Protocol Number: CV-NCOV-001

Official Title: A Phase 1, partially blind, placebo-controlled, dose-escalation, first-in-human, clinical trial to evaluate the safety, reactogenicity and immunogenicity after 1 and 2 doses of the investigational SARS-CoV2 mRNA vaccine CVnCoV administered intramuscularly in healthy adults.

NCT Number: NCT04449276

Document Date: 24-Jul-2020

CLINICAL TRIAL PROTOCOL

COVID-19:
A Phase 1, partially blind, placebo-controlled, dose-escalation, first-in-human, clinical trial to evaluate the safety, reactogenicity and immunogenicity after 1 and 2 doses of the investigational SARS-CoV-2 mRNA vaccine CVnCoV administered intramuscularly in healthy adults

Protocol Number:	CV-NCOV-001
EudraCT Number:	2020-001286-36
Investigational product:	CV07050101 (referred to as CVnCoV)
Phase:	Phase 1
Sponsor:	CureVac AG Schumannstrasse 27 60325 Frankfurt Germany
Short Title:	Safety, reactogenicity and immunogenicity of CVnCoV in healthy adults
Protocol Version:	3.0
Protocol Date:	24 July 2020

PROTOCOL VERSION HISTORY:

Version 1.0 dated 28 May 2020

Version 2.0 dated 12 June 2020

PROTOCOL APPROVAL SIGNATURES

Protocol Title: COVID-19: A Phase 1, partially blind, placebo-controlled, dose-escalation, first-in-human, clinical trial to evaluate the safety, reactogenicity and immunogenicity after 1 and 2 doses of the investigational SARS-CoV-2 mRNA vaccine CVnCoV administered intramuscularly in healthy adults

Protocol Number: CV-NCOV-001

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

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

Sponsor Signatory

[redacted]

CureVac AG

Medical Responsible Person

[redacted]

CureVac AG

Head of Clinical Operations

[redacted]

CureVac AG

Statistician

[redacted]

[redacted]

PROTOCOL APPROVAL SIGNATURES

Protocol Title: COVID-19: A Phase 1, partially blind, placebo-controlled, dose-escalation, first-in-human, clinical trial to evaluate the safety, reactogenicity and immunogenicity after 1 and 2 doses of the investigational SARS-CoV-2 mRNA vaccine CVnCoV administered intramuscularly in healthy adults

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Sponsor Signatory

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Medical Responsible Person

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Head of Clinical Operations

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Statistician

[redacted]

[redacted]

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Head of Clinical Operations

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Statistician

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INVESTIGATOR SIGNATURE PAGE

Protocol Title: COVID-19: A Phase 1, partially blind, placebo-controlled, dose-escalation, first-in-human, clinical trial to evaluate the safety, reactogenicity and immunogenicity after 1 and 2 doses of the investigational SARS-CoV-2 mRNA vaccine CVnCoV administered intramuscularly in healthy adults

Protocol Number: CV-NCOV-001

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, Good Clinical Practice (GCP), and relevant International Council on Harmonization (ICH) guidelines.

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

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

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

Investigator Signatory

Name

Address

Signature

Date

SAE hotline and medical monitor contacts

SAE Hotline	
SAE reporting to PRA 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.	
Europe	
Name of primary Contact:	[redacted]
Address:	
Phone:	
Fax:	
Email:	

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LIST OF ABBREVIATIONS

AE	Adverse event
AESI	Adverse event of special interest
ANA	Antinuclear antibody
ARI	Acute respiratory infection
BLRM	Bayesian logistic regression model
BMI	Body mass index
CCL	Chemokine ligand
CEPI	Coalition for Epidemic Preparedness Innovations
CMI	Cell-mediated immunity
CoV	Coronavirus
CRO	Contract research organization
CTL	Cytotoxic T lymphocyte
CVnCoV	Investigational SARS-CoV-2 mRNA vaccine
DDS	Dose-determining set
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
DSMB	Data and safety monitoring board
E	Envelope
ECG	Electrocardiogram
eCRF	Electronic case report form
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EWOC	Escalation with overdose control
FDA	US Food and Drug Administration
FIH	First-in-human
GCP	Good Clinical Practice
GMT	Geometric mean titer
hCG	Human chorionic gonadotropin
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICS	Intracellular cytokine staining
IEC	Independent Ethics Committee
IFN	Interferon
Ig	Immunoglobulin
IL	Interleukin

IM	Intramuscularly
IMP	Investigational medicinal product
IP-10	IFN-γ-induced protein 10
IRB	Institutional Review Board
iSRC	Internal safety review committee
IUD	Intrauterine device
IUS	Intrauterine systems
IVRS	Interactive voice response system
LLOQ	Lower limit of quantification
LNP	Lipid nanoparticles
M	Membrane
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
mRNA	Messenger ribonucleic acid
N	Nucleocapsid
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
pIMD	Potential immune-mediated disease
PT	Preferred Term
RBD	Receptor binding domain
RNA	Ribonucleic acid
RT-PCR	Reverse transcription polymerase chain reaction
S	Spike
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS	Severe acute respiratory syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SOC	System Organ Class
SOP	Standard operating procedure
TSH	Thyroid stimulating hormone
VDE	Vaccine dependent disease enhancement
WHO	World Health Organization

1 SYNOPSIS

Name of Investigational Vaccine:	CVnCoV	
Sponsor:	CureVac AG	
Coordinating Investigator:	[redacted]	
Title of Trial:	COVID-19: A Phase 1, partially blind, placebo-controlled, dose-escalation, first-in-human, clinical trial to evaluate the safety, reactogenicity and immunogenicity after 1 and 2 doses of the investigational SARS-CoV-2 mRNA vaccine CVnCoV administered intramuscularly in healthy adults.	
Rationale:	Coronaviruses are a large family of zoonotic viruses causing respiratory disease, ranging from a common cold to severe diseases such as Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) in humans. In December 2019, an outbreak of respiratory disease caused by a novel coronavirus strain was reported in Wuhan City, Hubei Province, China. The novel coronavirus was named "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2), while the disease associated with it is referred to as COVID-19. The virus has spread to different parts of China and an increasing number of countries worldwide and on 12 March 2020 the World Health Organization (WHO) announced that the outbreak was characterized as a pandemic. In spite of the severity of respiratory disease caused by emerging coronaviruses, there is currently no licensed vaccine available for prevention of coronavirus-associated disease. In partnership with the Coalition for Epidemic Preparedness Innovations (CEPI), CureVac AG is developing a new SARS-CoV-2 (mRNA) vaccine formulated with lipid nanoparticles (referred to as CVnCoV). This first-in-human (FIH) Phase 1 trial will evaluate the safety, reactogenicity and immunogenicity of CVnCoV at different dose levels using an adaptive dose-finding design. This will allow dose escalation or de-escalation using predefined safety criteria and select the CVnCoV dose for further clinical development. Throughout the trial, cases of COVID-19 disease will be identified and documented for later pooling of cases across trials in the clinical development program.	
Trial Duration for Each Subject:	Approximately 13 months for each subject.	**Phase:** 1
Objectives:	All objectives will be analyzed in all subjects, in those subjects retrospectively SARS-CoV-2 seronegative at baseline, and in those subjects retrospectively SARS-CoV-2 seropositive at baseline. ***Primary*** • To evaluate the safety and reactogenicity profile after 1 and 2 dose administrations of CVnCoV at different dose levels. ***Secondary*** • To evaluate the humoral immune response after 1 and 2 dose administrations of CVnCoV at different dose levels. ***Exploratory*** • To evaluate the cell-mediated immune response after 1 and 2 dose administrations of CVnCoV at different dose levels in all subjects from the assigned site(s).	

	• To evaluate the innate immune response after 1 and 2 dose administrations of CVnCoV at different dose levels in all open-label sentinel subjects. • To identify and assess cases of COVID-19 disease. • To describe the rate of asymptomatic infections with SARS-CoV-2.
Overall Design:	This FIH trial will evaluate the safety, reactogenicity and immunogenicity of different dose levels of CVnCoV using an adaptive dose-finding design to determine the CVnCoV dose for further clinical development. Due to the adaptive design of the trial, the actual number of subjects enrolled might be lower or higher than the target numbers. Subjects will be enrolled in 2 age categories (18-40 years and 41-60 years) with an equal distribution across each category. The trial will include subjects with no history of COVID-19 disease as well as subjects with SARS-CoV-2 positive serology. The SARS-CoV-2 serology status at baseline will be evaluated retrospectively to allow separate analyses of subjects retrospectively SARS-CoV-2 seronegative at baseline and subjects retrospectively SARS-CoV-2 seropositive at baseline. To ensure the open-label sentinel subjects in each dose level are seronegative, the SARS-CoV-2 serological status will be determined prior to enrollment during eligibility assessment in these subjects. Additionally, assessment of SARS-CoV-2 serological status may also be performed in the observer-blind placebo-controlled part of the trial, to identify subjects with SARS-CoV-2 positive serology. Three provisional CVnCoV dose levels (2, 4 and 8µg) will be evaluated as indicated in Synopsis Table 1. To ensure the safety of the subjects, specified safety data will be reviewed on a predefined schedule by an internal safety review committee (iSRC) with oversight provided by an independent data safety monitoring board (DSMB). All subjects will be administered a second vaccine dose on Day 29 with the same dose level or placebo as administered on Day 1. Additional potential dose levels that could be assessed are 1, 3 and 6µg, depending on the reactogenicity/safety findings after vaccination with respectively 2, 4 and 8µg dose levels; as well as 12, 16 and/or 20µg. A schematic overview of the design is provided in Synopsis Figure 1.

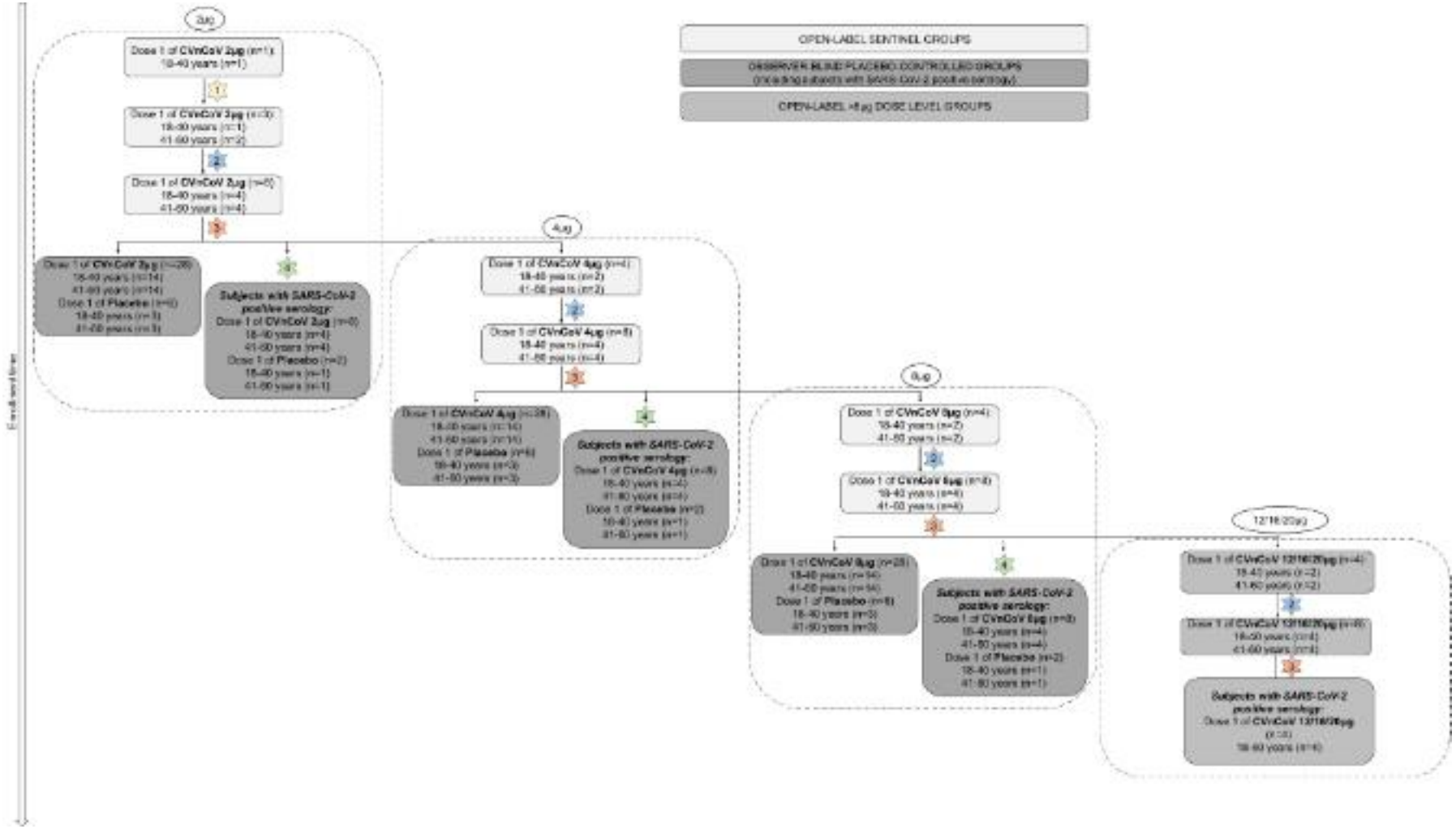
Synopsis Table 1 Provisional dose levels during dose escalation

Number of subjects vaccinated per CVnCoV dose level (µg)*							
2µg		**4µg**		**8µg**		**12/16/20µg****	
18-40 years	**41-60 years**	**18-40 years**	**41-60 years**	**18-40 years**	**41-60 years**	**18-40 years**	**41-60 years**
1	-	-	-	-	-		
Post-vaccination observation for 24 hours**		-	-	-	-		
1	2	-	-	-	-		
Safety review of 24-hour post dose 1 data (iSRC+DSMB Chair)		-	-	-	-		
4	4	-	-	-	-		
Safety review of 60-hour post dose 1 data (iSRC+DSMB)							
18 + 4 placebo***	18 + 4 placebo***	2	2	-	-		
-	-	*Safety review of 24-hour post dose 1 data (iSRC+DSMB Chair)*		-	-		
-	-	4	4	-	-		
Safety review of 60-hour post dose 1 data (iSRC+DSMB)							
-	-	18 + 4 placebo***	18 + 4 placebo***	2	2		
-	-	-	-	*Safety review of 24-hour post dose 1 data (iSRC+DSMB Chair)*			
-	-	-	-	4	4		
Safety review of 60-hour post dose 1 data (iSRC+DSMB)							
-	-	-	-	18 + 4 placebo***	18 + 4 placebo***	2	2
-	-	-	-	-	-	*Safety review of 24-hour post dose 1 data (iSRC+DSMB Chair)*	
-	-	-	-	-	-	4	4
Safety review of 60-hour post dose 1 data (iSRC+DSMB)							
-	-	-	-	-	-	**18 to 60 years**	
-	-	-	-	-	-	4*****	

Light grey shaded cells indicate the open-label sentinel groups.
Dark grey shaded cells indicate the observer-blind placebo-controlled groups.
* Provisional dose levels of 2, 4 and 8µg will be evaluated. Additional potential dose levels that could be assessed are 1, 3 and 6µg, depending on the reactogenicity/safety findings after vaccination with respectively 2, 4 and 8µg dose levels; as well as 12, 16 and/or 20µg.
** If any Grade 3 ARs are reported within 24 hours following vaccination, the iSRC and DSMB Chair will be consulted before continuation of enrollment of the next open-label sentinel subjects.
*** Including approximately 4 + 1 subjects with SARS-CoV-2 positive serology.

**** The next dose level will only be given to subjects once initial data from the previous dose level have been reviewed by the iSRC and DSMB, e.g., if 12µg is investigated, it will only be administered after review of the 8µg data (post dose 1 in 12 sentinel subjects), and if the dose level is then escalated to 16µg, it will only be administered after review of the 12µg data (post dose 1 in 12 sentinel subjects).
***** Subjects with SARS-CoV-2 positive serology.

Synopsis Figure 1 Overview of staggered enrollment and dose escalation



The 12, 16 and/or 20µg dose levels will only be given to subjects once initial data from the previous dose level have been reviewed by the iSRC and DSMB, not in parallel.

	On the first vaccination day, the first open-label sentinel subject aged 18-40 years confirmed to be SARS-CoV-2 seronegative will be enrolled and vaccinated with CVnCoV at the lowest dose level (2µg). The subject will be observed for 24 hours after vaccination. If any Grade 3 adverse reactions, defined as solicited systemic, solicited local and unsolicited Grade 3 adverse events (AEs) considered as related to the trial vaccine according to the Investigator, are reported within 24 hours following vaccination, the iSRC and DSMB Chair will be consulted. In case no safety concerns are identified, the next open-label sentinel group of 3 subjects (1 aged 18-40 years and 2 aged 41-60 years) confirmed to be SARS-CoV-2 seronegative will be enrolled and vaccinated with CVnCoV at the lowest dose level (2µg). The subjects should be vaccinated at least 60 minutes apart. Safety and reactogenicity data reported during an observation period of at least 24 hours after vaccination from these first 4 subjects will be collected and reviewed by the iSRC and DSMB Chair. In this review, the iSRC and DSMB Chair will review all available safety data, but focus specifically on Grade 3 adverse reactions and any serious adverse event (SAE) considered as related to the trial vaccine according to the Investigator. Based on this review, the iSRC and DSMB Chair will decide on the subsequent vaccination of an additional open-label sentinel group of 8 subjects (4 aged 18-40 years and 4 aged 41-60 years, confirmed to be SARS-CoV-2 seronegative) with the same dose level on the next vaccination day (at least 36 hours after the first vaccination day). Safety and reactogenicity data of subjects vaccinated on the first and second vaccination days will then be collected for at least 60 hours post-vaccination from each subject and reviewed by the iSRC and the DSMB. Based on this review, the iSRC and DSMB will recommend on continuation of enrollment at the same dose level (start of randomized expansion in observer-blind placebo-controlled groups) and initiation of enrollment in the next dose level: • In case of **continuation of enrollment at the 2µg dose level**, an additional 44 subjects will be enrolled, including 10 subjects with SARS-CoV-2 positive serology. Of these 44 subjects, 36 (18 aged 18-40 years and 18 aged 41-60 years) will receive CVnCoV at the 2µg dose level, including approximately 8 subjects with SARS-CoV-2 positive serology. The other 8 subjects (4 aged 18-40 years and 4 aged 41-60 years) will receive placebo in an observer-blind manner, including approximately 2 subjects with SARS-CoV-2 positive serology. • In case of **dose escalation**, a newly enrolled open-label sentinel group of 4 subjects (2 aged 18-40 years and 2 aged 41-60 years) confirmed to be SARS-CoV-2 seronegative will receive the next higher dose (4µg) or an intermediate dose depending on iSRC and DSMB recommendations. The subjects should be vaccinated at least 60 minutes apart. In case of favorable outcome of the review by the iSRC and DSMB Chair of at least 24-hour post-vaccination data and a maximum number of 2 subjects with Grade 3 adverse reactions, an additional open-label sentinel group of 8 subjects (4 aged 18-40 years and 4 aged 41-60 years, confirmed to be SARS-CoV-2 seronegative) will receive the same dose level on the next vaccination day (at least 36 hours after the first vaccination day within this dose level). For each subsequent step, continuation of enrollment within a dose level in a placebo-controlled observer-blind manner and dose escalation will be assessed by the iSRC and DSMB based on 60-hour post-vaccination safety data for each subject, including all available post-vaccination data from previously vaccinated subjects. The scheme for staggered

	enrollment and dose escalation in Synopsis Figure 1 will be pursued if no safety concerns are found by the iSRC or DSMB. Once the open-label sentinel phase has been successfully concluded for a given dose level, enrollment will no longer be restricted to subjects with no history of COVID-19 disease or negative serology to SARS-CoV-2, but will also include subjects with SARS-CoV-2 positive serology. These subjects will be enrolled at pre-defined site(s). For each dose level, the iSRC will review at least 24-hour post-vaccination safety data from the first 4 seropositive subjects. These first 4 seropositive subjects within each dose level should be vaccinated at least 60 minutes apart. Vaccination of additional subjects at that dose level and/or vaccination of subjects with SARS-CoV-2 positive serology at a higher dose level will only proceed upon favorable outcome of this iSRC review. All subjects will be administered a second vaccine dose on Day 29 with the same dose level of CVnCoV or placebo as administered on Day 1. When safety data will be available at least 60 hours post dose 2 for all subjects within a dose level, the iSRC and DSMB will review all available safety (and, if available, immunogenicity) data to confirm the safety of the dose level after the second dose.
Adaptations to the Trial:	Depending on the safety and immunogenicity of the provisional dose levels, additional dose levels might be evaluated. In each case, the enrollment schedule will be performed as described in the design section above. For dose levels >8µg, the enrollment schedule will be performed as described in the design section above for the first 12 sentinel subjects. After a review of the post dose 1 data from these subjects, 4 subjects (aged 18 to 60 years) with SARS-CoV-2 positive serology will be enrolled to receive the same CVnCoV dose level. These 4 open-label subjects will have the same assessments as subjects in the observer-blind placebo-controlled groups and are included when reference is made to the observer-blind placebo-controlled groups throughout this protocol. In case the lowest dose of 2µg fails to meet the predefined safety criteria, a dose de-escalation to 1µg will be initiated. In case the 4µg dose level fails to meet the predefined safety criteria, a dose de-escalation to 3µg can be initiated. Similarly, in case the 8µg dose level fails to meet the predefined safety criteria, a dose de-escalation to 6µg can be initiated.
Trial Visits/Contacts:	**For subjects in the open-label sentinel groups:** • 12 protocol-scheduled visits on Day 1, Day 2, Day 8, Day 15, Day 29, Day 30, Day 36, Day 43, Day 57, Day 120, Day 211 and Day 393 and 2 protocol-scheduled telephone contacts (safety calls) on Day 3 and Day 31. **For subjects in the observer-blind placebo-controlled groups:** • 10 protocol-scheduled visits on Day 1, Day 8, Day 15, Day 29, Day 36, Day 43, Day 57, Day 120, Day 211 and Day 393 and 4 protocol-scheduled telephone contacts (safety calls) on Day 2, Day 3, Day 30 and Day 31.
Collection of Blood Samples:	At each protocol-scheduled visit, blood samples will be taken for safety and/or immunogenicity testing. The maximum total volume of blood taken over the trial period from each subject will be (Table 1): • 625mL for subjects in the open-label sentinel groups, • 540mL for subjects in the observer-blind placebo-controlled groups.

Safety Assessments:	Reactogenicity will be assessed daily on each vaccination day and the following 7 days via collection of solicited local AEs (injection-site pain, redness, swelling, and itching) and systemic AEs (headache, fatigue, chills, myalgia, arthralgia, nausea/vomiting, and diarrhea) using diary cards. In addition, other indicators of safety will be collected (e.g., body temperature). Diary cards will also be used for collection of unsolicited AEs on each vaccination day and the following 28 days. SAEs, adverse events of special interest (AESIs) and AEs leading to vaccine withdrawal or trial discontinuation will be collected throughout the trial. AESIs to be monitored throughout the trial include potential immune-mediated diseases (pIMDs) and COVID-19 disease. In case of confirmed COVID-19, a disease-specific diary card will be completed by the subject or the treating health care provider. Non-serious intercurrent medical conditions that may affect the immune response to vaccination will also be collected throughout the trial.
Laboratory Testing for COVID-19 Disease:	As part of the eligibility assessment, a polymerase chain reaction (PCR) for SARS-CoV-2 will be performed. Additionally, for the 12 open-label sentinel subjects in each dose level, the SARS-CoV-2 serological status will be determined using site-specific diagnostics prior to enrollment to ensure they are seronegative. This may also be performed for subjects in the observer-blind placebo-controlled part of the trial to identify subjects with SARS-CoV-2 positive serology. At several pre-defined timepoints during the trial, IgM and IgG serology will be assessed. Testing will be done for SARS-CoV-2 spike protein to evaluate vaccine-induced immune responses as well as for SARS-CoV-2 N-antigen (not contained in the vaccine construct) to evaluate immune responses induced by natural infection. This will allow to retrospectively define the subject's (baseline) serology status for the group/cohorts analysis. Any subject with clinical suspicion of SARS-CoV-2 infection will undergo appropriate testing and referral within the local healthcare system as appropriate. Subjects with confirmed SARS-CoV-2 infections should not receive any (additional) vaccine dose, but will be closely monitored for disease patterns and severity.
Planned Number of Subjects:	The target is to enroll 56 subjects per dose level for ≤8µg and 16 subjects per dose level for >8µg as follows: • 12 subjects per dose level in the open-label sentinel groups • 44 subjects per dose level in the observer-blind placebo-controlled groups for the provisional dose levels of 2, 4 and 8µg, and 4 open-label subjects per dose level for >8µg
Criteria for Inclusion and Exclusion:	**Inclusion criteria for all subjects:** Subjects will be enrolled in this trial only if they meet **all** of the following criteria: 1. Healthy male and female subjects aged 18 to 60 years inclusive. Healthy subject is defined as an individual who is in good general health, not having any mental or physical disorder requiring regular or frequent medication. 2. Expected to be compliant with protocol procedures and available for clinical follow-up through the last planned visit.

	3. Physical examination and laboratory results without clinically significant findings according to the Investigator's assessment. 4. Body mass index (BMI) ≥18.0 and ≤30.0kg/m^2 (≥18.0 and ≤32.0kg/m^2 for subjects with SARS-CoV-2 positive serology). 5. Females: 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). 6. Females of childbearing potential must use highly effective methods of birth control from 1 month before the first administration of the trial vaccine until 3 months following the last administration. The following methods of birth control are considered highly effective when used consistently and correctly: o Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal); o Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable); o Intrauterine devices (IUDs); o Intrauterine hormone-releasing systems (IUSs); o Bilateral tubal occlusion; o Vasectomized partner; o Sexual abstinence (periodic abstinence [e.g., calendar, ovulation, symptothermal and post-ovulation methods] and withdrawal are not acceptable). **Exclusion criteria:** Subjects will not be enrolled in this trial if they meet **any** of the exclusion criteria. <u>The following criterion applies to all open-label sentinel subjects:</u> 1. Subjects with SARS-CoV-2 positive serology as confirmed by testing at enrollment. <u>The following criteria apply to all subjects, except those with SARS-CoV-2 positive serology:</u> 2. Subjects considered at the Investigator's discretion to be at increased risk to acquire COVID-19 disease (including, but not limited to, health care workers with direct involvement in patient care or care of long-term care recipients). 3. History of confirmed COVID-19 disease or known exposure to an individual with confirmed COVID-19 disease or SARS-CoV-2 infection within the past 2 weeks.

	<u>The following criteria apply to all subjects:</u> 4. 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. 5. Receipt of any other vaccines within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to enrollment in this trial or planned receipt of any vaccine within 28 days of trial vaccine administration. 6. Receipt of any investigational SARS-CoV-2 or other coronavirus vaccine prior to the administration of the trial vaccine. 7. Any treatment with immunosuppressants or other immune-modifying drugs (including, but not limited to, corticosteroids, biologicals and Methotrexate) within 6 months prior to the administration of the trial vaccine or planned use during the trial, with the exception of topically-applied steroids. Corticosteroids used in the context of COVID-19 disease of subjects with SARS-CoV-2 positive serology are not exclusionary. 8. Any medically diagnosed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination, including known human immunodeficiency virus infection, hepatitis B virus infection and hepatitis C virus infection. 9. History of potential immune mediated disease (refer to Appendix 9). 10. History of angioedema. 11. Any known allergy, including allergy to any component of CVnCoV or aminoglycoside antibiotics. A history of hay fever or seasonal allergies (pollinosis) that does not require current treatment (e.g., anti-histamines) during the vaccination period (1 month before first vaccination until 1 month after last vaccination) is not exclusionary. 12. History of or current alcohol and/or drug abuse. 13. Subjects who are active smokers, were active smokers within the last year (including any vaping in the last year) or have a total smoking history ≥10 pack years. 14. Acute or currently active SARS-CoV-2 infection as confirmed by reactive PCR within 3 days of first trial vaccine administration. 15. History of confirmed SARS or MERS. 16. Administration of immunoglobulins (Igs) and/or any blood products within the 3 months preceding the administration of any dose of the trial vaccine. 17. Presence or evidence of significant acute or chronic medical or psychiatric illness. Significant medical or psychiatric illnesses include but are not limited to: o Respiratory disease (e.g., chronic obstructive pulmonary disease, asthma) requiring daily medications currently or any treatment of respiratory disease exacerbations (e.g., asthma exacerbation) in the last 5 years. o Respiratory disease with clinically significant dyspnea in the last 5 years (except COVID-19 disease in subjects with SARS-CoV-2 positive serology). o Asthma medications: inhaled, oral, or intravenous (IV) corticosteroids, leukotriene modifiers, long- and short-acting beta agonists, theophylline, ipratropium, biologics.

	○ Significant cardiovascular disease (e.g., congestive heart failure, cardiomyopathy, ischemic heart disease, history of stroke, peripheral artery disease, pulmonary embolism) or history of myocarditis or pericarditis as an adult. ○ Elevated blood pressure or hypertension, even if well-controlled. ○ Diabetes mellitus type 1 or 2. ○ History of any neurological disorders or seizures including Guillain-Barré syndrome, with the exception of febrile seizures during childhood. ○ Current or past malignancy, unless completely resolved without sequelae for >5 years. 18. Foreseeable non-compliance with protocol as judged by the Investigator. 19. For females: pregnancy or lactation. 20. History of any anaphylactic reactions. 21. Subjects with impaired coagulation or any bleeding disorder in whom an intramuscular injection or a blood draw is contraindicated. 22. Subjects employed by the Sponsor, Investigator or trial site, or relatives of research staff working on this trial.
Endpoints:	***Primary*** • The frequencies of Grade 3 adverse reactions and any SAE considered as related to the trial vaccine within at least 24 hours after the first vaccination by dose level, for decisions on subsequent vaccination of an additional open-label sentinel group with the same dose level. • The frequencies of Grade 3 adverse reactions and any SAE considered as related to the trial vaccine within at least 60 hours after the first vaccination by dose level, for decisions on dose escalation as well as continuation of enrollment at the same dose level in the observer-blind placebo-controlled part of the trial. • The frequencies, intensities and duration of solicited local AEs on each vaccination day and the following 7 days by dose and dose level, for the characterization of the safety and reactogenicity profile. • The frequencies, intensities, duration and relationship to trial vaccination of solicited systemic AEs on each vaccination day and the following 7 days by dose and dose level, for the characterization of the safety and reactogenicity profile. • The occurrence, intensities and relationship to trial vaccination of unsolicited AEs on each vaccination day and the following 28 days by dose and dose level, for the characterization of the safety and reactogenicity profile. • The occurrence and relationship to trial vaccination of SAEs and AESIs at predefined time points throughout the trial, for the characterization of the safety and reactogenicity profile.

	Secondary* *On Day 8, Day 15, Day 29, Day 36, Day 43, Day 57, Day 120, Day 211 and Day 393:* • The proportion of subjects seroconverting for SARS-CoV-2 spike protein antibodies, as measured by ELISA. *In subjects who did not get exposed to SARS-CoV-2 before the trial, or during the trial before the applicable sample was collected, as measured by ELISA to SARS-CoV-2 N-antigen, seroconversion is defined as an increase in titer in antibodies against SARS-CoV-2 spike protein versus baseline.* *In subjects seropositive for SARS-CoV-2 at baseline, seroconversion is defined as a 2-fold increase in titer in antibodies against SARS-CoV-2 spike protein versus baseline.* • Individual SARS-CoV-2 spike protein-specific antibody levels in serum, as measured by ELISA. • Geometric mean titers (GMTs) of serum SARS-CoV-2 spike protein antibodies, as measured by ELISA, in subjects who did not get exposed to SARS-CoV-2 before the trial or during the trial before the applicable sample was collected, as measured by ELISA to SARS-CoV-2 N-antigen. • The proportion of subjects seroconverting for SARS-CoV-2 neutralizing antibodies, as measured by an activity assay. *In subjects who did not get exposed to SARS-CoV-2 before the trial or during the trial before the applicable sample was collected, as measured by ELISA to SARS-CoV-2 N-antigen, seroconversion is defined as an increase in titer in SARS-CoV-2 neutralizing antibodies versus baseline.* *In subjects seropositive for SARS-CoV-2 at baseline, seroconversion is defined as a 2-fold increase in titer in SARS-CoV-2 neutralizing antibodies versus baseline.* • Individual SARS-CoV-2 neutralizing antibody levels in serum. • GMTs of serum SARS-CoV-2 neutralizing antibodies, as measured by an activity assay, in subjects who did not get exposed to SARS-CoV-2 before the trial or during the trial before the applicable sample was collected, as measured by ELISA to SARS-CoV-2 N-antigen. ** Samples may be used for assay validation and additional studies of the mechanism of action of the vaccine.* ***Exploratory**** *Cell-mediated immune response* *On Day 29, Day 36 and Day 211** in peripheral blood mononuclear cells (PBMCs) from all subjects at the assigned site(s):* • The frequency and functionality of SARS-CoV-2 spike-specific T-cell response after antigen stimulation. *Intracellular cytokine staining (ICS) to investigate Th1 response and production of Th2 markers (e.g. secreted IL-5) will be used to investigate whether vaccination induces a Th1 shift from baseline. Further T-cell immune response maybe investigated with other technologies like ELISpot or CyTOF.* • The proportion of subjects with a detectable increase in SARS-CoV-2 spike-specific T-cell response. *** Testing of samples collected on Day 211 will be done only in subjects categorized as T-cell responders on Day 29 and/or Day 36.*

	Innate immune response *On Day 2, Day 8, Day 29, Day 30 and Day 36 in all open-label sentinel subjects:* • Serum cytokine concentrations, including but not limited to interferon (IFN)-α, IFN-γ, interleukin (IL)-6, chemokine ligand (CCL) 2 and IFN-γ-induced protein 10 (IP 10). • Gene expression profiling. ** Samples may be used for assay validation and additional studies of the mechanism of action of the vaccine.* *Evaluation of infection* • Number of subjects with virologically-confirmed SARS-CoV-2 infection as measured by reverse transcription (RT)-PCR at clinically determined time points throughout the trial. • Number of subjects with asymptomatic SARS-CoV-2 infection as measured by retrospective serology at predefined time points.
Safety Monitoring Committees:	An iSRC will be established consisting of the Principal Investigator at each trial site, the Medical Monitor and medical representatives of the Sponsor. The iSRC and DSMB Chair will review all available safety data obtained during at least 24 hours post-vaccination for each open-label sentinel subject vaccinated on the first vaccination day per dose level, and assess for Grade 3 adverse reaction(s) and any SAE considered as related to the trial vaccine according to the Investigator. Based on this review, the iSRC and DSMB Chair will decide on the enrollment of the subjects planned on the next vaccination day within each dose level. The iSRC will also perform ongoing safety assessments for subjects beyond the first 24 hours on all available data. The iSRC will review at least 24-hour post-vaccination safety data from the first 4 seropositive subjects enrolled at each dose-level. In addition, the iSRC together with the DSMB will review all available safety data obtained during at least 60 hours post-vaccination for each subject to recommend on continuation of enrollment at the same dose level and dose escalation. If no stopping rule is met, the DSMB Chair can decide to allow trial progression without obtaining a DSMB quorum. The DSMB may recommend additional measures including modification or halt of the trial.
Sample Size Justification:	This trial is designed to be primarily descriptive and hence, its sample size was not determined based on formal statistical power calculations.
Analysis Sets:	**Safety Set:** The safety set will consist of all subjects who received at least 1 dose of trial vaccine and for whom any post-vaccination safety data are available. **Immunogenicity Set:** The immunogenicity set will include all subjects who received at least 1 dose of trial vaccine and for whom the baseline blood sample and at least one additional blood sample are available for analysis.
Statistical Methodology:	***Missing data/discontinuation:*** Due to the dose escalation and exploratory design of the trial; no imputation of missing values will be done for any analysis (except the imputation for missing partial dates of AEs and concomitant medication). Reasons for discontinuation from the trial or trial vaccination will be listed and summarized. Currently no replacement of drop-out subjects is foreseen.

Statistical Analyses:	***Analysis of Demographics and Other Baseline Characteristics:*** Data will be summarized with respect to demographic and baseline characteristics, medical history, immune response measurements, and all safety measurements using descriptive statistics (quantitative data) and contingency tables (qualitative data) by dose level and arm. ***Safety Analyses*** The safety analyses will be performed for all subjects, for subjects retrospectively SARS-CoV-2 seronegative at baseline, and for subjects retrospectively SARS-CoV-2 seropositive at baseline. ***Solicited AEs:*** The number and percentage of subjects with at least 1 solicited AE of any kind, by severity grade, for local AEs, systemic AEs, and overall, will be summarized, after the first vaccination, after the second vaccination and after any vaccination. The results will be tabulated by dose level and arm. 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. ***Immunogenicity Analysis:*** Descriptive statistics for the immunogenicity endpoints will be provided by arm for each dose level. Data will be presented after each vaccine dose. Individual values and GMT of SARS-CoV-2 spike protein antibody levels and of SARS-CoV-2 neutralizing antibodies, percentages of immune cell populations and cellular responders will be summarized for each dose level in all subjects, in those subjects retrospectively SARS-CoV-2 seronegative at baseline, and in those subjects retrospectively SARS-CoV-2 seropositive at baseline. For subjects who do not get exposed to SARS-CoV-2 before the trial, or during the trial before the applicable sample was collected (as confirmed by a titer increase in antibodies to SARS-CoV-2 N-antigen or a PCR-positive swab during the trial), percentages of subjects seroconverting for SARS-CoV-2 spike-protein antibodies and SARS-CoV-2 neutralizing antibodies will be summarized at each dose level. In addition, for the open-label sentinel groups, levels of cytokines and changes in gene transcripts will be summarized. This analysis may also be performed separately in subjects retrospectively SARS-CoV-2 seronegative at baseline and subjects retrospectively SARS-CoV-2 seropositive at baseline.

2 SCHEDULE OF ACTIVITIES

Table 1 Schedule of Trial Assessments and Procedures

	Vaccination Period													Follow-up		End of Trial
Contact Type	**Clinic Visit**	**Clinic Visit/ Phone Call[a]**		**Phone Call**	**Clinic Visit**			**Clinic Visit/ Phone Call[a]**		**Phone Call**	**Clinic Visit**			**Clinic Visit**		**Clinic Visit**
Visit Number	**1[b]**	**2**	**-**	**-**	**3**	**4**	**5**	**6**	**-**	**-**	**7**	**8**	**9**	**10**	**11**	**12**
Visit Window (days)	**n/a**	**-0/+0**	**-0/+0**	**-0/+0**	**-0/+1**	**-0/+1**	**-0/+4**	**-0/+0**	**-0/+0**	**-0/+0**	**-0/+1**	**-0/+1**	**-0/+4**	**±14**	**±14**	**-0/+30**
Trial Day	**1**	**2**	**2**	**3**	**8**	**15**	**29**	**30**	**30**	**31**	**36**	**43**	**57**	**120**	**211**	**393**
Anchoring	**-**	**1**	**1**	**1**	**1**	**1**	**1**	**29**	**29**	**29**	**29**	**29**	**29**	**29**	**29**	**29**
Signed informed consent	X															
Inclusion/exclusion criteria	X															
Demographics	X															
Medical history	X															
Vaccination																
Review of criteria for delay or cancellation of vaccination[c]	X						X									
Administration of CVnCoV or placebo (including 4h observation)	X						X									
Safety Monitoring																
Physical examination[d]	X[e]						X									X
Symptom-directed physical examination[d]		X			X	X		X			X	X	X	X	X	
Vital signs[d,f]	X	X			X	X	X	X			X	X	X	X	X	X
ECG	X															
Diary dispensing[g]	X						X									
Diary (re)training[g]	X	X			X	X	X	X			X	X				
Diary review[g]		X			X	X	X	X			X	X	X			
Diary reminder[g]		X	X[h]	X[h]	X	X		X	X[h]	X[h]	X	X				
Diary collection[g]							X						X			
Solicited AEs[g]	X	X			X		X	X			X					
Unsolicited AEs[g]	X	X			X	X	X	X			X	X	X			
SAEs[i]	X	X			X	X	X	X			X	X	X	X	X	X

	Vaccination Period													Follow-up		End of Trial
Contact Type	**Clinic Visit**	**Clinic Visit/ Phone Call[a]**		**Phone Call**	**Clinic Visit**			**Clinic Visit/ Phone Call[a]**		**Phone Call**	**Clinic Visit**			**Clinic Visit**		**Clinic Visit**
Visit Number	**1[b]**	**2**	**-**	**-**	**3**	**4**	**5**	**6**	**-**	**-**	**7**	**8**	**9**	**10**	**11**	**12**
Visit Window (days)	**n/a**	**-0/+0**	**-0/+0**	**-0/+0**	**-0/+1**	**-0/+1**	**-0/+4**	**-0/+0**	**-0/+0**	**-0/+0**	**-0/+1**	**-0/+1**	**-0/+4**	**±14**	**±14**	**-0/+30**
Trial Day	**1**	**2**	**2**	**3**	**8**	**15**	**29**	**30**	**30**	**31**	**36**	**43**	**57**	**120**	**211**	**393**
Anchoring	**-**	**1**	**1**	**1**	**1**	**1**	**1**	**29**	**29**	**29**	**29**	**29**	**29**	**29**	**29**	**29**
Intercurrent medical conditions[i]	X	X			X	X	X	X			X	X	X	X	X	X
AEs leading to premature 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[j]	X			X	X	X	X			X	X	X	X	X	X
Safety lab (~9mL)[k]	X	X			X			X			X					
Safety lab in case of abnormal result at previous visit (~9mL)[k]						X	X					X	X	X	X	X
Serum pregnancy test (~3mL)[l]	X															
Urine pregnancy test[m]	X						X									
TSH, thyroid antibodies, ANA (~3mL)[n]	X															
Swab collection for PCR testing[o]	X															
In the open-label sentinel subjects in each dose level: Antibody diagnostics (serum) (~6mL)[p]	X															
Immunogenicity[q]																
ELISA (serum) (~12mL)[r]	X[s]				X	X	X[s]				X	X	X	X	X	X
SARS-CoV-2 neutralizing activity (serum) (~12mL)	X[s]				X	X	X[s]				X	X	X	X	X	X
In all open-label sentinel subjects: Cytokine assessment (serum) (~6mL)	X[s]	X			X		X[s]	X			X					
In all open-label sentinel subjects: Gene expression profiling (PAXgene® blood RNA system) (~5mL)	X[s]	X			X		X[s]	X			X					
In all subjects from assigned site(s): Cell-mediated immunity (~40-64mL)[t]	X[s]						X[s]				X[u]				X	
Maximum total blood volume (mL)	120	20	-	-	45	35	85	20		-	85	35	35	35	75	35
Trial end																**X**

AE: adverse event; AESI: adverse event of special interest; ANA: antinuclear antibody; ECG: electrocardiogram; ELISA: enzyme-linked immunosorbent assay; PBMC: peripheral blood mononuclear cell; PCR: polymerase chain reaction; RNA: ribonucleic acid; SAE: serious adverse event; TSH: thyroid-stimulating-hormone

a. The Day 2 and Day 30 contacts will only be conducted as visits for subjects in the open-label sentinel groups.
b. Procedures to establish subject eligibility may be performed within 21 days prior to trial vaccine administration. If all information to establish eligibility is available, these procedures can be done on the same day including the trial vaccine administration. Eligibility criteria, including laboratory results, need to be reviewed on the day of vaccination prior to trial vaccine administration.
c. See Section 6.3 for an overview of the criteria leading to delay or cancellation of vaccine administration. In case of delay, the vaccination should take place within the allowed time windows. The reasons for delay or cancellation should be documented in the subject chart.
d. Physical examination and vital signs must be performed/measured by a qualified healthcare professional. See Section 9.2.4 for an overview of the required assessments.
e. If the complete physical examination to establish eligibility was performed within 21 days prior to trial vaccine administration, a symptom-directed physical examination should be performed on the day of vaccination prior to trial vaccine administration.
f. Vital signs will be measured pre- and post-vaccination prior to discharge. Subjects will be observed for 4 hours 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. Diaries for recording of post-vaccination solicited/unsolicited AEs. Solicited AEs occurring on the day of vaccination (Day 1 and Day 29) and for the following 7 days and unsolicited AEs occurring on the day of vaccination (Day 1 and Day 29) and for the following 28 days will be recorded by the subject on the diary cards.
h. During the phone calls, the subject´s general well-being should be checked and the subject should be reminded to complete the safety information on the diary cards.
i. SAEs, AESIs (including COVID-19 disease), intercurrent medical conditions that may affect the immune response to vaccination and AEs leading to trial or trial vaccine withdrawal will be collected throughout the trial.
j. Concomitant medication/vaccination taken within 6 months prior to enrollment should be recorded to establish eligibility.
k. See Appendix 3 for an overview of the safety laboratory assessments.
l. A 3mL blood sample will be taken for pregnancy testing of women of childbearing potential.
m. Urine pregnancy tests will be performed before each vaccination for women of childbearing potential, unless the serum pregnancy test was performed less than 3 days before and yielded a negative result.
n. A blood sample will be drawn for potential retrospective measurement of TSH, thyroid antibodies and ANA in case of the occurrence of clinical autoimmune events during the trial (other autoantibodies might be investigated as well depending on the possible clinical autoimmune event).
o. Swabs for COVID-19 disease testing will also be collected in case the subject displays symptoms of acute respiratory infection (including, but not limited to COVID-19 disease), if operationally possible (see Section 9.4).
p. Antibody diagnostics may also be performed in the observer-blind placebo-controlled part of the trial to identify subjects with SARS-CoV-2 positive serology.
q. See Section 9.3 for an overview of the immunogenicity assessments.
r. IgG and IgM ELISA will be performed on SARS-CoV-2 spike protein to investigate seroconversion and on SARS-CoV-2 N-antigen for determination of seronegativity to natural infection.
s. Baseline blood samples on Day 1 and Day 29 must be collected on the day of vaccination prior to vaccination.
t. The blood volume to be collected for cellular immune response will be 64mL on Day 1 and 40mL on Days 29, 36 and 211.
u. In case Visit 7 (Day 36) cannot take place (e.g., due to a public health emergency), the blood sample for cell-medicated immunity assessment should be taken at Visit 8 (Day 43).

3 INTRODUCTION

3.1 Background

3.1.1 Coronaviruses

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

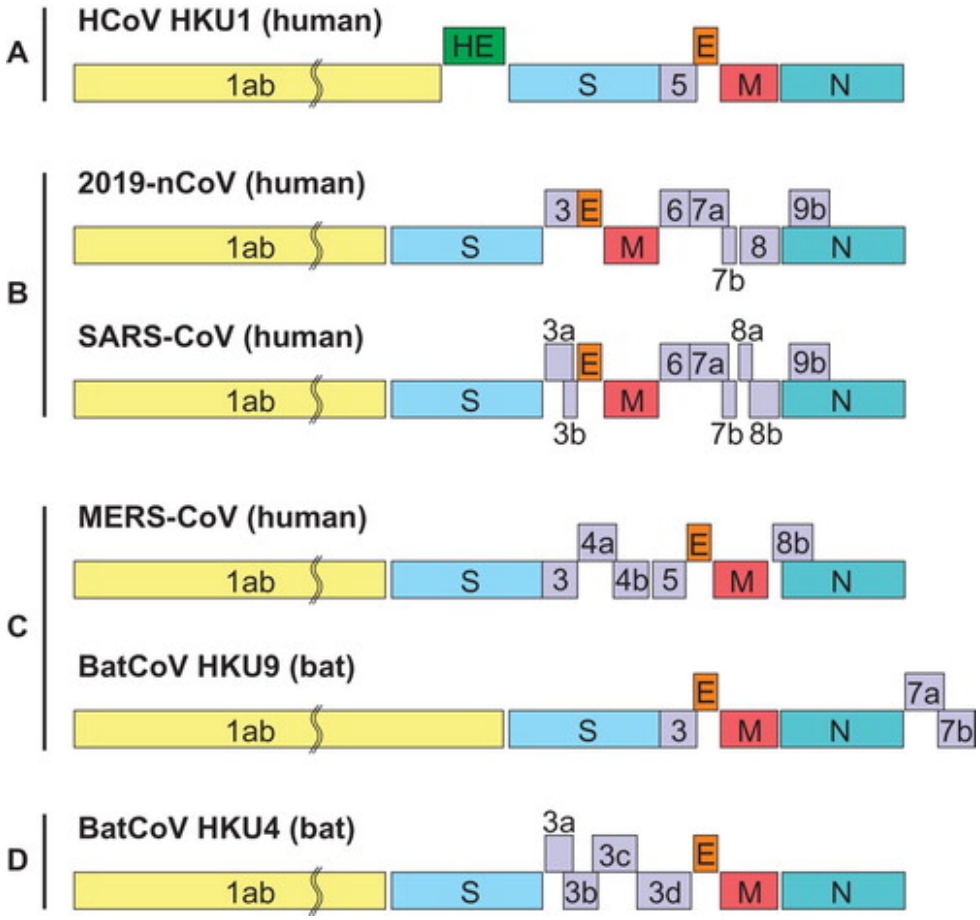
There are 4 genera of CoVs, namely, Alphacoronavirus (αCoV), Betacoronavirus (βCoV), Deltacoronavirus (δCoV) and Gammacoronavirus (γCoV) [3]. Evolutionary analyses have shown that bats and rodents are the gene sources of most αCoVs and βCoVs, while avian species are the gene sources of most δCoVs and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

Prior to December 2019, when clusters of pneumonia cases with unknown etiology were detected in Wuhan City, Hubei Province, China, only 2 additional strains of CoVs had caused outbreaks of severe acute respiratory disease in humans: the severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). On 9 January 2020, a novel CoV, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was officially identified as the cause of an outbreak of viral pneumonia in Wuhan. In the following weeks, the virus spread rapidly within China and an increasing number of countries worldwide. On 7 January 2020, the International Health Regulations (2005) Emergency Committee agreed that the outbreak met the criteria for a Public Health Emergency of International Concern. On 12 March 2020, the World Health Organization (WHO) announced that the outbreak was characterized as a pandemic.

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

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

Figure 1 Genome organization of SARS-CoV-2* compared with other betacoronaviruses



* SARS-CoV-2 was initially named 2019-nCoV as indicated in the figure.
Source: Chan *et al.*, 2020 [3]

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

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

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

3.1.2 COVID-19 Disease

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

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

In early stages of the outbreak, the reported case-fatality rate in China was 17% [19]. In admitted patients in Wuhan, mortality reached 25% in the middle of the epidemic. Similarly high death rates are recorded in those requiring intensive care: in a large retrospective cases series on COVID-19 confirmed patients admitted to intensive care units (Lombardy, Italy), mortality reached 26% [20]. The global mortality rate is currently around 4% [21].

According to the 2020 World Health Statistics, the COVID-19 pandemic is causing significant loss of life, disrupting livelihoods, and threatening the recent advances in health and progress towards global sustainable development goals [22]. On 22 July 2020, according to WHO, 14 765 256 cases have been confirmed globally, including 612 054 deaths [21].

3.2 Trial Rationale

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

(FIH) Phase 1 trial will evaluate the safety, reactogenicity and immunogenicity of CVnCoV at different dose levels. Since it is considered critical to establish the safety and reactogenicity in participants with pre-existing immune responses, to allow vaccination in efficacy and other large future clinical trials as well as future public health vaccination campaigns without the need to incorporate baseline serology assessments in all participants or potential vaccines, the trial will also enroll previously infected subjects to allow evaluation of the safety and reactogenicity in the context of pre-existing immunity. CVnCoV has been developed with CureVac's proprietary RNActive® technology platform, which uses chemically unmodified mRNA molecules as a basis for vaccination.

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 more detailed epidemiological information.

3.3 Risk/Benefit Assessment

3.3.1 Known Potential Risks

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

As with every vaccination and based on previous clinical experience with other RNActive® vaccines, local reactions, i.e., pain, redness, itching and swelling at the injection site, and systemic adverse events (AEs), i.e., fever, headache, fatigue, chills, myalgia, arthralgia, nausea/vomiting and diarrhea, are expected side effects that typically resolve within 24 hours after the vaccination with or without corrective treatment with antipyretics [23, 24, 25, 26]. After administration of CureVac's Rabies mRNA investigational vaccine formulated with LNP (CV7202), in addition to the systemic AEs described above, a few subjects experienced decreased appetite, night sweats and tachycardia.

As for every vaccine, the occurrence of allergic/anaphylactic reactions cannot be excluded and emergency equipment for the treatment of such reactions must be available at the trial site. These events are unexpected and constitute a potential important medical risk. So far, no allergic/anaphylactic reactions have been observed in the completed and ongoing clinical trials after repeated administration of protamine-formulated RNActive® vaccines, nor after administration of CV7202 at different dose levels (1µg, 2µg and 5µg) in the first-in-human (FIH) CV-7202-104 trial.

Vaccine Dependent Disease Enhancement (VDE) describes a phenomenon in which pre-existing immunity is not enough to neutralize viral infection and may lead to severe disease progression. The risk of antibody-dependent enhancement (ADE), and more generally VDE, by CVnCoV is considered low. The factors that are postulated to contribute to VDE (based on observations in animal studies for SARS or MERS) are the use of inactivated virus, recombinant wild-type non-stabilized S-protein, nucleoprotein vaccines, alum or other adjuvants inducing a Th2 bias; by design these factors are not applicable to CVnCoV.

The design rationale for the stabilized pre-fusion S-protein in CVnCoV was also based on the strategy used for MERS-CoV [27] and has been shown to lead to a better ratio of functional (virus neutralizing titers [VNT]) to binding antibodies (enzyme-linked immunosorbent assay [ELISA] titers) for eliciting a more protective immune response.

Based on its design and mode-of-action, it is expected that CVnCoV, an mRNA vaccine candidate expressing pre-fusion stabilized full-length S-protein, is unlikely to induce VDE. Furthermore, CVnCoV is inducing a balanced immune response, as observed in preclinical studies and documented in the Investigator's Brochure, and previous evidence that RNA vaccines are triggering TLR-stimulation (TLR7) resulting in type I interferon (IFN) induction [28]. Indeed, current pharmacology data with CVnCoV indicate induction of type I IFN with no (interleukin [IL]-4 and IL-13) or very low (IL-5) induction of cytokines indicative of a Th2 response. Th2 response has been shown to be associated with enhanced disease in animal models (refer to Section 4.1.2 of the Investigator's Brochure, in vivo Pharmacology Studies) [29]. While the VDE risk to subjects vaccinated with CVnCoV in the clinic are considered minimal, nevertheless, the potential risk for VDE will be evaluated in this trial designed to address the high unmet medical need due to the COVID-19 pandemic. As part of the clinical assessment in this trial, neutralizing antibodies will be determined and the induction of Th1 response will be investigated by cellular immunomonitoring with the specific aim to assess the risk of VDE prior to enrolling a larger number of subjects into Phase 2/3 clinical trials. Participants who experience COVID-19 disease during the trial will be followed closely to ensure clinical symptoms and safety data are collected and disease progression can be monitored and reported. In parallel with this trial, animal challenge models will be evaluated before initiation of the Phase2/3 trials.

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

Based on this information, the preclinical data package and measures to minimize potential VDE risk for human subjects are considered sufficient to initiate this FIH trial.

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

Developmental toxicity studies have not been performed for CVnCoV. No histopathological alterations in the reproductive organs were identified in the local tolerance or repeat-dose toxicology studies in rat or rabbit, and toxicologically relevant levels of RNA were not detected in reproductive organs in the biodistribution study. Therefore, the teratogenicity risk is deemed low. However, given that human data on pregnancies is not available, the teratogenic risk associated with CVnCoV administration cannot be ruled out at this moment. For this reason, inclusion of female subjects of childbearing potential requires use of a highly effective contraceptive measure from 1 month before the first administration of the trial vaccine until 3 months following the last administration.

Due to the theoretical possibility of non-specific immune stimulating properties of CVnCoV, it cannot be excluded that pre-existing potential immune mediated diseases (pIMDs) may be aggravated, become clinically apparent for the first time or triggered after vaccination

with CVnCoV. Such reactions have been very rarely described after administration of other vaccines but the causal relationship between vaccination and the induction or aggravation of pIMDs is uncertain and is therefore a theoretical risk. These events are considered unexpected for CVnCoV.

In addition, a list of AEs of special interest (AESIs) to be monitored following administration of investigational SARS-CoV-2 vaccines has been identified by the Brighton Collaboration Safety Platform for Emergency vACcines (SPEAC) Project. If any suspected AESI (pIMD, COVID-19 disease or other AE specific to SARS-CoV-2 vaccines or the target disease) should occur in a subject who received CVnCoV, a diagnostic workup should be performed by a specialist depending on the type of suspected reaction (e.g., endocrinologist for suspected autoimmune thyroiditis) and this condition will be monitored and documented throughout the trial.

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

3.3.2 Known Potential Benefits

Subjects receiving the investigational CVnCoV vaccine may not directly benefit from this vaccination since the immune response has not yet been evaluated in humans and it is thus not known if the vaccine is effective in protecting against COVID-19 disease. Furthermore, no correlate of protection or threshold of protection has been established for COVID-19 disease up to now. Subjects participating in this trial may benefit from having regular health checks as part of the trial procedures (e.g., physical examination, vital signs assessment, electrocardiogram [ECG]).

3.3.3 Assessment of Potential Risks and Benefits

To minimize the risk for subjects participating in this FIH trial, an internal safety review committee (iSRC) and data safety monitoring board (DSMB) will oversee the safety of the participating subjects on a specified schedule throughout the trial (see Section 9.2.6). All subjects will be closely observed on site for 4 hours after administration of each vaccine dose.

Potential important medical risks associated with CVnCoV, as specified in Section 3.3.1, can be managed at clinical trial sites in a Phase 1 setting should they occur.

4 TRIAL OBJECTIVES AND ENDPOINTS

4.1 Objectives

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

Primary objectives:

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

Secondary objective:

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

Exploratory objectives:

- To evaluate the cell-mediated immune response after 1 and 2 dose administrations of CVnCoV at different dose levels in all subjects from the assigned site(s).
- To evaluate the innate immune response after 1 and 2 dose administrations of CVnCoV at different dose levels in all open-label sentinel subjects.
- To identify and assess cases of COVID-19 disease.
- To describe the rate of asymptomatic infections with SARS-CoV-2.

4.2 Endpoints

Primary endpoints:

- The frequencies of Grade 3 adverse reactions and any serious adverse event (SAE) considered as related to the trial vaccine within at least 24 hours after the first vaccination by dose level, for decisions on subsequent vaccination of an additional open-label sentinel group with the same dose level.
- The frequencies of Grade 3 adverse reactions and any SAE considered as related to the trial vaccine within at least 60 hours after the first vaccination by dose level, for decisions on dose escalation as well as continuation of enrollment at the same dose level in the observer-blind placebo-controlled part of the trial.
- The frequencies, intensities and duration of solicited local AEs on each vaccination day and the following 7 days by dose and dose level, for the characterization of the safety and reactogenicity profile.
- The frequencies, intensities, duration and relationship to trial vaccination of solicited systemic AEs on each vaccination day and the following 7 days by dose and dose level, for the characterization of the safety and reactogenicity profile.
- The occurrence, intensities and relationship to trial vaccination of unsolicited AEs on each vaccination day and the following 28 days by dose and dose level, for the characterization of the safety and reactogenicity profile.
- The occurrence and relationship to trial vaccination of SAEs and AESIs at predefined time points throughout the trial, for the characterization of the safety and reactogenicity profile.

Secondary endpoints*:

On Day 8, Day 15, Day 29, Day 36, Day 43, Day 57, Day 120, Day 211 and Day 393:

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

  In subjects who did not get exposed to SARS-CoV-2 before the trial, or during the trial before the applicable sample was collected, as measured by ELISA to SARS-CoV-2 N-antigen, seroconversion is defined as an increase in titer in antibodies against SARS-CoV-2 spike protein versus baseline.

  In subjects seropositive for SARS-CoV-2 at baseline, seroconversion is defined as a 2-fold increase in titer in antibodies against SARS-CoV-2 spike protein versus baseline.
- Individual SARS-CoV-2 spike protein-specific antibody levels in serum, as measured by ELISA.
- Geometric mean titers (GMTs) of serum SARS-CoV-2spike protein antibodies, as measured by ELISA, in subjects who did not get exposed to SARS-CoV-2 before the trial, or during the trial before the applicable sample was collected, as measured by ELISA to SARS-CoV-2 N-antigen.
- The proportion of subjects seroconverting for SARS-CoV-2 neutralizing antibodies, as measured by an activity assay.

  In subjects who did not get exposed to SARS-CoV-2 before the trial, or during the trial before the applicable sample was collected, as measured by ELISA to SARS-CoV-2 N-antigen, seroconversion is defined as an increase in titer in SARS-CoV-2 neutralizing antibodies versus baseline.

  In subjects seropositive for SARS-CoV-2 at baseline, seroconversion is defined as a 2-fold increase in titer in SARS-CoV-2 neutralizing antibodies versus baseline.
- Individual SARS-CoV-2 neutralizing antibody levels in serum.
- GMTs of serum SARS-CoV-2 neutralizing antibodies, as measured by an activity assay, in subjects who did not get exposed to SARS-CoV-2 before the trial, or during the trial before the applicable sample was collected, as measured by ELISA to SARS-CoV-2 N-antigen.

** Samples may be used for assay validation and additional studies of the mechanism of action of the vaccine.*

Exploratory endpoints*:

Cell-mediated immune response

*On Day 29, Day 36 and Day 211** in peripheral blood mononuclear cells (PBMCs) from all subjects at the assigned site(s):*

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

  Intracellular cytokine staining (ICS) to investigate Th1 response and production of Th2 markers (e.g. secreted IL-5) will be used to investigate whether vaccination induces a Th1 shift from baseline. Further T-cell immune response may be investigated with other technologies like ELISpot or CyTOF.

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

*** Testing of samples collected on Day 211 will be done only in subjects categorized as T-cell responders on Day 29 and/or Day 36.*

Innate immune response
On Day 2, Day 8, Day 29, Day 30 and Day 36 in all open-label sentinel subjects:

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

** Samples may be used for assay validation and additional studies of the mechanism of action of the vaccine.*

Evaluation of infection

- Number of subjects with virologically-confirmed SARS-CoV-2 infection as measured by reverse transcription polymerase chain reaction (RT-PCR) at clinically determined time points throughout the trial.
- Number of subjects with asymptomatic SARS-CoV-2 infection as measured by retrospective serology at predefined time points.

5 TRIAL DESIGN

5.1 Overall Design

This is a Phase 1, partially blind, placebo-controlled, dose escalation FIH trial of intramuscularly (IM) administered CVnCoV. This trial will evaluate the safety, reactogenicity and immunogenicity of 3 provisional CVnCoV dose levels (2, 4 and 8µg) using an adaptive dose-finding design. This will allow dose escalation or de-escalation using predefined safety criteria and select the CVnCoV dose for further clinical development. To ensure the safety of the subjects, specified safety data will be reviewed on a predefined schedule by an iSRC and a DSMB. An overview of the staggered enrolment and safety monitoring is provided in Figure 2.

An adaptive 2-parameter Bayesian logistic regression model (BLRM) for dose escalation with overdose control (EWOC) will be used in the escalation to guide determination of the safety of each dose level, while decisions of dose level expansion in the sentinel groups of 4 subjects is based on a maximum number of 2 subjects with Grade 3 adverse reactions.

Subjects will be enrolled in 2 age categories (18-40 years and 41-60 years) with an equal distribution across each category. The trial will include subjects with no history of COVID-19 disease as well as subjects with SARS-CoV-2 positive serology. The SARS-CoV-2 serology status at baseline will be evaluated retrospectively to allow separate analysis of subjects retrospectively SARS-CoV-2 seronegative at baseline and subjects retrospectively SARS-CoV-2 seropositive at baseline. To ensure the open-label sentinel subjects in each dose level are seronegative, the SARS-CoV-2 serological status will be determined prior to enrollment during eligibility assessment in these subjects. Additionally, assessment of SARS-CoV-2 serological status may also be performed in the observer-blind placebo-controlled part of the trial, to identify subjects with SARS-CoV-2 positive serology.

Due to the adaptive design of the trial, the actual number of subjects enrolled might be lower or higher than the target numbers.

Throughout the trial, cases of COVID-19 disease will be identified and documented for later pooling of cases across trials in the clinical development program.

5.2 Dose Escalation Steps

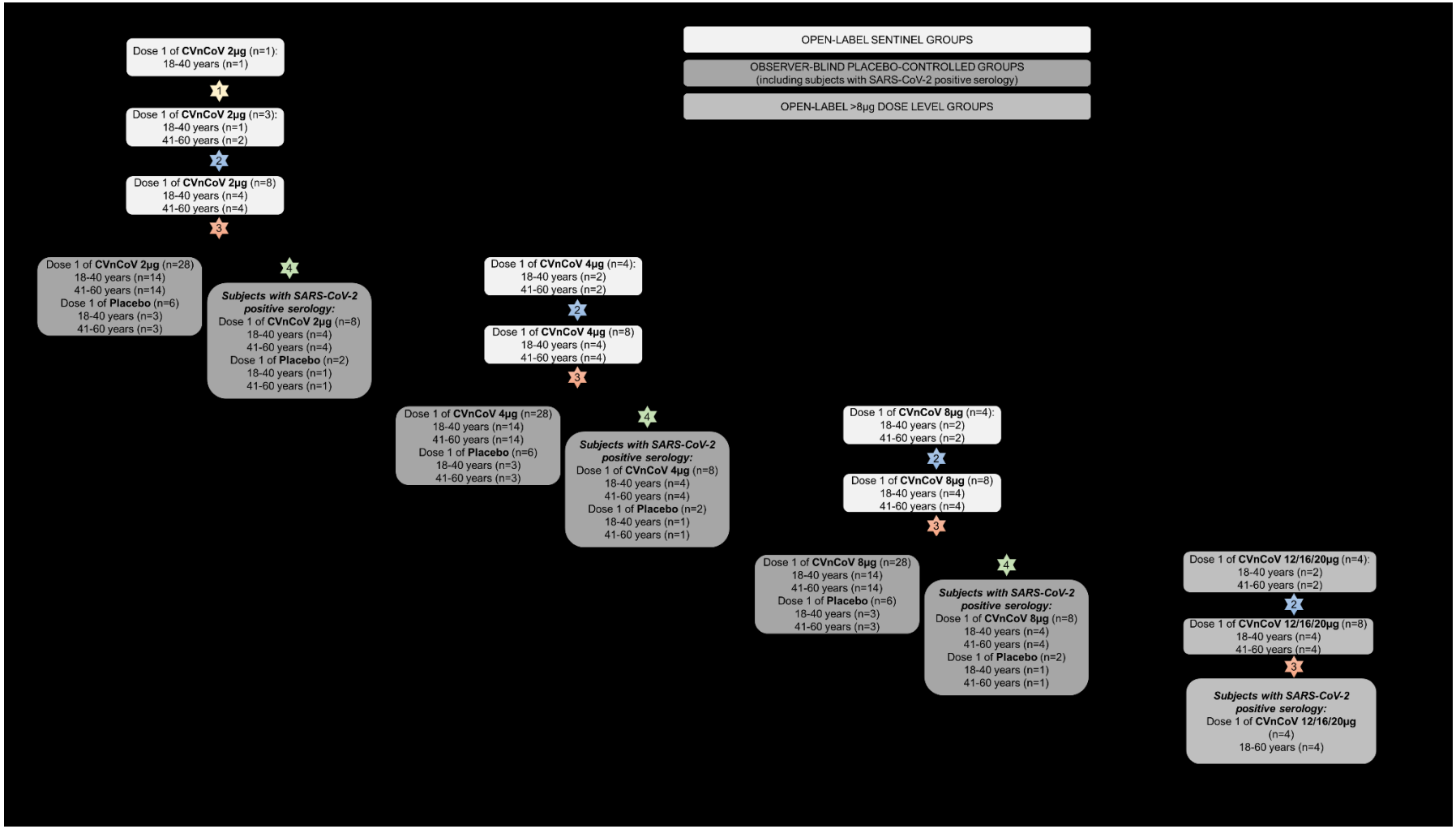
The starting dose of CVnCoV is 2µg. Dose escalation steps will follow the scheme indicated in Table 2. In each dose escalation step, subjects will be equally distributed across the 2 age categories (with the exception of subjects with SARS-CoV-2 positive serology who receive dose levels >8µg).

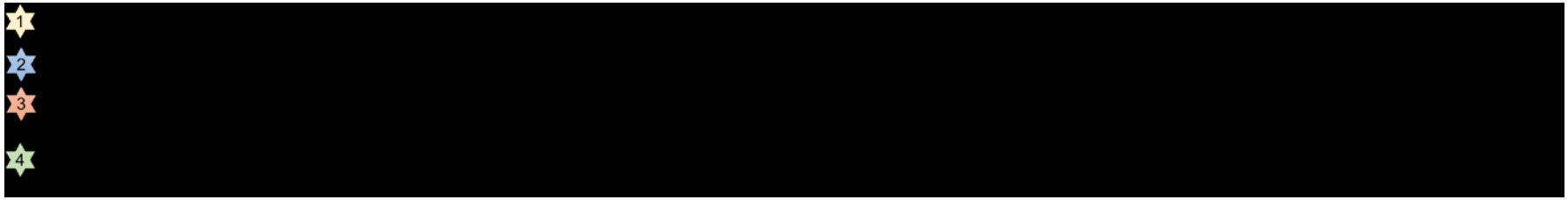
Additional potential dose levels that could be assessed are 1, 3 and 6µg, depending on the reactogenicity/safety findings after vaccination with respectively 2, 4 and 8µg dose levels; as well as 12, 16 and/or 20µg.

All subjects will be administered a second vaccine dose on Day 29 with the same dose level of CVnCoV or placebo as administered on Day 1. When safety data will be available at least 60 hours post dose 2 for all subjects within a dose level, the iSRC and DSMB will

review all available safety (and, if available, immunogenicity) data to confirm the safety of the dose level after the second dose.

Figure 2 Overview of staggered enrollment and dose escalation





The 12, 16 and/or 20µg dose levels will only be given to subjects once initial data from the previous dose level have been reviewed by the iSRC and DSMB, not in parallel.

Table 2 Provisional dose levels during dose escalation

Number of subjects vaccinated per CVnCoV dose level (µg)*							
2µg		**4µg**		**8µg**		**12/16/20µg****	
18-40 years	**41-60 years**	**18-40 years**	**41-60 years**	**18-40 years**	**41-60 years**	**18-40 years**	**41-60 years**
1	-	-	-	-	-		
Post-vaccination observation for 24 hours**		-	-	-	-		
1	2	-	-	-	-		
Safety review of 24-hour post dose 1 data (iSRC+DSMB Chair)		-	-	-	-		
4	4	-	-	-	-		
Safety review of 60-hour post dose 1 data (iSRC+DSMB)							
18 + 4 placebo***	18 + 4 placebo***	2	2	-	-		
-	-	*Safety review of 24-hour post dose 1 data (iSRC+DSMB Chair)*		-	-		
-	-	4	4	-	-		
Safety review of 60-hour post dose 1 data (iSRC+DSMB)							
-	-	18 + 4 placebo***	18 + 4 placebo***	2	2		
-	-	-	-	*Safety review of 24-hour post dose 1 data (iSRC+DSMB Chair)*			
-	-	-	-	4	4		
Safety review of 60-hour post dose 1 data (iSRC+DSMB)							
-	-	-	-	18 + 4 placebo***	18 + 4 placebo***	2	2
-	-	-	-	-	-	*Safety review of 24-hour post dose 1 data (iSRC+DSMB Chair)*	
-	-	-	-	-	-	4	4
Safety review of 60-hour post dose 1 data (iSRC+DSMB)							
-	-	-	-	-	-	**18 to 60 years**	
-	-	-	-	-	-	4*****	

Light grey shaded cells indicate the open-label sentinel groups.
Dark grey shaded cells indicate the observer-blind placebo-controlled groups.
* Provisional dose levels of 2, 4 and 8µg will be evaluated. Additional potential dose levels that could be assessed are 1, 3 and 6µg, depending on the reactogenicity/safety findings after vaccination with respectively 2, 4 and 8µg dose levels; as well as 12, 16 and/or 20µg.
** If any Grade 3 ARs are reported within 24 hours following vaccination, the iSRC and DSMB Chair will be consulted before continuation of enrollment of the next open-label sentinel subjects.
*** Including approximately 4 + 1 subjects with SARS-CoV-2 positive serology.

**** The next dose level will only be given to subjects once initial data from the previous dose level have been reviewed by the iSRC and DSMB, e.g., if 12µg is investigated, it will only be administered after review of the 8µg data (post dose 1 in 12 sentinel subjects), and if the dose level is then escalated to 16µg, it will only be administered after review of the 12µg data (post dose 1 in 12 sentinel subjects).
***** Subjects with SARS-CoV-2 positive serology.

On the first vaccination day, the first open-label sentinel subject aged 18-40 years confirmed to be SARS-CoV-2 seronegative will be enrolled and vaccinated with CVnCoV at the lowest dose level (2µg). The subject will be observed for 24 hours after vaccination. If any Grade 3 adverse reactions, defined as solicited systemic, solicited local and unsolicited Grade 3 adverse events (AEs) considered as related to the trial vaccine according to the Investigator, are reported within 24 hours following vaccination, the iSRC and DSMB Chair will be consulted. In case no safety concerns are identified, the next open-label sentinel group of 3 subjects (1 aged 18-40 years and 2 aged 41-60 years) confirmed to be SARS-CoV-2 seronegative will be enrolled and vaccinated with CVnCoV at the lowest dose level (2µg). The subjects should be vaccinated at least 60 minutes apart. Safety and reactogenicity data reported during an observation period of at least 24 hours after vaccination from these first 4 subjects will be collected and reviewed by the iSRC and DSMB Chair. In this review, the iSRC and DSMB Chair will review all available safety data, but focus specifically on Grade 3 adverse reactions, defined as solicited systemic, solicited local and unsolicited Grade 3 AEs considered as related to the trial vaccine according to the Investigator, and any SAE considered as related to the trial vaccine according to the Investigator. Based on this review, the iSRC and DSMB Chair will decide on the subsequent vaccination of an additional open-label sentinel group of 8 subjects (4 aged 18-40 years and 4 aged 41-60 years, confirmed to be SARS-CoV-2 seronegative) with the same dose level on the next vaccination day (at least 36 hours after the first vaccination day).

Safety and reactogenicity data of subjects vaccinated on the first and second vaccination days will then be collected for at least 60 hours post-vaccination from each subject and reviewed by the iSRC and the DSMB. Based on this review, the iSRC and DSMB will recommend on continuation of enrollment at the same dose level (start of randomized expansion in observer-blind placebo-controlled groups) and initiation of enrollment in the next dose level:

- In case of **continuation of enrollment at the 2µg dose level**, an additional 44 subjects will be enrolled, including 10 subjects with SARS-CoV-2 positive serology. Of these 44 subjects, 36 subjects (18 aged 18-40 years and 18 aged 41-60 years) will receive CVnCoV at the 2µg dose level, including approximately 8 subjects with SARS-CoV-2 positive serology. The other 8 subjects (4 aged 18-40 years and 4 aged 41-60 years) will receive placebo in an observer-blind manner, including approximately 2 subjects with SARS-CoV-2 positive serology.
- In case of **dose escalation**, a newly enrolled open-label sentinel group of 4 subjects (2 aged 18-40 years and 2 aged 41-60 years) confirmed to be SARS-CoV-2 seronegative will receive the next higher dose (4µg) or an intermediate dose depending on iSRC and DSMB recommendations guided by the BLRM. The subjects should be vaccinated at least 60 minutes apart. In case of favorable outcome of the review by the iSRC and DSMB Chair of at least 24-hour post-vaccination data and a maximum number of 2 subjects with Grade 3 adverse reactions, an additional open-label sentinel group of 8 subjects (4 aged 18-40 years and 4 aged 41-60 years, confirmed to be SARS-CoV-2 seronegative) will receive the same dose level on the next vaccination day (at least 36 hours after the first vaccination day).

For each subsequent step, continuation of enrollment within a dose level in a placebo-controlled observer-blind manner and dose escalation will be assessed by the iSRC and DSMB based on 60-hour post-vaccination safety data for each subject, including all available post-vaccination data from previously vaccinated subjects. The scheme for

staggered enrollment and dose escalation in Figure 2 will be pursued if no safety concerns are found by the iSRC or DSMB.

Once the open-label sentinel phase has been successfully concluded for a given dose level, enrollment will no longer be restricted to subjects with no history of COVID-19 disease or negative serology to SARS-CoV-2, but will also include subjects with SARS-CoV-2 positive serology. These subjects will be enrolled at pre-defined site(s). For each dose level, the iSRC will review at least 24-hour post-vaccination safety data from the first 4 seropositive subjects. These first 4 seropositive subjects within each dose level should be vaccinated at least 60 minutes apart. Vaccination of additional subjects at that dose level and/or vaccination of subjects with SARS-CoV-2 positive serology at a higher dose level will only proceed upon favorable outcome of this iSRC review.

5.3 Adaptations to the Trial

Depending on the safety and immunogenicity of the provisional dose levels, additional dose levels might be evaluated. In each case, the enrollment schedule will be performed as described in Section 5.2.

For dose levels >8µg, the enrollment schedule will be performed as described in Section 5.2 for the first 12 sentinel subjects. After a review of the post dose 1 data from these subjects, 4 subjects (aged 18 to 60 years) with SARS-CoV-2 positive serology will be enrolled to receive the same CVnCoV dose level. These 4 open-label subjects will have the same assessments as subjects in the observer-blind placebo-controlled groups and are included when reference is made to the observer-blind placebo-controlled groups throughout this protocol.

In case the lowest dose of 2µg fails to meet the predefined safety criteria, a dose de-escalation to 1µg will be initiated. In case the 4µg dose level fails to meet the predefined safety criteria, a dose de-escalation to 3µg can be initiated. Similarly, in case the 8µg dose level fails to meet the predefined safety criteria, a dose de-escalation to 6µg can be initiated.

5.4 Stopping Rules

5.4.1 Individual Stopping Rules

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

The stopping rules are met in case any of the following events occur on the day of vaccination or following 7 days (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 48 hours to Grade ≤2,
  - Transient Grade 3 local AE that resolved within 48 hours to Grade ≤2.

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

5.4.2 Trial Suspension Rule

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

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

During the observer-blind placebo-controlled phase at each dose level, if >4 subjects experienced Grade 3 adverse reaction(s) after administration of CVnCoV at a particular dose level, vaccination will be put on hold for all subjects in the applicable dose level and any higher dose level. The DSMB will perform a comprehensive review of all relevant safety and reactogenicity data before making a decision to stop, continue or modify vaccination (including dose-de-escalation) with this and any higher dose level.

5.5 Scientific Rationale for Trial Design

This trial will evaluate the safety and reactogenicity of different CVnCoV dose levels using an adaptive Phase 1 dose-finding design. This will allow dose escalation or de-escalation using predefined safety criteria and select the CVnCoV dose for further clinical development. An adaptive 2-parameter BLRM for dose escalation with overdose control will be used in the escalation to guide determination of the safety of each dose level. The use of Bayesian response adaptive models for Phase 1 studies has been advocated by the European Medicines Agency (EMA) adopted guideline on small populations (EMA, 2006) and by Rogatko *et al.*, 2007 [37] and is one of the key elements of the US Food and Drug Administration (FDA)'s Critical Path Initiative.

As mentioned in the FDA Adaptive Designs for Clinical Trials of Drugs and Biologics Guidance for Industry, an adaptive design provides a variety of advantages over non-adaptive designs since adaptive designs allow the trial to adjust to information that was not available when the trial began. This advantage becomes especially important in exploratory Phase 1 dose-finding designs, as it improves understanding of vaccine effects. The adaptive design of this trial in combination with real-time safety monitoring facilitates dose-adjustment based on predefined vaccine reactogenicity criteria [33]. An adaptive design can make it possible to answer broader questions than normally feasible with a non-adaptive design [34,35]. The proposed design of the current trial saves sample size and efficiently assigns subjects to doses considered safe. This design therefore allows moving into further development of the CVnCoV vaccine more efficiently by allowing to move as per protocol to a lower dose level in case of too high reactogenicity, instead of having to pause and amend the trial protocol. This is of particular importance in view of the current pandemic situation, with a high medical need to develop a prophylactic vaccine to prevent COVID-19.

The visit schedule follows that of the FIH trial with CureVac's Rabies mRNA investigational vaccine (CV7202-104). The blood draws for immunogenicity will assess the induction and persistence of innate immune responses, antibody and T-cell responses induced by CVnCoV. Specifically, induction of antibody-responses will be analyzed 1, 2 and 4 weeks after the vaccination (Day 8, Day 15 and Day 29 following the first vaccination, and Day 36, Day 43 and Day 57 after the second vaccination, respectively). The persistence of the antibody response will be evaluated at Day 120, Day 211 and Day 393 (i.e., 3, 6 and 12 months after the second vaccination). Activation of innate immunity will be assessed in the open-label sentinel subjects in the first week after first and second vaccination (Day 1, Day 2 and Day 8 and Day 29, Day 30 and Day 36, respectively). The induction of cell-mediated immunity (CMI) will be analyzed in subjects from the assigned site(s) 1 week after the second vaccination (Day 36). In addition, memory responses will be analyzed in the follow-up period (Day 211).

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

Given the different dose levels of CVnCoV to be administered sequentially, the initial part of the dose escalation will be open with regard to the CVnCoV arm assignments. Dose escalation is scheduled to happen rapidly as compared to what is usually permitted according to EU guidelines on FIH studies. This is justified by the current pandemic situation, where the global population is at risk for infection and, in certain cases, severe disease and death, with no efficacious vaccine available. Clinical data are available from 42 subjects vaccinated with 1 or 2 doses of CureVac's Rabies mRNA investigational vaccine formulated with the same LNPs. These data, as well as the fact that dose escalation will be performed only when re-assuring safety/reactogenicity data are available from the subjects vaccinated with the level below, up to minimum 24 hours post-vaccination, allow to implement this more rapid progression from one dose level to the next, as per predefined stopping and escalation rules. The 24-hour interval post-vaccination was chosen since data from the ongoing Rabies clinical trial have shown that adverse reactions, including those that will be used to decide on further vaccination steps, almost exclusively started within 24 hours after vaccination, usually even in the evening or night after vaccination.

To reduce the risk of biased trial outcomes, the second part of the dose escalation will be conducted in a placebo-controlled observer-blind manner. Double-blinding is not possible due to the difference in appearance of the investigational vaccine and placebo.

5.6 Justification for Dose

Three provisional CVnCoV dose levels (2, 4 and 8 µg) will be evaluated, defined based on clinical data from the CV7202-104 trial with a Rabies vaccine using the same technology as well as non-clinical data. Refer to the Investigator's Brochure for an overview of these data.

Additional higher (12, 16 and/or 20µg), lower (1µg) and/or intermediate (3 and 6 µg) dose levels might be evaluated depending on the outcomes of the safety and reactogenicity evaluations and all available immunogenicity data. Identification of immunogenic dose

levels with lower mRNA content might be of particular importance for efficient vaccination in a worldwide viral outbreak setting.

5.7 End of Trial Definition

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

End of Trial is defined as the point at which the last subject has completed the last visit on Day 393.

6 TRIAL POPULATION

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

In this trial, subjects with no history of COVID-19 disease will be included as well as subjects with SARS-CoV-2 positive serology.

6.1 Inclusion Criteria For All Subjects

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

1. Healthy male and female subjects aged 18 to 60 years inclusive.

   Healthy subject is defined as an individual who is in good general health, not having any mental or physical disorder requiring regular or frequent medication.
2. Expected to be compliant with protocol procedures and available for clinical follow-up through the last planned visit.
3. Physical examination and laboratory results without clinically significant findings according to the Investigator's assessment.
4. Body mass index (BMI) ≥18.0 and ≤30.0kg/m^2 (≥18.0 and ≤32.0kg/m^2 for subjects with SARS-CoV-2 positive serology).
5. Females: 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 the serum pregnancy test was performed more than 3 days before).
6. Females of childbearing potential must use highly effective of birth control from 1 month 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 (IUDs);
   - Intrauterine hormone-releasing systems (IUSs);
   - Bilateral tubal occlusion;
   - Vasectomized partner;
   - Sexual abstinence (periodic abstinence [e.g., calendar, ovulation, symptothermal and post-ovulation methods] and withdrawal are not acceptable).

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

6.2 Exclusion Criteria

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

The following criterion applies to all open-label sentinel subjects:

1. Subjects with confirmed SARS-CoV-2 positive serology as confirmed by testing at enrollment.

The following criteria apply to all subjects, except those with SARS-CoV-2 positive serology:

2. Subjects considered at the Investigator's discretion to be at increased risk to acquire COVID-19 disease (including, but not limited to, health care workers with direct involvement in patient care or care of long-term care recipients).
3. History of confirmed COVID-19 disease or known exposure to an individual with confirmed COVID-19 disease or SARS-CoV-2 infection within the past 2 weeks.

The following criteria apply to all subjects:

4. 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.
5. Receipt of any other vaccines within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to enrollment in this trial or planned receipt of any vaccine within 28 days of trial vaccine administration.
6. Receipt of any investigational SARS-CoV-2 or other CoV vaccine prior to the administration of the trial vaccine.
7. Any treatment with immunosuppressants or other immune-modifying drugs (including, but not limited to, corticosteroids, biologicals and Methotrexate) within 6 months prior to the administration of the trial vaccine or planned use during the trial, with the exception of topically-applied steroids. Corticosteroids used in the context of COVID-19 disease of subjects with SARS-CoV-2 positive serology are not exclusionary.
8. Any medically diagnosed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination, including known human immunodeficiency virus infection, hepatitis B virus infection and hepatitis C virus infection.
9. History of a pIMD (refer to Appendix 9).
10. History of angioedema.
11. Any known allergy, including allergy to any component of CVnCoV or aminoglycoside antibiotics. A history of hay fever or seasonal allergies (pollinosis) that does not require current treatment (e.g., anti-histamines) during the vaccination period (1 month before first vaccination until 1 month after last vaccination) is not exclusionary.
12. History of or current alcohol and/or drug abuse.

13. Subjects who are active smokers, were active smokers within the last year (including any vaping in the last year) or have a total smoking history ≥10 pack years.
14. Acute or currently active SARS-CoV-2 infection as confirmed by reactive PCR within 3 days of first trial vaccine administration.
15. History of confirmed SARS or MERS.
16. Administration of immunoglobulins (Igs) and/or any blood products within the 3 months preceding the administration of any dose of the trial vaccine.
17. Presence or evidence of significant acute or chronic medical or psychiatric illness. Significant medical or psychiatric illnesses include but are not limited to:
    - Respiratory disease (e.g., chronic obstructive pulmonary disease, asthma) requiring daily medications currently or any treatment of respiratory disease exacerbations (e.g., asthma exacerbation) in the last 5 years.
    - Respiratory disease with clinically significant dyspnea in the last 5 years (except COVID-19 disease in subjects with SARS-CoV-2 positive serology).
    - Asthma medications: inhaled, oral, or intravenous (IV) corticosteroids, leukotriene modifiers, long- and short-acting beta agonists, theophylline, ipratropium, biologics.
    - Significant cardiovascular disease (e.g., congestive heart failure, cardiomyopathy, ischemic heart disease, history of stroke, peripheral artery disease, pulmonary embolism) or history of myocarditis or pericarditis as an adult.
    - Elevated blood pressure or hypertension, even if well-controlled.
    - Diabetes mellitus type 1 or 2.
    - History of any neurological disorders or seizures including Guillain-Barré syndrome, with the exception of febrile seizures during childhood.
    - Current or past malignancy, unless completely resolved without sequelae for >5 years.
18. Foreseeable non-compliance with protocol as judged by the Investigator.
19. For females: pregnancy or lactation.
20. History of any anaphylactic reactions.
21. Subjects with impaired coagulation or any bleeding disorder in whom an IM injection or a blood draw is contraindicated.
22. Subjects employed by the Sponsor, Investigator or trial site, or relatives of research staff working on this trial.

6.3 Vaccine Delay Recommendations

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

- Subjects with a clinically significant (≥ Grade 2) active infection or other acute disease (as assessed by the Investigator) or temperature >38.0°C (>100.4°F), within 3 days of intended trial vaccination. Further dose administration should be delayed until the active infection or other acute disease has recovered to ≤ Grade 1 or the subject's

temperature has decreased to ≤38.0°C (≤100.4°F) for at least 3 days, if this still allows to vaccinate the subject as per the predefined interval. Temperature should be measured orally.

- Subjects who took antipyretic medication within 8 hours before intended trial vaccination.

In the event that a subject meets a criterion for delay of vaccination, the subject may receive the trial dose once the window for delay has passed, if clinically appropriate to vaccinate in the judgment of the Investigator and the time windows of the protocol can be respected (refer to Table 1).

There are also circumstances under which further vaccination is suspended in this trial, as detailed in Section 5.2 for the dose escalation steps and Section 5.4 for stopping rules. If these reactions occur, the subject(s) must not receive additional vaccinations but is/are encouraged to continue in trial participation for safety reasons, including collection of safety blood samples. Immunogenicity assessments may be performed also, at the Investigator's discretion.

6.4 Failure to Meet Eligibility Criteria

The Investigator must account for all subjects who sign an informed consent. If the subject is found to be not eligible (i.e., did not meet all inclusion criteria or met 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 one 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 tests value meeting one or more exclusion criteria, which are not in line with the medical history and clinical evaluation of the subjects may be re-tested to confirm the value of the tests, if still allowed within the enrollment period (Day -21 to Day 1). If not feasible, the subject should be re-assessed for eligibility.

7 TRIAL VACCINE

7.1 Trial Vaccine Administration

7.1.1 Description of the Trial Vaccines

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

The placebo administered in the control arms consists of 0.9% NaCl.

7.1.2 Dosing and Administration

The provisional dose levels to be administered are provided in Table 2. On the first vaccination day within each dose level, the 4 newly enrolled open-label sentinel subjects should be vaccinated at least 60 minutes apart. Also, the first 4 newly enrolled seropositive subjects within each dose level should be vaccinated at least 60 minutes apart. As detailed in Sections 5.2 and 5.3, additional higher, lower and/or intermediate dose levels may be evaluated depending on the outcome of the safety evaluations.

All subjects will be administered a second vaccine dose on Day 29 with the same dose level or placebo as administered on Day 1.

Injections must be performed IM by needle in the deltoid area (non-dominant arm) in all groups.

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.

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. All subjects must remain under direct supervision of personnel trained in the treatment of these reactions for 4 hours following administration of the trial IMP.

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 at the local pharmacy or a qualified Phase 1 unit according to the handling protocol provided by CureVac AG.

7.2.2 Product Storage and Stability

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

7.2.3 Accountability

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

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

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

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

7.3 Randomization and Blinding

In the initial part of dose escalation for the provisional dose levels of 2, 4 and 8µg, subjects will be enrolled in sentinel groups in an open manner. In the second part, subjects will be enrolled in placebo-controlled groups in an observer-blind manner within each dose level with a 4.5:1 ratio and stratified by the 2 age categories (18-40 and 41-60 years). Double-blinding is not possible due to the difference in appearance of the investigational vaccine and placebo.

Groups with a dose level >8µg will be open-label.

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

Emergency unblinding

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

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

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

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

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

If the code has been broken and there are no medical reasons for discontinuation, the subject may continue the trial.

7.4 Vaccine Compliance

The Investigator will record all injections (CVnCoV and placebo) 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 administration should be pursued.

7.8 Treatment After the End of Trial

No post-trial care will be provided.

8 DISCONTINUATION/WITHDRAWAL CRITERIA

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

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

Subjects who received at least 1 dose of trial vaccine will be encouraged to continue participation until the end of the trial for safety assessments. Assessments of solicited AEs and associated phone calls 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 discontinued trial vaccine administration. Immunogenicity assessments may be performed at the Investigator's discretion, if the subject agrees.

8.1 Discontinuation of Trial Vaccine Administration

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

- Consent withdrawal by the subject.

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

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

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

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

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

- Pregnancy (see Section 9.2.2).

  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.

- Clinical suspicion of SARS-CoV-2 infection (as specified in Section 9.4).

- 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.

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

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

The trial can also be terminated by the Regulatory Authority for any reason or if recommended by the iSRC or DSMB, or at a site level by the Independent Ethics Committee or Institutional Review Board (IEC/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

For each procedure, subjects are to be assessed by the same Investigator or site personnel whenever possible.

In case subjects are not be 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). This is in accordance with EMA's "*Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic Version 3* (28/04/2020)", which states that "*Where a trial participant is unable to attend the site, other measures, such as home nursing, if possible given social distancing needs, or contact via phone or telemedicine means, may be required to identify adverse events and ensure continuous medical care and oversight.*". There will likely be further updates to this guidance, and the Sponsor will take these into consideration for decision-making during the course of the trial.

Blood samples for humoral immune response assessment on Day 29, Day 43 and Day 57 and for CMI assessment on Day 36 should be collected via a home visit within the protocol-specified time window. Blood sampling for immunogenicity assessment at other time points may be postponed to the next possible visit, in case of a public health emergency. If visits, phone-contacts or sample collection cannot be performed within the protocol-defined windows, in such extraordinary circumstances as a public health emergency, it will be acceptable to perform these tasks outside of these windows.

Alternatively, electronic diaries may be used during the trial for collection of safety-related information, in which case systems will be adjusted accordingly.

9.1 Schedule of Trial Assessments and Procedures

Refer to the Schedule of Activities (Table 1). The trial procedures apply to all subjects, independent if they had a history of COVID-19 disease or SARS-CoV-2 positive serology and independent of the serology status at baseline as per retrospective analysis.

9.1.1 Visit 1: Day 1

Note that procedures to establish subject eligibility, recording of demographic information and medical history may be performed within 21 days prior to trial vaccine administration, i.e., spread out over more than 1 day. If all information to establish eligibility is available, these procedures can be done on the same day including the trial vaccine administration. Eligibility criteria, including laboratory results, need to be reviewed on the day of vaccination prior to trial vaccine administration.

9.1.1.1 Pre-vaccination Procedures

- Obtain the signed informed consent form.

  Signed informed consent must be obtained prior to the subject entering into the trial, and before any protocol-directed procedures are performed (see Section 12.4).
- Review inclusion/exclusion criteria (see Section 6.1 and 6.2).
- Record demographic information.

- Record medical history.
- Record concomitant medication and vaccination, including recurring medication for intermittent conditions, if taken within 6 months prior to enrollment in this trial.
- Perform a complete physical examination, including height and weight (see Section 9.2.4). If the complete physical examination to establish eligibility was performed within 21 days prior to trial vaccine administration, a symptom-directed physical examination should be performed on the day of vaccination prior to trial vaccine administration.
- Measure vital signs (body temperature, pulse, blood pressure, see Section 9.2.4).
- Carry out a 12-lead ECG (see Section 9.2.4).
- Collect a swab sample for detection of SARS-CoV-2 infection by PCR.
- Collect a blood sample for safety and immunogenicity assessment (~115mL for open-label sentinel subjects and ~105mL for observer-blind placebo-controlled subjects [see Table 1).
- **For the open-label sentinel subjects in each dose level:** Collect a blood sample (~6mL) for determination of SARS-CoV-2 serology status. This may also be performed for subjects in the observer-blind placebo-controlled part of the trial to identify subjects with SARS-CoV-2 positive serology.

9.1.1.2 Vaccination Procedures

- Check inclusion/exclusion criteria (see Section 6.1 and 6.2) and review prohibited medications listed as an exclusion criterion (see Section 6.2).
- Review criteria for delay of vaccination (see Section 6.3).
- Collect a blood sample for a serum pregnancy test (hCG) (~3mL) to establish eligibility for female subjects of childbearing potential.
- Conduct a urine pregnancy test for female subjects of childbearing potential, unless the serum pregnancy test to establish eligibility was performed less than 3 days before.
- Collect a blood sample (~3mL) for potential retrospective baseline testing of autoantibodies (TSH, thyroid antibodies and anti-nuclear antibody [ANA] and other autoantibodies), in case of the occurrence of clinical autoimmune events.
- Administer the trial vaccine dose according to the subject's assignment.

9.1.1.3 Post-vaccination Procedures

- Observe the subject on site for at least 4 hours following vaccination for safety monitoring.
- Issue the diary card and instruct the subject to record solicited AEs occurring on the day of vaccination and the following 7 days and unsolicited AEs occurring on the day of vaccination and the following 28 days.
- Train the subject how to measure solicited AEs and how to complete the diaries.
- Train the subject on when and how to contact the site to report acute respiratory infection (ARI) symptoms to detect COVID-19 like illnesses (see Section 9.4).

- Record safety data, including solicited AEs, unsolicited AEs, SAEs, intercurrent medical conditions that may affect the immune response to vaccination, AEs leading to premature discontinuation and AESIs.
- At the end of the observation period:
  - Measure vital signs (body temperature, pulse, blood pressure, see Section 9.2.4).
  - The subject may not be discharged until vital signs are within normal range or have returned to pre-vaccination levels.

9.1.2 Visit 2: Day 2 – Only for Open-Label Sentinel Subjects

- Record concomitant medication and vaccination, including recurring medication for intermittent conditions.
- Perform a symptom-directed physical examination (see Section 9.2.4).
- Measure vital signs (body temperature, pulse, blood pressure, see Section 9.2.4).
- Review the diary card and remind the subject to continue recording solicited and unsolicited AEs in the diary card.
- Re-train the subject how to measure solicited AEs and how to complete the diaries.
- Re-train the subject on when and how to contact the site to report ARI symptoms to detect COVID-19 like illnesses (see Section 9.4).
- Record safety data, including solicited AEs, unsolicited AEs, SAEs, intercurrent medical conditions that may affect the immune response to vaccination, AEs leading to premature discontinuation and AESIs.
- Collect a blood sample for safety and immunogenicity assessment (~20mL, see Table 1).

9.1.3 Phone Call: Day 2 – Only for Observer-Blind Placebo-Controlled Subjects

The purpose of this safety call is to inquire on the subject's general well-being and to assess reactogenicity.

- All Grade 3 solicited and unsolicited AEs and all SAEs reported by the subject during the call must be reported to the medical monitor without delay, on the same day of awareness by the site, to allow assessing Grade 3 adverse reactions and SAEs considered as related to the trial vaccine according to the Investigator in real time.
- Remind the subject to continue recording solicited and unsolicited AEs in the diary card.

9.1.4 Phone Call: Day 3

The purpose of this safety call is to inquire on the subject's general well-being and to assess reactogenicity.

- All Grade 3 solicited and unsolicited AEs and all SAEs reported by the subject during the call must be reported to the medical monitor without delay, on the same day of awareness by the site, to allow assessing Grade 3 adverse reactions and SAEs considered as related to the trial vaccine according to the Investigator in real time.

- Remind the subject to continue recording solicited and unsolicited AEs in the diary card.

9.1.5 Visit 3: Day 8

- Record concomitant medication and vaccination, including recurring medication for intermittent conditions.
- Perform a symptom-directed physical examination (see Section 9.2.4).
- Measure vital signs (body temperature, pulse, blood pressure, see Section 9.2.4).
- Review the diary card and remind the subject to continue recording unsolicited AEs in the diary card.
- Re-train the subject how to complete the diaries.
- Re-train the subject on when and how to contact the site to report ARI symptoms to detect COVID-19 like illnesses (see Section 9.4).
- Record safety data, including solicited AEs, unsolicited AEs, SAEs, intercurrent medical conditions that may affect the immune response to vaccination, AEs leading to premature discontinuation and AESIs.
- Collect a blood sample for safety and immunogenicity assessment (~45mL for open-label sentinel subjects and ~35mL for observer-blind placebo-controlled subjects [see Table 1]).

9.1.6 Visit 4: Day 15

- Record concomitant medication and vaccination, including recurring medication for intermittent conditions.
- Perform a symptom-directed physical examination (see Section 9.2.4).
- Measure vital signs (body temperature, pulse, blood pressure, see Section 9.2.4).
- Review the diary card and remind the subject to continue recording unsolicited AEs.
- Re-train the subject how to complete the diaries.
- Re-train the subject on when and how to contact the site to report ARI symptoms to detect COVID-19 like illnesses (see Section 9.4).
- Record safety data, including unsolicited AEs, SAEs, intercurrent medical conditions that may affect the immune response to vaccination, AEs leading to premature discontinuation and AESIs.
- Collect a blood sample for immunogenicity assessment (~24mL, see Table 1).
- Collect a blood sample for safety assessment in case of an abnormal value for any of the safety parameters at the previous visit (~9mL, see Table 1).

9.1.7 Visit 5: Day 29

9.1.7.1 Pre-vaccination Procedures

- Record concomitant medication and vaccination, including recurring medication for intermittent conditions.
- Perform a complete physical examination (see Section 9.2.4).
- Measure vital signs (body temperature, pulse, blood pressure, see Section 9.2.4).

- Collect and review the diary card issued after Dose 1.
- Collect a blood sample for immunogenicity assessment (~75mL for open-label sentinel subjects and ~65mL for observer-blind placebo-controlled subjects [see Table 1]).
- Collect a blood sample for safety assessment in case of an abnormal value for any of the safety parameters at the previous visit (~9mL, see Table 1).

9.1.7.2 Vaccination Procedures

- Check criteria for discontinuation of trial vaccination (see Section 8.1) and review prohibited medications listed as an exclusion criterion (see Section 6.2).
- Review criteria for delay of vaccination (see Section 6.3).
- Conduct a urine pregnancy test for female subjects of childbearing potential.
- Administer the trial vaccine dose according to the subject's assignment.

9.1.7.3 Post-vaccination Procedures

- Observe the subject on site for at least 4 hours following vaccination for safety monitoring.
- Issue the diary card and instruct the subject to record solicited AEs occurring on the day of vaccination and the following 7 days and unsolicited AEs occurring on the day of vaccination and the following 28 days.
- Re-train the subject how to measure solicited AEs and how to complete the diaries.
- Re-train the subject on when and how to contact the site to report ARI symptoms to detect COVID-19 like illnesses (see Section 9.4).
- Record safety data, including solicited AEs, unsolicited AEs, SAEs, intercurrent medical conditions that may affect the immune response to vaccination, AEs leading to premature discontinuation and AESIs.
- At the end of the observation period:
  - Measure vital signs (body temperature, pulse, blood pressure, see Section 9.2.4).
  - The subject may not be discharged until vital signs are within normal range or have returned to pre-vaccination levels.

9.1.8 Visit 6: Day 30 – Only for Open-Label Sentinel Subjects

- Record concomitant medication and vaccination, including recurring medication for intermittent conditions.
- Perform a symptom-directed physical examination (see Section 9.2.4).
- Measure vital signs (body temperature, pulse, blood pressure, see Section 9.2.4).
- Review the diary card and remind the subject to continue recording solicited and unsolicited AEs in the diary card.
- Re-train the subject how to measure solicited AEs and how to complete the diaries.
- Re-train the subject on when and how to contact the site to report ARI symptoms to detect COVID-19 like illnesses (see Section 9.4).

- Record safety data, including solicited AEs, unsolicited AEs, SAEs, intercurrent medical conditions that may affect the immune response to vaccination, AEs leading to premature discontinuation and AESIs.
- Collect a blood sample for safety and immunogenicity assessment (~20mL, see Table 1).

9.1.9 Phone Call: Day 30 – Only Observer-Blind Placebo-Controlled Subjects

The purpose of this safety call is to inquire on the subject's general well-being and to assess reactogenicity.

- All Grade 3 solicited and unsolicited AEs and all SAEs reported by the subject during the call must be reported to the medical monitor without delay, on the same day of awareness by the site, to allow assessing Grade 3 adverse reactions and SAEs considered as related to the trial vaccine according to the Investigator in real time.
- Remind the subject to continue recording solicited and unsolicited AEs in the diary card.

9.1.10 Phone Call: Day 31

The purpose of this safety call is to inquire on the subject's general well-being and to assess reactogenicity.

- All Grade 3 solicited and unsolicited AEs and all SAEs reported by the subject during the call must be reported to the medical monitor without delay, on the same day of awareness by the site, to allow assessing Grade 3 adverse reactions and SAEs considered as related to the trial vaccine according to the Investigator in real time.
- Remind the subject to continue recording solicited and unsolicited AEs in the diary card.

9.1.11 Visit 7: Day 36

- Record concomitant medication and vaccination, including recurring medication for intermittent conditions.
- Perform a symptom-directed physical examination (see Section 9.2.4).
- Measure vital signs (body temperature, pulse, blood pressure, see Section 9.2.4).
- Review the diary card and remind the subject to continue recording unsolicited AEs in the diary card.
- Re-train the subject how to complete the diaries.
- Re-train the subject on when and how to contact the site to report ARI symptoms to detect COVID-19 like illnesses (see Section 9.4).
- Record safety data, including solicited AEs, unsolicited AEs, SAEs, intercurrent medical conditions that may affect the immune response to vaccination, AEs leading to premature discontinuation and AESIs.
- Collect a blood sample for safety and immunogenicity assessment (~85mL for open-label sentinel subjects and ~75mL for observer-blind placebo-controlled subjects [see Table 1]).

Note: In case Visit 7 (Day 36) cannot take place (e.g. due to a public health emergency), the blood sample for CMI assessment should be taken at Visit 8 (Day 43).

9.1.12 Visit 8: Day 43

- Record concomitant medication and vaccination, including recurring medication for intermittent conditions.
- Perform a symptom-directed physical examination (see Section 9.2.4).
- Measure vital signs (body temperature, pulse, blood pressure, see Section 9.2.4).
- Review the diary card and remind the subject to continue recording unsolicited AEs in the diary card.
- Re-train the subject how to complete the diaries.
- Re-train the subject on when and how to contact the site to report ARI symptoms to detect COVID-19 like illnesses (see Section 9.4).
- Record safety data, including unsolicited AEs, SAEs, intercurrent medical conditions that may affect the immune response to vaccination, AEs leading to premature discontinuation and AESIs.
- Collect a blood sample for immunogenicity assessment (~24mL, see Table 1).
- Collect a blood sample for safety assessment in case of an abnormal value for any of the safety parameters at the previous visit (~9mL, see Table 1).

9.1.13 Visit 9: Day 57

- Record concomitant medication and vaccination, including recurring medication for intermittent conditions.
- Perform a symptom-directed physical examination (see Section 9.2.4).
- Measure vital signs (body temperature, pulse, blood pressure, see Section 9.2.4).
- Collect and review the diary card.
- Re-train the subject on when and how to contact the site to report ARI symptoms to detect COVID-19 like illnesses (see Section 9.4).
- Record safety data, including unsolicited AEs, SAEs, intercurrent medical conditions that may affect the immune response to vaccination, AEs leading to premature discontinuation and AESIs.
- Collect a blood sample for immunogenicity assessment (~24mL, see Table 1).
- Collect a blood sample for safety assessment in case of an abnormal value for any of the safety parameters at the previous visit (~9mL, see Table 1).

9.1.14 Visit 10: Day 120 (Follow-up Visit)

- Record concomitant medication and vaccination, including recurring medication for intermittent conditions.
- Perform a symptom-directed physical examination (see Section 9.2.4).
- Measure vital signs (body temperature, pulse, blood pressure, see Section 9.2.4).

- Re-train the subject on when and how to contact the site to report ARI symptoms to detect COVID-19 like illnesses (see Section 9.4).
- Record safety data, including SAEs, intercurrent medical conditions that may affect the immune response to vaccination, AEs leading to premature discontinuation and AESIs.
- Collect a blood sample for immunogenicity assessment (~24mL, see Table 1).
- Collect a blood sample for safety assessment in case of an abnormal value for any of the safety parameters at the previous visit (~9mL, see Table 1).

9.1.15 Visit 11: Day 211 (Follow-up Visit)

- Record concomitant medication and vaccination, including recurring medication for intermittent conditions.
- Perform a symptom-directed physical examination (see Section 9.2.4).
- Measure vital signs (body temperature, pulse, blood pressure, see Section 9.2.4).
- Re-train the subject on when and how to contact the site to report ARI symptoms to detect COVID-19 like illnesses (see Section 9.4).
- Record safety data, including SAEs, intercurrent medical conditions that may affect the immune response to vaccination, AEs leading to premature discontinuation and AESIs.
- Collect a blood sample for immunogenicity assessment (~64mL, see Table 1).
- Collect a blood sample for safety assessment in case of an abnormal value for any of the safety parameters at the previous visit (~9mL, see Table 1).

9.1.16 End of Trial Visit: Day 393

The end of trial visit will be performed 365 days (-0/+30 days) after the last trial vaccine administration. This includes subjects who prematurely discontinued vaccination during the trial. The following assessments should be performed:

- Record concomitant medication and vaccination, including recurring medication for intermittent conditions.
- Perform a complete physical examination (see Section 9.2.4).
- Measure vital signs (body temperature, pulse, blood pressure, see Section 9.2.4).
- Record safety data, including SAEs, intercurrent medical conditions that may affect the immune response to vaccination, AEs leading to premature discontinuation and AESIs.
- Collect a blood sample for immunogenicity assessment (~24mL, see Table 1).
- Collect a blood sample for safety assessment in case of an abnormal value for any of the safety parameters at the previous visit (~9mL, see Table 1).

9.2 Safety Assessments

9.2.1 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 11.

9.2.1.1 Solicited Adverse Events

Diary cards will be distributed to all subjects for collection of solicited local AEs (injection-site pain, redness, swelling and itching) and solicited systemic AEs (fever, headache, fatigue, chills, myalgia, arthralgia, nausea/vomiting and diarrhea) on the day of vaccination and the following 7 days.

Temperature should be measured orally.

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

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

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

Table 3 Intensity Grading* for Solicited Local Adverse Events

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

*FDA toxicity grading scale [36].

Table 4 Intensity Grading* for Solicited Systemic Adverse Events

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

*FDA toxicity grading scale [36]; IV = Intravenous.

9.2.1.2 Unsolicited Adverse Events and Serious Adverse Events

Unsolicited AEs occurring on the day of vaccination and the following 28 days will be recorded by the subject on the diary card.

The occurrence of AEs (serious and non-serious) will be assessed by non-directive questioning of the subject at each visit. AEs volunteered by the subject during or between visits as subject diary card entries or detected through observation, physical examination, laboratory test, or other assessments during the entire trial, will be recorded in the eCRF. Subjects should be instructed to report immediately any AEs with serious symptoms, subjective complaints or objective changes in their well-being to the Investigator or the

site personnel, regardless of the perceived relationship between the event and the trial vaccine.

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

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

9.2.1.3 Adverse Events of Special Interest

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

- AEs with a suspected immune-medicated etiology (pIMDs, see Appendix 9),
- COVID-19 disease,
- other AEs relevant to SARS-CoV-2 vaccine development or the target disease (see Appendix 10).

AESIs will be collected throughout the trial.

9.2.2 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 11 for details on the reporting and follow-up of pregnancies.

9.2.3 Safety Laboratory Assessments

Blood samples for determination of hematology (complete blood count, including differential and platelets), clinical biochemistry and coagulation will be analyzed as indicated in the Schedule of Activities on Day 1 and one and 7 days after each vaccine dose administration (Days, 2, 8, 30 and 36) (refer to Table 1). At all other visits, safety laboratory assessment will only be done in case an abnormal value was observed at the previous visit. An overview of the safety laboratory tests is provided in Appendix 3.

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

On Day 1, the total blood drawn for safety laboratory assessment is ~15mL for all subjects. Blood will be taken for potential retrospective baseline measurement of TSH, thyroid antibodies and ANA in case of the occurrence of (a) clinical autoimmune event(s) during the trial (other autoantibodies might be investigated as well depending on the possible clinical autoimmune event).

Laboratory data will be graded according with the FDA toxicity grading scale [36]. These guidelines however are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

9.2.4 Vital Signs, Physical Examination, and ECG

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

At specific trial visits (see Table 1), a complete **physical examination** will be performed, including examination of general appearance, eyes/ears/nose/throat, head/neck/thyroid, lymph node areas, cardiovascular system, lung/chest, abdomen and genitourinary system, extremities and neurological examination, skin examination, measurement of weight and height. At all other trial visits, a symptom-directed physical examination may be performed.

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

9.2.5 Medical and Surgical History

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

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

9.2.6 Safety Monitoring Committees

Specified safety data will be reviewed by an iSRC and an external and independent DSMB. The iSRC will consist of the Principal Investigator at each trial site, the Medical Monitor and medical representatives of the Sponsor. Details on the composition, objectives, and role and responsibilities of the iSRC and DSMB will be described in separate charters, agreed with the respective committee members and Sponsor. The charters will also define and document the content of the safety and/or immunogenicity summaries, and general procedures (including communications). The iSRC and DSMB review will be based on unblinded data.

The iSRC and DSMB Chair will review all available safety data obtained during at least 24 hours post-vaccination for each open-label sentinel subject vaccinated on the first vaccination day per dose level, and assess for Grade 3 adverse reaction(s) and any SAE considered as related to the trial vaccine according to the Investigator. Based on this review, the iSRC and DSMB Chair will decide on the enrollment of the subjects planned on the next vaccination day within each dose level. For each dose level, the iSRC will review at least 24-hour post-vaccination safety data from the first 4 seropositive subjects. Vaccination of additional seropositive subjects at that dose level and/or vaccination of subjects with SARS-CoV-2 positive serology at a higher dose level will only proceed upon favorable outcome of this iSRC review. The iSRC will also perform ongoing safety assessments for subjects beyond the first 24 hours on all available data.

In addition, the iSRC together with the DSMB will review all available safety data obtained during at least 60 hours post-vaccination for each subject to recommend on continuation of enrollment at the same dose level and dose escalation. If no stopping rule is met, the DSMB Chair can decide to allow trial progression without obtaining a DSMB quorum.

During the observer-blind placebo-controlled phase at each dose level, if >4 subjects experienced Grade 3 adverse reaction(s) after administration of CVnCoV at a particular dose level, vaccination will be put on hold for all subjects in the applicable dose level and any higher dose level. The DSMB will perform a comprehensive review of all relevant safety and reactogenicity data before making a decision to stop, continue or modify vaccination (including dose-de-escalation) with this and any higher dose level.

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

If a stopping rule or trial suspension rule is limited to subjects with SARS-CoV-2 positive serology, vaccination will only be put on hold for subjects with SARS-CoV-2 positive serology.

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

After completion of vaccination for all subjects, the DSMB will continue to review safety data every 3 months, or more frequently if needed based on the safety data.

9.3 Immunogenicity Assessments

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

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

9.3.1 Humoral Immune Response

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

The humoral immune response will be evaluated on Day 1, Day 8, Day 15, Day 29, Day 36, Day 43, Day 57, Day 120, Day 211 and Day 393.

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

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

9.3.2 Innate Immune Response – Only for Open-Label Sentinel Subjects

The innate immune response will only be evaluated in subjects in the open-label sentinel groups.

Measurement of serum cytokines, including but not limited to IFN-α, IFN-γ, IL-6, CCL2 and IP-10, will be performed on Day 1, Day 2, Day 8, Day 29, Day 30 and Day 36.

In addition, gene expression changes will be determined using the PAXgene® blood RNA system by transcriptome profiling on Day 1, Day 2, Day 8, Day 29, Day 30 and Day 36.

9.3.3 Cell-Mediated Immunity

CMI will only be evaluated in subjects from the assigned site(s).

The frequency and functionality of SARS-CoV-2 spike-specific T-cell response after antigen stimulation will be determined in PBMC in comparison to baseline. For example, intracellular cytokine staining (ICS) to investigate Th1 response and production of Th2 markers (e.g. secreted IL-5) will be used to investigate whether vaccination induces a Th1 shift from baseline. Further T-cell immune response maybe investigated with other technologies like ELISpot or CyTOF.

CMI assessment will be performed on Day 1 (baseline), Day 29, Day 36 and Day 211. Note that testing on Day 211 will only be performed on subjects who are determined as T-cell responders on Day 29 and/or Day 36.

9.4 Laboratory Testing for COVID-19 Disease

As part of the eligibility assessment, PCR for SARS-CoV-2 will be performed. Additionally, for the 12 open-label sentinel subjects in each dose level, the SARS-CoV-2 serological status will be determined using site-specific diagnostics prior to enrollment to ensure they are seronegative. This may also be performed for subjects in the observer-blind placebo-controlled part of the trial to identify subjects with SARS-CoV-2 positive serology.

At several pre-defined timepoints during the trial, IgM and IgG serology will be assessed. Testing will be done for SARS-CoV-2 spike protein to evaluate vaccine-induced immune responses as well as for SARS-CoV-2 N-antigen (not contained in the vaccine construct) to evaluate immune responses induced by natural infection. This will allow to retrospectively identify the subject's (baseline) serology status for the group/cohorts analysis.

Any subject with clinical suspicion of SARS-CoV-2 infection will undergo appropriate testing and referral within the local healthcare system as appropriate. Subjects with confirmed SARS-CoV-2 infections should not receive any (additional) vaccine dose, but will be closely monitored for disease patterns and severity.

Subjects will be instructed to contact the site if they observe any of the following symptoms:

Cough, shortness of breath, difficulty breathing, fever ≥37.8°C, fatigue, myalgia, chills, wheezing, nasal congestion, runny nose, sore throat, headache, diarrhea, or new olfactory and taste disorders.

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

If the subject displays symptoms of ARI (including, but not limited to COVID-19 disease), the Investigator will collect appropriate specimens as soon as feasible and perform PCR and serological assays at the discretion of the Investigator or treating physician to establish laboratory measures of infection with SARS-CoV-2. Each of those assays will

be repeated 7-14 days after the initial assessment as well. In order to assess severity of disease, subjects will document disease progression on a symptom log and Investigators will document additional clinical parameters based on hospital records, if applicable.

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

10 STATISTICAL CONSIDERATIONS

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

10.1 Sample Size Determination

This trial is designed to estimate the probability that the true rate of adverse reactions for each dose lies in an acceptable safety range (see Section 10.3.5.1) and to describe the safety profile of CVnCoV. Hence, its sample size was not determined based on formal statistical power calculations.

During the trial, a minimum of 12 subjects evaluable for the dose determining set (DDS-2, as defined in Section 10.2) will be vaccinated per dose level until completion of the dose escalation. After completion of the open-label sentinel phase, subjects will be enrolled in placebo-controlled groups in an observer-blind manner within each dose level with a 4.5:1 ratio and stratified by the 2 age categories (18-40 and 41-60 years). For an overview of the distribution of subjects, refer to Figure 2.

It is estimated that approximately 56 subjects per dose level will be enrolled, including 48 CVnCoV and 8 placebo recipients, for ≤8µg and 16 subjects per dose level, all CVnCoV recipients, for >8µg. The actual number of subjects will depend on the number of dose levels/groups that are tested.

The trial is designed to provide, by combining data from the open-label sentinel and the observer-blind placebo-controlled phases, a reasonable precision for the rate of subjects with Grade 3 adverse reaction(s). Table 5 provides the estimate and 95% credibility interval for given observed numbers of subjects for a sample size of 48 subjects per dose level (assuming a Beta (0.5,0.5) prior distribution).

Table 5 Estimate rate of subjects with Grade 3 adverse reaction(s) and 95% credibility interval per dose level

N subjects with Grade 3 adverse reaction(s)	Estimate (95% credibility interval) in %	Probability adverse reaction rate <33%
0	1 (0 - 5.1)	100
2	5.1 (0.9 - 12.7)	100
4	9.2 (2.9 - 18.6)	100
6	13.3 (5.4 - 24)	99.9
8	17.3 (8.2 - 29)	99.4
10	21.4 (11.2 - 33.8)	96.7
12	25.5 (14.5 - 38.5)	88.2
14	29.6 (17.8 - 43)	71.,0
16	33.7 (21.3 - 47.3)	47.3
18	37.8 (24.9 - 51.6)	25.1
20	41.8 (28.5 - 55.8)	10.2

N = Number of subjects

Table 6 provides probabilities (in %) that the following condition is met for assumed true rates of adverse reactions and a sample size of 48 subjects per arm: There is a ≥80% probability that the true rate of Grade 3 adverse reaction(s) is <33%.

For example, assuming a true adverse reactions rate of 20%, the condition is met with a probability of 91.6%.

Table 6 Probabilities that the rate of Grade 3 adverse reactions is <33% is ≥80% for given 'true' adverse reactions rates during dose escalation

True rate of adverse reactions	Probability (%)
0.05	100
0.1	100
0.15	99.1
0.2	91.6
0.25	69.8
0.3	39.7
0.35	16.1

The number of placebo subjects is chosen to have a minimum number of subjects to descriptively evaluate the onset and the level of humoral immune response taking into account that there are 2 age groups, 2 possible SARS-CoV-2 status at baseline, 3 different doses levels and a placebo group (Table 7). A total of 24 placebo subjects, of whom 18 are expected to have a SARS-CoV-2 negative serology before the trial start, will provide a reasonable number in the placebo group to differentiate between each of the age groups receiving CVnCoV individually and all subjects on a dose level versus all placebo recipients.

Despite the small sample size for the placebo group within a dose level, a pooled within-trial analysis of all placebo recipients could provide a sufficient number to assess differences between CVnCoV and placebo recipients by providing anchoring information on 'no dose' for regression analyses. With the given number, an exploratory t-test might be conducted assuming a large vaccination effect, which cannot be quantified yet. As the effect is unknown since this is the FIH trial, no assumptions and power analyses were conducted. This trial will however allow to generate a hypothesis for the Phase 2/3 trials.

Table 7 Distribution of subjects

	Subjects with no history of COVID-19		**Subjects with SARS-Cov-2 positive serology**	
	CVnCoV	**Placebo**	**CVnCoV**	**Placebo**
2/4/8µg: 18-40 years	20	9	4	3
2/4/8µg: 41-60 years	20	9	4	3
2/4/8µg: all age groups	40	18	8	6

In addition, even in the absence of statistical power, the inclusion of blinding and placebo subjects can reduce biases in AE reporting occurring in open-label trials.

10.2 Populations for Analyses

Safety Set:

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

The ***dose-determining set 1 (DDS-1)*** will consist of the first 4 subjects in a dose level of the safety set, who have either experienced Grade 3 adverse reactions or SAEs considered as related to the trial vaccine according to the Investigator at any time during the first 24 hours, or completed the 24-hour observation period without experiencing Grade 3 adverse reactions or SAEs considered as related to the trial vaccine according to the Investigator. The DDS-1 will be used for the first dose expansion decision at a particular dose level. The minimum vaccination and safety evaluation requirements will have been met if the subject has received the planned dose of CVnCoV, has been observed for at least 24 hours following the first vaccine administration and has completed the required safety evaluation. Subjects who do not meet these requirements will be regarded as ineligible for inclusion in the dose-determining set. Since DDS-1 is only used during dose escalation, DDS-1 is not reported in the tables but Grade 3 adverse reactions and SAEs considered as related to the trial vaccine according to the Investigator used for the analyses are marked in the listings.

The ***dose-determining set 2 (DDS-2)*** will consist of all subjects in the safety set, who have either experienced Grade 3 adverse reactions or SAEs considered as related to the trial vaccine according to the Investigator at any time during the first 60 hours, or completed the 60-hour observation period without experiencing Grade 3 adverse reactions or SAEs considered as related to the trial vaccine according to the Investigator. The DDS-2 set will be used for dose escalation decisions and for decisions to continue enrollment after the 60-hour safety reviews.

Immunogenicity Set:

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

10.3 Statistical Analyses

10.3.1 General Considerations

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

A statistical analysis plan (SAP) will be prepared and finalized at the latest prior to database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all trial objectives and the handling of missing data.

Data from this trial may be pooled with data from potential follow-up trials, e.g. in different age groups.

10.3.2 Demographic, Medical History and Other Baseline Characteristics

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

10.3.3 Trial Vaccine Administration

The administrations of CVnCoV or placebo 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 assumption is that the rate of subjects with Grade 3 adverse reactions will be similar in subjects independent of baseline serology status (seronegative or seropositive) and therefore similar in subjects with no history of COVID-19 disease and subjects with SARS-CoV-2 positive serology. Both groups will be analyzed together for the primary analysis of Grade 3 adverse reactions. Additional subgroup analyses will be performed for subjects retrospectively SARS-CoV-2 seronegative at baseline and subjects retrospectively SARS-CoV-2 seropositive at baseline.

An adaptive Bayesian logistic regression model (BLRM) guided by the escalation with overdose control (EWOC) principle will be used for the dose escalation while decisions of dose level expansion in the sentinel groups of 4 subjects is based on a maximum number of 2 subjects with Grade 3 adverse reactions. Of note, dose escalation can also not proceed if any SAE considered as related to the trial vaccine according to the Investigator occurs. The use of Bayesian response adaptive models for Phase 1 studies has been advocated by the EMA adopted guideline on small populations (EMA, 2006) and by Rogatko *et al.*, 2007 [37] and is one of the key elements of the FDA's Critical Path Initiative.

A modified 2-parameter BLRM will be used for dose escalation [38]. Standardized doses will be used such that one of the doses (d*) equals 1, e.g., doses are rescaled as d/d*. Consequently, α is equal to the odds of the probability of intolerance at d*. All information currently available about the dose-adverse reaction relationship of CVnCoV is summarized in a prior distribution. This prior distribution is then updated after each group of subjects with all of the adverse reactions data available in the safety set from the current trial. Once updated, the distribution summarizes the probability that the true rate of adverse reactions for each dose lies in the following categories:

- 0% to <33%: targeted tolerance; and
- ≥33% to 100%: intolerance.

The EWOC principle mandates that any dose of CVnCoV that has more than a 50% chance of being in the intolerance category is not considered for the next dose administrations [38, 39]. A clinical synthesis of the available safety and reactogenicity information (including adverse reactions that are not Grade 3 adverse reactions), laboratory values and, if available, immune response information as well as the recommendations from the Bayesian model and the iSRC/DSMB will be used to determine the dose level(s) for the next group at a dose-escalation teleconference. In any case where there is a change in dose level to be administered to the next enrolled subjects, a new model will be defined using a Meta-Analytic-Predictive prior, based on the observed data.

The frequency of Grade 3 adverse reactions and SAEs considered as related to the trial vaccine according to the Investigator will be tabulated by dose level after 24 hours and 60 hours post-vaccination and information about the Grade 3 adverse reactions and SAEs considered as related to the trial vaccine according to the Investigator will be listed by dose level.

Bayesian Logistic Regression Model

The objective of the design is to determine the highest dose with less than 50% risk of a true Grade 3 adverse reaction rate being equal to or above 33%. The dose escalation will be guided by a modified Bayesian 2-parameter logistic regression model with overdose control.

The model is formulated as follows:

$\text{logit}(p(d)) = \log(\alpha) + \beta * \log(d/d^*)$,

where $\text{logit}(p) = \log(p/(1-p))$. $p(d)$ represents the probability of having a Grade 3 adverse reaction in the first 24 hours at dose d, $d^* = 8\mu g$ is the reference dose, allowing for the interpretation of α as the odds of an adverse reaction at dose d^*, and $\theta = (\log(\alpha), \log(\beta))$ with $\alpha, \beta > 0$ is the parameter vector of the model.

Since a Bayesian approach is applied, a prior distribution $\pi(\theta)$ for the unknown parameter vector θ needs to be specified. This prior distribution will be specified as a multivariate normal distribution, i.e.,

$\pi(\theta) = MVN(\mu, \Sigma)$

the multivariate normal distribution with mean vector μ and covariance matrix Σ, with

$$\Sigma_i = \begin{pmatrix} \sigma_{i,11}^2 & \sigma_{i,11}\sigma_{i,22}\rho_i \\ \sigma_{i,11}\sigma_{i,22}\rho_i & \sigma_{i,22}^2 \end{pmatrix}$$

Prior derivation

Since no prior information is available, the uncertainty about the dose-tolerance relationship is expressed by a mixture distribution composed of a main component (*a priori* assuming 10% and 20% adverse reaction probabilities at 2µg and 8µg, respectively), a low tox (*a priori* assuming 5% and 15% adverse reaction probabilities at 2µg and 8µg, respectively) and a high tox component (*a priori* assuming 25% and 50% adverse reaction probabilities at 2µg and 8µg, respectively). All mixture components are attached with high uncertainty expressed by unit variances of the coefficients. A summary of the prior probabilities of Grade 3 adverse reactions at different doses, as well as the corresponding probability of targeted and overdosing, are shown in Table 9. Graphically, the prior medians with accompanying 95% credible intervals are shown in Figure 3. The uncertainty around the medians is large, showing the low amount of in-men information this prior provides.

Table 8 Summary of prior distribution

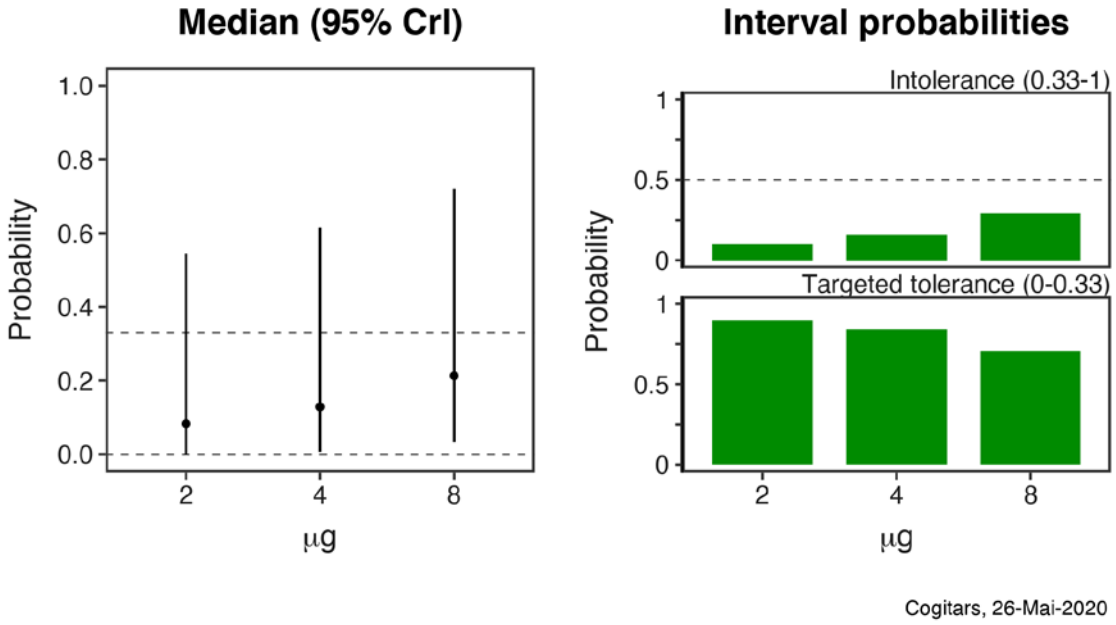
Prior Component	Mixture Weight	Mean Vector	STD Vector	Correlation
Main	0.8	-1.386	1	0
		-0.536	1	
Low tox	0.1	-1.735	1	0
		-0.136	1	
High tox	0.1	0.000	1	0
		-0.233	1	
		-0.761	1	

Table 9 Prior probabilities of Grade 3 adverse reaction at selected doses

Dose (µg)	Probability of true adverse reaction rate in		Mean	STD	Quantiles		
	[0-0.33)	[0.33-1]			2.5%	50%	97.5%
2	0.898	0.102	0.133	0.145	0	0.083	0.545
4	0.841	0.159	0.179	0.161	0.007	0.128	0.615
8	0.708	0.292	0.26	0.185	0.034	0.213	0.721

Doses in bold type meet the overdose criterion, P(overdose) < 0.20.
* STD = standard deviation.

Figure 3 Prior medians and 95% credibility intervals



The highest acceptable dose may be considered reached if both of the following criteria is fulfilled:

1. The posterior probability of the true Grade 3 adverse reaction rate in the target interval [0%-33%) is at least 50% and the probability of being above the target is below 50%.
2. At least 12 subjects have been vaccinated with this dose level.

Statistical model assessment

The model was assessed using 2 different metrics:

1. **Hypothetical data scenarios:** For various potential data constellations as they could occur in the actual trial, the maximal next doses as allowed by the model and by the 200% escalation limit are investigated. Data scenarios thus provide a way to assess the “on-trial” behavior of the model.
2. **Simulated operating characteristics:** These illustrate for different assumed true dose-tolerance relationships, how often a correct dose would be declared as highest acceptable dose by the model. They are a way to assess the “long-run” behavior of the model.

In summary, the model showed very good behavior as assessed by these metrics. More details can be found in Appendix 6.

10.3.5.2 Descriptive Safety Analysis

The safety measurements will include:

1. AEs (type, intensity, frequency and relationship to trial vaccination), i.e., incidence and severity of AEs for both solicited local (injection-site pain, redness, swelling, and itching) and systemic events (fever, headache, fatigue, chills, myalgia, arthralgia, nausea/vomiting and diarrhea) occurring on the day of vaccination and the following 7 days) and unsolicited events (occurring on the day of vaccination and the following 28 days).
2. SAEs and AESIs throughout the trial.

The descriptive safety analyses will be performed for all subjects, for subjects retrospectively SARS-CoV-2 seronegative at baseline, and for subjects retrospectively SARS-CoV-2 seropositive at baseline.

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

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

Unsolicited AEs: Unsolicited AEs, SAEs and AESIs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) by System Organ Class (SOC) and Preferred Term (PT). The frequency and percentage of subjects reporting these events will be tabulated at the SOC and PT levels for each dose level and dose. 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

10.3.6 Secondary and Exploratory Analysis

Descriptive statistics for the secondary and exploratory immunogenicity endpoints will be provided by arm for each dose level. Data will be presented after each vaccine dose.

Individual values and GMT of SARS-CoV-2 spike protein antibody levels and of SARS-CoV-2 neutralizing antibodies, percentages of immune cell populations and cellular responders will be summarized for each dose level in all subjects, in those subjects retrospectively SARS-CoV-2 seronegative at baseline, and in those subjects retrospectively SARS-CoV-2 seropositive at baseline. For subjects who do not get exposed to SARS-CoV-2 before the trial, or during the trial before the applicable sample was collected (as confirmed by a titer increase in antibodies to SARS-CoV-2 N-antigen or a PCR-positive swab during the trial), percentages of subjects seroconverting for SARS-CoV-2 spike-protein antibodies and SARS-CoV-2 neutralizing antibodies will be summarized at each dose level. In addition, for the open-label sentinel groups, levels of cytokines and changes in gene transcripts will be summarized. This analysis may also be performed separately in subjects retrospectively SARS-CoV-2 seronegative at baseline and subjects retrospectively SARS-CoV-2 seropositive at baseline.

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

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

10.3.7 Missing Data

Analysis of vaccination variables will be done on a valid case basis, i.e., for missing observations, no imputation for missing data, such as last observation carried forward, will be applied. For SARS-CoV-2 spike protein antibodies, concentration values marked as below the lower limit of quantification (LLOQ) will be set to 0.5*LLOQ.

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

Currently no replacement of drop-out subjects is foreseen.

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

For start date:

- If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to missing.

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

For resolution date:

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

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

10.3.8 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 heath 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.

Each dose escalation step is considered as an interim analysis (refer to Section 5.2 for the dose escalation steps).

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Electronic Case Report Forms

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

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

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

11.2 Audit and Inspection

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

11.3 Monitoring

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

In accordance with GCP, and regulatory requirements, the trial monitor will carry out source document verification at regular intervals to ensure that the data collected in the eCRF are accurate and reliable. The frequency of monitoring visits will be determined by the rate of subject recruitment.

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

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

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

An electronic medical record may be the source document; however, the 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 EMA.

11.4 Data Management and Coding

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

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

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

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

12 ETHICS

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

12.4 Informed Consent

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

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

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

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

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

13 DATA HANDLING AND RECORD KEEPING

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

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

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

13.1 Data Protection

All information generated in this trial is considered highly confidential and must not be disclosed to any person or entity not directly involved with the trial unless prior written consent is gained from the Sponsor. However, authorized regulatory officials, 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 (acc. to Art. 35 GDPR).

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

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

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

13.2 Clinical Trial Report

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

13.3 Publication Policy

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

14 REFERENCES

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15 APPENDICES

Appendix 1 Responsibilities of the Investigator

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

The Investigator agrees to assume the following responsibilities:

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

Appendix 2 Emergency Procedures

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

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

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

Appendix 3 Safety Laboratory Assessments

The tests detailed in Table 10 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 10 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 COVID-19 Symptoms Log

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

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

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

Appendix 5 Case Definition for COVID-19 Disease

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

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

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

Appendix 6 Statistical Appendix Including Model Performance and Data Scenarios

The model was assessed by 2 different metrics: hypothetical on-trial data scenarios and long-run operating characteristics.

Hypothetical Data Scenarios

Exemplary hypothetical data scenarios are shown in Table 11 to Table 13. These scenarios reflect potential on-trial data constellations and related escalation as allowed by the model and the 200% escalation limit. For each scenario, the probability of overdosing for the current dose, as well as the next potential dose and related probabilities of target-dosing are shown.

These settings illustrate the adaptive behavior of the model which takes into account all observed data from previous dose levels and show a reasonable behavior of the model.

Table 11 **Escalation from 2µg to 4µg:** Escalate to 4µg if not more than 4 in 12 subjects experience a Grade 3 adverse reaction.

Scenario	Dose	#AR	#Pat	CD - P(OD)	Next Dose	ND - P(TD)	ND - P(OD)
1	2	0	12	0.000	4	0.994	0.006
2	2	4	12	0.269	4	0.524	0.476
3	2	5	12	0.496	2	0.504	0.496

CD=Current dose
P(OD)= Probability of overdose
ND= Next dose
P(TD)= Probability of target dose
P(OD)= Probability of overdose

Table 12 **Escalation from 4µg to 8µg:** Only borderline scenarios are provided with maximum number of Grade 3 adverse reactions at 4µg which just allow to escalate. 3 to 4 adverse reactions at 4µg support escalation to 8µg depending on the outcome on previous dose levels.

Scenario	Dose	#AR	#Pat	CD - P(OD)	Next Dose	ND - P(TD)	ND - P(OD)
3	2	0	12				
	4	4	12	0.052	8	0.599	0.401
4	2	1	12				
	4	4	12	0.106	8	0.568	0.432
5	2	2	12				
	4	3	12	0.094	8	0.658	0.342
6	2	3	12				
	4	3	12	0.193	8	0.558	0.442
7	2	4	12				
	4	2	12	0.18	8	0.61	0.39

Table 13 **Confirmation of 8µg:** Scenarios represent the situations with the maximum number of Grade 3 adverse reactions at 8µg which still allow to confirm the highest dose level. 3 to 5 adverse reactions at 8µg support confirmation of safety of 8 µg depending on the outcome in previous dose levels.

Scenario	Dose	#AR	#Pat	CD - P(OD)	Next Dose	ND - P(TD)	ND - P(OD)
8	2	0	12				
	4	0	12				
	8	5	12	0.391	8	0.609	0.391
9	2	0	12				
	4	2	12				
	8	5	12	0.452	8	0.548	0.452
10	2	0	12				
	4	3	12				
	8	4	12	0.328	8	0.672	0.328
11	2	0	12				
	4	4	12				
	8	4	12	0.402	8	0.598	0.402
12	2	1	12				
	4	1	12				
	8	5	12	0.321	8	0.679	0.321
13	2	1	12				
	4	3	12				
	8	5	12	0.497	8	0.503	0.497
14	2	1	12				
	4	4	12				
	8	4	12	0.433	8	0.567	0.433
15	2	2	12				
	4	2	12				
	8	5	12	0.431	8	0.569	0.431
16	2	2	12				
	4	3	12				
	8	4	12	0.375	8	0.625	0.375
17	2	2	12				
	4	4	12				
	8	4	12	0.484	8	0.516	0.484
18	2	3	12				
	4	3	12				
	8	4	12	0.44	8	0.56	0.44

Operating Characteristics

Operating characteristics are a way to assess the long-run behavior of a model. Under an assumed true dose-tolerance curve, metrics such as the probability of recommending a dose with true Grade 3 adverse reaction rate in the target interval can be approximated via simulation. Table 14 describes 3 assumed true scenarios which were used to assess the operating characteristics of the model. These scenarios reflect a wide range of possible cases as follows:

- Scenario 1 (P): aligned with prior means

- Scenario 2 (H): high-intolerance scenario
- Scenario 3 (LH): low-intolerance followed by high-intolerance

Table 14 Assumed True Dose-Tolerance Scenarios

Scenario				
	Dose	2	4	8
1(P)	P(Grade 3 adverse reactions)	**0.13**	**0.18**	**0.26**
2(H)		**0.30**	0.50	0.60
3(LH)		**0.15**	**0.30**	0.45

Bold numbers indicate true adverse reaction rates in the target interval [0-0.33).

For each of these scenarios, 500 trials were simulated. It was then assessed how often a dose was declared safe with true Grade 3 adverse reaction rate in the targeted or over-dose range. Furthermore, the average, minimum and maximum number of subjects per trial and the average number of Grade 3 adverse reactions per trial are reported. Results are shown in Table 15.

Table 15 Hypothetical Data Scenarios

Scenario	% of trials recommending a dose with true Grade 3 adverse reaction rate in		Stopped	# Subjects	# Grade 3 adverse reactions
	Target dose	Overdose	% of trials	Mean (Min - Max)	Mean (Min - Max)
1 (P)	98.2	0	1.8	33.58 (4 - 36)	6.21 (0 - 11)
2 (H)	56.4	21	22.6	18.79 (4 - 36)	7.18 (3 - 15)
3 (LH)	74.2	24	1.8	28.75 (4 - 36)	7.66 (3 - 13)

In Scenario 1, which reflects the case that the true dose-tolerance relationship is aligned with prior means, 98.2% of the simulated trials declared a dose as safe with true Grade 3 adverse reaction rate in the targeted dose range, while 1.8% of the simulated trials were stopped without declaring a dose to be safe.

In Scenario 2 (high-intolerance scenario), the starting dose has already 30% probability of observing at least 1 Grade 3 adverse reaction at the first dose level. This contributes to the increased percentage of 22.6% of all simulated trials for which the trial is stopped since none of the doses is considered tolerable anymore. This is an expected situation for a high-intolerance scenario. Despite the high intolerance probabilities assumed, only 21% of the simulated trials declared a dose safe with true Grade 3 adverse reaction rate in the overdose range.

Scenario 3, 74.2% of the simulated trials declared a dose safe with true Grade 3 adverse reaction rate in the targeted dose range and in only 1.8% the trial was stopped, while in 24% of the trials, a safe dose in the overdose range was declared.

The mean subject numbers ranged from 18.79 subjects (high scenario) to 33.58 subjects (prior means scenario) and the maximum number of subjects was 36. Mean numbers of grade 3 ARs ranged from 6.21 to 7.66.

In summary, the operating characteristics demonstrate a good precision of the highest acceptable dose determination.

Appendix 7 Trial Governance Considerations

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

Appendix 8 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 9 Potential Immune-Mediated Diseases

Current list of pIMDs:

Gastrointestinal disorders:

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

Liver disorders:

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

Metabolic diseases:

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

Musculoskeletal disorders:

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

Neuro-inflammatory disorders:

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

Skin disorders:

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

Vasculitides:

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

Others:

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

Appendix 10 Adverse Events of Special Interest for SARS-CoV-2 Vaccines

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

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

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

Cardiac disorders:

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

Hematological disorders:
- o Thrombocytopenia

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

Renal disorders:
- o Acute kidney injury

Gastrointestinal disorders
- o Liver injury

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

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

Other:
- o Serious local/systemic AR following immunization

Appendix 11 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 one of two 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 [36]. **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 one 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 9.2.1. • 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 CRF extends from the time the subject gives informed consent until the end of the trial, for the period described in Section 9.2.1. • 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 12 Biological Samples and Record Retention

Biological Samples Retention and Destruction

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

Retention of Trial Records

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

Appendix 13 Protocol Amendment History

The trial was initiated using protocol version 2.0; changes made between versions 1.0 and 2.0 are therefore not listed here.

Protocol version 3.0: 24 July 2020
This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

None of the below changes affect the safety and well-being of subjects; the benefit-risk ratio remains favorable. The DSMB for this trial has determined that the dose-levels evaluated thus far have shown an acceptable safety/reactogenicity profile.

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
Title	Addition of “COVID-19” at start of title	Request of Competent Authority
Throughout	Addition of details for dose escalation to 12, 16 and/or 20µg	To increase the dose to >8µg based on safety and available immunogenicity data after iSRC and DSMB review, and not only after immunogenicity data from the second dose is available.
Synopsis, Schedule of Assessments, 5.1. Overall Design, 9.1.1.1. Pre-vaccination Procedures and 9.4. Laboratory Testing for COVID-19 Disease	Addition of the possibility to perform site-specific diagnostics prior to enrollment to test subjects’ serological status also in the observer-blind placebo-controlled part of the trial	To allow the sites to conduct this test to identify subjects with SARS-CoV-2 positive serology as part of the protocol
Synopsis and 5.2. Dose Escalation Steps	Post-vaccination observation for the first subject vaccinated with CV-nCoV 2µg was extended from “until midnight” to “for 24 hours”	Request of Ethical Committee

Section # and Name	Description of Change	Brief Rationale
Synopsis and 6.1. Inclusion Criteria	Addition of the following to criterion 4: Body mass index (BMI) ≥18.0 and ≤30.0kg/m^2 *(≥18.0 and ≤32.0kg/m^2 for subjects with SARS-CoV-2 positive serology)*.	To facilitate recruitment of subjects with SARS-CoV-2 positive serology, who are only recruited after evaluation of reactogenicity/safety of seronegative sentinel subjects
Synopsis and 6.2. Exclusion Criteria	Addition of the following to criterion 7: Any treatment with immunosuppressants or other immune-modifying drugs (including, but not limited to, corticosteroids, biologicals and Methotrexate) within 6 months prior to the administration of the trial vaccine or planned use during the trial, with the exception of topically-applied steroids. *Corticosteroids used in the context of COVID-19 disease of subjects with SARS-CoV-2 are not exclusionary.*	To facilitate recruitment of subjects with SARS-CoV-2 positive serology, who are only recruited after evaluation of reactogenicity/safety of seronegative sentinel subjects. Those subjects may have had COVID-19 disease and may have received corticosteroids as part of the treatment. This should not lead to exclusion
Synopsis and 6.2. Exclusion Criteria	Addition of the following to criterion 11: Any known allergy, including allergy to any component of CVnCoV or aminoglycoside antibiotics. *A history of hay fever or seasonal allergies (pollinosis) that does not require current treatment (e.g., anti-histamines) during the vaccination period (1 month before first vaccination until 1 month after last vaccination) is not exclusionary*.	To facilitate recruitment. Seasonal allergies are not seen as a risk factor, in particular if not requiring treatment

Section # and Name	Description of Change	Brief Rationale
Synopsis and 6.2. Exclusion Criteria	Addition of the following to criterion 17: Respiratory disease with clinically significant dyspnea in the last 5 years *(except COVID-19 disease in subjects with SARS-CoV-2 positive serology)*.	To facilitate recruitment of subjects with SARS-CoV-2 positive serology, who are only recruited after evaluation of reactogenicity/safety of seronegative sentinel subjects. Those subjects may have had COVID-19 disease which should not exclude them from participation in the trial
8. Discontinuation/ Withdrawal Criteria	Addition of the following text "Assessments of solicited AEs and associated phone calls 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 discontinued trial vaccine administration."	Only relevant visits need to be conducted for any subjects who prematurely discontinued trial vaccine administration
9.2.3. Safety Laboratory Assessments	Removed reference to the Common Terminology Criteria for Adverse Events	The FDA toxicity grading scale will be used for grading laboratory data
Appendix 5 Case Definition for COVID-19 Disease	Update of the case definition for COVID-19 disease	To comply with the new Coalition for Epidemic Preparedness Innovations definition
Throughout	Removal of the requirement for "known" SARS-CoV-2 positive serology	To facilitate recruitment of subjects with SARS-CoV-2 positive serology
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized