Protocol Number: CV-NCOV-003

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

NCT Number: NCT04860258

Document Date: 27 July 2021

AMENDMENT TO CLINICAL TRIAL PROTOCOL VERSION 2.0

COVID-19:
A Phase 3 multicenter clinical trial to evaluate the safety, reactogenicity and immunogenicity of the investigational SARS-CoV-2 mRNA vaccine CVnCoV in adults 18 years of age and above with co-morbidities

Protocol Number:	CV-NCOV-003
EudraCT Number:	2020-004070-22
Investigational product:	CV07050101 (referred to as CVnCoV)
Phase:	Phase 3
Sponsor:	CureVac AG Schumannstrasse 27 60325 Frankfurt Germany
Short Title:	Safety, reactogenicity and immunogenicity of CVnCoV in adults 18 years of age and above with co-morbidities
Version and Date:	Amendment 1 dated 27 July 2021, to Protocol Version 2.0 dated 29 March 2021

AMENDMENT APPROVAL SIGNATURES

Protocol Title: COVID-19: A Phase 3 multicenter clinical trial to evaluate the safety, reactogenicity and immunogenicity of the investigational SARS-CoV-2 mRNA vaccine CVnCoV in adults 18 years of age and above with co-morbidities

Protocol Number Protocol CV-NCOV-003, Version 2.0 Amendment 1

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.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

Sponsor Signatory
[redacted]
CureVac AG

Sponsor Medical Responsible Person
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CureVac AG

Clinical Project Manager
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CureVac AG

Statistician
[redacted]

[redacted]

INVESTIGATOR SIGNATURE PAGE

Protocol Title: COVID-19: A Phase 3 multicenter clinical trial to evaluate the safety, reactogenicity and immunogenicity of the investigational SARS-CoV-2 mRNA vaccine CVnCoV in adults 18 years of age and above with co-morbidities

Protocol Number: Protocol CV-NCOV-003, Version 2.0 Amendment 1

Confidentiality and GCP Compliance Statement

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

Once the Independent Ethics Committee (IEC) has approved the protocol amendment, I will not modify this amendment without obtaining prior approval of CureVac and of the IEC. I will submit the protocol amendment 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. Assigned numbers on all electronic case report forms (eCRFs) and laboratory samples will identify all subjects. CureVac or its representatives or regulatory agencies may review clinical information. 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

Rationale of the Amendment to Protocol Version 2.0

This amendment describes the changes to be implemented into protocol version 2.0 in the context of the pause of Trial CV-NCOV-003.

In line with protocol section 5.2.2 "Pausing of the Trial," the DSMB convened to review the available CVnCoV data across ongoing trials, and notably the available safety data of the pivotal phase 2b/3 trial CV-NCOV-004. The DSMB confirmed a favourable safety profile for CVnCoV. The second Interim Analysis data on efficacy from CV-NCOV-004 suggested age dependent efficacy with inconclusive efficacy data in the group > 60 years of age. In consultation with Investigators, a decision has been taken to stop further enrolment into CV-NCOV-003 and amend the current protocol version 2.0 to clarify that all subjects shall undergo safety and immunogenicity follow-up for 3 months following the last CVnCoV dose. Due to the change in risk/benefit profile, there is sufficient scientific and medical rationale to support an enrolment halt of all ages with comorbidities and for enrolled subjects to complete study activities, allowing standard of care COVID vaccination procedures to be followed by the Investigators or the subject's primary care physician.

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

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

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

Subjects will be provided with adequate information about the changes to the study, in accordance with applicable local regulations and in line with protocol section 12.4 "Informed Consent".

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

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

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

Table 2 Amended Schedule of Activities

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

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

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

CLINICAL TRIAL PROTOCOL

COVID-19:
A Phase 3 multicenter clinical trial to evaluate the safety, reactogenicity and immunogenicity of the investigational SARS-CoV-2 mRNA vaccine CVnCoV in adults 18 years of age and above with co-morbidities

Protocol Number:	CV-NCOV-003
EudraCT Number:	2020-004070-22
Investigational product:	CV07050101 (referred to as CVnCoV)
Phase:	Phase 3
Sponsor:	CureVac AG Schumannstrasse 27 60325 Frankfurt Germany
Short Title:	Safety, reactogenicity and immunogenicity of CVnCoV in adults 18 years of age and above with co-morbidities
Protocol Version:	2.0
Protocol Date:	29 March 2021

PROTOCOL VERSION HISTORY:

Version 1.0 dated 03 March 2021

Version 2.0 dated 29 March 2021

PROTOCOL APPROVAL SIGNATURES

Protocol Title: COVID-19: A Phase 3 multicenter clinical trial to evaluate the safety, reactogenicity and immunogenicity of the investigational SARS-CoV-2 mRNA vaccine CVnCoV in adults 18 years of age and above with co-morbidities

Protocol Number: CV-NCOV-003

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- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and reg[redacted]

Sponsor Signatory

[redacted]

CureVac AG

Sponsor Medical Responsible Person

[redacted]

CureVac AG

Clinical Project Manager

[redacted]

CureVac AG

Statistician

[redacted]

[redacted]

INVESTIGATOR SIGNATURE PAGE

Protocol Title: COVID-19: A Phase 3 multicenter clinical trial to evaluate the safety, reactogenicity and immunogenicity of the investigational SARS-CoV-2 mRNA vaccine CVnCoV in adults 18 years of age and above with co-morbidities

Protocol Number: CV-NCOV-003

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.

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CureVac to other clinical Investigators, regulatory agencies or other health authorities as required may disclose information developed in this clinical trial.

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:

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]

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LIST OF ABBREVIATIONS

ABPM	Ambulatory blood pressure monitoring
AE	Adverse event
AESI	Adverse event of special interest
CA	Competent authority
CEPI	Coalition for Epidemic Preparedness Innovations
CI	Credibility interval
CMI	Cell-mediated immunity
CoV	Coronavirus
COVID-19	Coronavirus Disease 2019
CRO	Contract research organization
CVnCoV	Investigational SARS-CoV-2 mRNA vaccine
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	estimated glomerular filtration rate
FDA	US Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMC	Geometric mean concentration
GMFC	Geometric mean of the fold change
GMT	Geometric mean titer
HbA1c	Hemoglobin A1c
HBPM	Home blood pressure monitoring
hCG	Human chorionic gonadotropin
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFN	Interferon
IL	Interleukin
IM	Intramuscular(ly)

IMP	Investigational medicinal product
IRB	Institutional Review Board
iSRC	Internal safety review committee
LLOQ	Lower limit of quantification
LNP	Lipid nanoparticles
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
MET	Metabolic equivalent threshold
mRNA	Messenger ribonucleic acid
N	Nucleocapsid
NICE	National Institute for Health and Care Excellence
NYHA	New York Heart Association
PCR	Polymerase chain reaction
pIMD	Potential immune-mediated disease
PPI	Per protocol immunogenicity subset
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
US	United States
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 3 multicenter clinical trial to evaluate the safety, reactogenicity and immunogenicity of the investigational SARS-CoV-2 mRNA vaccine CVnCoV in adults 18 years of age and above with co-morbidities	
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 Coronavirus Disease 2019 (COVID-19). The virus spread to different parts of China and an increasing number of countries worldwide and on 30 January 2020 the World Health Organization (WHO) announced the outbreak under International Health Regulations (IHR) as a public health emergency of international concern (PHEIC); the WHO's highest level of alarm. On 12 March 2020, the WHO announced the outbreak as a pandemic. In view of the severity of respiratory disease caused by emerging coronaviruses, development of a vaccine has been undertaken by several pharmaceutical companies, and there are now emergency authorized vaccines available for prevention of COVID-19, in several countries worldwide. CureVac AG is developing a new SARS-CoV-2 messenger ribonucleic acid (mRNA) vaccine formulated with lipid nanoparticles (referred to as CVnCoV) which is in advanced Phase 2/3 clinical development. The safety, reactogenicity and immunogenicity of this vaccine is being evaluated for the first time in humans in the dose-finding trial CV-NCOV-001 and in the dose-confirmation trial CV-NCOV-002. The data from these trials confirmed the selection of the 12-µg dose level for further evaluation in Phase 2b and Phase 3 trials which started in December 2020. This current trial will be conducted to assess the safety, reactogenicity and immunogenicity of CVnCoV in adults 18 years of age and above with co-morbidities known to increase the risk for (severe) COVID-19, when administered as 2 doses according to a 0 (Day 1) and 1-month (Day 29) vaccination schedule.	
Trial Duration for Each Subject:	Approximately 13 months for each subject (at least 12 months following the last vaccination)	**Phase:** 3

Objectives:	All objectives will be analyzed in all subjects overall, as well as per underlying co-morbidity. ***Primary*** • To evaluate the safety and reactogenicity profile after 1 and 2 dose administrations of CVnCoV. • To evaluate the humoral immune responses 14 days after 2 dose administrations of CVnCoV. ***Secondary*** • To evaluate the humoral immune responses after 1 and 2 dose administrations of CVnCoV at different time points during the trial. ***Exploratory*** • To evaluate the occurrence of laboratory-confirmed cases of COVID-19 after 1 and 2 doses of CVnCoV. • To evaluate the cell-mediated immune (CMI) response after 1 and 2 dose administrations of CVnCoV in a subset of subjects.
Overall Design:	This is a Phase 3 open-label, single-arm trial to assess the safety, reactogenicity and immunogenicity of CVnCoV in an adult population with co-morbidities known to increase the risk for (severe) COVID-19. The selected co-morbidities which will be investigated are obesity, chronic cardiovascular disease, chronic kidney disease, chronic obstructive pulmonary disease (COPD), human immunodeficiency virus (HIV) infection, type 2 diabetes mellitus and post-renal transplantation. Male and female subjects ≥18 years of age with 1 or more of the above co-morbidities will be eligible for the trial, with a life expectancy of at least 1 year as per the Investigator's assessment. Eligible subjects at screening must have no overt clinical symptoms or signs of COVID-19. Subjects will be enrolled into 1 trial group: • CVnCoV (n = 1,200): CVnCoV 12 µg on Day 1 and Day 29. The CVnCoV dose level to be administered in this trial was selected based on data from trial CV-NCOV-001 and confirmed in trial CV-NCOV-002. The 12-µg dose level is currently being investigated in large-scale Phase 2b/3 trials in subjects 18 years of age and above, both in subjects in the CV-NCOV-004 "Herald" trial and also in health care workers in the CV-NCOV-005 trial. **Stratification Based on Co-Morbidities** Subjects will be stratified post-hoc into different pre-defined co-morbidities or combinations thereof. To be eligible for the trial, subjects' medical condition(s) must be controlled and stable as per the clinical Investigator's judgment at the time of recruitment. For the purpose of enrollment in this trial, stratification of co-morbidities will be based on the subject's main medical condition that increases their risk of severe illness from COVID-19. In some cases, subjects may have several high-risk co-morbidities. For these scenarios, the main co-morbidity as determined by the Investigator will be used for enrollment stratification. Data analyses, however, will take into consideration all pre-defined co-morbidities of interest in the trial population.

	For chronic kidney disease, COPD, chronic cardiovascular disease and diabetes mellitus, the first 25 subjects enrolled in each co-morbidity will be restricted to those with mild to moderate disease (as defined below in the section "*Case definitions co-morbidities*"). These first 25 subjects per co-morbidity will be followed up for safety and reactogenicity for at least 1 week after the first dose. An assessment of these data will be performed by CureVac's internal Safety Review Committee (iSRC) and Data Safety Monitoring Board (DSMB) Chair overviewing the clinical development program of CVnCoV. After the favorable safety evaluation of CVnCoV on these 25 subjects, subjects with more severe forms of the co-morbidity may be enrolled as per the Investigator's decision. For obesity, HIV and renal transplant, no distinction will be made between the initial 25 subjects that can be enrolled and any further enrollments. As described above, for subjects with multiple high-risk co-morbidities, the subject's main medical condition as determined by the Investigator will be used for enrollment stratification. A minimum of at least 50 subjects will be enrolled in each co-morbid condition with a maximum of ~200 subjects.
Case Definitions Co-morbidities:	Subjects with the following selected co-morbidities are at increased risk of severe illness from COVID-19 and will be included in the trial. Life expectancy of at least 1 year as per the Investigators' assessment is required for inclusion of the subject into the trial. • **Chronic kidney disease**: Kidney function will be ascertained from a serum creatinine measurement done within the last 6 months, converted into estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, with impaired kidney function defined as eGFR <60 mL/min/1.73 m². o Mild chronic kidney disease is defined as an eGFR between 60-89 mL/min/1.73 m^2. o Moderate chronic kidney disease is defined as an eGFR between 31-59 mL/min/1.73 m^2 with stable therapy and good maintenance over at least 6 months [23]. • **COPD** (including emphysema and chronic bronchitis). o Mild COPD with or without cough or sputum production is defined as forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) <0.7 and FEV_1 ≥80% predicted. o Moderate COPD with or without cough or sputum production is defined as FEV_1/FVC <0.7 and FEV_1 ≥50%, but <80% predicted with stable treatment (GOLD Criteria for COPD severity). • **Obesity** with body mass index of >32 kg/m². • **Chronic cardiovascular disease** (heart failure, structural heart disorder, coronary artery disease, cardiomyopathies, arterial hypertension), including the following: o Heart failures (according to New York Heart Association [NYHA] classification [24]): - Class I: No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).

	- Class II: Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath). o A structural heart disorder - without symptoms - with symptoms. o Coronary artery disease: - Mild with metabolic equivalent threshold (MET)[1] <3, stable with medication. - Moderate with MET >3 – 5.9, stable with medication. o Cardiomyopathies of non-infective and metabolic origin: - Mild with MET <3, stable with medication. - Moderate with MET >3 – 5.9, stable with medication. o Hypertension (National Institute for Health and Care Excellence [NICE] categorization [26]): - Stage 1 hypertension: Clinic blood pressure ranging from 140/90 mmHg to 159/99 mmHg and subsequent ambulatory blood pressure monitoring (ABPM) daytime average or home blood pressure monitoring (HBPM) average blood pressure ranging from 135/85 mmHg to 149/94 mmHg. - Stage 2 hypertension: Clinic blood pressure of 160/100 mmHg or higher but less than 180/120 mmHg and subsequent ABPM daytime average or HBPM average blood pressure of 150/95 mmHg or higher. • **Chronic HIV infection with stable aviremia (<50 copies/mL) and CD4 count >350/mL** as documented by blood samples taken within 12 months before enrollment. (Viral load <50 copies/mL with transient changes of 50-350 copies/mL is allowed.) • **Type 2 diabetes mellitus**, controlled with medication [hemoglobin A1c (HbA1c) <58 mmol/mol (7.45%)]; [(HbA1c in % - 2.15) x 10.929 = HbA1c in mmol/mol]; • **Subjects with a renal transplant** at least a year ago under stable conditions for at least 6 months with medications, categorized as low risk of rejection. Following inclusion of 25 cases of mild to moderate conditions under chronic kidney disease, COPD, chronic cardiovascular disease and diabetes mellitus, more severe conditions can be included into the trial upon iSRC and DSMB Chair approval and subjected to the clinical Investigator's decision.

[1] MET is defined as the amount of oxygen consumed while sitting at rest and is equal to 3.5 mL O_2 per kg body weight/min and is roughly equivalent to the expenditure of 1 kcal per kilogram of body weight per hour; 1 MET is the rate of energy expenditure while at rest. A 4 MET activity expends 4 times the energy used by the body at rest. Light MET is <3, moderate is 3 to 5.9 and vigorous is ≥6.0. MET 1 can take care of him/herself and may not maintain themselves and gets constraints on exertion. MET 4 can climb a flight of stairs or walk up a hill and can participate in other strenuous activities; >2-3 METs is fit normal person with well controlled with medication [25].

	• Under cardiovascular disease the following cases can be included: o Heart failures (according to NYHA classification [24]) Class III: Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea (shortness of breath). o Coronary artery disease: Severe with MET >6, stable with medication. o Cardiomyopathies of non-infective and metabolic origin: Severe with MET >6, stable with medication. o Hypertension (NICE categorization [26]): Stage 3 or severe hypertension: Clinic systolic blood pressure of 180 mmHg or higher or clinic diastolic blood pressure of 120 mmHg or higher. • Under diabetes mellitus, cases of uncontrolled diabetes mellitus with recent HbA1c of >59 mmol/mol (7.45%) with medication can be included. For uncontrolled diabetes mellitus, HbA1c should be within <10% variation and the subject should not have any history of diabetic ketoacidosis or episode of severe symptomatic hypoglycemia within the past 3 months.
Trial Visits/ Contacts:	• 10 protocol-scheduled visits on Day -7, Day 1, Day 2, Day 29, Day 30, Day 43, Day 57, Day 120, Day 211 and Day 393. • 1 protocol-scheduled safety contact to collect diary card data on Day 9 for the first 25 subjects enrolled in the co-morbidities chronic kidney disease, COPD, chronic cardiovascular disease and diabetes mellitus. • 2 protocol-scheduled phone contacts on Day 15 and Day 302. In addition, subjects will be contacted once per week to be reminded to report symptoms of COVID-19.
Collection of Blood Samples:	Blood samples will be taken for safety and/or immunogenicity testing according to the Schedule of Activities (Table 1). The total volume of blood taken over the trial period from each subject will be approximately 136 mL in the subset of subjects participating in the immunological assessments and the safety laboratory testing. For the subset of subjects in whom the CMI will be assessed, the maximum volume of blood for these analyses will be 12 mL.
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 paper diary cards. 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 be contacted by phone to verify whether they had any health concerns since the last visit. Since no control group is included in the trial, the subjects will serve as their own control for reactogenicity and safety assessments. For this purpose, the subjects will complete the pre-vaccination diary card on a daily basis as of Day -7 (i.e., during 1 week before the first vaccination) to give an indication of their normal life with co-morbidities. Solicited systemic AEs as well as unsolicited AEs will

	need to be collected similar to what is done during the 7 days after vaccination. Subjects with any Grade 3 solicited or unsolicited AEs are asked to report this to the Investigator. Unscheduled visits will be performed when deemed necessary for safety assessments by the clinical Investigator and to ensure data integrity. Serious AEs (SAEs), AEs of special interest (AESIs), and AEs leading to vaccine withdrawal or trial discontinuation will be collected throughout the trial. AESIs to be monitored include potential immune-mediated diseases (pIMDs), AESIs for SARS-CoV-2 vaccines, and non-serious intercurrent medical conditions that may affect the immune response to vaccination. In case of confirmed COVID-19, a disease-specific diary will be completed by the subject and/or the treating health care provider in case of hospitalization.
Laboratory Testing for COVID-19:	Subjects will be screened for any symptoms or signs of COVID-19. Subjects who suffered from COVID-19 within the last six months prior to screening will not be enrolled in the trial. Subjects will be contacted once per week to enquire if they have developed any of the following symptoms*: • Fever or chills • Shortness of breath or difficulty breathing • New loss of taste or smell • Cough • Fatigue • Muscle or body aches • Headache • Sore throat • Congestion or runny nose • Nausea or vomiting • Abdominal pain • Diarrhea *FDA Guidance for Industry, Development and Licensure of Vaccines to Prevent COVID-19, June 2020. During every clinic visit and phone call, subjects will be instructed and reminded to call the trial site should they develop any of these symptoms. If any of these symptoms are observed, the Investigator will collect appropriate nasopharyngeal samples as soon as feasible to do a rapid diagnostic antigen test on site. In case of a positive result of the rapid test, another specimen will be sent to the central lab for confirmatory reverse transcription polymerase chain reaction (RT-PCR) to evaluate for infection with SARS-CoV-2. If the rapid test is negative, a specimen may be sent to the central lab at the clinical Investigator's discretion. For positive RT-PCR tests, viral RNA of SARS-CoV-2 will be sequenced to identify spike (S) protein variants. Any subject with clinical suspicion of SARS-CoV-2 infection following vaccination will undergo appropriate testing and referral within the local healthcare system as appropriate. Subjects with confirmed SARS-CoV-2 infection after the first vaccine dose administration should only receive the second dose of CVnCoV 2 weeks after complete recovery and if it falls under the time window as per Table 1.

Planned Number of Subjects:	Approximately 1,200 subjects will be enrolled.
Criteria for Inclusion and Exclusion:	**Inclusion criteria:** Subjects will be enrolled in this trial only if they meet **all** of the following criteria: 1. Male and female subjects ≥18 years of age with 1 or more co-morbidities as defined by the case definitions specified in the section "*Case definitions co-morbidities*". 2. For the co-morbidities chronic kidney disease, COPD, chronic cardiovascular disease and diabetes mellitus, the first 25 subjects per co-morbidity should include only mild to moderate cases as described in the section "*Case definitions co-morbidities*". Thereafter, more severe conditions may be recruited (see the section "*Overall design*") following iSRC and DSMB Chair approval. 3. Subject has no overt clinical signs or symptoms of COVID-19. 4. Subject has to sign the informed consent form (ICF) before any trial procedures. 5. Subjects with a life expectancy of at least 1 year as per the Investigator's assessment. 6. Expected to be compliant with protocol procedures and available for clinical follow-up through the last planned visit. 7. Physical examination without acute clinically significant findings according to the Investigator's assessment. 8. Female subjects: At the time of enrollment, negative human chorionic gonadotropin (hCG) pregnancy test (serum) for women presumed to be of childbearing potential on the day of enrollment. On Day 1 (pre-vaccination): negative urine pregnancy test (hCG), (only required if serum pregnancy test was performed more than 3 days before). Note: Women that are postmenopausal (defined as amenorrhea for ≥ 12 consecutive months prior to screening without an alternative medical cause) or permanently sterilized will be considered as not having reproductive potential. 9. 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; • Same sex relationships.

	Sexual abstinence [periodic abstinence (e.g., calendar, ovulation symptothermal and post-ovulation methods)] and withdrawal are not acceptable methods. Refer to the Clinical Trial Facilitation Group recommendations on contraception and pregnancy testing for further details [22]. **Exclusion criteria:** Subjects will not be enrolled in this trial if they meet **any** of the exclusion criteria. 1. A previous clinical and laboratory-confirmed diagnosis of COVD-19 within the last six months prior to screening. 2. 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. 3. 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. Planned vaccination with an inactivated influenza vaccine is permitted. 4. Receipt of any investigational, authorized or licensed SARS-CoV-2, other coronavirus vaccine or any other lipid nanoparticle (LNP) containing mRNA vaccine prior to the administration of the trial vaccine. For authorized or licensed SARS-CoV-2: planned administration during the trial up to 6 weeks after the foreseen date of second dose administration of CVnCoV. 5. Any treatment with immunosuppressants or other immune-modifying drugs (including, but not limited to, corticosteroids, biologicals, and methotrexate) for >14 days in total within 6 months prior to the administration of the trial vaccine or planned use during the trial. For corticosteroid use, this means prednisone or equivalent, 0.5 mg/kg/day for 14 days or more. The use of inhaled, topical, or localized injections of corticosteroids (e.g., for joint pain/inflammation) is permitted. Note: This exclusion does not apply to the renal transplant cases and is at the Investigator's discretion for subjects with other co-morbidities (e.g., COPD). 6. Any medically diagnosed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination, excluding the co-morbidities specified in the section "*Case definitions co-morbidities*". (Subjects with chronic HIV infection with controlled Hep B infection with therapy or aviremic Hep C may be eligible for the trial, based on the Investigator's judgment). 7. History of immune-mediated or autoimmune disease. 8. History of anaphylaxis or allergy to any component of CVnCoV or aminoglycoside antibiotics. 9. History of or current alcohol and/or drug abuse. 10. History of confirmed SARS or MERS disease. 11. Administration of immunoglobulins and/or any blood products within the 3 months preceding the administration of any dose of the trial vaccine. 12. Presence of evidence of significant uncontrolled acute or chronic medical or psychiatric illness, excluding the co-morbidities specified in the section "*Case definitions co-morbidities*".

	Significant medical or psychiatric illnesses include but are not limited to: • Uncontrolled respiratory disease • 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. 13. Foreseeable non-compliance with protocol, as judged by the Investigator. 14. For female subjects: pregnancy or lactation. 15. 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. However, use of anticoagulants is accepted in certain co-morbidities according to the clinical Investigator's judgment and if the INR remains ≤3. 16. Subjects employed by the Sponsor, Investigator, or trial site, or relatives of research staff working on this trial.
Endpoints:	***Primary*** *Safety* • The frequency, intensity, and duration of solicited local AEs on each vaccination day and the following 7 days. • The frequency, intensity, duration, and relationship to trial vaccination of solicited systemic AEs on each vaccination day and the following 7 days. • The occurrence, intensity and relationship to trial vaccination of unsolicited AEs on each vaccination day and the following 28 days. • The occurrence and relationship to trial vaccination of SAEs and AESIs throughout the trial. *Immunogenicity* *On Day 43:* • The proportion of subjects seroconverting for SARS-CoV-2 S protein receptor-binding domain (RBD) antibodies, as measured by an immunoassay. • Individual SARS-CoV-2 S protein RBD-specific antibody levels in serum, as measured an immunoassay. • Geometric mean titers (GMTs) of serum SARS-CoV-2 S protein RBD antibodies, as measured by an immunoassay. • *In a subset of subjects**: the proportion of subjects seroconverting for SARS-CoV-2 neutralizing antibodies, as measured by an activity assay. • *In a subset of subjects**: individual SARS-CoV-2 neutralizing antibody levels in serum, as measured by an activity assay. • *In a subset of subjects**: GMTs of serum SARS-CoV-2 neutralizing antibodies, as measured by an activity assay. ***Secondary*** *On Day 29, Day 120, Day 211 and Day 393:* • The proportion of subjects seroconverting for SARS-CoV-2 S protein RBD antibodies, as measured by an immunoassay.

	• Individual SARS-CoV-2 S protein RBD-specific antibody levels in serum, as measured by an immunoassay. • GMTs of serum SARS-CoV-2 S protein RBD antibodies, as measured by an immunoassay. *In a subset of subjects*, on Day 29 and Day 120:* • The proportion of subjects seroconverting for SARS-CoV-2 neutralizing antibodies, as measured by an activity assay. • Individual SARS-CoV-2 neutralizing antibody levels in serum, as measured by an activity assay. • GMTs of serum SARS-CoV-2 neutralizing antibodies, as measured by an activity assay. ***Exploratory*** *Occurrence of confirmed COVID-19 cases* • Number of subjects with RT-PCR-confirmed SARS-CoV-2 infection as measured by RT-PCR at clinically determined time points throughout the trial. • Number of subjects with asymptomatic SARS-CoV-2 infection as measured by serological titers of nucleocapsid antibodies on Day 1, Day 43, Day 120 and Day 393. *CMI response* *On Day 1, Day 29, Day 43 and Day 120 in peripheral blood stimulated with antigen, in a subset of subjects*:* • The SARS-CoV-2 S-specific T cell response, as measured by cytokine and chemokine expression after antigen stimulation using a standardized whole blood collection and culture system. ** The subset of subjects to participate in neutralizing activity and CMI response testing shall consist of approximately 25 subjects for each co-morbidity (up to a maximum of 175 subjects):* • *Twelve subjects from each co-morbidity will be enrolled as part of the first 25 cases.* • *The other 13 subjects will be enrolled as part of the next 25 enrolled subjects for each co-morbidity.*
Sample Size Justification:	The trial is designed to provide a reasonable precision for an estimate of the number of subjects seroconverting for SARS-CoV-2 S protein RBD-specific antibodies and an acceptable rate of Grade 3 adverse reactions (defined as solicited local Grade 3 AEs, and solicited systemic or unsolicited Grade 3 AEs considered as related to the trial vaccine).
Analysis Sets:	***Immunogenicity set*** The immunogenicity set will include all subjects who received at least 1 dose of CVnCoV and for whom the baseline blood sample and at least 1 additional blood sample are available for analysis. ***Safety Set*** The safety set will consist of all subjects who received at least 1 dose of CVnCoV and for whom any post-vaccination safety data are available. ***Per Protocol Immunogenicity Subset*** The Per Protocol Immunogenicity subset (PPI) will include all subjects who: • Received both doses within the windows defined in the protocol. • Have no major protocol deviations expected to impact the immunogenicity outcomes as specified in the statistical analysis plan (SAP).

	• Have not received medical treatments (such as blood products, immunoglobulin therapy) that may interfere with any of the proposed immunogenicity measurements. • Have at least 1 blood sample collected starting at 14 days (Day 43) post-second vaccination available for analysis. The PPI will be the primary analysis population for SARS-CoV-2 RBD of S protein antibody responses and SARS-CoV-2 viral neutralizing antibody responses in the subset studied.
Statistical Analyses:	***Analysis of Demographics and Other Baseline Characteristics*** Data will be summarized with respect to demographic characteristics (age, gender), medical history and all safety measurements using descriptive statistics (quantitative data) and contingency tables (qualitative data). Medical history will only be listed. Subjects will be stratified (post-hoc) by pre-defined co-morbidities. Subjects with multiple co-morbidities will contribute to the different corresponding strata. ***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 and after the second vaccination. 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*** The following analyses will be done for SARS-CoV-2 RBD of the S protein antibody concentrations and for neutralizing antibodies titers: • Geometric mean concentrations (GMC) / GMT by group will be summarized with their 95% credibility interval at each blood sampling time point for all evaluable subjects and then separately in subjects seronegative at baseline and in subjects seropositive at baseline. • The fold change from baseline will be computed for seropositive subjects at baseline and geometric mean of the fold change (GMFC) by group will be displayed with their 95% CI at each blood sampling time point after baseline.

	• The number and percentage of subjects SARS CoV-2 seronegative at baseline for whom a seroconversion is observed will be summarized and presented at each blood sampling time point after baseline with exact 95% CI. Seroconversion is defined as detectable antibodies in the serum [≥ lower limit of quantification (LLOQ)]. Data will be presented after each vaccine dose. ***Missing Data/Discontinuation*** Concentration values of RBD and neutralizing antibodies marked as below the lower limit of quantification (LLOQ) will be set to 0.5*LLOQ. No imputation of missing values will be performed for any analysis (except the imputation for missing partial dates of AEs and concomitant medication). Currently no replacement of discontinued or withdrawn subjects is foreseen. This plan may be affected if an important percentage of subjects opt to receive any of the authorized/licensed COVID-19 vaccines, in which case enrollment of additional subjects into this trial will be considered.

2 SCHEDULE OF ACTIVITIES

Table 1 Schedule of Trial Assessments and Procedures

	Screening	Vaccination Period									Follow-up		End of Trial
Visit Number	**1**	**2**	**3**	**Safety contact[a]**	**Phone contact**	**4**	**5**	**6**	**7**	**8**	**9**	**Phone contact**	**10**
Visit Window (days)	**-7/+0**	**n/a**	**-0/+0[q]**	**-0/+7**	**-2/+4**	**-3/+14**	**-0/+0[q]**	**-2/+4**	**-2/+4**	**-2/+4**	**-7/+7**	**-7/+7**	**-0/+30**
Trial Day	**-7**	**1**	**2**	**9**	**15**	**29**	**30**	**43**	**57**	**120**	**211**	**302**	**393**
Signed informed consent[b]	X												
Inclusion/exclusion criteria[b]	X	X				X							
Demographics	X												
Medical history	X												
Review of criteria for delay or cancellation of vaccination[c]		X				X							
Investigational vaccine administration (including 1 hour observation)		X				X							
Physical examination[d]	X	X[e]				X							X
Symptom-directed physical examination		(X)[e]	X				X	X	X				
Vital signs[d]	X	X[f]	X			X[f]	X	X	X				X
ECG	X												
Diary dispensation / (re)training[g]	X	X	X			X	X	X					
Diary review[g]		X	X	X		X	X	X	X				
Solicited AEs collected by diary[g]	X[h]	X	X	X		X	X						
Unsolicited AEs collected by diary[g]	X[h]	X	X	X		X	X	X	X				
SAEs[i]	X	X	X	X	X	X	X	X	X	X	X	X	X
Intercurrent medical conditions[i]	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs leading to vaccine withdrawal or trial discontinuation[i]		X	X	X	X	X	X	X	X	X	X	X	X
AESIs[i]		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication/vaccination	X	X[j]	X	X	X	X	X	X	X	X	X	X	X

	Screening	Vaccination Period									Follow-up		End of Trial
Visit Number	**1**	**2**	**3**	**Safety contact[a]**	**Phone contact**	**4**	**5**	**6**	**7**	**8**	**9**	**Phone contact**	**10**
Visit Window (days)	**-7/+0**	**n/a**	**-0/+0[q]**	**-0/+7**	**-2/+4**	**-3/+14**	**-0/+0[q]**	**-2/+4**	**-2/+4**	**-2/+4**	**-7/+7**	**-7/+7**	**-0/+30**
Trial Day	**-7**	**1**	**2**	**9**	**15**	**29**	**30**	**43**	**57**	**120**	**211**	**302**	**393**
Safety laboratory (~8 mL)[k] - 50 subjects per co-morbidity	X	X[o]	X			X[o]	X	(X)[l]	X	(X)[l]			
Serum pregnancy test (~3 mL)[m]	X												
Urine pregnancy test[m]		X				X							
Nasopharyngeal swab collection for rapid diagnosis on site and PCR testing[n]	(X)[n]												
Binding antibody to RBD of S (spike) protein of SARS-CoV-2 (~4mL blood)		X[o]				X[o]		X		X	X		X
Binding antibody to the N (nucleocapsid) protein of SARS-CoV-2 (~4 mL blood)		X[o]						X		X			X
Subset of 25 subjects per co-morbidity: SARS-CoV-2 neutralizing activity (6 mL blood)[p]		X[o]				X[o]		X		X	X		X
Subset of 25 subjects per co-morbidity: Cell-mediated immunity (3 mL)[p]		X[o]				X[o]		X		X			
Maximum total blood volume (mL)	~8	~25	~8	-	-	~21	~8	~17	~8	~17	~10	-	~14
Trial end													X

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

a. The safety contact is only applicable for the first 25 subjects enrolled in the co-morbidities chronic kidney disease, COPD, chronic cardiovascular disease and diabetes mellitus to collect diary card data. The safety/reactogenicity data entered in the week after the first vaccination (i.e. all data recorded until Day 8 inclusively) has to be received by site and entered into EDC as soon as possible. The site and the subject should agree on the best way to transfer this data. It can be done via different means such as a site visit, phone call or a transfer of the diary to site.
b. Procedures to establish subject eligibility will be performed within 7 days prior to trial vaccine administration along with consent collection and physical examinations and paper diary training. Eligibility criteria need to be reviewed on the day of vaccination prior to trial vaccine administration.
c. See Section 6.4 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 eCRF.
d. 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.
e. If results of a complete physical examination performed within 7 days prior to trial vaccine administration are available and sufficient in view of the protocol requirements, a symptom-directed physical examination should be performed on the day of vaccination prior to trial vaccine administration.
f. Vital signs will be measured pre- and post-vaccination prior to discharge. Subjects will be observed for 1 hour following each vaccination. Vital signs must be within normal or clinically non-relevant abnormal ranges or have returned to pre-vaccination values for the subject to be discharged.
g. Solicited and unsolicited AEs will be recorded in diaries. Diaries will be dispensed at Visit 1, Visit 2 and Visit 4.
h. Subjects should complete the diary card for solicited systemic AEs as well as unsolicited AEs on a daily basis as of Day -7 (i.e., during 1 week before the first vaccination) to give an indication of their normal life with co-morbidities.

i. SAEs, AESIs (including COVID-19), intercurrent medical conditions that may affect the immune response to vaccination, and AEs leading to vaccine withdrawal or trial discontinuation will be collected throughout the trial.
j. 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 medication/vaccination taken within 1 month prior to enrollment should be recorded to establish eligibility and any exception if relevant.
k. Safety laboratory testing will be performed in the first 50 subjects enrolled and vaccinated from each co-morbidity. See Appendix 3 for an overview of the safety laboratory assessments.
l. At Visit 6 and Visit 8 the safety laboratory only needs to be done if the previous result was abnormal.
m. A blood sample for serum pregnancy testing will be taken from women of childbearing potential at screening 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.
n. Swabs for COVID-19 testing will be collected in case the subject displays symptoms of acute respiratory infection (including, but not limited to COVID-19) (see Section 9.3).
o. Blood samples on Day 1 and Day 29 must be collected prior to vaccination.
p. This will include 12 subjects for each co-morbidity condition enrolled as part of the first 25 cases and 13 subjects enrolled as part of the next 25 subjects for each co-morbidity.
q. In case a subject cannot come to site on the day after the vaccination due to vaccination reactions/side effects it is acceptable to conduct this visit within a window of +2 days.

Total blood volume taken is approximately 136 mL in the subset of subjects participating in the immunological assessments and the safety laboratory testing, separated over 10 times.

3 INTRODUCTION

3.1 Background

3.1.1 Coronaviruses

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

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

Prior to December 2019, when clusters of pneumonia cases with unknown etiology were detected in Wuhan City, Hubei Province, China, only 2 additional strains of CoVs had caused outbreaks of severe acute respiratory disease in humans: the severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2003 and 2012 respectively with the host jump of coronaviruses from bat to humans. On 9 January 2020, a novel CoV, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was officially identified as the cause of an outbreak of viral pneumonia in Wuhan. In the following weeks, the virus spread rapidly within China and then globally. On 30 January 2020, the World Health Organization (WHO) announced the outbreak its highest alert under International Health Regulations (IHR) as a Public Health Emergency of International Concern (PHEIC), raising alarm for all the member states and on 12 March 2020, declared it as a pandemic.

3.1.2 COVID-19

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 [5,6]. The most common symptoms of COVID-19 include fever, cough, dyspnea, and occasionally watery diarrhea. 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 [7-10]. Chemosensory dysfunction, such as anosmia and dysgeusia, have increasingly been reported.

The global mortality rate is currently around 2% [11]. 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 [11]. As of 1 March 2021, according to WHO, >113.6 million cases have been confirmed globally, including over >2.5 million deaths [11].

3.2 Trial Rationale

In view of the severity of respiratory disease caused by emerging coronaviruses, development of a vaccine has been undertaken by several pharmaceutical companies, and there are now emergency authorized vaccines available for prevention of COVID-19, in several countries worldwide. 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 when administered as a 2-dose 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, reactogenicity and immunogenicity of this vaccine is being evaluated in the first-in-human dose-finding trial CV-NCOV-001 and in the dose-confirmation trial CV-NCOV-002. At this time, different dose levels (2, 4, 6, 8, 12, 16 and 20 µg) have been tested in 250 healthy adults 18 to 60 years of age in the CV-NCOV-001 trial and the dose levels of 6 and 12 µg have been tested in >600 individuals 18-60 and >60 years of age in the CV-NCOV-002 trial. The data from the CV-NCOV-001 trial confirmed the selection of the 12-µg dose level for further evaluation in Phase 2b and Phase 3 trials which started in December 2020. A total of >6,000 subjects have received the active dose of the vaccine till end of February 2021.

This trial will be conducted to assess the safety, reactogenicity and immunogenicity of CVnCoV in adults ≥18 years of age with co-morbidities known to increase the risk for (severe) COVID-19, when administered as 2 doses according to a 0 (Day 1) and 1-month (Day 29) vaccination schedule. The dose level to be administered in this trial was selected based on data from the trials CV-NCOV-001 and CV-NCOV-002.

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

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

[redacted]

[redacted]

[redacted]

Furthermore, CureVac consulted with external regulatory and scientific experts, including the Coalition for Epidemic Preparedness Innovations (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 and are being evaluated, as recommended by Wang and colleagues [20]. These approaches are in line with those agreed upon for COVID-19 vaccine development by the International Coalition of Medicines Regulatory Authorities [21].

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

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

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

CVnCoV has not been investigated in an adult population with co-morbidities known to increase the risk for (severe) COVID-19. The safety and reactogenicity as well as immunogenicity of CVnCoV in this population will be investigated in the current trial.

The current trial is designed to observe if these comorbid subjects have additional risks to vaccination to assess risk-benefit ratio.

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 further evaluated in humans and it is thus not known if the vaccine is effective in protecting against COVID-19. Furthermore, no correlate of protection or threshold of protection has been established for COVID-19. 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).

3.3.3 Assessment of Potential Risks and Benefits

To minimize the risk for subjects participating in this trial, a DSMB will oversee the safety of the subjects throughout the trial.

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 overall, as well as per underlying co-morbidity.

4.1.1 Primary

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

4.1.2 Secondary

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

4.1.3 Exploratory

- To evaluate the occurrence of laboratory-confirmed cases of COVID-19 after 1 and 2 doses of CVnCoV.
- To evaluate the cell-mediated immune (CMI) response after 1 and 2 dose administrations of CVnCoV in a subset of subjects.

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

Safety

- The frequency, intensity, and duration of solicited local AEs on each vaccination day and the following 7 days.
- The frequency, intensity, duration, and relationship to trial vaccination of solicited systemic AEs on each vaccination day and the following 7 days.
- The occurrence, intensity and relationship to trial vaccination of unsolicited AEs on each vaccination day and the following 28 days.
- The occurrence and relationship to trial vaccination of SAEs and AESIs throughout the trial.

Immunogenicity

On Day 43:

- The proportion of subjects seroconverting for SARS-CoV-2 S protein RBD antibodies, as measured by an immunoassay.
- Individual SARS-CoV-2 S protein RBD-specific antibody levels in serum, as measured by an immunoassay.
- Geometric mean titers (GMTs) of serum SARS-CoV-2 S protein RBD antibodies, as measured by an immunoassay.
- *In a subset of subjects**: the proportion of subjects seroconverting for SARS-CoV-2 neutralizing antibodies, as measured by an activity assay.
- *In a subset of subjects**: individual SARS-CoV-2 neutralizing antibody levels in serum, as measured by an activity assay.
- *In a subset of subjects**: GMTs of serum SARS-CoV-2 neutralizing antibodies, as measured by an activity assay.

4.2.2 Secondary

On Day 29, Day 120, Day 211 and Day 393:

- The proportion of subjects seroconverting for SARS-CoV-2 S protein RBD antibodies, as measured by an immunoassay.
- Individual SARS-CoV-2 S protein RBD-specific antibody levels in serum, as measured by an immunoassay.
- GMTs of serum SARS-CoV-2 S protein RBD antibodies, as measured by an immunoassay.

In a subset of subjects, on Day 29 and Day 120:*

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

4.2.3 Exploratory

Occurrence of confirmed COVID-19 cases

- Number of subjects with reverse transcription polymerase chain reaction (RT-PCR)-confirmed SARS-CoV-2 infection as measured by RT-PCR at clinically determined time points throughout the trial.
- Number of subjects with asymptomatic SARS-CoV-2 infection as measured by serological titers of nucleocapsid antibodies on Day 1, Day 43, Day 120 and Day 393.

CMI response

On Day 1, Day 29, Day 43 and Day 120 in peripheral blood stimulated with antigen in a subset of subjects:*

- The SARS-CoV-2 S-specific T cell response, as measured by cytokine and chemokine expression after antigen stimulation using a standardized whole blood collection and culture system.

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

- *Twelve subjects for each co-morbidity will be enrolled as part of the first 25 cases.*
- *The other 13 subjects will be enrolled as part of the next 25 enrolled subjects for each co-morbidity.*

5 TRIAL DESIGN

5.1 Overall Design

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

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

Subjects will be enrolled into 1 trial group:

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

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

The trial contains 10 protocol-scheduled visits and 2 protocol-scheduled phone contacts as detailed in Table 1. In addition, there will be a protocol-scheduled safety contact to collect diary card data on Day 9 for the first 25 subjects enrolled in the co-morbidities chronic kidney disease, COPD, chronic cardiovascular disease and diabetes mellitus (see below for details on the stratification).

Stratification Based on Co-Morbidities

Subjects will be stratified post-hoc into different pre-defined co-morbidities or combinations thereof. To be eligible for the trial, subjects' medical condition(s) must be controlled and stable as per the Investigator's judgment at the time of recruitment. For the purpose of enrollment in this trial, stratification of co-morbidities will be based on the subject's main medical condition that increases their risk of severe illness from COVID-19. In some cases, subjects may have several high-risk co-morbidities. For these scenarios, the main co-morbidity as determined by the Investigator will be used for enrollment stratification. Data analyses, however, will take into consideration all pre-defined co-morbidities of interest in the trial population.

For chronic kidney disease, COPD, chronic cardiovascular disease and diabetes mellitus, the first 25 subjects enrolled in each co-morbidities will be restricted to those with mild to moderate disease (as defined in Section 6.3).

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

in these 25 subjects and following iSRC and DSMB Chair approval, subjects with more severe forms of the co-morbidity may be enrolled as per the Investigator's decision.

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

5.2 Stopping/Pausing Rules for Safety

5.2.1 Individual Subject Stopping Rules

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

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

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

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

5.2.2 Pausing of the Trial

The decision to pause the trial (i.e., temporary stopping of enrollment and vaccinations) due to a safety signal will be based on a recommendation from the DSMB in consultation with the Sponsor (see Section 9.1.6). The DSMB may recommend pausing the trial for a safety concern following a review of accumulating safety data presented at the regularly scheduled DSMB meetings or from an ongoing review of AEs, which include but are not limited to, suspected unexpected serious adverse reactions (SUSARs); all SAEs judged as related to trial vaccine; concerning SAEs (e.g., AESIs); and all life-threatening SAEs and deaths. These events will be monitored by the DSMB (which is for entire COVID-19 vaccine clinical development trials encompassing CV-NCOV-001, -002, -004, -005 and -003) on a regular basis during the trial. The selected AEs and procedures for the safety review are described in detail in the DSMB Charter.

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

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

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

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

5.3 Scientific Rationale for Trial Design

This trial will evaluate the safety, reactogenicity and immunogenicity of CVnCoV in adults ≥18 years of age with co-morbidities known to increase the risk for (severe) COVID-19. As this population is at higher risk of SARS-CoV-2 infection, it is critical to investigate CVnCoV in this population and determine if the vaccine is safe and well tolerated. While subjects with co-morbidities are also included in other Phase 3 trials in the program, the current trial will ensure investigation of CVnCoV in a trial population with very well characterized co-morbidities.

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

5.4 Justification for Dose

CVnCoV will be evaluated at the dose level of 12 µg, defined based on clinical data from the ongoing trials CV-NCOV-001 and CV-NCOV-002. Refer to the Investigator's Brochure for an overview of the CVnCoV clinical and non-clinical data.

5.5 End of Trial Definition

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

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

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. Male and female subjects ≥18 years of age with 1 or more co-morbidities as defined by the case definitions in Section 6.3.
2. For the co-morbidities chronic kidney disease, COPD, chronic cardiovascular disease and diabetes mellitus, the first 25 subjects per co-morbidity should include only mild to moderate cases as described in Section 6.3. Thereafter, more severe conditions may be recruited (see Section 5.1) following iSRC and DSMB Chair approval.
3. Subject has no overt clinical signs or symptoms of COVID-19.
4. Subject has to sign the informed consent form (ICF) before any trial procedures.
5. Subjects with a life expectancy of at least 1 year as per the Investigator's assessment.
6. Expected to be compliant with protocol procedures and available for clinical follow-up through the last planned visit.
7. Physical examination without acute clinically significant findings according to the Investigator's assessment.
8. Female subjects: At the time of enrollment, negative human chorionic gonadotropin (hCG) pregnancy test (serum) for women presumed to be of childbearing potential on the day of enrollment. On Day 1 (pre-vaccination): negative urine pregnancy test (hCG) (only required if serum pregnancy test was performed more than 3 days before).

   Note: Women that are postmenopausal (defined as amenorrhea for ≥ 12 consecutive months prior to screening without an alternative medical cause) or permanently sterilized will be considered as not having reproductive potential.
9. 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;
- Same sex relationships.

Sexual abstinence [periodic abstinence (e.g., calendar, ovulation, symptothermal and post-ovulation methods)] and withdrawal are not acceptable methods.

Refer to the Clinical Trial Facilitation Group recommendations on contraception and pregnancy testing for further details [22].

6.2 Exclusion Criteria

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

1. A previous clinical and laboratory-confirmed diagnosis of COVID-19 within the last six months prior to screening.
2. 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.
3. 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. Planned vaccination with an inactivated influenza vaccine is permitted.
4. Receipt of any investigational, authorized or licensed SARS-CoV-2, other coronavirus vaccine or any other LNP-containing mRNA vaccine prior to the administration of the trial vaccine. For authorized or licensed SARS-CoV-2: planned administration during the trial up to 6 weeks after the foreseen date of second dose administration of CVnCoV.
5. Any treatment with immunosuppressants or other immune-modifying drugs (including, but not limited to, corticosteroids, biologicals, and methotrexate) for >14 days in total within 6 months prior to the administration of the trial vaccine or planned use during the trial. For corticosteroid use, this means prednisone or equivalent, 0.5 mg/kg/day for 14 days or more. The use of inhaled, topical, or localized injections of corticosteroids (e.g., for joint pain/inflammation) is permitted.

   Note: This exclusion does not apply to the renal transplant cases and is at the Investigator's discretion for subjects with other co-morbidities (e.g., COPD).
6. Any medically diagnosed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination, excluding the co-morbidities specified in Section 6.3.

   (Subjects with chronic HIV infection with controlled Hep B infection with therapy or aviremic Hep C may be eligible for the trial, based on the Investigator's judgment).
7. History of immune-mediated or autoimmune disease.
8. History of anaphylaxis or allergy to any component of CVnCoV or aminoglycoside antibiotics.

9. History of or current alcohol and/or drug abuse.
10. History of confirmed SARS or MERS disease
11. Administration of immunoglobulins and/or any blood products within the 3 months preceding the administration of any dose of the trial vaccine.
12. Presence or evidence of significant uncontrolled acute or chronic medical or psychiatric illness, excluding the co-morbidities specified in Section 6.3. Significant medical or psychiatric illnesses include but are not limited to:
    - Uncontrolled respiratory disease.
    - 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.
13. Foreseeable non-compliance with protocol, as judged by the Investigator.
14. For female subjects: pregnancy or lactation.
15. Subjects with impaired coagulation or any bleeding disorder in whom an intramuscular (IM) 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. However, use of anticoagulants is accepted in certain co-morbidities according to the clinical Investigator's judgment and if the INR remains ≤3.
16. Subjects employed by the Sponsor, Investigator, or trial site, or relatives of research staff working on this trial.

6.3 Case Definitions Co-morbidities

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

- **Chronic kidney disease:** Kidney function will be ascertained from the serum creatinine measurement within the last 6 months, converted into estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, with impaired kidney function defined as eGFR <60 mL/min/1.73m².
    - Mild chronic kidney disease is defined as an eGFR between 60-89 mL/min/1.73 m^2.
    - Moderate chronic kidney disease is defined as an eGFR between 31-59 mL/min/1.73 m^2 with stable therapy and good maintenance over at least 6 months [23].

- **Chronic obstructive pulmonary disease** (COPD) (including emphysema and chronic bronchitis).
  - Mild COPD with or without cough or sputum production is defined as forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) <0.7 and FEV_1 ≥80% predicted.
  - Moderate COPD with or without cough or sputum production is defined as FEV_1/FVC <0.7 and FEV_1≥50%, but <80% predicted with stable treatment (GOLD Criteria for COPD severity).
- **Obesity** with body mass index >32 kg/m².
- **Chronic cardiovascular disease** (heart failure, structural heart disorder, coronary artery disease, cardiomyopathies, arterial hypertension), including the following:
  - Heart failures (according to New York Heart Association [NYHA] classification [24]):
    - Class I: No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
    - Class II: Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
  - A structural heart disorder
    - without symptoms
    - with symptoms.
  - Coronary artery disease:
    - Mild with metabolic equivalent threshold (MET)[2] <3, stable with medication.
    - Moderate with MET >3 – 5.9, stable with medication.
  - Cardiomyopathies of non-infective and metabolic origin:
    - Mild with MET <3, stable with medication.
    - Moderate with MET >3 – 5.9, stable with medication.
  - Hypertension (National Institute for Health and Care Excellence [NICE] categorization [26]):
    - Stage 1 hypertension: Clinic blood pressure ranging from 140/90 mmHg to 159/99 mmHg and subsequent ambulatory blood pressure monitoring (ABPM) daytime average or home blood pressure monitoring (HBPM) average blood pressure ranging from 135/85 mmHg to 149/94 mmHg.

[2] MET is defined as the amount of oxygen consumed while sitting at rest and is equal to 3.5 mL O_2 per kg body weight/min and is roughly equivalent to the expenditure of 1 kcal per kilogram of body weight per hour; 1 MET is the rate of energy expenditure while at rest. A 4 MET activity expends 4 times the energy used by the body at rest. Light MET is <3, moderate is 3 to 5.9 and vigorous is ≥6.0. MET 1 can take care of him/herself and may not maintain themselves and gets constraints on exertion. MET 4 can climb a flight of stairs or walk up a hill and can participate in other strenuous activities; >2-3 METs is fit normal person with well controlled with medication [25].

- Stage 2 hypertension: Clinic blood pressure of 160/100 mmHg or higher but less than 180/120 mmHg and subsequent ABPM daytime average or HBPM average blood pressure of 150/95 mmHg or higher.

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

Following inclusion of 25 cases of mild to moderate conditions under chronic kidney disease, COPD, chronic cardiovascular disease and diabetes mellitus, more severe conditions can be included into the trial upon iSCR and DSMB Chair approval and subjected to the clinical Investigator's decision (refer to Section 5.1 for details on the stratification based on co-morbidities).

- Under cardiovascular disease, the following cases can be included:
  - Heart failures (according to NYHA classification [24]) Class III: Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea (shortness of breath).
  - Coronary artery disease: Severe with MET >6, stable with medication.
  - Cardiomyopathies of non-infective and metabolic origin: Severe with MET >6, stable with medication.
  - Hypertension (NICE categorization [26]): Stage 3 or severe hypertension: Clinic systolic blood pressure of 180 mmHg or higher or clinic diastolic blood pressure of 120 mmHg or higher.
- Under diabetes mellitus, cases of uncontrolled diabetes mellitus with recent HbA1c of >59 mmol/mol (7.45%) with medication can be included. For uncontrolled diabetes mellitus, HbA1c should be within <10% variation and the subject should not have any history of diabetic ketoacidosis or episode of severe symptomatic hypoglycemia within the past 3 months.

6.4 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 and SARS-CoV-2 infection is either not clinically suspected or testing is negative) or body 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 body 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. Body temperature should be measured orally and by using the thermometer provided to the subject at Visit 1.

- For subjects who develop laboratory-confirmed COVID-19 after the first dose but prior to receiving the second dose of CVnCoV, once the subject has recovered from COVID-19, the subject can be vaccinated with the second dose of CVnCoV, following two weeks of complete recovery if within the per protocol defined allowed time windows as specified in Table 1.
- Subjects who took antipyretic medication within 8 hours before intended trial vaccination (this is not applicable to the intake of low dose acetylsalicylic acid taken for prevention of cardiac disease).

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

In case of any complications, the subsequent vaccination may be stopped or delayed.

6.5 Failure to Meet Eligibility Criteria

The Investigator must account for all subjects who sign an 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 -7 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 containing 12 µg mRNA. The IMP is composed of the active pharmaceutical ingredient, an mRNA that encodes the stabilized full-length S protein, and 4 lipid components: cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), PEG-ylated lipid, and a cationic lipid.

7.1.2 Dosing and Administration

All subjects will be administered a first vaccine dose of CVnCoV on Day 1 and a second vaccine dose on Day 29.

Injections must be performed 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 1 hour 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, as presented in

1. Review and provide a signature as approval of the content of the clinical trial report (to be reported by the coordinating Investigator).

Appendix 2. 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 and 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 CVnCoV 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

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

7.4 Vaccine Compliance

The Investigator will record all CVnCoV injections 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.

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 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 CVnCoV should be pursued.

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 for the second 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. Blood samples for immunogenicity assessments may be taken at the Investigator's discretion.

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.

- SARS-CoV-2 infection, virologically confirmed by positive RT-PCR test (as specified in Table 1).

  Note: Subjects who develop laboratory-confirmed COVID-19 after the first vaccine dose administration should only receive the second vaccine dose 2 weeks after getting fully recovered and if it falls under the time windows (see Section 6.4).

- 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.
- Wants to receive authorized/licensed vaccine.
- 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 available 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. For each procedure, subjects are to be assessed by the same Investigator or site personnel whenever possible.

After each vaccination, subjects should be monitored for 1 hour at the site before discharge from the hospital for measurement of vital signs (see Section 9.1.4) and inspection of injection site.

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 can be performed within 7 days prior to trial vaccine administration, i.e., spread out over more than 1 day. Eligibility criteria need to be reviewed on the day of vaccination prior to trial vaccine administration. However, completion of the diary card for baseline, before vaccination, should start only on Day -7.

The total volume of blood taken over the trial period from each subject will be approximately 136 mL in the subset of subjects participating in the immunological assessments and the safety laboratory testing. For the subset of subjects in whom the CMI will be assessed, the maximum volume of blood for these analyses will be 12 mL. 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 9.

Subjects with any Grade 3 solicited or unsolicited AEs are asked to immediately report these to the Investigator. Unscheduled visits will be performed when deemed necessary for safety assessments by the clinical Investigator and to ensure data integrity.

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

9.1.1.1 Solicited Adverse Events

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

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

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

Solicited AEs will be assessed on an intensity scale of absent, mild, moderate, and severe (Table 2 and Table 3). In case of related Grade 3 solicited or unsolicited AEs reported for more than 1 day in the diary, the subject will be questioned to establish the total duration of the AE as exactly as possible and this information will be recorded in the eCRF.

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

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

Table 2 Intensity Grading for Solicited Local Adverse Events

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

Based on the United States Food and Drug Administration toxicity grading scale [27].

Table 3 Intensity Grading for Solicited Systemic Adverse Events

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

Based on the United States Food and Drug Administration toxicity grading scale [27].

9.1.1.2 Unsolicited Adverse Events and Serious Adverse Events

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

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

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

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

9.1.1.3 Adverse Events of Special Interest

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

- AEs with a suspected immune-mediated etiology (pIMDs, see Appendix 7).
- Other AEs relevant to SARS-CoV-2 vaccine development or the target disease (see Appendix 8 for the current list of AESIs and see Section 9.3 for details on laboratory testing for COVID-19).
- Non-serious intercurrent medical conditions that may affect the immune response to vaccination will also be collected throughout the trial.

AESIs will be collected throughout the trial.

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 9 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 Table 1 in the first 50 subjects enrolled and vaccinated from each co-morbidity condition. Blood samples on Day 1 and Day 29 must be collected prior to vaccination. 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 to establish eligibility at screening. 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 (US FDA) toxicity grading scale [27]. Any institutional normal reference ranges should be provided to demonstrate that they are appropriate.

A laboratory abnormality is however only considered an AE if considered clinically significant in the medical and scientific judgment of the Investigator.

9.1.4 Vital Signs, Physical Examination, and Electrocardiogram

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. At the vaccination visits on Day 1 and Day 29, vital signs will be measured pre- and post-vaccination prior to discharge. Subjects will be observed for 1 hour 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.

A complete physical examination should be performed at the time points specified in Table 1, except if results of a complete physical examination performed within 7 days prior to Day 1 are available and sufficient in view of the protocol requirements, 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, extremities and neurological examination, skin examination, and measurement of weight and height. At the other trial visits, a symptom-directed physical examination will be performed at the discretion of the Investigator.

An electrocardiogram (ECG) with conventional 12-lead traces will be recorded at the screening 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.

Any changes in severity of the underlying condition will be monitored. Increases in severity meeting the definition of an SAE and considered to be related to the trial vaccine will be reported as a SUSAR (see Appendix 9).

Information should be provided on medical and surgical history and concomitant medical conditions specifying those ongoing on Day -7.

9.1.6 Safety Monitoring Committees

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

As described in Section 5.1, for the co-morbidities chronic kidney disease, COPD, chronic cardiovascular disease and diabetes mellitus, the first 25 subjects per co-morbidity should include only mild to moderate cases. The iSRC and DSMB Chair will perform an assessment of the safety and reactogenicity data up to at least 1 week after the first dose, prior to proceding with enrollment of subjects with more severe forms of the co-morbidity as per the Investigator's decision.

In addition, as part of the risk-benefit analysis, the DSMB will periodically monitor COVID-19 cases for signals of VDE (see Section 3.3.1).

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

9.2 Immunogenicity Assessments

An overview of the timing of blood sample collection for immunogenicity assessment is provided in Table 1. Blood samples on Day 1 and Day 29 must be collected prior to vaccination.

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

The immune response induced by vaccination with CVnCoV will be evaluated by 2 assays at the time points specified in Table 1:

- Binding antibodies to the SARS-CoV-2 RBD of the S protein measured in serum by an immunoassay for all subjects.
- Viral neutralizing antibodies directed against SARS-CoV-2 measured in serum by a functional activity assay for a subset of approximately 25 subjects per co-morbidity. This will include 12 subjects for each co-morbidity enrolled as part of the first 25 cases and 13 subjects enrolled as part of the next 25 subjects for each co-morbidity.

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

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

9.2.3 Cell-Mediated Immunity

CMI will only be evaluated in approximately 25 subjects per co-morbidity at the time points specified in Table 1. This will include 12 subjects for each co-morbidity enrolled as part of the first 25 cases and 13 subjects enrolled as part of the next 25 subjects for each co-morbidity.

The induction, by the vaccine, of SARS-CoV-2 S protein-specific T-cell responses after antigen stimulation will be measured by secretion of T cell specific cytokines and chemokines (including but not limited to IFN-gamma, TNF-alpha, IL-2, IFN-γ-induced protein 10 [IP-10], IL-4, IL-5, IL-17, IL-21) after antigen stimulation using a standardized whole blood collection and culture system.

9.3 Laboratory Testing for COVID-19

Subjects will be screened for any symptoms or signs of COVID-19. Subjects who suffered from COVID-19 within the last six months prior to screening will be not be enrolled into the trial.

Subjects will be contacted once per week to enquire if they developed any of the following symptoms*:

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

*FDA Guidance for Industry, Development and Licensure of Vaccines to Prevent COVID-19, June 2020 [28].

During every clinic visit and phone call, subjects will be instructed and reminded to call the trial site if they develop any of these symptoms.

If any of these symptoms are observed, the Investigator will collect appropriate nasopharyngeal samples as soon as feasible to do a rapid diagnostic antigen test on site. In case of a positive result of the rapid test, another specimen will be sent to the central lab for confirmatory RT-PCR to evaluate for infection with SARS-CoV-2. If the rapid test is negative, a specimen may be sent to the central lab at the clinical Investigator's discretion.

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

Any subject with clinical suspicion of SARS-CoV-2 infection following vaccination will undergo appropriate testing and referral within the local healthcare system as appropriate. Subjects with confirmed SARS-CoV-2 infection after the first vaccine dose administration should only receive the second dose of CVnCoV 2 weeks after complete recovery and if it falls within the per protocol-defined allowed time window as specified in Table 1.

The currently available case definition for COVID-19 is provided in Appendix 4.

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size Determination

The sample size of the trial ensures that sufficient safety and immunogenicity data will be available in a population with co-morbidities. We aim to enroll 1,200 subjects.

The trial is designed to provide a reasonable precision for an estimate of the number of subjects seroconverting for SARS-CoV-2 S protein RBD-specific antibodies and an acceptable rate of Grade 3 adverse reactions (defined as solicited local Grade 3 AEs, and solicited systemic or unsolicited Grade 3 AEs considered as related to the trial vaccine). Table 4 provides the estimate and 95% credibility interval (CI) for the observed numbers of subjects seroconverting for SARS-CoV-2 S protein antibodies for sample sizes of 150 (providing characteristics for a pre-defined co-morbidity) and 1,200 assuming a Beta (1.9, 0.1) priors for seroconversion for SARS-CoV-2 S protein antibodies and Beta (0.5, 1.5) priors for Grade 3 adverse reactions are assumed.

Table 4 Estimate of Number of Subjects Seroconverting for SARS-CoV-2 S Protein Antibodies and 95% Credibility Interval

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

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

Table 5 provides probabilities (in %) that the following 2 conditions are simultaneously met for assumed true adverse reaction rates and for assumed true rates of subjects seroconverting for SARS-CoV-2 S protein antibodies and for different sample sizes:

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

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

Table 5 Probabilities (in %) for Assumed True Adverse Reaction Rates and for Assumed True Rates of Subjects with Seroconverting for SARS-CoV-2 S Protein Antibodies and Different Sample Sizes

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

10.2 Populations for Analyses

Immunogenicity set

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

Safety Set

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

Per Protocol Immunogenicity Subset

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

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

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

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. The safety and immunogenicity analyses will be done overall.

An 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.

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

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

10.3.2 Demographic, Medical History and Other Baseline Characteristics

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

10.3.3 Trial Vaccine Administration

The administrations of CVnCoV 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:

2. 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).
3. SAEs and AESIs throughout the trial.

Solicited AEs: For reactogenicity assessment, 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 and after the second vaccination. 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.

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% CI based on the Beta (0.5, 0.5) prior distribution 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. 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 with 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 and a listing will be provided.

10.3.5.2 Primary Immunogenicity Analysis

No formal hypothesis on immunogenicity will be tested. Descriptive statistics for the immunogenicity endpoints will be provided.

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

- Geometric mean concentrations (GMC) / GMT by group will be summarized with their 95% CI at each blood sampling time point for all evaluable subjects and then separately in subjects seronegative at baseline and in subjects seropositive at baseline.
- The fold change from baseline will be computed for seropositive subjects at baseline and geometric mean of the fold change (GMFC) by group will be displayed with their 95% CI at each blood sampling time point after baseline.
- The number and percentage of subjects SARS-CoV-2 seronegative at baseline for whom a seroconversion is observed will be summarized and presented at each blood sampling time point after baseline with exact 95% CI. Seroconversion is defined as detectable antibodies in the serum [≥ lower limit of quantification (LLOQ)].

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

The analyses of CMI in terms of induction by the vaccine of SARS-CoV-2 S protein-specific T-cell responses will be detailed in the SAP.

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

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 the RBD and neutralizing antibodies, concentration values marked as below the lower limit of quantification (LLOQ) will be set to 0.5*LLOQ.

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

Currently no replacement of discontinued or withdrawn subjects is foreseen. This plan may be affected if an important percentage of subjects opt to receive any of the authorized/licensed COVID-19 vaccines, in which case an enrollment of additional subjects into this trial will be considered.

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), as presented in Appendix 5, will check eCRF entries against source documents according to the guidelines of Good Clinical Practice (GCP). The ICF 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 following the local guidelines.

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

and closed before database lock. Protocol deviations will be classified as important or non-important 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. 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. Any changes to the approved version of this protocol will require formal approvals by the IEC(s), as specified in Appendix 6. 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.

The responsibilities of the Investigators are further described in Appendix 1.

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. Biological samples and record retention are described in Appendix 10.

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

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15 APPENDICES

Appendix 1 Responsibilities of the Investigator

Clinical research trials 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 (to be reported by the coordinating Investigator).

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 6 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 6 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
Serum/Urine Pregnancy Tests	Human chorionic gonadotropin

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

Appendix 4 Case Definition for COVID-19

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 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 5 Trial Governance Considerations

CureVac AG is the Sponsor of this trial. PRA Health Sciences is the CRO appointed to coordinate the conduct of this trial.

Appendix 6 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 7 Potential Immune-Mediated Diseases

Current list of pIMDs:

Gastrointestinal disorders:

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

Liver disorders:

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

Metabolic diseases:

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

Musculoskeletal disorders:

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

Neuro-inflammatory disorders:

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

Skin disorders:

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

Vasculitides:

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

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

Appendix 8 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:
- Anaphylaxis
- Vasculitides
- Enhanced disease following immunization
- Multisystem inflammatory syndrome in children
- Subacute thyroiditis

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

Cardiac disorders:

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

Hematological disorders:
- Thrombocytopenia

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

Renal disorders:
- Acute kidney injury

Gastrointestinal disorders
- Liver injury
- Pancreatitis

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

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

Other:

- Serious local/systemic adverse reaction following immunization
- Rhabdomyolysis

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

Appendix 9 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 [27]. **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 10 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.