. History of angioedema (known C1 inhibitor deficiency). 9. History of anaphylaxis or allergy to any component of CVnCoV or aminoglycoside antibiotics. 10. History of or current alcohol and/or drug abuse.

	11. Subjects who are active smokers, were active smokers within the last year (including any vaping in the last year), or have a total smoking history ≥10 pack years. A pack year is calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked. 12. History of virologically-confirmed SARS, MERS, or COVID-19 disease or known exposure (without any personal protective equipment) to an individual with confirmed COVID-19 disease or SARS-CoV-2 infection within the past 2 weeks. 13. Administration of immunoglobulins and/or any blood products within the 3 months preceding the administration of any dose of the trial vaccine. 14. Presence or evidence of significant uncontrolled acute or chronic medical or psychiatric illness. Significant medical or psychiatric illnesses include but are not limited to: o Uncontrolled respiratory disease (e.g., chronic obstructive pulmonary disease, asthma), including use of the following asthma medications: intravenous corticosteroids, leukotriene modifiers, biologics. o Uncontrolled cardiovascular disease (e.g., congestive heart failure, cardiomyopathy, ischemic heart disease, history of stroke, peripheral artery disease, pulmonary embolism). o History of myocarditis or pericarditis as an adult. o Diabetes mellitus (insulin-dependent). o Uncontrolled neurological disorders or Guillain-Barré syndrome or history of seizure, except for febrile seizures during childhood. o Current or past malignancy, unless completely resolved without sequelae for >5 years. 15. Foreseeable non-compliance with protocol, as judged by the Investigator. 16. For female subjects: pregnancy or lactation. 17. Subjects with impaired coagulation or any bleeding disorder in whom an intramuscular injection or a blood draw is contraindicated. This includes subjects on treatment with anticoagulants (e.g., vitamin K antagonists, novel oral anticoagulants, and heparin). Use of platelet aggregation inhibitors is not exclusionary. 18. Subjects employed by the Sponsor, Investigator, or trial site, or relatives of research staff working on this trial. 19. Subjects considered at the Investigator's discretion to be at increased risk of exposure to COVID-19 disease.
Endpoints:	Any immunogenicity samples may also be used for assay validation and additional studies of the mechanism of action of the vaccine. ***Primary*** • The frequencies, intensities, and duration of solicited local AEs on Day 1 and Day 29 and the following 7 days by dose and group. • The frequencies, intensities, duration, and relationship to trial vaccination of solicited systemic AEs on Day 1 and Day 29 and the following 7 days by dose and group. • The occurrence, intensities and relationship to trial vaccination of unsolicited AEs on Day 1 and Day 29 and the following 28 days by dose and group. • The occurrence and relationship to trial vaccination of SAEs and AESIs throughout the trial.

	On Day 29 and Day 43: • The proportion of subjects seroconverting for SARS-CoV-2 spike protein antibodies, as measured by enzyme-linked immunosorbent assay (ELISA). • Individual SARS-CoV-2 spike protein-specific antibody levels in serum, as measured by ELISA. • Geometric mean titers (GMTs) of serum SARS-CoV-2 spike protein antibodies, as measured by ELISA. • The proportion of subjects seroconverting for SARS-CoV-2 neutralizing antibodies, as measured by an activity assay. • Individual SARS-CoV-2 neutralizing antibody levels in serum. • GMTs of serum SARS-CoV-2 neutralizing antibodies, as measured by an activity assay. ***Secondary*** • The frequencies, intensities, and duration of solicited local AEs on the day of the booster administration and the following 7 days by group. • The frequencies, intensities, duration, and relationship to trial vaccination of solicited systemic AEs on the day of the booster administration and the following 7 days by group. • The occurrence, intensities and relationship to trial vaccination of unsolicited AEs on the day of the booster administration and the following 28 days by group. *On Day 57 (only for subjects receiving the booster dose on Day 57), Day 85 (only for subjects receiving the booster dose on Day 57), Day 180 (only for subjects receiving the booster dose on Day 57 or Day 180), Day 208 (only for subjects receiving the booster dose on Day 180), and Day 393 (only for subjects receiving the booster dose on Day 180):* • The proportion of subjects seroconverting for SARS-CoV-2 spike protein antibodies, as measured by ELISA. • Individual SARS-CoV-2 spike protein-specific antibody levels in serum, as measured by ELISA. • GMTs of serum SARS-CoV-2 spike protein antibodies, as measured by ELISA. • The proportion of subjects seroconverting for SARS-CoV-2 neutralizing antibodies, as measured by an activity assay. • Individual SARS-CoV-2 neutralizing antibody levels in serum. • GMTs of serum SARS-CoV-2 neutralizing antibodies, as measured by an activity assay. ***Exploratory*** <u>*CMI response*</u> *On Day 1, Day 29, and Day 43 in peripheral blood mononuclear cells (PBMCs) in a subset of subjects:* • The frequency and functionality of SARS-CoV-2 spike-specific T-cell response after antigen stimulation. *Intracellular cytokine staining (ICS) to investigate Th response will be used to investigate whether vaccination induces a Th1 shift from*

	baseline. Further T-cell immune responses may be investigated with other technologies like ELISpot or CyTOF. • The proportion of subjects with a detectable increase in SARS-CoV-2 spike-specific T-cell response. *Innate immune response* *On Day 1 and Day 2 in a subset of subjects:* • Serum cytokine concentrations, including but not limited to interferon (IFN)-α, IFN-γ, IL-6, chemokine ligand (CCL) 2, and IFN-γ-induced protein 10 (IP 10). *Evaluation of infection* • Number of subjects with virologically-confirmed SARS-CoV-2 infection as measured by RT-PCR at clinically determined time points throughout the trial.
Sample Size Justification:	The trial is designed to provide a reasonable precision for an estimate of the number of subjects with seroconverting for nCoV spike protein antibodies and an acceptable rate of Grade 3 adverse reactions.
Analysis Sets:	***Safety Set*** The safety set will consist of all subjects who received at least 1 dose of trial vaccine and for whom any post-vaccination safety data are available. ***Immunogenicity Set*** The immunogenicity set will include all subjects who received at least 1 dose of trial vaccine and for whom the baseline blood sample and at least 1 additional blood sample are available for analysis.
Statistical Methodology:	***Missing Data/Discontinuation*** Due to the exploratory design of the trial, no imputation of missing values will be done for any analysis (except the imputation for missing partial dates of AEs and concomitant medication). Reasons for discontinuation from the trial or trial vaccination will be listed and summarized. Currently no replacement of drop-out subjects is foreseen.
Statistical Analyses:	***Analysis of Demographics and Other Baseline Characteristics*** Data will be summarized with respect to demographic characteristics (age, gender), medical history, baseline immune status, and all safety measurements using descriptive statistics (quantitative data) and contingency tables (qualitative data) by dose level and group. Medical history will only be listed. ***Primary Safety Analyses*** Solicited AEs: The number and percentage of subjects with at least 1 solicited AE of any kind, by severity grade, for local AEs, systemic AEs, and overall, will be summarized, after the first vaccination, after the second vaccination, after the booster vaccination (if applicable), and after any vaccination. The results will be tabulated by dose level and group. For subjects with more than 1 episode of the same event, the maximum severity will be used for tabulations. In addition, the frequencies and severity of each solicited AE will be summarized for each vaccination day and the following 7 days. Similar tabulations will be performed for solicited systemic AEs considered as related to the trial vaccine. The duration and severity of solicited AEs will be analyzed at subject level. Unsolicited AEs: Unsolicited AEs, 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 these events will be tabulated at the SOC and PT levels. Additional similar tabulations will be performed to evaluate severity and relationship to the trial vaccine. ***Primary Immunogenicity Analysis*** Percentages of subjects seroconverting for nCoV spike protein antibodies and values of antibody levels, percentages of subjects seroconverting for nCoV-neutralizing antibodies and GMTs and percentages of immune cell populations and cellular responders will be summarized for each dose level. Antibody levels for nCoV spike protein antibodies and GMTs for nCoV-neutralizing antibodies will be summarized for each dose level for subjects previously exposed to SARS-CoV-2 as indicated by confirmed positive SARS-CoV-2 serology at baseline. Data will be presented after each vaccine dose. In addition, levels of cytokines will be summarized for a subset of subjects.

2 SCHEDULE OF ACTIVITIES

Table 1 Schedule of Trial Assessments and Procedures

	Primary Vaccination Period								Booster Vaccination Period								End of Trial	
Visit Number	**1[a]**	**2**	**Phone contact**	**3**	**Phone contact**	**4**	**Phone contact[b]**	**5[c]**	**Phone contact[c]**	**6[c]**	**Prompt**	**7**	**Phone contact[d]**	**8[d]**	**Prompt**	**Phone contact**	**9[w]**
Visit Window (days)	**n/a**	**-0/ +0**	**-0/ +0**	**-2/ +4**	**-2/ +4**	**-0/ +0**	**-2/ +4**	**-2/ +4**	**-2/ +4**	**-0/ +0**	**-2/ +4**	**-2/ +4**	**-10/ +10**	**-0/ +0**	**-2/ +4**	**-2/ +4**	**-0/ +30**	**-0/ +30**
Trial Day	**1**	**2**	**7[e]**	**15**	**29**	**30**	**43**	**57**	**57**	**58**	**85**	**120**	**180**	**181**	**208**	**270**	**393**	**393**
Anchoring	**-**	**1**	**1**	**1**	**1**	**29**	**29**	**29**	**57**	**57**	**57**	**29**	**1**	**180**	**180**	**180**	**180**	**180**
Signed informed consent	X																	
Inclusion/exclusion criteria	X																	
Demographics	X																	
Medical history	X																	
Vaccination																		
Review of criteria for delay or cancellation of vaccination[f]	X				X				X				X[g]					
Investigational vaccine administration (including 30-minute observation)	X				X				X				X[g]					
Safety Monitoring																		
Physical examination[h]	X[i]				X				X				X[g]					
Symptom-directed physical examination[h]		X					X				X				X			
Vital signs[h,j]	X	X			X		X		X		X		X		X			
ECG	X																	
Diary (re)training[k]	X	X			X		X		X				X[g]					
Diary review[k]		X	X	X	X	X	X	X		X	X			X	X			
Diary reminder[k]		X		X		X	X	X	X	X			X[g]	X				
Solicited AEs[k]	X	X		X	X	X	X	X	X	X	X		X[g]	X	X			
Unsolicited AEs[k]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Primary Vaccination Period								Booster Vaccination Period								End of Trial	
Visit Number	**1[a]**	**2**	**Phone contact**	**3**	**Phone contact**	**4**	**Phone contact[b]**	**5[c]**	**Phone contact[c]**	**6[c]**	**Prompt**	**7**	**Phone contact[d]**	**8[d]**	**Prompt**	**Phone contact**	**9[w]**
Visit Window (days)	**n/a**	**-0/ +0**	**-0/ +0**	**-2/ +4**	**-2/ +4**	**-0/ +0**	**-2/ +4**	**-2/ +4**	**-2/ +4**	**-0/ +0**	**-2/ +4**	**-2/ +4**	**-10/ +10**	**-0/ +0**	**-2/ +4**	**-2/ +4**	**-0/ +30**	**-0/ +30**
Trial Day	**1**	**2**	**7[e]**	**15**	**29**	**30**	**43**	**57**	**57**	**58**	**85**	**120**	**180**	**181**	**208**	**270**	**393**	**393**
Anchoring	**-**	**1**	**1**	**1**	**1**	**29**	**29**	**29**	**57**	**57**	**57**	**29**	**1**	**180**	**180**	**180**	**180**	**180**
SAEs[l]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Intercurrent medical conditions[l]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs leading to premature discontinuation[l]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AESIs[l]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication/vaccination	X[m]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety laboratory (~9 mL)[n]	X	X			X						X				X			
Safety laboratory in case of abnormal result at previous visit (~9 mL)[n]							X		X				X					
Serum pregnancy test (~3 mL)[o]	X																	
Urine pregnancy test[o]	X				X				X[g]				X[g]					
TSH, thyroid antibodies, ANA (~3 mL)[p]	X																	
Nasopharyngeal swab collection for RT-PCR testing[q]	X																	
Immunogenicity[r]																		
ELISA (serum) (~12 mL)[s]	X[t]				X[t]		X		X[t]		X		X[t,v]		X			X
Only in subjects in the initial phase of the trial: SARS-CoV-2 neutralizing activity (serum) (~12 mL)	X[t]				X[t]		X		X[t]		X		X[t,v]		X			X

	Primary Vaccination Period								Booster Vaccination Period								End of Trial	
Visit Number	**1[a]**	**2**	**Phone contact**	**3**	**Phone contact**	**4**	**Phone contact[b]**	**5[c]**	**Phone contact[c]**	**6[c]**	**Prompt**	**7**	**Phone contact[d]**	**8[d]**	**Prompt**	**Phone contact**	**9[w]**
Visit Window (days)	**n/a**	**-0/ +0**	**-0/ +0**	**-2/ +4**	**-2/ +4**	**-0/ +0**	**-2/ +4**	**-2/ +4**	**-2/ +4**	**-0/ +0**	**-2/ +4**	**-2/ +4**	**-10/ +10**	**-0/ +0**	**-2/ +4**	**-2/ +4**	**-0/ +30**	**-0/ +30**
Trial Day	**1**	**2**	**7[e]**	**15**	**29**	**30**	**43**	**57**	**57**	**58**	**85**	**120**	**180**	**181**	**208**	**270**	**393**	**393**
Anchoring	**-**	**1**	**1**	**1**	**1**	**29**	**29**	**29**	**57**	**57**	**57**	**29**	**1**	**180**	**180**	**180**	**180**	**180**
Subset of subjects from each CVnCoV group at predefined site(s): Cell-mediated immunity (~40-64 mL)[u]	X[t]				X[t]		X											
Subset of subjects from each CVnCoV group at predefined site(s): Cytokine assessment (serum) (~6 mL)	X[t]	X																
Maximum total blood volume (mL)	109	15			73		73		33		33		33		33			33
Trial end																	**X**	

AE: adverse event; AESI: adverse event of special interest; ANA: antinuclear antibody; ECG: electrocardiogram; ELISA: enzyme-linked immunosorbent assay; Ig: immunoglobulin; RT-PCR: reverse transcription polymerase chain reaction; SAE: serious adverse event; TSH: thyroid-stimulating hormone

a. Procedures to establish subject eligibility may be performed within 21 days prior to trial vaccine administration. If all information to establish eligibility is available, these procedures can be done on the same day including the trial vaccine administration. Eligibility criteria need to be reviewed on the day of vaccination prior to trial vaccine administration.
b. Phone contact on Day 57 is not required for subjects receiving an open-label booster vaccination on Day 57.
c. This will only take place for subjects receiving an open-label booster vaccination on Day 57.
d. This will only take place for subjects receiving an open-label booster vaccination on Day 180.
e. Phone contact can be made on Day 7 at the site's discretion to review the eDiary with the subject, but is not mandatory, and does not replace other scheduled phone contacts
f. See Section 6.3 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.
g. Only applicable for subjects receiving an open-label booster vaccination on Day 57/Day 180.
h. Physical examination and vital signs must be performed/measured by a qualified healthcare professional. See Section 9.1.4 for an overview of the required assessments.
i. 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.
j. Vital signs will be measured pre- and post-vaccination prior to discharge. Subjects will be observed for 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.
k. Solicited and unsolicited AEs will be recorded in diaries.
l. SAEs, AESIs (including COVID-19 disease), intercurrent medical conditions that may affect the immune response to vaccination, and AEs leading to trial or trial vaccine withdrawal will be collected throughout the trial.
m. Immunosuppressants or other immune-modifying drugs, with the exception of topically-applied, inhaled, or intranasal steroids, taken within 6 months prior to enrollment and any other concomitant medication/vaccination taken within 1 month prior to enrollment should be recorded to establish eligibility.

n. See Appendix 3 for an overview of the safety laboratory assessments.
o. A blood sample for serum pregnancy testing will be taken from women of childbearing potential on Day 1 prior to vaccination to establish eligibility. Urine pregnancy tests will be performed before each vaccination, unless the serum pregnancy test was performed less than 3 days before and yielded a negative result.
p. A blood sample will be drawn for potential retrospective measurement of TSH, thyroid antibodies, and ANA in case of the occurrence of clinical autoimmune events during the trial (other autoantibodies might be investigated as well depending on the possible clinical autoimmune event).
q. Swabs for COVID-19 disease testing will also be collected in case the subject displays symptoms of acute respiratory infection (including, but not limited to COVID-19 disease), if operationally possible (see Section 9.3).
r. See Section 9.2 for an overview of the immunogenicity assessments.
s. ELISA will be performed on SARS-CoV-2 spike (S) protein to investigate immune responses to vaccination and on SARS-CoV-2 nucleocapsid (N) protein to determine immune response to natural infection.
t. Baseline blood samples on Day 1, Day 29, Day 57, and Day 180 must be collected prior to vaccination.
u. The blood volume to be collected for cellular immune response will be 64 mL on Day 1 and 40 mL on Days 29 and 43.
v. Only for subjects receiving 6 µg and for subjects receiving the 12 µg booster dose on Day 57 or Day 180.
w. Only for subjects who received the booster on Day 180 and who had not received a licensed/authorized vaccine before the End of Trial visit.

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 phosphorlated 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.

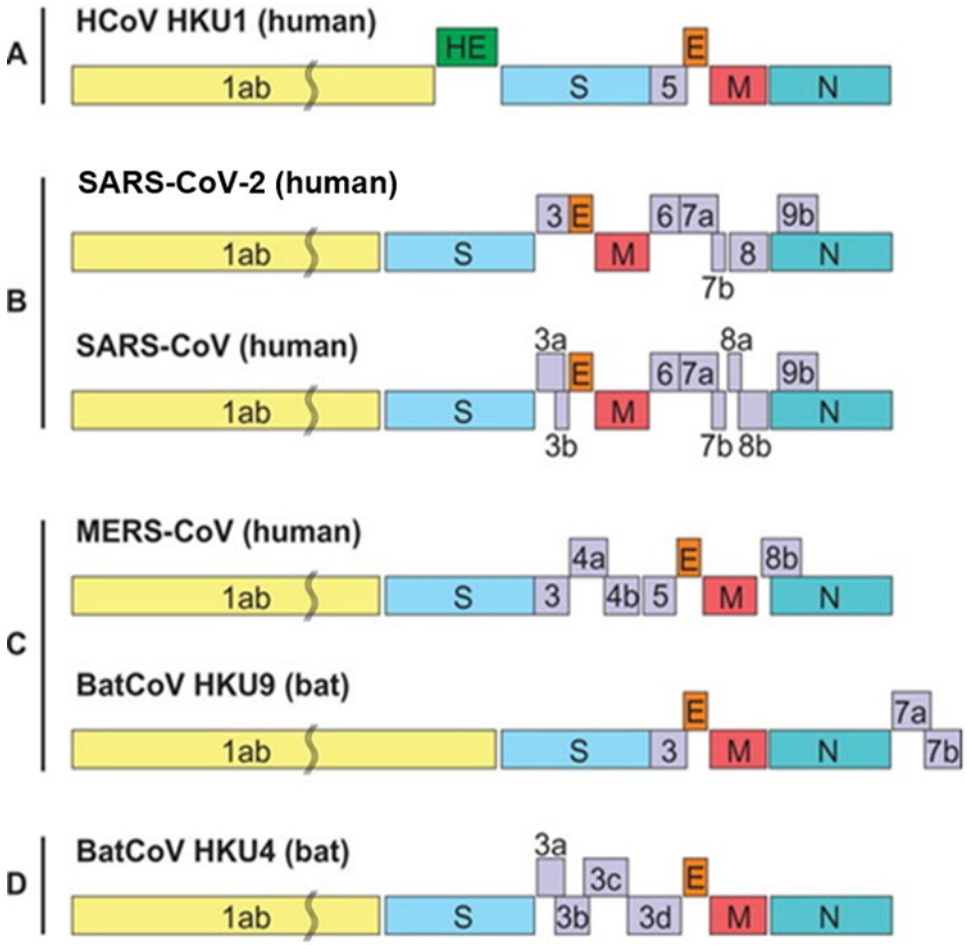
There are 4 genera of CoVs, namely, Alphacoronavirus (αCoV), Betacoronavirus (βCoV), Deltacoronavirus (δCoV), and Gammacoronavirus (γCoV) [3]. Evolutionary analyses have shown that bats and rodents are the gene sources of most αCoVs and βCoVs, while avian species are the gene sources of most δCoVs and 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 09 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 then globally. On 07 January 2020, the International Health Regulations (2005) Emergency Committee agreed that the outbreak met the criteria for a Public Health Emergency of International Concern. On 12 March 2020, the World Health Organization (WHO) announced that the outbreak was characterized as a pandemic.

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

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

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



Source: Chan *et al.*, 2020 [3]

The S gene of SARS-CoV-2 appears 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 level of amino acids, 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 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 core 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.

3.1.2 COVID-19 Disease

SARS-CoV-2 is transmitted mainly through close contact and respiratory droplets. The mean incubation period is 4 to 6 days with about 95% of patients developing symptoms within 14 days after infection [10,11]. The most common symptoms of COVID-19 disease 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 currently around 3% [21].

According to the 2020 World Health Statistics, the COVID-19 pandemic is causing significant loss of life, disrupting livelihoods, and threatening the recent advances in health and progress towards global sustainable development goals [22]. On 11 October 2020, according to WHO, 37 109 851 cases have been confirmed globally, including 1 070 355 deaths [21].

3.2 Trial Rationale

In partnership with the Coalition for Epidemic Preparedness Innovations (CEPI), CureVac AG is developing a new SARS-CoV-2 messenger ribonucleic acid (mRNA) vaccine formulated with lipid nanoparticles (LNP), referred to as CVnCoV, for the prevention of COVID-19 disease when administered as a 2-dose primary vaccination schedule. CVnCoV was developed with CureVac's proprietary RNActive® technology platform, which uses chemically unmodified mRNA molecules as a basis for vaccination. The safety and immunogenicity of this vaccine was evaluated for the first time in humans in the dose-finding trial CV-NCOV-001.

This second trial was conducted to confirm the safety and immunogenicity of CVnCoV at different dose levels in adults >60 years of age (i.e., 61 years or older) when administered according to a 0 (Day 1), 1-month (Day 29) primary vaccination schedule. The dose levels to be administered in this trial will be selected based on data from Trial CV-NCOV-001. For this elderly population, higher dose levels than the dose levels investigated for adults 18 to 60 years of age will be considered to address potentially reduced immunogenicity in

the context of immunosenescence. In addition, the safety and immunogenicity of a booster dose of CVnCoV administered at approximately 2 months (Day 57) or 6 months (Day 180) after the first dose will be evaluated in a subgroup of subjects.

In order to bridge to the population evaluated in Trial CV-NCOV-001, adults 18 to 60 years will also be enrolled in this trial.

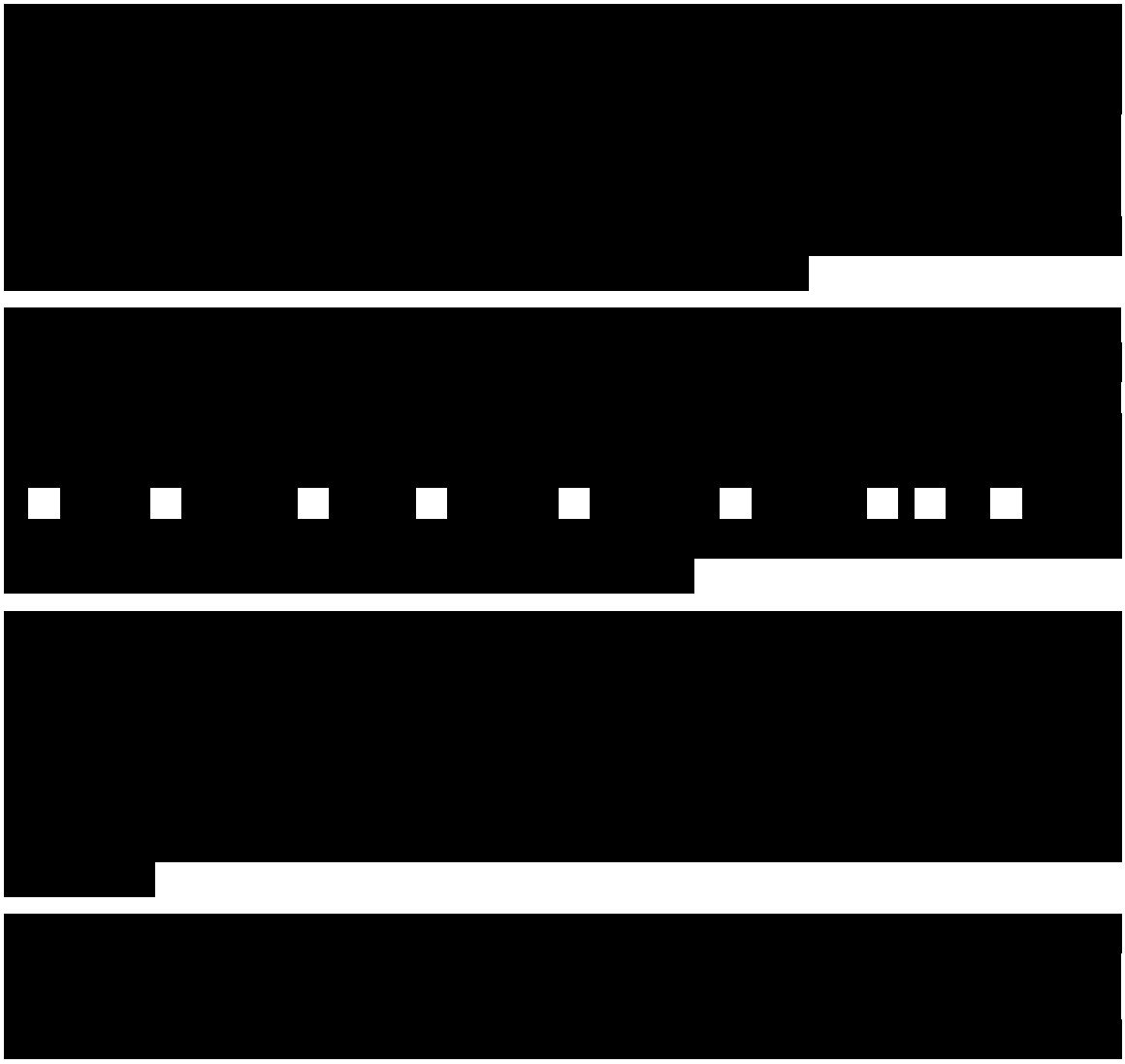
For further clinical development and for the expansion cohorts, the selected dose of 12 µg will generate comprehensive safety and immunogenicity data for CVnCoV.

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

3.3 Risk/Benefit Assessment

3.3.1 Known Potential Risks

Evidence from non-clinical studies shows that CVnCoV is well tolerated in relevant animal species and no safety risks have been identified.



[redacted]

Furthermore, CureVac is consulting with external regulatory and scientific experts, including CEPI, 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, as recommended by Wang and colleagues [30]. These approaches are in line with those agreed upon for COVID-19 vaccine development by the International Coalition of Medicines Regulatory Authorities [31].

[redacted]

During the very early stages of manufacture of CVnCoV, kanamycin is used. Although there is no evidence of residual kanamycin in the final investigational medicinal product (IMP), subjects with a previous class I allergic reaction to aminoglycosides should be excluded from vaccination with CVnCoV as a measure of precaution.

[redacted]

[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, COVID-19 disease or other AE specific to SARS-CoV-2 vaccines or the target disease) 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 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.

Active Controls

Common side effects of both the hepatitis A vaccine and pneumococcal vaccine are the same as for every vaccine and include injection site reactions, loss of appetite, fever, and headache.

3.3.2 Known Potential Benefits

Subjects receiving the investigational CVnCoV vaccine may not directly benefit from this vaccination since the immune response is still being evaluated in humans. Furthermore, no correlate of protection or threshold of protection has been established for COVID-19 disease. 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, electrocardiogram [ECG]).

Active Controls

Active controls were selected for this trial to offer a certain level of benefit to the subjects in the control groups. Subjects 18 to 60 years of age will receive the hepatitis A vaccine and subjects >60 years of age (i.e., 61 years or older) will receive the pneumococcal vaccine. These vaccines are considered to provide some benefit to subjects in the respective age categories.

3.3.3 Assessment of Potential Risks and Benefits

To minimize the risk for subjects participating in this trial, a data safety monitoring board (DSMB) will oversee the safety of the subjects on a specified schedule. The DSMB will also convene if any serious adverse events (SAEs) related to the vaccine occurs. If any dose levels other than those already administered in Trial CV-NCOV-001 are investigated in this trial, an internal safety review committee (iSRC) will review the safety and reactogenicity data on a continuous basis.

Potential important medical risks associated with CVnCoV, as specified in Section 3.3.1, can be managed at the clinical trial sites, should they occur.

4 TRIAL OBJECTIVES AND ENDPOINTS

4.1 Objectives

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

4.1.1 Primary

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

4.1.2 Secondary

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

4.1.3 Exploratory

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

4.2 Endpoints

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

4.2.1 Primary

- The frequencies, intensities, and duration of solicited local AEs on Day 1 and Day 29 and the following 7 days by dose and group.
- The frequencies, intensities, duration, and relationship to trial vaccination of solicited systemic AEs on Day 1 and Day 29 and the following 7 days by dose and group.
- The occurrence, intensities and relationship to trial vaccination of unsolicited AEs on Day 1 and Day 29 and the following 28 days by dose and group.
- The occurrence and relationship to trial vaccination of SAEs and AESIs throughout the trial.

On Day 29 and Day 43:

- The proportion of subjects seroconverting for SARS-CoV-2 spike protein antibodies, as measured by ELISA.

- Individual SARS-CoV-2 spike protein-specific antibody levels in serum, as measured by ELISA.
- Geometric mean titers (GMTs) of serum SARS-CoV-2 spike protein antibodies, as measured by ELISA.
- The proportion of subjects seroconverting for SARS-CoV-2 neutralizing antibodies, as measured by an activity assay.
- Individual SARS-CoV-2 neutralizing antibody levels in serum.
- GMTs of serum SARS-CoV-2 neutralizing antibodies, as measured by an activity assay.

4.2.2 Secondary

- The frequencies, intensities, and duration of solicited local AEs on the day of the booster administration and the following 7 days by group.
- The frequencies, intensities, duration, and relationship to trial vaccination of solicited systemic AEs on the day of the booster administration and the following 7 days by group.
- The occurrence, intensities and relationship to trial vaccination of unsolicited AEs on the day of the booster administration and the following 28 days by group.

On Day 57 (only for subjects receiving the booster dose on Day 57), Day 85 (only for subjects receiving the booster dose on Day 57), Day 180 (only for subjects receiving the booster dose on Day 57 or Day 180), Day 208 (only for subjects receiving the booster dose on Day 180), and Day 393 (only for subjects receiving the booster dose on Day 180):

- The proportion of subjects seroconverting for SARS-CoV-2 spike protein antibodies, as measured by ELISA.
- Individual SARS-CoV-2 spike protein-specific antibody levels in serum, as measured by ELISA.
- GMTs of serum SARS-CoV-2 spike protein antibodies, as measured by ELISA.
- The proportion of subjects seroconverting for SARS-CoV-2 neutralizing antibodies, as measured by an activity assay.
- Individual SARS-CoV-2 neutralizing antibody levels in serum.
- GMTs of serum SARS-CoV-2 neutralizing antibodies, as measured by an activity assay.

4.2.3 Exploratory

CMI response

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

- The frequency and functionality of SARS-CoV-2 spike-specific T-cell response after antigen stimulation.
  Intracellular cytokine staining (ICS) to investigate Th response will be used to investigate whether vaccination induces a Th1 shift from baseline. Further T-cell

immune response may be investigated with other technologies like ELISpot or CyTOF.

- The proportion of subjects with a detectable increase in SARS-CoV-2 spike-specific T-cell response.

Innate immune response

On Day 1 and Day 2 in a subset of subjects:

- Serum cytokine concentrations, including but not limited to IFN-α, IFN-γ, IL-6, chemokine ligand (CCL) 2, and IFN-γ-induced protein 10 (IP 10).

Evaluation of infection

- Number of subjects with virologically-confirmed SARS-CoV-2 infection as measured by RT-PCR at clinically determined time points throughout the trial.

5 TRIAL DESIGN

5.1 Overall Design

This is a Phase 2a, partially blind, active-controlled, dose-confirmation trial to assess the safety and immunogenicity of provisionally selected CVnCoV dose levels of 6 and 12 µg in an older adult population. The design of the trial will allow an increase or decrease in dose based on data from Trial CV-NCOV-001 and this trial (see Section 5.2). An overview of the planned number of subjects to be enrolled per trial group and the vaccination schedule is provided in Table 2.

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

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

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

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

The 6 µg and 12 µg groups will be enrolled sequentially, i.e., enrollment in the 12 µg groups will only be initiated once Groups 1 and 2 have been fully enrolled. Group 2 (subjects >60 years, for 6 µg) will be initiated in 4 sentinel subjects. These subjects should be vaccinated at least 60 minutes apart. Safety and reactogenicity data reported during an observation period of at least 24 hours after vaccination will be collected and reviewed by an iSRC. In this review, the iSRC will review all available safety data, but focus specifically on Grade 3 adverse reactions. Based on this review, the iSRC will decide on continuation of enrollment of subjects at this dose level. In a next step, 8 additional sentinel subjects will be enrolled. Safety and reactogenicity data reported during an observation

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

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

5.2 Change in Dose Level

Other possible dose levels to be administered in this trial will continuously be assessed based on the ongoing Trial CV-NCOV-001 in adults aged 18 to 60 years. In case additional dose levels are investigated in this trial, such a dose level will be initiated in additional sentinel subjects in the same manner as described in Section 5.1. If the dose level of 12 µg is considered too reactogenic for adults aged 18 to 60 years in the CV-NCOV-001 trial, the dose level in this trial would be reduced from 12 µg to 8 µg.

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

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

5.3 Expansion Cohorts

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

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

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

Table 2 Trial Groups and Vaccination Schedule

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

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

5.4 Stopping Rules

5.4.1 Individual Stopping Rules

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

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

- An allergic/anaphylactic reaction considered as related to the trial vaccine.
- Any SAE considered as related to the trial vaccine.
- Any Grade 3 AE considered related to the trial vaccine, with the following exceptions:
  - Transient Grade 3 systemic AE (fever, headache, fatigue, chills, myalgia, arthralgia, nausea/vomiting, and diarrhea) considered related to the trial vaccine that resolved within 48 hours to Grade ≤2.
  - Transient Grade 3 local AE that resolved within 48 hours to Grade ≤2.

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

5.4.2 Trial Suspension Rule

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

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

5.5 Scientific Rationale for Trial Design

This trial will evaluate the safety, reactogenicity, and immunogenicity of different CVnCoV dose levels in an elderly population (>60 years of age [i.e., 61 years or older]). As the elderly are affected most by SARS-CoV-2, it is critical to investigate CVnCoV in this population and determine an appropriate dose and regimen.

A booster dose will be administered at approximately 2 months (Day 57) or at 6 months (Day 180) after the first dose of the primary regimen to address potentially reduced immunogenicity in the context of immunosenescence in this elderly population. Furthermore, a 0, 1, 6-month schedule is commonly used for licensed vaccines because it allows for an extended period for affinity maturation before the later boost.

The duration of the trial is appropriate for mRNA vaccines, allowing a minimum of 365 days of safety follow-up after the last primary dose for all subjects, to collect and evaluate safety data as needed.

The hepatitis A and pneumococcal vaccines were selected as control because hepatitis A and pneumococcal disease occur in the countries in which the trial is being conducted; subjects will therefore benefit from this control to some degree.

5.6 Justification for Dose

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

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

5.7 End of Trial Definition

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

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

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.

6.1 Inclusion Criteria

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

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

   A healthy subject is defined as an individual who is in good general health, according to the Investigator's assessment. Chronic health conditions are acceptable if the condition is considered well controlled with treatment according to the discretion of the Investigator.

2. Expected to be compliant with protocol procedures and available for clinical follow-up through the last planned visit.

3. Subjects who are able to understand and willing to provide informed consent.

4. Physical examination without clinically significant findings according to the Investigator's assessment.

5. Body mass index (BMI) ≥18.0 and ≤32.0 kg/m^2.

6. Female subjects of childbearing potential: at the time of enrollment, negative human chorionic gonadotropin (hCG) pregnancy test (serum) for female subjects presumed to be of childbearing potential on the day of enrollment. On Day 1 (pre-vaccination): negative urine pregnancy test (required if serum pregnancy test was performed more than 3 days before).

7. Female subjects of childbearing potential must use highly effective methods of birth control from 2 weeks before the first administration of the trial vaccine until 3 months following the last administration. The following methods of birth control are considered highly effective when used consistently and correctly:

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

Male subjects should be instructed not to get their partners pregnant until 3 months after the last administration.

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

6.2 Exclusion Criteria

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

1. Use of any investigational or non-registered product (vaccine or drug) other than the trial vaccine within 28 days preceding the administration of the trial vaccine, or planned use during the trial period.
2. Receipt of any other vaccines within 28 days prior to enrollment in this trial or planned receipt of any vaccine within 28 days of trial vaccine administration (primary dose or booster dose).
3. Receipt of any investigational or licensed/authorized SARS-CoV-2 or other coronavirus vaccine prior to the administration of the trial vaccine.
4. Any treatment with immunosuppressants or other immune-modifying drugs (including, but not limited to, corticosteroids, biologicals, and methotrexate) within 6 months prior to the administration of the trial vaccine or planned use during the trial, with the exception of topically-applied, inhaled, or intranasal steroids.
5. Use of hormonal therapy for gender reassignment.
6. Any medically diagnosed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination, including known human immunodeficiency virus infection, hepatitis B virus infection, and hepatitis C virus infection.
7. History of immune-mediated or autoimmune disease.
8. History of angioedema (known C1 inhibitor deficiency).
9. History of anaphylaxis or allergy to any component of CVnCoV or aminoglycoside antibiotics.
10. History of or current alcohol and/or drug abuse.
11. Subjects who are active smokers, were active smokers within the last year (including any vaping in the last year), or have a total smoking history ≥10 pack years. A pack year is calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked.
12. History of virologically-confirmed SARS, MERS, or COVID-19 disease or known exposure (without any personal protective equipment) to an individual with confirmed COVID-19 disease or SARS-CoV-2 infection within the past 2 weeks.
13. Administration of immunoglobulins and/or any blood products within the 3 months preceding the administration of any dose of the trial vaccine.

14. Presence or evidence of significant uncontrolled acute or chronic medical or psychiatric illness. Significant medical or psychiatric illnesses include but are not limited to:

    - Uncontrolled respiratory disease (e.g., chronic obstructive pulmonary disease, asthma), including use of the following asthma medications: intravenous corticosteroids, leukotriene modifiers, biologics.
    - Uncontrolled cardiovascular disease (e.g., congestive heart failure, cardiomyopathy, ischemic heart disease, history of stroke, peripheral artery disease, pulmonary embolism).
    - History of myocarditis or pericarditis as an adult.
    - Diabetes mellitus (insulin-dependent).
    - Uncontrolled neurological disorders or Guillain-Barré syndrome or history of seizure, except for febrile seizures during childhood.
    - Current or past malignancy, unless completely resolved without sequelae for >5 years.

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

6.3 Vaccine Delay Recommendations

After enrollment, subjects may encounter clinical circumstances that warrant a delay of trial vaccine administration. These situations are listed below:

- Subjects with a clinically significant (Grade ≥2) active infection or other acute disease (as assessed by the Investigator) or temperature >38.0°C (>100.4°F), within 3 days of intended trial vaccination. Further dose administration 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) for at least 3 days, if this still allows to vaccinate the subject as per the predefined interval. Temperature should be measured orally.
- Subjects who took antipyretic medication within 8 hours before intended trial vaccination.

In case of delay, the vaccination should take place within the allowed time windows specified in Table 1.

6.4 Failure to Meet Eligibility Criteria

The Investigator must account for all subjects who sign an informed consent form (ICF). If the subject is found to be not eligible (i.e., did not meet all inclusion criteria or met one or more exclusion criteria), the Investigator should document this in the subject's source data and electronic case report form (eCRF).

Re-doing the full assessments for eligibility assessment as per Table 1 or re-testing (i.e., re-doing a single assessment) is allowed if the reason for ineligibility is a transient event.

An example of a condition under which re-assessment may be considered includes:

- Subjects who required treatment for an acute illness that resolved (e.g., a urinary tract infection) may be re-assessed once the illness resolved or the medical problem stabilized.

An example of a condition under which re-testing may be considered includes:

- Subjects who have clinical laboratory test value(s) that are not in line with the medical history and clinical evaluation of the subjects may be re-tested to confirm the value of the tests, if still allowed within the enrollment period (Day -21 to Day 1). If not feasible, the subject should be re-assessed for eligibility.

7 TRIAL VACCINE

7.1 Trial Vaccine Administration

7.1.1 Description of the Trial Vaccine

CVnCoV is an investigational LNP-formulated RNActive® SARS-CoV-2 vaccine. The IMP is composed of the active pharmaceutical ingredient, an mRNA that encodes Wsmpv-SP, and 4 lipid components: cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), PEG-ylated lipid, and a cationic lipid.

7.1.2 Description of the Active Controls

The active controls used in this trial will be a licensed hepatitis A vaccine and a licensed pneumococcal vaccine. These vaccines will be prepared, stored, handled, and administered in accordance with the package inserts.

7.1.3 Dosing and Administration

The provisional dose levels to be administered are provided in Table 2.

Injections must be performed intramuscularly (IM) by needle 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 instruction for injection described in the trial-specific pharmacy manual must be followed. An intravascular injection is highly unlikely at this site due the lack of larger blood vessels.

Subjects should be observed for 30 minutes following each vaccination. Since there is a theoretical risk of anaphylactic reactions, the 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. If anaphylaxis or severe hypersensitivity reactions occur following IMP administration, no further doses should be given.

7.2 Preparation/Handling/Storage/Accountability

7.2.1 Preparation

Mixing of CVnCoV and 0.9% NaCl to produce dosing solutions for IM injection will occur according to the handling manual provided by CureVac AG.

7.2.2 Product Storage and Stability

CVnCoV is presented as an aqueous solution and stored below -60°C.

7.2.3 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.
- Unique subject identifier.
- Date and quantity of trial vaccine dispensed to each subject.
- Initials of the person preparing the dose.
- Initials of the person administering the vaccine.

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

7.3 Randomization and Blinding

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

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

The Sponsor and safety monitoring committees will be unblinded for data from the randomized groups, but will take appropriate measures to ensure subject blinding is kept at site level until database lock.

7.3.1 Emergency Unblinding

In case of urgent medical conditions and if further treatment decisions must be based on the knowledge of the trial vaccine, the respective subjects might be unblinded.

The Investigator can request individual subject unblinding by using the interactive voice response system (IVRS) and preferably after contacting the Sponsor.

Individual unblinding should only occur in emergency situations for reasons of subject safety when knowledge of the IMP is essential for the clinical management or welfare of the subject.

The identity of the IMP 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 IVRS.

When the blind is broken, the date, exact timing and reason must be fully documented in the source documents and entered into the eCRF, as applicable. 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 the trial.

7.3.2 Licensed/Authorized Vaccine

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

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

7.4 Vaccine Compliance

The Investigator will record all injections (CVnCoV and active control) administered in the subject's eCRF page.

7.5 Misuse and Overdose

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

Definition 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) should be treated symptomatically with physical measures, paracetamol or non-steroidal anti-inflammatory drugs.

7.6 Concomitant Therapy and Vaccines

Concomitant medication and vaccines including the reason for administration must be recorded in the subject's eCRF. As outlined in Section 6.3, vaccination will be delayed in subjects who take antipyretic medication within 8 hours before intended trial vaccination, however, prophylactic paracetamol can be taken after vaccination and should be documented in the subject's eCRF.

For additional information, refer to Section 6.2.

7.7 Therapy Leading to Discontinuation

If a subject requires therapy listed as an exclusion criterion in Section 6.2 (with the exception of a licensed/authorized SARS-CoV-2 vaccine) and which cannot be delayed, discontinuation would be considered to ensure integrity of the trial data, following individual case review, but safety follow-up until 12 months after the last dose of the primary regimen should be pursued.

Licensed/authorized SARS-CoV-2 vaccines are allowed. Receipt of any other investigational SARS-CoV-2 vaccine or vaccines against any other virus from the coronavirus family is prohibited during the trial.

7.8 Treatment After the End of Trial

This trial will investigate a prophylactic vaccine and therefore post-trial care is not applicable.

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. Assessments of solicited AEs and associated phone calls or electronic prompts (by e.g., text message) for the second (and booster) dose will not be necessary if a subject received only 1 dose. Overall, only relevant visits need to be conducted for any subjects who prematurely discontinue from trial product administration. Immunogenicity assessments may be performed at the Investigator's discretion, if the subject agrees.

8.1 Discontinuation of Trial Vaccine Administration

The primary reason for discontinuation of further administrations of trial vaccine doses 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).

- 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 9.1.2).

  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.

- Virologically-confirmed SARS-CoV-2 infection (as specified in Section 9.3).

- Trial terminated by the Sponsor (in which case the minimum safety follow-up of 1 year after the last trial vaccine dose would be performed).

- Major protocol deviation.
- Other.

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

8.2 Withdrawal from the Trial

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

- Continued participation jeopardizes the subject’s health, safety, or rights.
- The subject has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the subject’s health or the subject is unwilling to continue because of the AE. The reasons for not performing further safety or immunogenicity assessments should be documented.
- The subject did not return to the trial site and multiple attempts (at least 3) 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.

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

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

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:

- Safety reasons: the incidence of AEs in this or any other trial using the same or 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 trial site is unlikely to be able to recruit sufficient subjects within the agreed time frame.
- The trial 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 a regulatory authority for any reason or if recommended by the iSRC or DSMB, or at a site level by the Independent Ethics Committee (IEC) or

Institutional Review Board (IRB). The Sponsor may close an individual trial site prematurely for reasons such as poor protocol compliance or unsatisfactory recruitment of subjects.

8.4 Lost to Follow-Up

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

9 TRIAL ASSESSMENTS AND PROCEDURES

The Schedule of Activities is detailed in Table 1. The trial procedures apply to all subjects, independent of the serology status at baseline per retrospective analysis. For each procedure, subjects are to be assessed by the same Investigator or site personnel whenever possible.

In case subjects are not able to come to the site for protocol-specified 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).

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. If all information to establish eligibility is available, these procedures can be done on the same day including the trial vaccine administration. Eligibility criteria need to be reviewed on the day of vaccination prior to trial vaccine administration.

The maximum total volume of blood taken over the trial period from any subject will be approximately 279 mL (or 435 mL for subjects in who CMI and cytokines will be assessed). The blood volumes to be collected for each parameter are specified in Table 1.

9.1 Safety Assessments

9.1.1 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.

Unscheduled visits will be performed when deemed necessary for safety assessments or to ensure data integrity.

Subjects with any Grade 3 solicited or unsolicited AEs reported electronically by the subject will be contacted by the Investigator, and subjects who did not enter any diary information will be prompted and then contacted in case of non-response within 24 hours.

9.1.1.1 Solicited Adverse Events

Solicited local AEs (injection site pain, redness, swelling, and itching) and solicited systemic AEs (fever, headache, fatigue, chills, myalgia, arthralgia, nausea/vomiting, and diarrhea) will be recorded on the day of vaccination and the following 7 days using a diary (electronic or paper).

Temperature should be measured orally.

Solicited AEs will be assessed on an intensity scale of absent, mild, moderate, and severe (Table 3 and Table 4). In case of related Grade 3 solicited or unsolicited AEs reported for more than 1 day in the diary, the subject will be questioned to establish the total duration of the AE as exactly as possible and this information will be recorded in the eCRF.

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

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

Table 3 Intensity Grading for Solicited Local Adverse Events

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

Based on the United States Food and Drug Administration toxicity grading scale [33].

Table 4 Intensity Grading for Solicited Systemic Adverse Events

Adverse Event	Grade	Definition
Fever	0	<38°C
	1	≥38 – 38.4°C
	2	≥38.5 – 38.9°C
	3	≥39°C
Headache	0	Absent
	1	Mild, no interference with activity
	2	Moderate, some interference with 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 activity
	2	Moderate, some interference with activity
	3	Significant, prevents activity
Chills	0	Absent
	1	Mild, no interference with activity
	2	Moderate, some interference with activity
	3	Significant, prevents activity
Myalgia	0	Absent
	1	Mild, no interference with activity
	2	Moderate, some interference with activity
	3	Significant, prevents activity
Arthralgia	0	Absent
	1	Mild, no interference with activity
	2	Moderate, some interference with activity
	3	Significant, prevents activity
Nausea/ Vomiting	0	Absent
	1	Mild, no interference with activity and/or 1 – 2 episodes/ 24 hours
	2	Moderate, some interference with activity and/or >2 episodes/ 24 hours
	3	Significant, prevents daily activity, requires outpatient intravenous hydration
Diarrhea	0	Absent
	1	2 – 3 loose stools or <400 g/24 hours
	2	4 – 5 stools or 400 – 800 g/24 hours
	3	6 or more watery stools or >800 g/24 hours or requires outpatient intravenous hydration

Based on the United States Food and Drug Administration toxicity grading scale [33].

9.1.1.2 Unsolicited Adverse Events and Serious Adverse Events

Diaries will also be used for collection of unsolicited AEs on each vaccination day and the following 28 days. In addition, subjects will receive a prompt (by e.g., a phone call or text message) to verify whether the subjects had any health concerns since the last visit.

The occurrence of AEs (serious and non-serious) will be assessed by non-directive questioning of the subject at each visit. AEs volunteered by the subject during or between visits in the diary or detected through observation, physical examination, laboratory test, or other assessments during the entire trial, will be recorded in the eCRF, if they fall within

the reporting period. Subjects should be instructed to report immediately any AEs with serious symptoms, subjective complaints or objective changes in their well-being to the Investigator or the site personnel, regardless of the perceived relationship between the event and the trial vaccine.

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

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

9.1.1.3 Adverse Events of Special Interest

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

- AEs with a suspected immune-medicated etiology (pIMDs, see Appendix 8),
- COVID-19 disease,
- other AEs relevant to SARS-CoV-2 vaccine development or the target disease (see Appendix 9).

AESIs will be collected throughout the trial.

9.1.2 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.

9.1.3 Safety Laboratory Assessments

Blood samples for determination of hematology (complete blood count, including differential and platelets), clinical biochemistry, and coagulation will be analyzed as indicated in the Schedule of Activities. An overview of the safety laboratory tests is provided in Appendix 3.

In addition, a blood sample for serum pregnancy testing will be taken from women of childbearing potential on Day 1 prior to vaccination to establish eligibility. Urine pregnancy tests will be performed before each vaccination, unless the serum pregnancy test was performed less than 3 days before and yielded a negative result.

Laboratory data will be graded according with the United States Food and Drug Administration (FDA) toxicity grading scale [33]. Any institutional normal reference ranges should be provided to demonstrate that they are appropriate.

9.1.4 Vital Signs, Physical Examination, and ECG

Vital signs (body temperature, systolic/diastolic blood pressure, and heart rate) will be recorded in a standardized manner after the subject has rested in the sitting position for 5 minutes.

A complete physical examination should be performed at the time points specified in Table 1, except if a complete physical examination to establish eligibility was performed within 21 days prior to Day 1, in which case a symptom-directed physical examination can

be performed on Day 1 prior to the vaccine administration. The complete physical examination will include: general appearance, eyes/ears/nose/throat, head/neck/thyroid, lymph node areas, cardiovascular system, lung/chest, abdomen and genitourinary system, extremities and neurological examination, skin examination, and measurement of weight and height.

An ECG with conventional 12-lead traces will be recorded on Day 1 for all subjects. Additionally, ECGs should be performed as clinically indicated.

9.1.5 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.

9.1.6 Safety Monitoring Committees

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

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

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

9.2 Immunogenicity Assessments

An overview of the timing of blood sample collection for immunogenicity assessment is provided in Table 1.

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

If a subject receives a licensed/authorized vaccine, no further immunogenicity samples will be collected/analyzed after receipt of the licensed/authorized vaccine. Immunogenicity samples on Day 393 will only be collected from subjects who attend this visit at the site,

ie, subjects who received the Day 180 booster AND who had not received a licensed/authorized vaccine before this visit.

9.2.1 Humoral Immune Response

The humoral immune response elicited by the vaccine will be evaluated by measurement of SARS-CoV-2 spike protein-specific antibodies in serum by ELISA and SARS-CoV-2 neutralizing antibodies in serum by an activity assay.

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

Seroconversion will be defined as:

- Subjects seronegative at baseline (in addition to a negative serostatus at baseline, such subjects would also not have been exposed to SARS-CoV-2 during the trial before the applicable sample was collected, as confirmed by a titer increase in antibodies to SARS-CoV-2 N-antigen or a RT-PCR-positive swab during the trial): an increase in antibody titer against SARS-CoV-2 spike protein versus baseline.
- Subjects seropositive at baseline: a 2-fold increase in antibody titer against SARS-CoV-2 spike protein versus baseline.

To further evaluate the humoral immune response, cross-reactivity with other viral antigens might be analyzed.

9.2.2 Cell-Mediated Immunity

CMI will only be evaluated in approximately 20 subjects per CVnCoV group at assigned site(s).

The frequency and functionality of SARS-CoV-2 spike-specific T-cell response after antigen stimulation will be determined in PBMC in comparison to baseline. For example, ICS to investigate Th response will be used to investigate whether vaccination induces a Th1 shift from baseline. Further T-cell immune response may be investigated with other technologies like ELISpot or CyTOF.

9.2.3 Innate Immune Response

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

9.3 Laboratory Testing for COVID-19 Disease

As a baseline assessment, a RT-PCR test for SARS-CoV-2 will be performed in all subjects. Testing will be done for SARS-CoV-2 spike protein to evaluate vaccine-induced immune responses as well as for SARS-CoV-2 N-antigen (not contained in the vaccine construct) to evaluate immune responses induced by natural infection. This will allow to retrospectively define the subject's serology status, including the baseline status for the by-group/cohort analysis.

Subjects will be prompted once or twice per week to report if the subjects have any of the following symptoms: cough, shortness of breath, difficulty breathing, fever ≥37.8°C, fatigue, myalgia, chills, wheezing, nasal congestion, runny nose, sore throat, headache, diarrhea, or new olfactory and taste disorders.

A COVID-19 symptoms log listing these symptoms will be provided to subjects with RT-PCR-confirmed COVID-19 disease (refer to Appendix 4 for an example symptom log).

If any of these symptoms are observed, the Investigator will collect appropriate samples as soon as feasible and locally perform RT-PCR and/or serological assays as locally available to evaluate for infection with SARS-CoV-2. If a serological assay is performed, this should look at antibodies against N protein antigen, but not to antibodies against Spike viral antigen, as this is part of the vaccine. These assays will be repeated 7 to 14 days after the initial assessment.

Any subject with clinical suspicion of SARS-CoV-2 infection will undergo appropriate testing and referral within the local healthcare system as appropriate. Subjects with confirmed SARS-CoV-2 infections during the trial should not receive any additional vaccine dose, but will be closely monitored for disease patterns and severity. In order to assess severity of disease, subjects will document disease progression on a symptom log and Investigators will document additional clinical parameters based on hospital records, if applicable.

The currently available case definition for COVID-19 disease is provided in Appendix 5.

10 STATISTICAL CONSIDERATIONS

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

10.1 Sample Size Determination

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

Table 5 Sample Size

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

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

The trial is designed to provide a reasonable precision for an estimate of the number of subjects with seroconverting for nCoV spike protein antibodies and an acceptable rate of Grade 3 adverse reactions. Table 6 provides the estimate and 95% credibility interval for the observed numbers of subjects with seroconverting for nCoV spike protein antibodies for different sample sizes assuming a Beta (1.9,0.1) prior for seroconverting for nCoV spike protein antibodies and a Beta (0.5,1.5) prior for Grade 3 adverse reactions.

Table 6 Estimate of Number of Subjects with Seroconverting for nCoV Spike Protein Antibodies and 95% Credibility Interval

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

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

Table 7 provides probabilities (in %) that the following 2 conditions are simultaneously met for assumed true adverse reaction rates and for assumed true rates with seroconverting for nCoV spike protein antibodies and for different sample sizes:

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

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

Table 7 Probabilities (in %) for Assumed True Adverse Reaction Rates and for Assumed True Rates of Subjects with Seroconverting for nCoV Spike Protein Antibodies and Different Sample Sizes

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

10.2 Populations for Analyses

Safety Set

The safety set will consist of all subjects who received at least 1 dose of trial vaccine and for whom any post-vaccination safety data are available.

Immunogenicity Set

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

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

10.3 Statistical Analyses

10.3.1 General Considerations

All data obtained in this trial and documented in the eCRF will be listed and summarized with sample statistics or frequency tables as appropriate. In all tables, listings and figures, the dose groups will be reported from the lowest to the highest dose and by age group. The safety and immunogenicity analyses will be done overall and by baseline serology status for SARS-CoV-2.

The primary and secondary objectives and endpoints related to seroconversion for SARS-CoV-2 spike protein and SARS-CoV-2 neutralizing antibodies will, in addition to the immunogenicity set, be analyzed for subjects who:

- Received dose 1 and dose 2 of trial vaccine.
- Have baseline and Day 43 blood samples for immunogenicity assessment.
- Have no major protocol deviations expected to impact the immunogenicity outcomes.

A statistical analysis plan (SAP) will be prepared and finalized at the latest prior to database lock. 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.

Data on COVID-19 cases from this trial may be pooled with data from other trials investigating CVnCoV such as Trials CV-NCOV-004 and CV-NCOV-005.

10.3.2 Demographic, Medical History and Other Baseline Characteristics

Data will be summarized with respect to demographic characteristics (age, gender), medical history, baseline immune status, and all safety measurements using descriptive statistics (quantitative data) and contingency tables (qualitative data) by dose level and group. Medical history will only be listed.

10.3.3 Trial Vaccine Administration

The administrations of CVnCoV or the active control will be listed and the number of vaccinations will be summarized in contingency tables.

10.3.4 Concomitant Medication and Vaccinations

Concomitant medication/vaccination after the start of the trial vaccine will be listed and summarized by Anatomical Therapeutic Chemical term in contingency tables.

10.3.5 Primary Analysis

10.3.5.1 Primary Safety Analysis

The safety measurements will include:

1. AEs (type, intensity, frequency and relationship to trial vaccination), i.e., incidence and severity of AEs for both solicited local (injection site pain, redness, swelling, and itching) and solicited systemic events (fever, headache, fatigue, chills, myalgia, arthralgia, nausea/vomiting, and diarrhea) occurring on the day of vaccination and the

following 7 days) and unsolicited events (occurring on the day of vaccination and the following 28 days).

2. SAEs and AESIs throughout the trial.

Solicited AEs: For reactogenicity assessment, for each dose level and dose in each phase, the number and percentage of subjects with at least 1 solicited AE of any kind, by severity grade, for local, systemic, and overall, will be summarized after the first vaccination, after the second vaccination, after the booster vaccination (if applicable), and after any vaccination. In addition, results from the expansion phase will be tabulated by group. For subjects with more than 1 episode of the same event, the maximum severity will be used for tabulations. In addition, for each dose level and dose in the dose escalation and expansion phases, the frequencies and severity of each solicited AE will be summarized for each vaccination day and the following 7 days. Similar tabulations will be performed for solicited systemic AEs considered as related to the trial vaccine. The duration and severity of solicited AEs will be analyzed at subject level.

In addition, other indicators of safety (e.g., body temperature) will be collected and summarized. The number and percentage of subjects with Grade 3 adverse reaction(s) or SAEs considered as related to the trial vaccine according to the Investigator with the 95% credibility interval based on the Beta (0.5,0.5) prior distribution for each dose level and dose will be calculated and summarized.

Unsolicited AEs: Unsolicited AEs, 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 these events will be tabulated at the SOC and PT levels for each dose level and dose in the dose escalation and expansion phases. Additional similar tabulations will be performed to evaluate severity and relationship to the trial vaccine. AEs that are reported as related to the trial vaccine will be considered trial vaccine-related; missing classifications concerning trial vaccine relationship will also be considered trial vaccine-related.

Safety laboratory values will be classified into low/normal/high based on laboratory normal ranges. Each parameter will be presented by descriptive statistics at each visit including change from baseline. Shift tables normal ranges will be presented. All laboratory values will be listed. A separate listing for abnormal lab values will be presented.

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

10.3.5.2 Primary Immunogenicity Analysis

Percentages of subjects seroconverting for nCoV spike protein antibodies and values of antibody levels, percentages of subjects seroconverting for nCoV-neutralizing antibodies and GMTs and percentages of immune cell populations and cellular responders will be summarized for each dose level. Antibody levels for nCoV spike protein antibodies and GMTs for nCoV-neutralizing antibodies will be summarized for each dose level for subjects previously exposed to SARS-CoV-2 as indicated by confirmed positive SARS-CoV-2 serology at baseline. Data will be presented after each vaccine dose. In addition, levels of cytokines will be summarized for a subset of subjects.

10.3.6 Missing Data

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

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

Currently no replacement for drop-out subjects is foreseen.

For safety data, some missing or partially missing variables will be imputed as follows:

For start date:

- If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to missing.
- If the AE start date year value is less than the vaccination start date year value, the AE started before the vaccination. Therefore:
  - If the AE year is lower than the vaccination year and the AE month is missing, the imputed AE start date is set to the mid-year point (i.e., 01JULYYYY).
  - If the AE year is lower than the vaccination year and the AE month is not missing, the imputed AE start date is set to the mid-month point (i.e., 15MONYYYY).
- If the AE start date year value is greater than the vaccination start date year value, the AE started after vaccination. Therefore, if the AE year is greater than the vaccination year and the AE month is missing, the imputed AE start date is set to the year start point (i.e., 01JANYYYY).

For resolution date:

- If date of resolution is completely missing, it is assumed that it resolved at the date of the end of the AE assessment period.
- If year is present, it is assumed that it resolved on 31 December of that year (i.e., 31DECYYYY), or at the end of the AE assessment period if earlier.
- If year and month are present, it is assumed that it resolved on the last day of that month, or at the end of the AE assessment period if earlier.

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

10.3.7 Interim Analysis

One or more interim analyses may be performed for this trial. The analyses will be based on a data snapshot. As this trial is of exploratory nature and no inferential statistics are planned, no adjustment for multiple testing will be done. Depending on the evolving state

of the current pandemic and the public health need, an early analysis may be performed, and a study report based on interim data may be written to engage with collaborators and/or regulators.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Electronic Case Report Forms

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

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

The Sponsor or the contract research organization (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 (European Union member state local or competent authorities) or foreign governments (e.g., US-FDA and others). 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. Data collection must be completed for each subject who signs an ICF. For subjects who failed to meet the eligibility criteria, only demographic data and reason for failure will be documented.

In accordance with GCP, and regulatory requirements, the trial monitor will perform 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.

The compliance with the protocol will be examined with regard to inclusion and exclusion criteria, therapies leading to elimination and timing and availability of planned assessments. Protocol deviations will be monitored on an ongoing basis during the trial

and closed before database lock. Protocol deviations will be classified as minor, major, or critical deviations. The detailed definitions of important protocol deviations leading to exclusion 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 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 the European Medicines Agency.

11.4 Data Management and Coding

All data derived from the trial will remain the property of the Sponsor. Data management of this trial will be performed by a CRO. The Sponsor assumes accountability for actions delegated to other individuals, e.g., the 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 standard operating procedures 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 (see Section 11.3). This may include electronic source document verification. Data entered into the eCRF will be validated as defined in the data validation plan.

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

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

12 ETHICS

12.1 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 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 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 IEC together with the approved ICF must be filed in the trial files.

The Investigators will report promptly to the 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 IEC as required. On completion of the trial, the 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 IEC(s), as well as other relevant trial documentation will be submitted to the regulatory authority(ies) of the participating country/ies, according to local/national requirements, for review and approval before the beginning of the trial.

Any relevant AEs will be reported to regulatory authorities according to the processes and regulations of each country.

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

12.4 Informed Consent

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

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

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

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

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

13 DATA HANDLING AND RECORD KEEPING

Essential documents are those documents that individually and collectively permit evaluation of the trial and quality of the data produced. After completion of the trial, all documents and data relating to the trial will be kept in an orderly manner by the Investigator in a secure trial file. This file will be available for audits by the Sponsor/CRO or inspections by the regulatory agencies. Essential documents should be retained for 15 years after end of the trial. It is the responsibility of the Sponsor to inform the 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 a CRO (i.e., acting as a data processor), governed by a contract and strictly according to and subject to the General Data Protection Regulation (GDPR) and any applicable data protection rules and regulations. The Sponsor and the CRO (data processor) will 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 the subjects. 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, 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 GDPR).

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

The subject must be informed that his/her personal trial-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the ICF. 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 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 will ensure that this report meets the standards of the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3).

13.3 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 studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by mutual agreement. Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

14 REFERENCES

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

17. Deng Y, Liu W, Liu K, et al. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 (COVID-19) in Wuhan, China: a retrospective study. Chin Med J. 2020 Mar 20.
18. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. The Lancet Respiratory Medicine. 2020 Feb 24; https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30079-5/abstract
19. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) [cited 2020 Mar 24]; https://www.who.int/publications-detail/report-of-the-who-china-joint-mission-on-coronavirus-disease-2019-(covid-19)
20. Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. JAMA. 2020 Apr 6; https://doi.org/10.1001/jama.2020.5394
21. WHO Coronavirus disease (COVID-19) Weekly Epidemiological Update, 12 October 2020. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20201012-weekly-epi-update-9.pdf
22. World Health Statistics 2020: Monitoring health for the SDGs, sustainable development goals. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO. https://apps.who.int/iris/bitstream/handle/10665/332070/9789240005105-eng.pdf?ua=1
23. Alberer M, Gnad-Vogt U, Hong HS, et al. Safety and immunogenicity of a mRNA rabies vaccine in healthy adults: an open-label, non-randomised, prospective, first-in-human phase 1 clinical trial. Lancet. 2017;390(10101):1511-1520.
24. Kübler H, Scheel B, Gnad-Vogt U, et al. Self-adjuvanted mRNA vaccination in advanced prostate cancer patients: a first-in-man phase I/IIa study. Journal for Immunotherapy of Cancer. 2015;3:26. doi:10.1186/s40425-015-0068-y.
25. Hong HS, Koch SD, Scheel B, et al. Distinct transcriptional changes in non-small cell lung cancer patients associated with multi-antigenic RNActive® CV9201 immunotherapy. Oncoimmunology. 2016;5(12):e1249560. doi:10.1080/2162402X.2016.1249560.
26. Rausch S, Schwentner C, Stenzl A, Bedke J. mRNA vaccine CV9103 and CV9104 for the treatment of prostate cancer. Hum Vaccin Immunother. 2014;10(11):3146-52.
27. Pallesen J, Wang N, Corbett KS, et al. Immunogenicity and structures of a rationally designed prefusion MERS-CoV spike antigen. Proc Natl Acad Sci USA. 2017; 114(35):E7348-E7357.
28. Fotin-Mleczek M, Duchardt KM, Lorenz C, et al. Messenger RNA-based vaccines with dual activity induce balanced TLR-7 dependent adaptive immune responses and provide antitumor activity. J Immunother. 2011;34(1):1-15.
29. Graham B. S., et al. Rapid COVID-19 vaccine development; 2020; Science 10.1126/science.abb8923; https://science.sciencemag.org/content/sci/early/2020/05/07/science.abb8923.full.pdf
30. Wang J and Zand MS. The potential for antibody-dependent enhancement of SARS-CoV-2 infection: Translational implications for vaccine development. Journal of Clinical and Translational Science. 2020;1-4.

31. Global regulatory workshop on COVID-19 vaccine development: Summary Report. International Coalition of Medicines Regulatory Authorities (ICMRA), 18 March 2020, https://www.pei.de/SharedDocs/Downloads/EN/newsroom-en/hp-news/icrma-report.pdf?__blob=publicationFile&v=2. Accessed 11 Jun 2020.
32. Clinical Trial Facilitation Group (CTFG) Recommendations related to contraception and pregnancy testing in clinical trials, September 2014. Available at: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf
33. US Department of Health and Human Services. Food and Drug Administration (FDA). Guidance for Industry. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. 2007. [Available from: https://www.fda.gov/media/73679/download; Accessed 14 July 2020].
34. Chen Z, Yuan Y, Li Z, et al. Dose escalation with over-dose and under-dose controls in Phase I/II clinical trials. Contemp Clin Trials. 2015;43:133-41.

15 APPENDICES

Appendix 1 Responsibilities of the Investigator

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

The Investigator agrees to assume the following responsibilities:

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

Appendix 2 Emergency Procedures

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

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

The 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.

Appendix 3 Safety Laboratory Assessments

The tests detailed in Table 8 will be performed by the local laboratory.

Additional tests may be performed at any time during the trial as determined necessary by the Investigator or required by local regulations.

Table 8 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	Complete blood count including differential and platelets
Clinical Chemistry/Biochemistry	Magnesium, creatinine, albumin and lactate dehydrogenase, C-reactive protein, gamma glutamyl transferase, blood urea nitrogen, bilirubin (direct/indirect), calcium, alkaline phosphatase, sodium, potassium, total protein, glutamic oxaloacetic transaminase/aspartate aminotransferase, glutamic pyruvic transaminase/alanine aminotransferase
Coagulation	Prothrombin time/international normalized ratio, activated partial thromboplastin time
Pregnancy Tests	Human chorionic gonadotropin

The Investigator must document his review of each laboratory safety report, by signing and dating the report.

Appendix 4 COVID-19 Symptoms Log

The following table provides an example of a COVID-19 symptom log. This may be adapted according to emerging understanding of COVID-19 disease.

Symptoms		**If yes, onset date (DD/MMM/YYYY)**	**If yes, resolution date (DD/MMM/YYYY)**
Fever (≥37.8°C)	☐ Yes ☐ No	___ /_____ /_____	___ /_____ /_____
Subjective fever (feeling feverish)	☐ Yes ☐ No	___ /_____ /_____	___ /_____ /_____
Chills	☐ Yes ☐ No	___ /_____ /_____	___ /_____ /_____
Muscle aches	☐ Yes ☐ No	___ /_____ /_____	___ /_____ /_____
Joint aches	☐ Yes ☐ No	___ /_____ /_____	___ /_____ /_____
Body aches	☐ Yes ☐ No	___ /_____ /_____	___ /_____ /_____
Fatigue	☐ Yes ☐ No	___ /_____ /_____	___ /_____ /_____
Runny nose	☐ Yes ☐ No	___ /_____ /_____	___ /_____ /_____
Sore throat	☐ Yes ☐ No	___ /_____ /_____	___ /_____ /_____
Altered voice (hoarseness)	☐ Yes ☐ No	___ /_____ /_____	___ /_____ /_____
Cough(new onset or worsening of chronic cough)	☐ Yes ☐ No If yes then: ☐ dry ☐ productive (with mucous production)	___ /_____ /_____	___ /_____ /_____
Shortness of breath	☐ Yes ☐ No If yes, then: ☐ when exercising ☐ at rest	___ /_____ /_____	___ /_____ /_____
Wheezes	☐ Yes ☐ No	___ /_____ /_____	___ /_____ /_____
Nausea or vomiting	☐ Yes ☐ No	___ /_____ /_____	___ /_____ /_____

Headache	☐ Yes ☐ No	___ /_____ /_____	___ /_____ /_____
Abdominal pain	☐ Yes ☐ No	___ /_____ /_____	___ /_____ /_____
Diarrhea (≥3 loose/looser than normal stools/24hr)	☐ Yes ☐ No	___ /_____ /_____	___ /_____ /_____
Altered or loss of smell	☐ Yes ☐ No	___ /_____ /_____	___ /_____ /_____
Altered or loss of taste	☐ Yes ☐ No	___ /_____ /_____	___ /_____ /_____
Loss of appetite	☐ Yes ☐ No	___ /_____ /_____	___ /_____ /_____
Seizures	☐ Yes ☐ No	___ /_____ /_____	___ /_____ /_____
Altered consciousness	☐ Yes ☐ No	___ /_____ /_____	___ /_____ /_____
Other, specify:_____	☐ Yes ☐ No	___ /_____ /_____	___ /_____ /_____

Appendix 5 Case Definition for COVID-19 Disease

According to CEPI's guidance "*COVID-19 Efficacy Endpoints in Interventional Trials: What Constitutes an Incident Clinical Disease Case and What Triggers Diagnostic Work-Up Version 2.0 dated 25 June 2020*", virologically-confirmed COVID-19 disease is defined as follows:

An RT-PCR-confirmed an acute illness that is clinically consistent with COVID-19 based on the presence of at least 1 new-onset symptom: a) persistent cough, b) dyspnea or tachypnea (RR >20/min), c) Low peripheral capillary oxygen saturation (SpO_2 <95% on room air) as measured by pulse-oximetry, d) chest pain, e) Radiographic findings consistent with LRTD, f) fever (defined as body temperature of ≥37.8°C, irrespective of method), g) myalgia, h) chills, i) loss of smell or taste, j) headache, k) sore throat, l) diarrhea.

There will likely be further updates to this guidance, and the Sponsor will take these into consideration during the course of the trial.

Appendix 6 Trial Governance Considerations

CureVac AG is the Sponsor of this trial. A CRO will coordinate the conduct of this trial.

Appendix 7 Protocol Changes

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 authority/authorities [CA(s)] and a favorable opinion of the 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 investigational medicinal product, 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 CA(s) and IEC(s) of the new events and the measures taken.

Appendix 8 Potential Immune-Mediated Diseases

Current list of pIMDs:

Gastrointestinal disorders:

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

Liver disorders:

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

Metabolic diseases:

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

Musculoskeletal disorders:

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

Neuro-inflammatory disorders:

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

Skin disorders:

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

Vasculitides:

- o Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis and temporal arteritis
- o Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg-Strauss syndrome (allergic granulomatous angiitis), Buerger's disease thromboangiitis obliterans, necrotizing vasculitis and anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), Henoch- Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis

Others:

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

Appendix 9 Adverse Events of Special Interest for SARS-CoV-2 Vaccines

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

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

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

Cardiac disorders:

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

Hematological disorders:
- o Thrombocytopenia

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

Renal disorders:
- o Acute kidney injury

Gastrointestinal disorders
- o Liver injury

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

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

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

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

Definition of an Adverse Event (AE)

Definition of an AE:

- An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.
- An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- All AEs fall into 1 of 2 categories: “non-serious” or “serious”.

Examples of an AE include:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to a known concomitant disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after administration of the trial vaccine even though it may have been present before the start of the trial.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either trial vaccine or a concomitant medication/vaccination.
- An adverse effect of the trial vaccine or concomitant medication/vaccination.
- An accident or injury.

Events NOT Meeting the AE Definition:

- Medical or surgical procedures or other therapeutic interventions themselves are not AEs, but the condition for which the surgery/intervention is required is an AE and should be documented accordingly.
- Planned surgical measures and the condition(s) leading to these measures are not AEs, if the condition(s) was (were) known before the period of observation (see below) and did not worsen during trial.

  In the latter case the condition should be reported as medical history.
- Situations where an untoward medical occurrence did not occur (e.g., social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the trial that do not worsen.

Death is not considered an AE but an outcome.

Definition of an SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:
• Results in death.
• Is life-threatening. The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
• Requires inpatient hospitalization or prolongation of existing hospitalization: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
• Results in persistent disability/incapacity The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
• Is a congenital anomaly/birth defect in the offspring of the subject.
• Is an important medical event: Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent 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 AE and SAE reported during the trial and assign it to one of the following categories [34]. **Absent** (Grade 0): No AE. **Mild** (Grade 1): An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities. **Moderate** (Grade 2): An event that causes sufficient discomfort to interfere with normal everyday activities. **Severe** (Grade 3): An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

Assessment of Causality

• The Investigator is obligated to assess the relationship between the trial vaccine and each occurrence of each AE/SAE. Causality will be determined as:
  • **Related**: There is a reasonable causal relationship between the trial vaccine and the AE.
  • **Unrelated**: There is no reasonable causal relationship between the trial vaccine and the AE.
• A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
• The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as underlying disease(s), concomitant therapy or vaccination, and other risk factors, as well as the temporal relationship of the event to the trial vaccine administration will be considered and investigated.
• The Investigator will also consult the Investigator's Brochure for CVnCoV in his/her assessment.
• For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
• There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the CRO. However, **it is very important that the Investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the CRO.**
• The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
• The causality assessment is 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 trial visit or until the last follow-up visit, for the period described in Section 9.1.1. • When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The Investigator will then record all relevant AE/SAE information in the eCRF. • SAEs need to be reported to the CRO within 24 hours (see section Reporting of SAEs). • It is **not** acceptable for the Investigator to send photocopies of the subject's medical records to the CRO in lieu of completion of the AE/SAE eCRF screen. • There may be instances when copies of medical records for certain cases are requested by the CRO. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the CRO. • The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. • AESIs and cases of overdose must be documented and medically assessed by the Investigator and the outcome described on the SAE/AESI/overdose/misuse report form. • Pregnancy must be documented and medically assessed by the Investigator and the outcome described on the Pregnancy Report Form which is to be sent to the CRO.
Follow-up of AEs and SAEs
• The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the CRO to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a subject dies during participation in the trial or during the follow-up period, the Investigator will provide the CRO with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed eCRF. • The Investigator will submit any updated SAE data to the CRO within 24 hours of receipt of the information.

Reporting of AEs

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

Reporting of SAEs

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

Determination of Expectedness, Reference Safety Information
• Expectedness will be determined by the CRO according to the designated Reference Safety Information provided in the current Investigator's Brochure. Any updates or substantial amendments will be considered accordingly.
Observation Period
• For the purpose of this trial, the period of observation for collection of AEs required to be reported in the eCRF extends from the time the subject gives informed consent until the end of the trial, for the period described in Section 9.1.1. • All AEs that occur in the course of the clinical trial regardless of the causal relationship should be monitored and followed up until the outcome is known or it is evident that no further information can be obtained. • There must be documented reasonable attempts to obtain follow-up information and outcome. • It is the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.
Post-Trial Events
• If the Investigator becomes aware of any SAE that occurred after the end of the trial but is considered to be caused by the trial vaccine(s), this must be reported to the CRO. • These SAEs will be processed by the CRO. Instructions for how to submit these SAEs will be provided in a handout in the Investigator Site File.

Reporting of Other Events

Reporting and Follow-up of Pregnancies
• Pregnancy is an exclusion criterion for enrollment in this trial, but subjects could potentially become pregnant during their active participation in this trial. • Any pregnancy in a subject having received a trial vaccine must be reported to the CRO within 24 hours of the site learning of its occurrence, using a pregnancy reporting form. If the subject becomes pregnant during the trial, she will not receive any further doses of any Sponsor-supplied trial vaccine. The pregnancy must be followed to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if the intended duration of safety follow-up for the trial has ended. • The trial site should maintain contact with pregnant subjects to obtain pregnancy outcome information. • Any complications during pregnancy (e.g., gestational diabetes or eclampsia) are to be considered as an AE; however, these complications could result in the event being an SAE. Spontaneous abortions, fetal death, stillbirth and congenital anomalies reported in the baby are always considered as SAEs. The pregnancy by itself will not be processed as an SAE. The Investigator will follow the subject until completion of the pregnancy and must assess the outcome in the shortest possible time but not more than 30 days within completion of the pregnancy. The

Investigator should notify the CRO of the outcome of the pregnancy by submitting a Follow-up Pregnancy Report.

Reporting and Follow-up of SUSARs and Other Regulatory Reporting

- Any SUSAR will be the subject of expedited reporting.
- The Sponsor and/or the CRO shall ensure that all relevant information about a SUSAR that is fatal or life-threatening is reported to the relevant competent authorities and IEC(s) within 7 days after knowledge by the Sponsor of such a case and that relevant follow-up information is communicated within an additional 8 days.
- The Sponsor will report all serious and unexpected AEs, which are judged by either the Investigator or the Sponsor as having a reasonable suspected causal relationship (suspected unexpected serious adverse reactions, SUSARs), to the competent authority, the concerned Independent Ethics Committee and Investigators according to applicable law.
- Post-trial SUSARs that occur after the subject has completed the clinical trial must be reported by the Investigator to the Sponsor.

Reporting and Follow-up of Misuse and Overdose

- Drug misuse and drug overdose should always be reported in the same format (i.e., on SAE form) and within the same timelines as a SAE, even if they may not result in an adverse outcome.
- When an “overdose” or “drug misuse” of the trial vaccine occurs without an AE, the Investigator should also complete an “SAE/AESI/overdose/misuse report form” and send this to the Sponsor’s safety contact.
- It should be clearly stated that no AE was observed. If no SAE is associated, misuse/overdose will be assessed as non-serious.
- In this case, there is no need to complete the “Averse Event” screen in the eCRF.

Product Quality Complaints

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

Appendix 11 Biological Samples and Record Retention

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.

Retention of Trial Records

Records and source documents pertaining to the conduct of the trial and the distribution of the investigational medicinal product (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.

Appendix 12 Protocol Amendment History

The trial was initiated using protocol version 1.0.

Protocol version 3.0: 03 December 2021
This amendment also consolidates changes made in local amendments for each site and therefore supersedes Version 2.2 for Panama and Version 2.4 for Peru.

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
Throughout	All subjects will be unblinded.	Following the results from the final efficacy analysis of the pivotal trial, CV-NCOV-004 (HERALD), all subjects will be unblinded.
Throughout	The Day 393 visit changed to a phone contact for subjects who did not receive the Day 180 booster. Only subjects who received a booster on Day 180 and who did not receive a licensed/authorized vaccine before this visit need to return to the site in person.	To protect the safety of subjects during increasing incidence rates of COVID-19 cases.
Throughout	Clarifications added that immunogenicity from Day 57 will only be evaluated as follows: Day 57: only subjects who receive the Day 57 booster. Day 85: only subjects who receive the Day 57 booster. Day 180: only subjects who receive the Day 57 or Day 180 booster. Day 208: only subjects who receive the Day 180 booster. Day 393: only subjects who receive the Day 180 booster.	Immunogenicity analyses at all time points for all subjects are not required.
Synopsis,	Removal of the exploratory objective and associated	This will not be analyzed.

Section # and Name	Description of Change	Brief Rationale
4.1.3 Exploratory Objectives, 4.2.3 Exploratory Endpoints	endpoint to describe the rate of asymptomatic infections.	
Synopsis Table 1, Table 2 Trial Groups and Vaccination Schedule	Updated dose level to be administered in the expansion phase from “to be determined” to 12 µg.	The optimal dose level for CVnCoV was determined to be 12 µg and that dose level was further investigated in the expansion phase.
Synopsis	In *Trial Visits/Contacts*, removal of “only for subjects receiving the booster dose on Day 180” for Day 180 visit.	Clarification that Day 180 visit is for all subjects.
Synopsis	In *Planned Number of Subjects*, the planned number of subjects in the initial phase was increased from 220 to 223.	3 more subjects than initially planned were enrolled.
Synopsis, 6.1 Inclusion Criteria	Addition of inclusion criterion: *Subjects who are able to understand and willing to provide informed consent.*	Standard criterion used across trials.
Synopsis, 6.1 Inclusion Criteria	Duration of the restriction on avoidance of partners of male subjects falling pregnant changed from the duration of the trial to 3 months after the last administration.	A period of 13 months (the entire duration of the trial) is not necessary. 3 months is consistent with the period for female subjects to use highly effective methods of birth control.
Synopsis, 6.2 Exclusion Criteria	Addition of “or licensed/authorized” to investigational SARS-CoV-2 vaccines.	Several vaccines against SARS-CoV-2 have since been licensed or authorized.
2 Schedule of Activities	Footnote added that immunogenicity samples on Day 180 are only to be collected from subjects who received the 6 µg dose or the booster on Day 57 or Day 180.	This sample is no longer needed for other subjects.

Section # and Name	Description of Change	Brief Rationale
2 Schedule of Activities	Footnote added that immunogenicity samples at the End of Trial visit are only to be collected from subjects who received the Day 180 booster and had not received an authorized/licensed vaccine before the End of Trial visit.	This sample is no longer needed for other subjects.
5.6 Justification for Dose	Updated to state that results from Trial CV-NCOV-001 showed that 12 µg is the optimal dose level.	Results from this trial have since become available.
7.7 Therapy Leading to Discontinuation	Text added that subjects may receive a licensed/authorized SARS-CoV-2 vaccine during the trial, but not any investigational vaccines or vaccines against any other coronavirus.	Several licensed/authorized vaccines have become available since the start of the trial.
9.2 Immunogenicity Assessments	Instruction added to not collect further immunogenicity samples if a subject receives a licensed/authorized vaccine.	Results from these samples would not contribute to the immunogenicity analyses of CVnCoV and collection thereof is therefore unnecessary.
Table 6	Correction in last column from 95.2 to 93.2.	Correction.
10.3.1 General Considerations	Additional immunogenicity analyses added.	Immunogenicity data will also be summarized separately for subjects who received both primary doses, who have baseline as well as Day 43 data available, and who have no major protocol deviations which could impact the immunogenicity outcomes.
Appendix 4 COVID-19 Symptoms Log	Change for fever criterion from >37.8°C to ≥37.8°C	Correction.
Throughout	PCR changed to RT-PCR.	Consistency.

Section # and Name	Description of Change	Brief Rationale
Throughout	Minor editorial and document formatting revisions and changes based on updated data.	-

Protocol version 2.0: 20 October 2020
This amendment is 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.

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
Medical Responsible Person Updated	[redacted] added as the Medical Responsible Person	To account for team member change.
SAE hotline and medical monitor contacts	Contact details for medical monitor updated.	To account for team member change.
Synopsis, 3.2 Trial Rationale	Addition of 12 and 16 µg to the following sentence: At this time, 6 dose levels (2, 4, 6, 8, 12, and 16 µg) have been tested in healthy adults 18 to 60 years of age.	Updated to include additional dose level tested in the ongoing Trial CV-NCOV-001.
Throughout	Revision of planned treatment groups. Dose in 8 µg cohort changed to 12 µg and groups within this cohort changed to: Group 3 (observer-blind): CVnCoV 12 µg on Day 1 and 12 µg on Day 29 (in subjects 18 to 60 years of age). Group 4 (observer-blind): CVnCoV 12 µg on Day 1 and 12 µg on Day 29 (in subjects >60	Increase in the dose level to be investigated based on the safety and immunogenicity data from Trial CV-NCOV-001.

Section # and Name	Description of Change	Brief Rationale
	years of age [i.e., 61 years or older]).	
Throughout	Change in the number of subjects in the initial phase of the trial.	Associated with the change in the initial groups.
Throughout	Addition of a booster dose of CVnCoV at Day 57 for a subgroup of subjects plus associated visits/contacts.	To investigate 2 different booster schedules.
2 Schedule of activities	Updated visit numbering.	To account for addition of a visit for the Day 57 booster dose and associated visits/contacts.
2 Schedule of activities	Addition of optional Phone Contact on Day 7.	To facilitate review of the eDiary with the subject at an earlier timepoint.
Synopsis, 2 Schedule of Activities, 9 Trial Assessments and Procedures	Maximum total volume of blood taken over the trial period from each subject increased.	Collection of blood samples will be performed at the visits on Day 57 and Day 85, which have been added for subjects who receive the Day 57 booster dose.
Synopsis, 4.2.1 Primary Endpoints	Wording of primary endpoints revised to specify “Day 1 and Day 29”.	To clarify that the primary safety endpoints are evaluated after the primary doses and the secondary safety endpoints after the booster dose.
Synopsis, 4.2.2 Secondary Endpoints	Secondary endpoints added to account for the following secondary objective: To evaluate the safety and reactogenicity profile after a booster dose administration of CVnCoV at different dose levels.	To clarify that the primary safety endpoints are evaluated after the primary doses and the secondary safety endpoints after the booster dose.
Synopsis, 5.1 Overall Design, 7.3 Randomization and Blinding	Addition of the following text: “Subjects in the initial phase will be randomized according to a 10:1 ratio to receive CVnCoV or	To clarify randomization ratio for the initial phase.

Section # and Name	Description of Change	Brief Rationale
	the active control in an observer-blinded manner."	
Synopsis, 5.2 Change in Dose Level	Revision of text relating to changes of dose level to allow for an increase up to 20 µg in the case of insufficient immunogenicity and a reduction in dose from 12 µg to 8 µg in the case reactogenicity is too high.	To facilitate changes in dose level.
5.5 Scientific Rationale for Trial Design	Removed rationale for inclusion of double dose group.	The double dose treatment group has been removed from the trial design as determined by the Steering Committee.
Synopsis, 6.1 Inclusion Criteria	Inclusion criterion 4 revised to account for an increase the upper limit of body mass index to: Body mass index (BMI) ≥18.0 and ≤32.0 kg/m^2	To facilitate recruitment.
Synopsis, 6.1 Inclusion Criteria	Addition of the following text to inclusion criterion 6: "Male subjects should be instructed not to get their partners pregnant during the study."	Clarification
Synopsis, 6.2 Exclusion Criteria	Addition of "(primary dose or booster dose)" to exclusion criterion 2: "Receipt of any other vaccines within 28 days prior to enrollment in this trial or planned receipt of any vaccine within 28 days of trial vaccine administration (primary dose or booster dose)".	Clarification
Synopsis, 6.2 Exclusion Criteria	Definition of pack year added to exclusion criterion 11.	Clarification

Section # and Name	Description of Change	Brief Rationale
Synopsis, 6.2 Exclusion Criteria	Addition of “virologically “ to exclusion criterion 12: “History of virologically-confirmed SARS, MERS, or COVID-19 disease or known exposure (without any personal protective equipment) to an individual with confirmed COVID-19 disease or SARS-CoV-2 infection within the past 2 weeks.”	Clarification
7.6 Concomitant Therapy and Vaccines	Addition of the following text: “As outlined in Section 6.3, vaccination will be delayed in subjects who take antipyretic medication within 8 hours before intended trial vaccination, however, prophylactic paracetamol can be taken after vaccination and should be documented in the subject’s eCRF.”	Clarification
7.1.3 Dosing and Administration	Removal of text detailing administration instructions for the double dose group.	The double dose treatment group has been removed from the trial design as determined by the Steering Committee.
9.1.1.1 Solicited Adverse Events	Removed the following text: “For Group 4 where 2 injections are given in opposite arms, the solicited local reactions will be documented separately. The severity and relatedness for each separate solicited local reaction should be assessed and recorded in the eCRF.”	The double dose treatment group has been removed from the trial design as determined by the Steering Committee.

Section # and Name	Description of Change	Brief Rationale
Synopsis, 9.3 Laboratory Testing for COVID-19 Disease	Text added to clarify procedure for performing RT-PCR and serological assays locally for subjects who have symptoms associated with COVID-19 disease.	Clarification
Synopsis, 9.3 Laboratory Testing for COVID-19 Disease	Addition of the following text detailing which antibody tests should be performed in subjects who have symptoms associated with COVID-19 disease: "If a serological assay is performed, this should look at antibodies against N protein antigen, but not to antibodies against Spike viral antigen, as this is part of the vaccine."	Clarification
Synopsis, Table 1 Trial Groups and Vaccination schedule Table 5 Sample size	Changed the number of subjects in Group 3 and Group 4 to 90 subjects each. Changed the number of subjects in Group 5 and Group 6 to 9 subjects each.	Group 3 with 90 subjects go against Group 5 with 9 subjects and Group 4 with 90 subjects will go against Group 6 with 9 subjects. This will give a 10:1 ratio. Group 1 and Group 2 were randomized at 10:1, but the blocks were not completed as this was not necessary from a safety perspective.
Throughout	Minor editorial and document formatting revisions.	Minor, therefore have not been summarized.