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STUDY PROTOCOL

A multi-center phase Ib trial to assess the safety, tolerability and immunogenicity of the candidate vaccine **MVA-SARS-2-ST** in adults

EudraCT No.	2021-000548-23
Protocol No.	UKE-SARS-COV-2-ST
Registration No.	NCT04895449
Version/Date	Version 3.0, 05-OCT-2021
Sponsor	University Medical Center Hamburg-Eppendorf Martinistr. 52 20246 Hamburg, Germany
Coordinating investigator	Prof. Marylyn M. Addo, MD, PhD, MSc, DTM&H University Medical Center Hamburg-Eppendorf I. Department of Medicine Martinistr. 52 20246 Hamburg, Germany [redacted]

SIGNATURES

Sponsor Signature

This protocol has been approved by University Medical Center Hamburg-Eppendorf.

B. Schwappach-Pignataro — 06.10.2021

Sponsor signature — Date

Prof. Dr. Blanche Schwappach-Pignataro
Dekanin und Mitglied im UKE-Vorstand

Sponsor name

Coordinating investigator Signature

I hereby confirm that I have acknowledged the protocol and agree to conduct the clinical trial in compliance with the protocol.

Coordinating investigator signature — Date

Coordinating investigator name

Statistician signature

I hereby confirm that I have acknowledged the protocol and agree to conduct the clinical trial in compliance with the protocol.

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Coordinating investigator signature

7. Oct 2021

Date

Prof. Dr. M. Addo

Coordinating investigator name

Statistician signature

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Coordinating investigator name	

Statistician signature

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Antonia Zapf	06 Oct 2021
Statistician signature	Date
Prof. Dr. Antonia Zapf	
Statistician name	

Summary of Changes

Summary of changes since last version of protocol (protocol version 1.0 to version 2.0)		
Amendment Number	**Date of Amendment**	**Section Affected by Change**
01	25-JUN-2021	Synopsis
Brief description of change: Update of timelines, secondary objectives and endpoints adapted, staggered approach adapted, responsibility of LSB added, confirmatory PCR test added in case of positive SARS-CoV-2 antigen test.		
01	25-JUN-2021	8.2/ 8.2.1
Brief description of change: Secondary objectives and endpoints adapted.		
01	25-JUN-2021	9.2
Brief description of change: Seronegative status of participants in phase Ib and phase IIa part A clarified.		
01	25-JUN-2021	9.3.2
Brief description of change: Exclusion 6 modified (seronegative status to be confirmed by SARS-CoV-2 antibody test at screening).		
01	25-JUN-2021	9.4.1
Brief description of change: Staggered approach adapted (3rd group).		
01	25-JUN-2021	9.4.6
Brief description of change: Vaccination with (conditionally) licensed COVID-19 vaccine permitted 6 weeks after 2nd vaccination.		
01	25-JUN-2021	9.4.7.3 & 9.4.7.4 & 9.7.2.9
Brief description of change: SARS-CoV-2 antibody test at screening added for phase Ib and phase IIa part A. Confirmatory PCR test added in case of positive SARS-CoV-2 antigen test.		
01	25-JUN-2021	9.11.1.3.1
Brief description of change: Handling of missing data added.		
01	25-JUN-2021	11
Brief description of change: LSB for Phase Ib added. Criteria for dose selection for phase IIa added.		

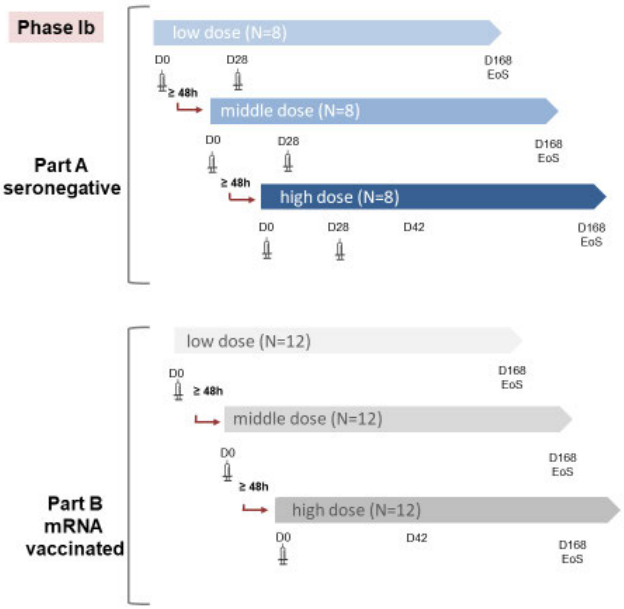
Summary of changes since last version of protocol (protocol version 2.0 to version 3.0)		
Amendment Number	**Date of Amendment**	**Section Affected by Change**
02	05-OCT-2021	Title Page
Brief description of change: Registration no. was added, Titel adapted.		
02	05-OCT-2021	Synopsis
Brief description of change:		

Part B with mRNA vaccinated subjects added and therefore update of primary and secondary objectives, inclusion and exclusion criteria, administered doses, duration of treatment. Phase IIa part of the study was deleted.		
02	05-OCT-2021	Study schedules
Brief description of change: Footnote m added to all parts: COVID-19 antigen test results may be used if test was performed within 4h before screening. Study schedule Part B added. Detailed time and events: Update of details for assessments at time point 0 hours after dose administration.		
02	05-OCT-2021	7.1 Background information and rationale
Brief description of change: Update of numbers of infections and cases of death.		
02	05-OCT-2021	7.4 Risk-benefit considerations
Brief description of change: Amount of blood collected from participants of Part B added and reference to Phase IIa deleted.		
02	05-OCT-2021	8.1 Primary objective
Brief description of change: Alignment of wording of primary objective in Part A with exclusion criteria: Subjects are SARS-CoV-2 seronegative. Primary objective for Part B added. Reference to Phase IIa deleted.		
02	05-OCT-2021	8.2 Secondary objectives
Brief description of change: Alignment of wording of secondary objectives in Part A with exclusion criteria: Subjects are SARS-CoV-2 seronegative. Secondary objective for Part B added. Reference to Phase IIa deleted.		
02	05-OCT-2021	9.1 Overall study design and plan-description
Brief description of change: Update of numbers of participants: Part A reduced to 8 subjects in each dose level, B with 12 subjects in each dose level. Reference to Phase IIa deleted. Figure 1 *Overall study design* updated accordingly.		
02	05-OCT-2021	9.2 Discussion of study design, including the choice of control groups
Brief description of change: Study population of Part B added. Reference to Phase IIa deleted.		
02	05-OCT-2021	9.3 Selection of study population
Brief description of change: Study population of Part B added. Reference to Phase IIa deleted.		
02	05-OCT-2021	9.3.1 Inclusion criteria
Brief description of change: Inclusion criterion for Part B added. Reference to Phase IIa deleted.		
02	05-OCT-2021	9.3.2 Exclusion criteria
Brief description of change: Update for distinction between Part A and Part B. Reference to Phase IIa deleted.		
02	05-OCT-2021	9.3.3 Reproductive potential
Brief description of change: Contraception requirements not applicable for females with exclusively same-sex sex partners.		

02	05-OCT-2021	9.4.1 Treatments administered
Brief description of change: Part B added. Reference to Phase IIa deleted.		
02	05-OCT-2021	9.4.7.2 Participant identification
Brief description of change: Numbering for Part B added. Clarification added: Assignment to Part A and Part B will be in parallel.		
02	05-OCT-2021	9.4.5 Blinding
Brief description of change: Reference to unblinding was deleted.		
02	05-OCT-2021	9.4.7.3 Screening, confinement and regular visits
Brief description of change: Updated according to the study schedules.		
02	05-OCT-2021	9.7.2.12 Reactogenicity
Brief description of change: Instructions for use of subject diary corrected.		
02	05-OCT-2021	9.11 Statistical methods planned in the protocol and determination of sample size
Brief description of change: Adaption of the Part B and deletion of the Phase IIa.		
02	05-OCT-2021	11 Safety Steering Committee (SSC)
Brief description of change: Safety steering committee instead of LSB/DSMB added. Section was renamed.		

1 SYNOPSIS

Name of sponsor/company: University Medical Center Hamburg-Eppendorf	**Individual study table referring to part of the dossier**	**(For national authority use only)**
Name of finished product: MVA-SARS-2-ST	**Volume:**	
Name of active ingredient: MVA-SARS-2-ST	**Page:**	
Title of study:	A multi-center, phase Ib trial to assess the safety, tolerability and immunogenicity of the candidate vaccine **MVA-SARS-2-ST** in adults	
Coordinating investigator	Prof. Dr. med. M. Addo	
Sponsor	University Medical Center Hamburg-Eppendorf	
CRO	CTC North GmbH & Co. KG, Hamburg	
Study centers:	2 to 5 study sites in Germany	
Protocol-No.	UKE-SARS-COV-2-ST	
EudraCT-No.	2021-000548-23	
Study period	Period will last for approx. 7 months per participant (screening to follow-up). Study Timelines: Total study duration (FPFV to LPLV) approx. 10 months FPFV JUL 2021 LPFV NOV 2021 LPLV MAY 2022	
Phase of development:	Phase Ib	
Objectives: **Primary objectives**	• To evaluate the safety, tolerability and reactogenicity of two intramuscular dose administrations of three dose levels of the candidate MVA-SARS-2-ST vaccine in healthy SARS-CoV-2 seronegative adults aged 18-64 years (Part A). • To evaluate the safety, tolerability and reactogenicity of one intramuscular dose administration of three dose levels of the candidate MVA-SARS-2-ST vaccine in healthy adults previously vaccinated against COVID-19 aged 18-64 years (Part B). •	
Secondary objectives	• To evaluate SARS-CoV-2-S1-binding and SARS-CoV-2 neutralizing antibodies in healthy SARS-CoV-2 seronegative adults induced by three dose levels after two administrations of MVA-SARS-2-ST vaccine (Part A). • To evaluate SARS-CoV-2-S1-binding and SARS-CoV-2 neutralizing antibodies in healthy adults vaccinated against COVID-19 induced by three dose levels after one administration of MVA-SARS-2-ST vaccine (Part B).	

Exploratory objectives	• To investigate Th1 and Th2 immune responses following vaccination. • To investigate the occurrence of antibody-dependent enhancement and vaccine-associated enhanced respiratory disease. • To identify and immunologically characterize cases of COVID-19. • To evaluate the rate of natural infection of SARS-CoV-2 during the clinical trial by monitoring antibodies against SARS-CoV-2 N protein. • To investigate sex differences in immunity to MVA-SARS-2-ST vaccination. • To investigate age-related immune responses to MVA-SARS-2-ST vaccination. • To examine vaccine-induced humoral immune responses and antibody functions, including vector-immunity, neutralizing and non-neutralizing antibody functions. • To evaluate MVA-SARS-2-ST-specific cellular immune responses after administration of MVA-SARS-2-ST vaccine. • To evaluate MVA-SARS-2-ST-induced B- and T-cell memory responses. • To evaluate innate immune responses induced by MVA-SARS-2-ST vaccine. • To evaluate early gene expression signatures induced by MVA-SARS-2-ST vaccine. • To evaluate pre-existing humoral and cellular immunity to coronaviruses. • To identify potential biomarkers and gene signatures of innate immune responses to MVA-SARS-2-ST vaccine and their correlation to dose, reactogenicity, and immune response.
Study design	Multi-center, phase Ib study, open-label, 2 parts to evaluate SARS-CoV-2 seronegative and previously SARS-CoV-2-vaccinated individuals. 

Methodology:	This will be a phase Ib, multi-center study in approximately 60 adults aged 18 years and older. PART A (24 seronegative subjects) • low dose ≥ 1 x 10^7 IU (N=8) • middle dose ≥ 5 x 10^7 IU (N=8) • high dose ≥ 1 x 10^8 IU (N=8) PART B (36 previously vaccinated subjects) • low dose ≥ 1 x 10^7 IU (N=12) • middle dose ≥ 5 x 10^7 IU (N=12) • high dose ≥ 1 x 10^8 IU (N=12) For safety reasons dose administration in each dose level for both Parts will be performed in at least three groups. 1st participant of each dose level will be vaccinated 24 hours before the next 3 participants and the rest of the participants will be vaccinated 24 hours after the second group of the respective dose level. Dose levels will commence in a staggered fashion. The next dose level of each Part will start at least 48 hours after all participants of the prior dose level of the respective Part have been vaccinated. Each participant will receive two single injections, 28 days apart (Part A) or one single injection (Part B). All participants will be followed up for safety until D 168. Part A and Part B will commence in parallel.
Number of participants:	60 Homogeneous sex distribution of no less than 25% of one sex is targeted.
Main criteria for inclusion:	**Key inclusion criteria** 1. Written informed consent. 2. Healthy male and female adults aged 18 – 64 at time of informed consent. 3. Body mass index 18.5 - 32.0 kg/m^2 and weight > 50 kg at screening. 4. Female participants: non-pregnant, non-lactating with negative pregnancy test. 5. Females who agree to comply with the applicable contraceptive requirements of the protocol. 6. ≥ 6 months fully vaccinated with a (conditionally) licensed mRNA vaccine against COVID-19 (Part B only).

	Key exclusion criteria 1. Receipt of any vaccine from 4 weeks prior to each trial vaccination (8 weeks for live vaccines) to 6 weeks after each trial vaccination. 2. Previous rMVA immunization. 3. Previous immunization with investigational vaccine against COVID-19. 4. Previous immunization with EUA/conditionally licensed vaccine against COVID-19 (not applicable to part B). 5. Evidence of active SARS-CoV-2 infection (positive SARS-CoV-2 antigen test followed by a confirmatory positive PCR test). 6. Known allergy to the components of the MVA-SARS-2-ST vaccine product or history of life-threatening reactions to vaccine containing the same substances. 7. Known history of anaphylaxis to vaccination or any allergy likely to be exacerbated by any component of the trial vaccines. 8. Evidence in the participant's medical history or in the medical examination that might influence either the safety of the participant or the absorption, distribution, metabolism or excretion of the investigational product. 9. Clinically relevant findings in ECG or significant thromboembolic events in medical history. 10. Any confirmed or suspected immunosuppressive or immunodeficient condition, cytotoxic therapy in the previous 5 years, and/or uncontrolled diabetes (HbA1c ≥ 7.0). 11. Any known chronic or active neurologic disorder, including seizures and epilepsy, excluding a single febrile seizure as a child.
Test product, dose and mode of administration:	**Test product:** MVA-SARS-2-ST **Dose:** Part A: Participants will receive 2 single doses of ≥ $1x10^7$ IU, ≥ $5 x 10^7$ IU, or ≥ $1 x 10^8$ IU MVA-SARS-2-ST in 0.5 mL (total injected volume 1 mL). Part B: Participants will receive 1 single dose of ≥ $1x10^7$ IU, ≥ $5 x 10^7$ IU, or ≥ $1 x 10^8$ IU MVA-SARS-2-ST in 0.5 mL (total injected volume 0.5 mL). Dose administration on day 0 (Part A and B) and day 28 (Part A) for each participant. **Mode of administration:** Intramuscular (i.m.)
Duration of treatment:	Part A: Participants will receive two single vaccine injections. First injection on day 0; second injection on day 28. Part B: Participants will receive one single vaccine injection on day 0.
Reference therapy, dose and mode of administration, batch number:	None

Criteria for evaluation:	**Primary endpoints:** The nature, frequency and severity of adverse events associated with MVA-SARS-2-ST vaccine will be collected and measured as follows: • Occurrence of solicited local reactogenicity signs and symptoms for 7 days after vaccination. • Occurrence of solicited systemic reactogenicity signs and symptoms for 7 days after vaccination. • Occurrence of unsolicited adverse events (AE) for 28 days after vaccination. • Change from baseline of safety laboratory measures. • Occurrence of serious adverse events (SAE) throughout the study period. **Secondary endpoints:** Immunogenicity • Humoral immunity: Amount of anti-SARS-CoV-2-S1-binding antibodies as measured by ELISA and detection of antibodies that neutralize SARS-CoV-2 (Part A & B). • Percentage of participants who seroconverted: The seroconversion measured by ELISA is defined as the detection of SARS-CoV-2-S1-specific antibodies if the baseline value was negative, or as an increase in the antibody titer by a factor of 4 or more compared to the baseline value (Part A). • Percentage of participants who showed an increase of the level of binding and neutralizing antibodies to baseline (Part B).
Safety:	Safety data (AEs, SAEs and vital signs) will be collected at all study visits. Laboratory safety tests (biochemistry, hematology and dipstick urinalysis) will be performed at screening, pre-dose and at defined study follow-up visit. It is planned to enroll all participants in a longitudinal follow-up study after end of study and have an additional 6-month follow-up for safety assessment.
Statistical methods:	Metric data will be summarized using descriptive statistics (number, mean, standard deviation, minimum, Q25, median, Q75 and maximum). Categorical data will be summarized by using frequency Tables (frequency and percent). Data will be analyzed in the entire study population as well as in subgroups. It is not planned to test any hypotheses in a confirmatory sense.

2 STUDY SCHEDULES

Table 1 Study schedule Part A

Phase of study	SCR	Ambulatory visits												End of study
Study visit (v)	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Study day	**-28 – -1**	**-1[i]**	**0**	**1**	**3**	**7 (±1)**	**14 (±3)**	**28**	**29**	**35 (±1)**	**42 (±3)**	**56 (±7)**	**84 (±7)**	**168 (±14)**
Study months			**0**					**1**				**2**	**3**	**6**
Informed consent	√													
I/E criteria	√		√[e,k]											
Medical history & demographics	√		√[e,g]											
Physical examination	√		√[a,e]					√[a,e]						√
Height and weight	√													√[j]
Vital signs	√		√[b]	√	√	√	√	√[b]	√	√	√	√	√	√
12-lead ECG	√													
COVID-19 antigen test	√ [m]		√	if applicable based on COVID-19 case definition[h]				√	if applicable based on COVID-19 case definition [h]					
PCR for SARS-CoV-2 as required	---------- continuously[h] ----------													
Vaccination			√[d]					√[d]						
Injection site & systemic events/ reactions assessment			√[c]	√	√	√	√	√[c]	√	√	√	√	√	√
Temperature	√		√[b]	√	√	√	√	√[b]	√	√	√	√	√	√
Training & dispensing diary			√					√						
Review & collection diary				√	√	√	√	√	√	√	√	√		
Adverse events & concomitant medication			√[c]	√	√	√	√	√[c]	√	√	√	√	√	√
AESI and SAE reporting			---------- continuously ----------											
Safety lab blood (clinical chemistry, hematology)	√	√[f,i]		√	√	√		√[e]	√	√	√	√	√	√

Phase of study	SCR	Ambulatory visits												End of study
Study visit (v)	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Study day	**-28 – -1**	**-1[i]**	**0**	**1**	**3**	**7 (±1)**	**14 (±3)**	**28**	**29**	**35 (±1)**	**42 (±3)**	**56 (±7)**	**84 (±7)**	**168 (±14)**
Study months			**0**					**1**				**2**	**3**	**6**
Urine pregnancy test	√													√
Serum pregnancy test		√[f,i]						√[e]						
Urine drug screen	√		√[e]					√[e]						
Safety urinalysis	√	√[f,i]						√[e]						√
HIV/HBV/HCV/SARS-CoV-2 serology	√													
Humoral responses			√[e]			√	√	√[e]		√	√	√	√	√
RNA blood sample			√[e]	√	√	√		√[e]	√	√				
PBMC freezing and plasma aliquots			√[e]	√	√	√	√	√[e]	√	√	√	√	√	√

[a] Symptom-targeted physical examination

[b] Please refer to Table 3 for frequency of vital signs and temperature examinations

[c] Please refer to Table 3 for frequency of adverse events and concomitant medication questioning

[d] Participants will be monitored and evaluated for AEs for at least 1 hour after vaccination and only be discharged if no clinically significant abnormalities, to be judged by an investigator, are measured and no unexpected side effects are observed

[e] Before immunization

[f] Samples do not need to be repeated if screening was performed ≤ 2 days before vaccination

[g] Update of medical history only

[h] When clinically indicated and at the discretion of the investigator

[i] Events can also be performed on day 0 (before immunization)

[j] Only weight

[k] Update only

[m] If COVID-19 antigen test was performed within 4 hours before the screening visit and if the test result is suitable to be used as source data for the clinical trial, e.g. a test done by the study site as part of the hygiene concept, the test does not need to be repeated at screening and the available test results can be used.

Table 2 Study schedule Part B

Phase of study	SCR	Ambulatory visits								End of study
Study visit (v)	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Study day	**-28 – -1**	**-1[i]**	**0**	**1**	**3**	**7 (±1)**	**14 (±3)**	**28 (±2)**	**56 (±7)**	**168 (±14)**
Study months			**0**					**1**	**2**	**6**
Informed consent	√									
I/E Criteria	√		√[e,k]							
Medical History & Demographics	√		√[e,g]							
Physical examination	√		√[a,e]							√
Height and weight	√									√[j]
Vital signs	√		√[b]	√	√	√	√			√
12-lead ECG	√									
COVID-19 antigen test	√[m]		√	if applicable based on COVID-19 case definition [h]						
PCR for SARS-CoV-2 as required	---------- continuously[h] ----------									
Vaccination			√[d]							
Injection site & systemic events/ reactions assessment			√[b]	√	√	√	√			√
Temperature	√		√[b]	√	√	√	√			√
Training & dispensing diary			√							
Review & collection diary				√	√	√	√	√		
Adverse events & concomitant medication			√[c]	√	√	√	√	√	√	√
AESI and SAE reporting			---------- continuously ----------							
Safety lab blood (clinical chemistry, hematology)	√	√[f,i]		√	√	√				√
Urine drug screen	√		√[e]							

Phase of study	SCR	Ambulatory visits								End of study
Study visit (v)	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Study day	**-28 – -1**	**-1[i]**	**0**	**1**	**3**	**7 (±1)**	**14 (±3)**	**28 (±2)**	**56 (±7)**	**168 (±14)**
Study months			**0**					**1**	**2**	**6**
Urine pregnancy test	√									√
Serum pregnancy test		√[f,i]								
Safety urinalysis	√	√[f,i]								√
HIV/HBV/HCV serology	√									
Humoral responses			√[e]			√	√	√	√	√
RNA blood sample[l]			√[e]	√	√	√				
PBMC freezing and plasma aliquots[l]			√[e]	√	√	√	√	√	√	√

[a] Symptom-targeted physical examination

[b] Please refer to Table 3 for frequency of vital signs and temperature examinations

[c] Please refer to Table 3 for frequency of Adverse Events and concomitant medication questioning

[d] Participants will be monitored and evaluated for AEs for at least 1 hour after vaccination and only be discharged if no clinically significant abnormalities, to be judged by the investigator, are measured and no other unexpected side effects are observed

[e] Before immunization

[f] Samples do not need to be repeated if screening was performed ≤ 2 days before vaccination

[g] Update of medical history only

[h] When clinically indicated and at the discretion of the investigator

[i] Events can also be performed on day 0 (before immunization)

[j] Only weight

[k] Update only

[m] If COVID-19 antigen test was performed within 4 hours before the screening visit and if the test result is suitable to be used as source data for the clinical trial, e.g. a test done by the study site as part of the hygiene concept, the test does not need to be repeated at screening and the available test results can be used.

Table 3 Detailed time and events

Study day	Time after dose administration (hours)	Vaccination	Vital signs	Temperature	Adverse events/ con Med	Injection site/ systemic reaction/ Events assessment
0	0[1]	√	√[1]	√[1]	Update Medical History	√ (within 5 minutes after vaccination
0	1 (±15 minutes)		√	√	√	√
28	0[1]	√	√[1]	√[1]	√[1]	√ (within 5 minutes after vaccination
28	1 (±15 minutes)		√	√	√	√

[1]Events must be completed within 30 minutes before vaccination.

3 TABLE OF CONTENTS

3.1 List of Tables

3.2 List of Figures

4 LIST OF ABBREVIATIONS

ADEM	Acute disseminated encephalomyelitis
ADR	Adverse Drug Reaction
AE	Adverse Event
AEFI	Adverse Event Following Immunization
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase Level
ALT	Alanine amino transferase
AST	Aspartate amino transferase
BP	Blood pressure
cm	Centimeter
CoV	Coronavirus
COVID-19	Coronavirus Disease 2019
CRO	Contract Research Organization
CRP	C-reactive protein
CSR	Clinical Study Report
CV	Coefficient of variation
DRM	Data review meeting
EC	Ethics Committee
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EDTA	Ethylene Diamine Tetra-acetic Acid
ELISA	Enzyme-linked Immunosorbent Assay
EliSpot	Enzyme-linked Immunosorbent Spot
ER	Emergency room
EU	European Union
FDA	Food and Drug Administration
FIH	First-in-human
FPFV	First Participant First Visit
GBS	Guillain Barré Syndrome
GCP	Good Clinical Practice
GCP-V	Regulations on the implementation of Good Clinical Practice in the conduct of clinical trials on medicinal products for human use (GCP Verordnung)
GeoCV	Geometric coefficient of variation
GeoM	Geometric mean
GGT	Gamma-glutamyl transferase
gms	grams
H	Hour
HBsAg	HBV surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HD	High Dose

HIV	Human Immunodeficiency Virus
i.m.	Intramuscular
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator site file
IU	Infectious Units
IMP	Investigational Medicinal Product
kg	Kilogram
LD	Low Dose
LDH	Lactate dehydrogenase
LPFV	Last participant first visit
LPLV	Last participant last visit
LSB	Local Safety Board
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MDRD	Creatinine clearance
Mean	Arithmetic mean
Med	Median
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
mg	Milligram
Min	Minute
mL	Milliliter
mmHg	Millimeters of mercury
MVA	Modified Vaccinia Virus Ankara
N	Number
NIBSC	National Institute for Biological Standards and Control
NOAEL	No Observed Adverse Event Level
PBMC	Peripheral Blood Mononuclear Cells
PCR	Polymerase Chain Reaction
PD	Protocol deviation
PFU	Plaque Forming Units
PI	Principal investigator
PR	Pulse rate
PRNT	Plaque Reduction Neutralization Test
PP	Per Protocol
QAU	Quality Assurance Unit
UMR	University Marburg
RBC	Red blood cells
RNA	Ribonucleic acid
RKI	Robert Koch-Institut
rMVA	Recombinant Modified Vaccinia Virus Ankara

SAE	Serious Adverse Event
SAP	Statistical analysis plan
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SCR	Screening
SD	Standard deviation
SOP	Standard Operating Procedure
SPEAC	Safety Platform for Emergency vACcines
SUSAR	Suspected unexpected Serious Adverse Reaction
Th1	T helper cell 1
Th2	T helper cell 2
TMF	Trial Master File
VNT	Virus Neutralization Test
WBC	White blood cells
WHO	World Health Organization
WNL	Within normal limits
WOCBP	Women of Childbearing Potential

5 ETHICS AND LEGAL ASPECTS

5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

This study will be planned and performed in accordance with

- The Declaration of Helsinki in its version of Fortaleza, 2013;
- EU Directive 2001/20/EC;
- EU Directive 2001/83/EC;
- ICH Guideline Good Clinical Practice E6(R2), of 9 November 2016;
- EMA Guideline on clinical evaluation of vaccines
- EMA Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic in its most current version
- Ergänzende Empfehlungen des BfArM und des PEI zur Europäischen Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic in its most current version

and other applicable laws.

5.2 Ethical conduct of the clinical trial

The sponsor authorizes CTC North for all necessary applications.

CTC North will submit all required documents according to local law to the responsible Ethics Committees (EC), as well as the Competent Authorities (CA) for approval. Approval by these authorities must be obtained prior to the start of the study in the respective study sites.

Copies of the original submission and approval documents will be sent to the sponsor and will be included in the Clinical Study Report (CSR). A list of the members of the EC will also be provided with the CSR.

5.3 Participant information and consent

Before any study specific procedures can take place, an investigator will explain to the participants the nature, significance and implications of the clinical trial. He/she will explain all methods, rules of conduct, and any restrictions which may apply. Possible effects and side effects will be discussed. Participants will be informed that they are free to withdraw from the clinical trial at any time, without giving any reason for doing so. They must be able to understand the full implications of their decision.

All participants will date and sign an informed consent form as evidence of consent. The investigator will also date and sign the informed consent form. The participant information sheet and the informed consent form of each participant will be filed in the investigator site file (ISF). A copy of the dated and signed consent form and the information sheet will be handed to participant after signature and before enrollment.

If new information about the vaccine that could be relevant for the willingness to continue participation of the study becomes available the participant will be informed by an investigator.

5.4 Confidentiality

The principal investigator (PI) at each study site must assure that participants' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code (i.e., consisting of an identification number, sex and year of birth) should be recorded on any form or biological sample submitted to the laboratory, sponsor, competent authority or EC. The PI must keep a participant identification log showing codes and names for all participants screened and for all participants enrolled in the trial.

5.5 Insurance

The sponsor is responsible for the appropriate insurance coverage for the participants.

5.6 Publication policy

The sponsor has to publish the result of this study considering applicable requirements of the BMBF. It is at the discretion of the sponsor to lead the publication activities. The trial will be registered at clinicaltrials.gov.

5.7 Qualification of the investigator

The PI and the deputy for each study site fulfill the requirements of applicable national law. Curriculum vitae of both will be filed in the trial master file (TMF).

For conducting the clinical trial, the respective PI may delegate tasks to investigators (or other qualified staff). This is to be documented properly. The PI is responsible for the adequate training and supervision of all delegates. No clinical trial related procedure must be performed by personnel which is not properly trained and delegated.

In the present document the mere term “investigator” refers to the PI or the deputy/deputies or investigators.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Sponsor	University Medical Center Hamburg-Eppendorf Martinistr. 52 20246 Hamburg, Germany
Coordinating investigator	Prof. Marylyn M. Addo, MD, PhD, MSc, DTM&H University Medical Center Hamburg-Eppendorf I. Department of Medicine Division of Infectious Diseases Martinistr. 52, 20246 Hamburg, Germany [redacted] [redacted] [redacted] [redacted]
Medical monitor	Dr. Olaf Degen University Medical Center Hamburg-Eppendorf MVZ Fachbereich Infektiologie Martinistr, 52,20246 Hamburg, Germany [redacted] [redacted] [redacted] [redacted]
CRO	CTC North GmbH & Co. KG at the University Medical Center Hamburg-Eppendorf Martinistr. 64, 20251 Hamburg, Germany
Responsibilities	Project management, regulatory submission, monitoring, data management, safety management
Overall project lead	Dr. Saskia Borregaard [redacted] [redacted] [redacted] [redacted]
Project manager	Laura Kaltenberg [redacted] [redacted] [redacted] [redacted]
Statistics	Prof. Dr. Antonia Zapf Institute of Medical Biometry and Epidemiology University Medical Center Hamburg-Eppendorf Martinistr. 52, 20246 Hamburg, Germany [redacted] [redacted] [redacted] [redacted]

Safety laboratory:
Safety laboratory analysis will be conducted at local laboratory at each involved study site.

Immunogenicity laboratories:

Humoral immunity	**T-cell Immunity and systems vaccinology**
Prof. Dr. Stephan Becker Institute for Virology Philipps University Marburg Hans Meerweinstr. 2 35043 Marburg, Germany	Prof. Dr. Marylyn M. Addo Department of Clinical Immunology of Infectious Diseases Bernhard-Nocht-Institute Bernhard Nocht Str. 74 20357 Hamburg, Germany
Humoral immunity/Vector immunity	**Humoral immunity**
Prof. Dr. Gerd Sutter Institute for Infectious Diseases and Zoonoses Ludwig-Maximilians-University Veterinärstr. 13 80539 Munich, Germany	Prof. Dr. Michael Hölscher Division of Infectious Diseases and Tropical Medicine Ludwig-Maximilians-University Leopoldstr. 5 80802 Munich, Germany
Humoral immunity	**Adaptive immune response**
Dr. Bart Haagmans Department of Viroscience, Ee1720 Erasmus Medical Centre Wytemaweg 80 3015CN Rotterdam, The Netherlands	PD. Dr. rer. nat. Geldmacher Division of Infectious Diseases and Tropical Medicine Klinikum of the University of Munich Leopoldstr. 5 80802 Munich, Germany
Adaptive immune response	**Humoral immunity**
Prof. Dr. Peter Kremsner, Dr. Meral Esen, Dr. Rolf Fendel Institute of Tropical Medicine University of Tübingen Wilhelmstraße 27 72074 Tübingen, Germany	PD Dr. Romans Wölfl Bundeswehr Institute of Microbiology Neuherbergstr. 11 80937 Munich, Germany
Sequencing projects	**Cellular immunity**
Prof. Dr. Andre Franke Institute of Clinical Molecular Biology (IKMB) Kiel University, Christian-Albrechts-Universität zu Kiel Rosalind-Franklin-Str. 12 24105 Kiel, Germany	Prof. Julian Schulze zur Wiesch Center for Internal Medicine University Medical Center Hamburg-Eppendorf Martinistr. 52, 20246 Hamburg, Germany
Humoral immune responses	**Adaptive immune responses**
Dr. Marc Lütgehetmann Center for Diagnostics Institute of Medical Microbiology, Virology and Hygiene University Medical Center Hamburg-Eppendorf Martinistr. 52, 20246 Hamburg, Germany	CEPI Centralised Lab Network European Laboratories/Collaborative Vaccine NEtwork

7 INTRODUCTION

7.1 Background information and rationale

SARS-CoV 2 and the need for a SARS-CoV-2 Vaccine

SARS-CoV-2 first emerged in December 2019 in Wuhan, China and quickly spread over the whole world with currently more than 213 million confirmed cases of primary infection leading to more than 4.4 million deaths in 192 countries [1]. The World Health Organization (WHO) declared the outbreak a “Public Health Emergency of International Concern” on 30th of January 2020 and, only 41 days later, on 11th of March, a pandemic [2].

Coronaviruses (CoV) are a large family of viruses that cause illness ranging from common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). SARS-CoV-2 is the causative agent of coronavirus disease 2019 (COVID-19), which is an infectious respiratory disease. Typical symptoms can include fever, cough, fatigue, shortness of breath, loss of smell and taste and diarrhea [3]. While most cases only report mild symptoms or are even asymptomatic, a severe form of pneumonia including acute respiratory distress syndrome, multi-organ failure, septic shock and blood clots can occur that can lead to death [4]. The overall infection fatality rate is currently estimated to be significantly lower compared to SARS and MERS. SARS-CoV-2 is easily transmitted by human-to-human contact.

MVA-SARS-2-ST represents a replication-deficient vector vaccine built on the recombinant Modified Vaccinia virus Ankara (MVA) platform. A first-in-human (FIH) trial (NCT04569383) with the a predecessor vaccine candidate, MVA-SARS-2-S, which expresses a non-stabilized full-length spike (S) glycoprotein of SARS-CoV-2, started in Hamburg in October 2020 (University Medical Center Hamburg-Eppendorf & CTC North GmbH & Co. KG) (see chapter 7.3). While the interim results of this study show that the vaccinations were well tolerated by subjects in both dose cohorts and no serious adverse events (SAEs) occurred, the immunogenicity analysis, however, showed that humoral immunity was lower than expected and, therefore, suboptimal. Vaccine candidates with pre-fusion-stabilized full-length spike glycoprotein of SARS-CoV-2 have recently shown remarkable efficacy while retaining a favourable safety profile, both in large phase III clinical trials as well as in real world scenarios [5, 6, 7].

The new vaccine candidate to be tested in this trial, MVA-SARS-2-ST, has been optimized to express a pre-fusion stabilized full-length spike (S) glycoprotein of SARS-CoV-2. Spike antigen is functionally implicated in virus cell entry and the target of naturally occurring neutralizing antibodies to coronaviruses. Multiple lines of evidence support the choice of S glycoprotein as vaccine target as described in detail below. The MVA vector platform, due to its replication-deficiency, is considered a safe, well-tolerated and immunogenic vaccine platform capable of inducing a multimodal humoral and cell-based immunological antigen response. MVA in its dozens of different clinical stage explorations in thousands of patients has never been associated with vaccine-related serious adverse events. The licensed IMVAMUNE®/IMVANEX® smallpox vaccine product line by Bavarian Nordic is based upon this platform.

7.2 Preclinical results

The experimental vaccine MVA-SARS-2-ST is currently being studied in mice and Syrian hamsters as outlined in the investigator’s brochure [8]. Animals were immunized using up-to-full-human-dose equivalents (1 x 10^8 plaque forming units [PFU]) in a prime-boost vaccination scheme via the intramuscular route. MVA-SARS-2-ST was well tolerated and led to the production of S antigen-specific CD8+ T cells and neutralizing antibodies.

Preclinical testing of the predecessor vaccine candidate MVA-SARS-2-S harboring the native SARS-CoV-2 S antigen sequence was done in mice, ferrets and Syrian hamsters. A combined preclinical proof-of-concept and safety study was performed in female BALB/c mice to obtain primary pharmacology and toxicology data for this construct. Animals were immunized in a prime-boost vaccination scheme using 1 x 10^7 or 1 x 10^8 PFU MVA-SARS-2-S via the intramuscular route. No evidence for a potential toxicity of the full human dose of MVA-SARS-2-S was observed. The repeated vaccination was well tolerated and caused no adverse events. A No Observed Adverse Event Level (NOAEL) was established for MVA-SARS-2-S of repeat i.m. administration of 1 x 10^8 PFU. Furthermore, MVA-SARS-2-S was shown to elicit humoral and cellular immune responses against SARS-CoV-2 (data unpublished).

Challenge experiments conducted with MVA-SARS-2-S in SARS-CoV-2 naturally susceptible hamsters and BALB/c mice transduced with the human ACE2 receptor demonstrated the protective capacity of MVA-SARS-2-ST. The knowledge gained from the experiments promise a benefit in respect to protection from COVID-19.

7.3 Clinical studies

The MVA platform is a promising vaccine platform, as multiple clinical trials against a variety of infectious diseases revealed a safe and immunogenic profile for MVA-based vaccines. Clinical trials showed the induction of multimodal humoral and cellular immune responses to the target antigen. More than 370 clinical trials testing MVA were published in PubMed.

From 2017 to 2019, a first-in-human trial (NCT03615911) with an MVA-MERS-S vaccine was performed in Hamburg (University Medical Center Hamburg-Eppendorf and CTC North GmbH & Co. KG) in 23 healthy adults using the same prime-boost regime as in this trial. Immunizations with MVA-MERS-S revealed a benign safety profile with only transient mild-to-moderate reactogenicity. The safety profile was similar after prime and boost immunization. Participants experienced no severe or serious adverse events. Local reactions, headache and fatigue were the most common AEs. All AEs resolved swiftly and without sequelae. Following booster immunization, 87% of all vaccines and 100% of high-dose vaccine recipients showed seroconversion using an S1-ELISA. Antibody titers measured by ELISA correlated well with MERS-S-specific neutralizing antibodies. MERS-CoV-S-specific T-cell responses were detected in 91% of all vaccine recipients. A dose-effect relationship was observed for reactogenicity but not for immunogenicity [9].

The first-in-human (FIH) trial (NCT04569383) with the predecessor vaccine candidate MVA-SARS-2-S included 30 healthy adults who were vaccinated with either a low dose ($1 \times 10^7 \pm 0.5$ log IU; N=15) or a high dose ($1 \times 10^8 \pm 0.5$ log IU; N=15) of the vaccine, using the same dosages and prime-boost regimen as in the MVA-MERS-S trial (days 0 and 28). The interim results of this study show that the vaccinations were well tolerated by subjects in both dose cohorts and no serious adverse events (SAEs) occurred. The majority of AEs were expected (local vaccine reactions, headache, fatigue/malaise, arthralgias, myalgias, gastrointestinal complaints, fever, and chills). Examinations of vital signs, temperature, and blood analyses including clinical chemistry and hematology (time points defined in the study protocol) also revealed no safety-relevant abnormalities.

7.4 Risk-benefit considerations

The participation in a phase Ib study will not be of direct benefit to the participants. Known risks related to the pharmacological properties of the investigational compound and/or study modalities are possible. To our best knowledge and judgement and based on the data available to date, the vaccine appears to be safe and no severe side effects and no unacceptable adverse drug reactions (ADR) are expected with this study. The used MVA vaccine vector has been extensively studied in clinical trials for other infectious diseases encompassing >6500 individuals, including children, cancer patients and immunocompromised hosts. The vaccine vector has had an excellent safety profile and unexpected adverse reactions conferred by the antigenic insert are not anticipated. A phase I study testing MVA-MERS-S by the coordinating investigator did not show any SAE and preliminary data from an ongoing MVA-SARS-2-S phase I clinical trial (NCT04569383) has only revealed mild to moderate adverse events in both dose groups.

All relevant preclinical studies required for the start of clinical development have been conducted. Preclinical data suggest a favorable safety and tolerability profile. Based on available information and the design of the study, the sponsor and the coordinating investigator consider the trial to be ethically acceptable. The duration of confinement, the medical surveillance and the chosen study design for the sequential dosing in all dose groups are considered adequate to ensure safety of the participants. Special consideration was given to frequent safety assessments as mandated and recommended by the Regulatory Authorities.

The selection of vaccine dose levels for this trial are based on preclinical data and data derived from previous clinical trials with the recombinant MVA vector technology. Vaccine dose levels of 1×10^7 IU and 1×10^8 IU have been found to be both safe and immunogenic. The rate of seroconversion was higher in the higher dose group in a previous small trial related to MVA-MERS-S. The current trial aims at contributing to dose finding for later phase clinical trials.

The vaccine recipients may benefit from protection against SARS-CoV-2 during the current COVID-19 pandemic. However, this trial is the first trial of MVA-SARS-2-ST in humans. Therefore, to date the risks-benefit ratio remains unknown. Participants will be strongly advised to not consider themselves protected against SARS-CoV-2 after vaccination at this stage of vaccine development.

Serious allergic reactions including anaphylaxis may occur and for this reason participants will be inoculated in a clinical area where advanced life support trained physicians, equipment and drugs are immediately available for the management of any serious adverse reactions. Participants will be closely

monitored and evaluated for AEs for at least 1 h after administration of vaccine with appropriate medical treatment readily available in case of a rare anaphylactic reaction.

In summary, preclinical and clinical data indicate a favorable safety and tolerability profile. So far, clinical trials with MVA vectors, including a phase 1 trial with MVA-SARS-2-S, have reported transient and spontaneously resolving adverse events and no serious adverse reactions. The duration of confinement and the medical surveillance are considered adequate to ensure maximal safety of the participants and have been established with guidance of the CA. Thus, considering the safety measures to minimize risks for study participants, the exposure of healthy participants with the MVA-SARS-2-ST vaccine is justified, since the potential risks and disadvantages for study participants are outweighed by the potential benefits for medical research, medical practice and eventually for individuals at risk of SARS-CoV-2 infection.

The total amount of blood collected from a participant will not exceed a maximum of 600 mL for participants of the Part A and 500mL for the participants in Part B over 7 months. These blood volumes should not endanger the otherwise healthy volunteers and do not exceed the volumes of voluntary blood donations. There may be slight bruising, local sensitivities, presyncopic symptoms associated with venipuncture or phlebitis, which may later lead to superficial vein thrombosis.

More detailed information about the known and expected benefits, risks and reasonably expected AEs of MVA-SARS-2-ST may be found in the IB [8].

Risk Assessment of conducting the clinical trial during the COVID-19 pandemic:

The sponsor and coordinating investigator carefully reviewed the feasibility, risk and benefits of starting a new clinical trial during the ongoing pandemic. Given the fact that MVA-SARS-2-ST represents a vaccine for the current COVID-19 pandemic, there is an immediate necessity to continue the MVA-SARS-2-ST vaccine development program. The safety of the trial participants is of primary importance, and all measures will be taken to minimize the risk to trial participants and prioritize trial participant safety and data validity.

8 STUDY OBJECTIVES

8.1 Primary objective

Part A:

This study is designed to evaluate the safety, tolerability and reactogenicity of two intramuscular dose administrations of three dose levels of the candidate MVA-SARS-2-ST vaccine in healthy SARS-CoV-2 seronegative adults aged 18-64 years.

Part B:

This study is designed to evaluate the safety, tolerability and reactogenicity of one intramuscular dose administration of three dose levels of the candidate MVA-SARS-2-ST vaccine in healthy adults previously vaccinated against COVID-19 aged 18-64 years.

8.1.1 Primary endpoints

The nature, frequency and severity of adverse events associated with MVA-SARS-2-ST vaccine will be collected and measured as followed:

- Occurrence of solicited local reactogenicity signs and symptoms for 7 days after vaccination.
- Occurrence of solicited systemic reactogenicity signs and symptoms for 7 days after vaccination.
- Occurrence of unsolicited adverse events (AE) for 28 days after vaccination.
- Change from baseline of safety laboratory measures.
- Occurrence of serious adverse events (SAE) throughout the study period.

8.2 Secondary objectives

Part A:

To evaluate SARS-CoV-2-S1 binding and SARS-CoV-2 neutralizing antibodies in healthy SARS-CoV-2 seronegative adults induced by three dosage levels after two administrations of MVA-SARS-2-ST vaccine.

Part B:

To evaluate SARS-CoV-2-S1 binding and SARS-CoV-2 neutralizing antibodies in healthy adults previously vaccinated against COVID-19 induced by three dosage levels after one administration of MVA-SARS-2-ST vaccine.

8.2.1 Secondary endpoints

Immunogenicity:

- Humoral immunity: Amount of anti-SARS-CoV-2-S1-binding antibodies as measured by ELISA and detection of antibodies that neutralize SARS-CoV-2 (Part A & B).
- Percentage of participants who seroconverted. The seroconversion measured by ELISA is defined as the detection of SARS-CoV-2-S1-specific antibodies if the baseline value was negative, or as an increase in the antibody titer by a factor of 4 or more compared to the baseline value (Part A).
- Percentage of participants who showed an increase of the level of binding and neutralizing antibodies to baseline (Part B).

8.3 Exploratory objectives

- To investigate Th1 and Th2 immune responses following vaccination.
- To investigate antibody-dependent enhancement and vaccine-associated enhanced respiratory disease.
- To identify and characterize cases of COVID-19.
- To evaluate the rate of natural infection of SARS-CoV-2 during the clinical trial by monitoring antibodies against SARS-CoV-2 N protein.
- To investigate sex differences in immunity to MVA-SARS-2-ST vaccination.
- To investigate age-related immune responses to MVA-SARS-2-ST vaccination.
- To examine vaccine-induced humoral immune responses and antibody functions, including vector-immunity, neutralizing and non-neutralizing antibody functions.
- To evaluate MVA-SARS-2-ST-specific cellular immune responses after administration of MVA-SARS-2-ST.
- To evaluate MVA-SARS-2-ST-induced B- and T-cell memory responses.
- To evaluate innate immune responses induced by MVA-SARS-2-ST.
- To evaluate early innate immunity gene expression signatures induced by MVA-SARS-2-ST.
- To evaluate pre-existing humoral and cellular immunity to coronaviruses.
- To identify potential biomarkers and gene signatures of innate immune responses to MVA-SARS-2-ST and their correlation to dose, reactogenicity, and immune response.

9 INVESTIGATIONAL PLAN

9.1 Overall study design and plan-description

This will be a phase Ib multi-center study in approximately 60 adults consisting of the following two parts:

Part A

24 healthy SARS-CoV-2 seronegative adults aged 18-64 years will receive:

- ≥ 1 x 10^7 IU MVA-SARS-2-ST (low dose, LD) (N= 8) or
- ≥ 5 x 10^7 IU MVA-SARS-2-ST (middle dose, MD) (N= 8) or

- ≥ 1 x 10^8 IU MVA-SARS-2-ST (high dose, HD) (N= 8)

Each participant will receive two single injections, 28 days apart (day 0 and 28).

Part B

36 healthy adults, previously vaccinated with a (conditionally) licensed mRNA vaccine aged 18-64 years will receive:

- ≥ 1 x 10^7 IU MVA-SARS-2-ST (low dose, LD) (N= 12) or
- ≥ 5 x 10^7 IU MVA-SARS-2-ST (middle dose, MD) (N= 12) or
- ≥ 1 x 10^8 IU MVA-SARS-2-ST (high dose, HD) (N= 12) or

Each participant will receive one single injection (day 0).

A schematic overview of study design is represented in the below

Figure 1 *Overall study design*.

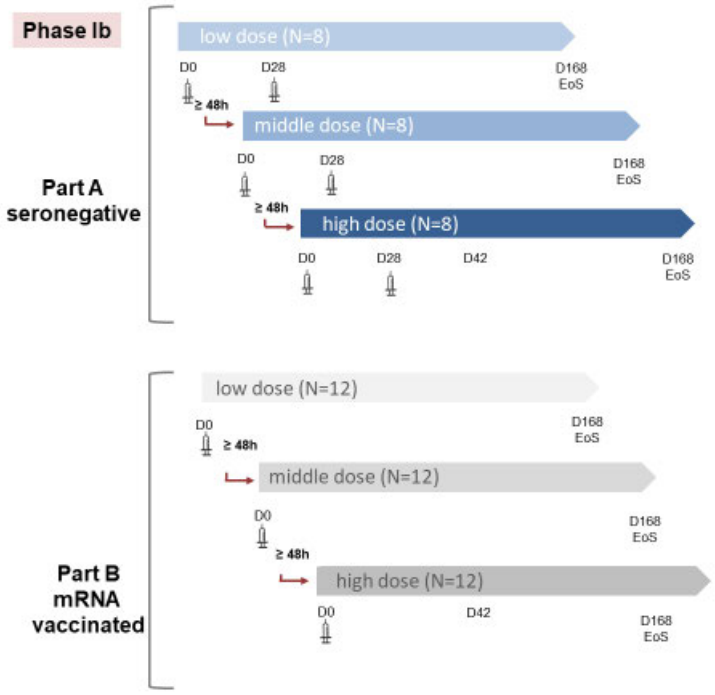


Figure 1 Overall study design

9.2 Discussion of study design, including the choice of control groups

In close coordination with the national Regulatory Authorities, the study design, including doses and schedule has been optimized to safely investigate the MVA-SARS-2-ST vaccine candidate. The study will be a phase Ib study in SARS-CoV-2 seronegative and fully with a (conditionally) licensed vaccine against COVID-19 vaccinated participants. In this phase Ib trial the primary focus will be on safety, tolerability and reactogenicity.

9.3 Selection of study population

In total, 60 male and female adults will be enrolled in this clinical trial. Participants will be recruited from the study centers' pool and public advertisement. Eligible participants will be allocated to one of the three dose cohorts [Parts A and B].

Homogeneous sex distribution of no less than 25% of one sex is targeted.

9.3.1 Inclusion criteria

The participant must not be enrolled before all inclusion criteria (including test results) are confirmed.

1. Ability to understand the participant information and to personally name, sign and date the informed consent to participate in the study.
2. Provided written informed consent.
3. Healthy male and female adults aged 18 – 64 at time of informed consent.
4. Chronic medical condition should be stable for the last 8 weeks (no hospitalization, no emergency room, no need for supplemental oxygen).
5. Participant may be on chronic or as needed medications if, in the opinion of the investigator they pose no additional risk to participant safety or assessment of reactogenicity and immunogenicity and do not indicate worsening of medical condition.
6. Body weight is defined in relation to height. Body mass index 18.5 – 32.0 kg/m^2 and weight > 50 kg at screening.
7. Non-pregnant, non-lactating female with a negative pregnancy test at screening and on dosing days (prior to vaccination).
8. Females of child-bearing potential who agree to comply with the applicable contraceptive requirements of the protocol (section 9.3.3) from at least 14 days prior to vaccination until day 56 or females who are permanently sterilized (at least 6 weeks post-sterilization).
9. The participant is co-operative and available for the entire study.
10. Part B: ≥ 6 months fully vaccinated with a (conditionally) licensed mRNA vaccine against COVID-19.

9.3.2 Exclusion criteria

Participants are excluded from the study if any of the following criteria are met at screening and/or on dosing days:

1. Receipt of any vaccine from 4 weeks prior to each trial vaccination (8 weeks for live vaccines) to 6 weeks after each trial vaccination.
2. Prior rMVA immunization.
3. Previous immunization with investigational vaccine against COVID-19.
4. Part A: Previous immunization with EU/conditionally licensed vaccine against COVID-19.
5. Evidence of an active SARS-CoV-2 infection (positive SARS-CoV-2 antigen test followed by a confirmatory positive PCR test).
6. Prior history of SARS-CoV-2 infection (documented by positive PCR test) according to medical history and/or antibody test (Part A only) at screening.
7. Known allergy to the components of the MVA-SARS-2-ST vaccine product or history of life-threatening reactions to vaccine containing the same substances.
8. Known history of anaphylaxis to vaccination or any allergy likely to be exacerbated by any component of the trial vaccines.
9. Participation in a clinical trial or use of an investigational product within 30 days or five times the half-life of the investigational product - whichever is longer - prior to receiving the first dose within this study.

10. Evidence in the participant's medical history or in the medical examination that might influence either the safety of the participant or the absorption, distribution, metabolism or excretion of the investigational products.
11. Clinically relevant findings in ECG or significant thromboembolic events in medical history.
12. Any positive result for HIV1/2, HCV antibody or HBs antigen testing.
13. Any confirmed or suspected immunosuppressive or immunodeficient condition, cytotoxic therapy in the previous 5 years, and/or uncontrolled diabetes (HbA1c > 7.0).
14. Participants with inflammatory, infectious and neuroinflammatory underlying disease which could cause an expected impairment of the blood brain barrier such as meningitis, multiple sclerosis, epilepsy, or Alzheimer's disease.
15. Any known chronic or active neurologic disorder, including seizures and epilepsy, excluding a single febrile seizure as a child.
16. Known history of Guillain-Barré Syndrome.
17. Active malignancy or history of metastatic or hematologic malignancy.
18. Suspected or known severe alcohol or illicit drug abuse within the past 5 years.
19. Moderate or severe illness and/or fever >38 °C within 1 week prior to vaccination.
20. Administration of immunoglobulins and/or any blood products within the 120 days preceding study entry or planned administration during the study period.
21. History of blood donation within 60 days of enrollment or plans to donate within the study.
22. Receipt of chronic (defined as more than 14 days) immune suppressants or other immune-modifying drugs within 6 months of screening.
    - For corticosteroids, this will mean prednisone, or equivalent, greater than or equal to 0.5 mg/kg/day.
    - Intranasal and inhaled steroids are allowed. Topical steroids are permitted provided they are not required to be applied to injection site.
23. Participants with skin lesions close to the injection site will be excluded.
24. Thrombocytopenia, contraindicating intramuscular vaccination based on investigator's judgment.
25. Participants with a significant infection or known inflammation.
26. Participants who are known or suspected not to comply with the study directives.
27. Any other significant finding or underlying medical condition, that in the opinion of the investigator, would increase the risk of the individual having an adverse outcome from participating in this study.
28. Investigator or employee of the study site or sponsor with direct involvement in the proposed study, or identified as an immediate family member (i.e., parent, natural or adopted child) of the investigator or employee with direct involvement in the proposed study.

9.3.3 Reproductive potential

The study population includes women of childbearing potential (WOCBP). WOCBP have to agree to comply with the applicable contraceptive requirements of the protocol as named below for the duration of the study. This does not apply for females who are permanently sterilized (at least 6 weeks post-sterilization) or are post-menopausal. Post-menopausal is defined as no menses for 12 months without alternative medical cause and ≥ 47 years.

Effective contraception is defined as a contraceptive method with failure rate of less than 1% per year when used consistently and correctly and when applicable, in accordance with the product label, for example:

- Oral contraceptives, either combined or progesterone alone;
- Injectable progesterone;
- Implants of etonogestrel or levonorgestrel;

- Estrogen vaginal ring;
- Percutaneous contraceptive patches;
- Intrauterine device or intrauterine system;
- Male partner sterilization at least 6 months prior to the female participant's entry into the study, and a monogamous relationship;
- Male condom combined with a vaginal spermicide (foam, gel, film, cream or suppository);
- Male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, film, cream, or suppository);
- Sexual abstinence (from at least 14 days prior first vaccination until end of study): acceptable only if it is the participant's preferred and usual form of birth control/lifestyle choice;
- Bilateral tubal occlusionVasectomised partner;

Condoms are to be used with the mentioned acceptable contraceptives.

Not applicable for females with exclusively same-sex sex partners.

9.3.4 Removal of participants from vaccination or assessment

The study in its entirety may be discontinued prematurely by the sponsor at any time (see below) for safety reasons. Individual participants may terminate their participation prematurely, or have their participation be terminated by the investigator.

Participants in Part A will not receive the second immunization if:

- A clinically significant acute illness occurs before vaccination. Minor illnesses (e.g. diarrhea or mild upper respiratory tract infection) do not affect second immunization;
- Fever (body temperature ≥ 38.0°C) within 24 hours prior to the planned time of vaccination;
- Allergic/anaphylactic reaction after the 1st vaccination considered as related to the trial vaccine;
- SARS-CoV-2 infection during day 0 to 28*;

In case any of the events occur before the first immunization, immunization may be postponed provided the screening window will not be exceeded.

* in case participant does not receive day 28 vaccination, no ambulatory visits on day 29 and day 35 will take place

9.3.4.1 Withdrawal of participants from the clinical trial

The circumstances that may lead to discontinuation of the study by an individual participant who will then be recorded as a drop-out include, but are not limited to, the following:

- Withdrawal for personal reasons;
- Circumstances in which the health of the participant would be endangered upon continued participation in the study;
- Participant non-compliance with study requirements;
- An AE, which requires discontinuation of the study involvement or results in inability to continue to comply with study procedures;
- Significant protocol violation;
- Lost-to follow-up;
- Pregnancy;
- Other (must be specified).

The reason for withdrawal will be recorded in the electronic case report form (eCRF). If withdrawal is due to an AE, appropriate follow-up visits or medical care will be arranged, with the agreement of the participant, until the AE has resolved, stabilized or a non-trial related causality has been assigned. The SSC may also recommend withdrawal of participants.

At least 3 documented attempts must be made within 2 weeks to contact any participant lost to follow-up at any time point prior to the last scheduled office visit. One of the documented attempts must include a written communication (e.g. post mail, courier) with acknowledgement of receipt requested (e.g. certified mail, registered mail) sent to the participant's last known address, requesting that they return any required material (e.g. diary) and return to the study site for final safety evaluations.

9.3.4.2 Handling of participants with premature study discontinuation

In the absence of a medical contraindication or significant protocol violation, every effort will be made by the investigator to keep the participant in the study (if participant received at least one vaccination). If a participant has to be withdrawn, all efforts will be made to complete and report the trial observations as thoroughly as possible. If a participant needs to be withdrawn, all efforts shall be made to follow safety of the participant as per protocol.

Participants who withdraw or are withdrawn from the study prior to the first injection (Part A and B) or participants who received the first vaccination but are withdrawn without medical reasons before the second vaccination will be replaced (Part A). An early termination visit will be performed for all drop-outs who received at least one vaccination. This visit may be a phone visit.

When a participant withdraws from the study after the first vaccination and before the planned end of the study period, all investigations scheduled for the end-of-study visit should be performed if the participant agrees. End-of-study evaluation will be completed at the time of the participant's withdrawal, with an explanation of the reason for this entered onto the respective "end-of-study" section of the eCRF as follows:

- Adverse event (specify);
- Death (specify);
- Protocol violation (specify);
- Medical condition (specify);
- Consent withdrawal, not due to AE;
- Lost to follow-up;
- Other (specify).

9.3.4.2.1 Replacement of participants

In case a participant will be replaced, the replacement participant will be assigned to the participant number as described in section 9.4.7.2. In the phase Ib the replacement participant will be assigned to the same treatment sequence as the participant he/she replaces.

9.3.4.3 Criteria for termination of the study (holding rules)

Safety holding rules will apply throughout the entire study period. Should a holding rule be activated, the investigator will inform the medical monitor and the sponsor. Study evaluation will be discussed with the SSC. The sponsor has to inform the CAs and the EC within the timelines defined by national law.

If the event(s) occur, the follow-up phase will continue. The discontinuation of a holding rule should be communicated to all entities in the same manner and timeframe as described above.

The SSC safety review will consider:

- The relationship of the AE to the IMP;
- The relationship of the AE to the IMP dose, or other possible causes of the event;
- If appropriate, additional screening or laboratory testing for other participants to identify those who may develop similar symptoms will be discussed.

All vaccines will be followed for safety until resolution or stabilization (if determined to be chronic sequelae) of their AE. For further details on AE grading please refer to 9.8.

The holding rules are as follows:

- Solicited (expected) local adverse events:

- If more than 2 injections in at least 2 participants are followed by Grade 3 solicited swelling or pain or Grade 4 redness beginning within 3 days after injection and persisting at Grade 3 (swelling or pain)/4 (redness) for > 48 hours

- Solicited (expected) systemic adverse events:
  - If more than 2 injections in at least 2 participants are followed by Grade 3 solicited systemic AE (or Grade ≥ 3 physical observations) beginning within 3 days after study injection and persisting at Grade ≥ 3 for >48 hours
- Unsolicited (unexpected) adverse events:
  - If more than 2 individuals develop a Grade ≥ 3 unsolicited AE (including laboratory AE and physical observations) that is considered probably or definitely related to injection and persists at Grade 3 for > 48 hours
- Any treatment related SAE
- A suspected unexpected serious adverse drug reaction (SUSAR) occurs that is life-threatening or results in death

Or

The sponsor may terminate the trial at any time or a Regulatory Authority may request the termination. In the case of study termination, investigators will be informed of the procedures to be followed to ensure adequate consideration is given to the protection of the participants' safety.

In case any holding or stopping rules apply, the sponsor needs to be informed within 24 hours. The sponsor has to inform the CAs and the EC within 15 days.

9.4 Treatments

9.4.1 Treatments administered

Part A

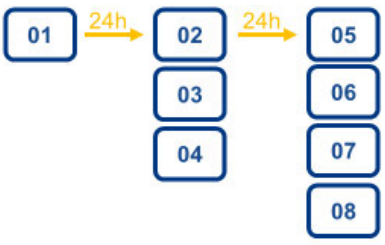
All eligible participants will be assigned to one of the dose cohorts (low dose, middle dose or high dose) according to the assignment list. Each participant will receive two vaccine injections administered as i.m. injections in the deltoid region of the upper arm muscle preferably of the non-dominant arm.

Part B

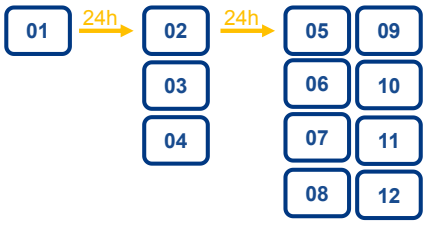
All eligible participants will be assigned to one of the dose cohorts (low dose, middle dose or high dose) according to the assignment list. Each participant will receive one vaccine injection administered as i.m. injection in the deltoid region of the upper arm muscle preferably of the non-dominant arm.

In case injection in the deltoid region of the upper arm muscle is not possible (e.g. due to medical or other contraindication), an alternative location can be used.

For safety reasons dose administration in each dose level of both Parts will be performed in at least three groups. Dose administration for the first participant at each dose levels will occur 24 hours prior to the next 3 participants. Dose administration for the three participants of the second group at each dose levels will occur 24 hours prior to the other participants of this dose level.



Part A



Part B

Vaccination in the next dose level can start 48 hours after all participants of the previous dose level of the respective Part received their 1st vaccination.

Dosing events are supervised by an investigator.

9.4.2 Identity of investigational medicinal products

Test-IMP:

Name:	MVA-SARS-2-ST
Dosage form:	Suspension for injection
Active substances:	MVA-SARS-2-ST
Route:	i.m. injections
Manufacturer:	IDT Biologika GmbH, Dessau

Additional information can be found in the investigator's Brochure [8].

An investigator or a delegated member of the study team will administer the IMP.

9.4.2.1 Packaging & labeling

IDT Biologika GmbH, Dessau, will supply the MVA-SARS-2-ST for the study. MVA-SARS-2-ST is labeled in accordance with the applicable laws and GCP guidelines.

9.4.2.2 Storage

The PI at each study site has the responsibility for ensuring that study medication is stored under appropriate conditions in a secure, limited-access location. Study medication is distributed by the pharmacy or by a nominated member of the unblinded study team.

MVA-SARS-2-ST must be stored in accordance with labeled storage conditions according to the pharmacy manual. Temperature monitoring is required at the storage location to ensure that the study medication is maintained within an established temperature range.

The PI is responsible for ensuring that the temperature is monitored throughout the total duration of the clinical trial and that records are maintained; the temperature must be monitored continuously such that at least minimum and maximum temperatures over a specific time period can be recorded and retrieved as required.

The sponsor has to be informed by the clinical trial site of any excursion from the established range as soon as the PI becomes aware of an excursion. The sponsor has then to confirm the stability of the vaccine before further use. Relevant temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the vaccine and will provide supportive documentation as necessary.

9.4.2.3 Shipment

The vaccine will be provided by IDT on behalf of the sponsor in sufficient quantity to the study sites.

9.4.2.4 Drug accountability

The PI at each study site has the overall responsibility for administering the IMP. The IMP must be administered in the manner specified in the study protocol and the pharmacy manual.

The investigator or a designee at the study sites will acknowledge receipt of the study medication documenting shipment content and condition. Damaged supplies will be replaced. Accurate records of all study medication received, dispensed, used, returned or destroyed must be maintained. No study medication may be destroyed or returned from the investigational site without prior knowledge and written consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state and national laws must be adhered to for the transfer.

All administrations will be documented in the site's drug accountability log or other study drug record. The PI is responsible for assuring the retrieval of all dispensed study supplies from participants.

The sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records.

As instructed by the sponsor all unused stocks and empty used boxes are sent to a nominated contractor or will be destroyed at the study site on behalf of the sponsor. Study medication being returned or destroyed must be counted and verified by PI or a designee. All certificates of delivery/drug receipts should be signed by the site representative to confirm contents of shipment. Shipment return forms must be signed prior to shipment by the study site. The sponsor must give authorization to return or destroy any study medication prior to shipment or destruction. Shipment of all returned study medication must comply with local, state, and national laws.

Based on the entries in the site drug accountability logs, it must be possible to reconcile study medication delivered with those used and returned. One hundred percent of the study medication must be accounted for and all discrepancies investigated and documented.

9.4.3 Method of assigning participants to treatment groups

Participants willing and eligible to participate in this study will be assigned to a dose cohort according to the assignment list. Assignment to the 2nd dose cohort will start after all participants for the 1st dose cohort are enrolled and assignment to the 3rd dose cohort will start after all participants for the 2nd dose cohort are enrolled.

9.4.4 Selection of doses in the study

The doses selected in this study represent dose levels with optimal immunogenicity and safety profile as observed in prior clinical trials using MVA-vector-based vaccines.

9.4.5 Blinding and unblinding

As this is an open-label study, no blinding procedures are necessary.

9.4.6 Prior and concomitant therapy

As outlined in Table 1 and Table 2**Fehler! Verweisquelle konnte nicht gefunden werden.** participants will be asked about concomitant use of medication.

All other concomitant therapies and change on pre-existing therapies must be recorded if administered in conjunction with an adverse event.

Prestudy therapies administered up to 30 days before the first dose of study vaccine must be recorded at screening.

Concomitant medication with a possible impact on study results such as corticosteroids, antihistamines, and vaccinations must not be used from first vaccination until day 56. Otherwise this has to be discussed with the PI, so that a decision about the further participation of the participant can be made.

For symptomatic management of flu-like symptoms/solicited AEs, the use of anti-pyretic drugs (e.g. paracetamol/ibuprofen) in the recommended daily dose is permitted.

Vaccination with a (conditionally) licensed COVID-19 vaccine is permitted 6 weeks or later after the 2nd immunization.

9.4.7 Treatment compliance

9.4.7.1 Admission to the clinical trial

Admission to the study will be effective upon the participant's arrival at the study ward. A participant will only be admitted to the study if the Informed Consent Form has been signed and all inclusion and none of the exclusion criteria are met. Should there be any doubts as to the state of health, a participant will not be admitted to the study.

Participants who fail to make themselves available upon commencement of the study or who cannot participate for personal reasons will be considered as not admitted to the study. They will be replaced by back-up participants who will be screened in surplus.

9.4.7.2 Participant identification

The PI of each site will keep a record relating the patient numbers and the names of all participants that have given their informed consent, to allow easy checking of data in patient files, when required. This

record will also include the date of the participant`s enrollment and completion, as well as participant who could not be included in the study for whatever reason.

Ascending screening numbers are to be assigned sequentially to all participants as they consent to take part in the study. The screening number will be a 4-digit number starting at 0001 following the site number (e.g. 01-0001).

The participant number is assigned to participants when they are enrolled into the study in order of appearance of the participants. This will be a 4-digit number starting at 1001 following the site number (e.g. 01-1001) for subjects in Part A and a 4-digit number starting at 5001 following the site number (e.g. 01-5001).

For screening failures, the screening number will be the identifying number used throughout the documentation.

For the Phase Ib participants who will replace a participant e.g. a withdrawn participant, will receive a screening number according to the above described scheme. In difference to the described participant number assignment, replacement participant will receive a 4-digit participant number which will consist of the old participant number (of the subject which should be replaced) plus 1000.

Participants who replace a participant will receive a screening number according to the above described scheme.

For the phase Ib allocation to a certain participant number will be done in successive order following screening and based on the participants' availability. Enrollment to Part A and Part B will be in parallel.

9.4.7.3 Screening, confinement and regular visits

9.4.7.3.1 Screening (day -28 to day -1) Part A and B

On the screening visit the following events will be performed:

- Informed consent
- Inclusion/exclusion criteria
- Medical history/ demographics
- Physical examination
- Height and weight
- Vital signs
- 12-lead ECG
- Temperature
- Safety laboratory blood (clinical chemistry, hematology)
- Urine pregnancy test
- Urine drug screen
- Safety urinalysis
- HIV/HBV/HCV serology
- COVID-19 antigen test (If COVID-19 antigen test was performed within 4 hours before the screening visit and if the test result is suitable to be used as source data for the clinical trial, e.g. a test done by the study site as part of the hygiene concept, the test does not need to be repeated at screening and the available test results can be used.)
- PCR for SARS-CoV-2 (only if required)
- SARS-CoV-2 antibody test (Part A only)

9.4.7.3.2 Pre-vaccination visit (day -1*) Part A and B

- Safety laboratory blood (clinical chemistry, hematology)
- Serum pregnancy test

- Safety urinalysis

*only applicable if screening visit is between day -28 and day -2, last antigen test to be performed within 2 days before the first vaccination.

9.4.7.3.3 Vaccination visits (day 0 and 28) Part A

- Update of inclusion/exclusion criteria (day 0 only)
- Update of medical history (day 0 only)
- Physical examination (symptom-targeted)
- Vaccination
- Training & dispensing of diary (day 0 only)
- Review & collection diary (day 28 only)
- COVID-19 antigen test
- PCR for SARS-CoV-2 (only if required)
- Urine drug screen
- Safety laboratory blood (clinical chemistry, hematology) (day 28 only)
- Serum pregnancy test (day 28 only)
- Safety urinalysis (day 28 only)
- Humoral responses
- RNA blood sample
- PBMC freezing and plasma aliquots

Before drug administration and one hour after dosing the following events will be performed **at 0 and 1 h (±15 minutes).**

- Vital signs (at 0 h before dose administration, and at 1 h [±15 minutes])
- Temperature (at 0 h before dose administration, and at 1 h [±15 minutes])
- Adverse events/ concomitant medication (at 1 h ±15 minutes after first dose administration and at 0 h before dose administration and 1 h ±15 minutes after dose administration on day 28)
- Injection site/ systemic events/reactions assessment (within 5 minutes and at 1 h ±15 minutes after dose administration).

9.4.7.3.4 Regular ambulatory visits Part A

Participants will return to the study ward for regular ambulatory visits on study day 1, 3, 7 (±1), 14 (±3), 29, 35 (±1), 42 (±3), 56 (±7) and 84 (±7).

On the ambulatory visits the following events will be performed:

- Temperature
- Vital signs
- Injection site & systemic events/reactions assessment
- Review & collection diary: only on day 1, 3, 7 (±1), 14 (±3), 29, 35 (±1), 42 (±3), and 56 (±7)
- Adverse events & concomitant medication assessment
- COVID-19 antigen test (only if required)
- PCR for SARS-CoV-2 (only if required)
- Safety lab blood (clinical chemistry, hematology) only on day 1, 3, 7 (±1), 29, 35 (±1), 42 (±3), 56 (±7) and 84 (±7)

- Humoral responses only on day 7 (±1), 14 (±3), 35 (±1), 42 (±3), 56 (±7) and 84 (±7)
- RNA blood sample only on day 1, 3, 7 (±1), 29 and 35 (±1)
- PBMC freezing and plasma aliquots

9.4.7.3.5 Vaccination visit (day 0) Part B

- Update of inclusion/exclusion criteria
- Update of medical history
- Physical examination (symptom-targeted)
- Vaccination
- Training & dispensing of diary
- COVID-19 antigen test
- PCR for SARS-CoV-2 (only if required)
- Urine drug screen
- Humoral responses
- RNA blood sample
- PBMC freezing and plasma aliquots

Before drug administration and one hour after dosing the following events will be performed **at 0 and 1 h (±15 minutes).**

- Vital signs (at 0 h before dose administration, and at 1 h [±15 minutes])
- Temperature (at 0 h before dose administration, and at 1 h [±15 minutes])
- Adverse events/ concomitant medication (at 1 h ±15 minutes after first dose administration and at 0 h before dose administration
- Injection site/ systemic events/reactions assessment (within 5 minutes after and at 1 h ±15 minutes after dose administration).

9.4.7.3.6 Regular ambulatory visits Part B

Participants will return to the study ward for regular ambulatory visits on study day 1, 3, 7 (±1), 14 (±3), 28 (±2), and 56 (±7).

On the ambulatory visits the following events will be performed:

- Temperature (only on day 1,3, 7 (±1) and 14 (±3))
- Vital signs (only on day 1,3, 7 (±1), and 14(±3))
- Injection site & systemic events/reactions assessment (only on day 1, 3, 7 (±1), and 14(±3))
- Review & collection diary: only on day 1, 3, 7 (±1), 14 (±3), 28 (±2)
- Adverse events & concomitant medication assessment
- COVID-19 antigen test (only if required)
- PCR for SARS-CoV-2 (only if required)
- Safety lab blood (clinical chemistry, hematology) (only on day 1,3 and 7 (±1))
- Humoral responses only on day 7 (±1), 14 (±3), 28 (±2), and 56 (±7)
- RNA blood sample only on day 1, 3 and 7 (±1)
- PBMC freezing and plasma aliquots

9.4.7.3.7 End of study / early termination visit Part A and B

An end-of-study follow-up visit will be performed on day 168 (±14) or upon early termination. The following events will be performed:

- Physical examination
- Weight
- Vital signs
- Injection site & systemic events/ reactions assessment
- Temperature
- COVID-19 antigen test (as required)
- PCR for SARS-CoV-2 (only if required)
- Adverse events & concomitant medication assessment
- Safety lab blood (clinical chemistry, hematology)
- Safety urinalysis
- Urine pregnancy test
- Humoral responses
- PBMC freezing and plasma aliquots

9.4.7.4 Unscheduled visit

Unscheduled visits may be performed at any time during the study. Depending on the reason for the unscheduled visit (e.g. AE, abnormal laboratory values), appropriate assessments will be performed based on the judgment of the investigator. Results of the assessment and any changes in concomitant treatment will be recorded in the eCRF. Specifically, to assess for antibody dependent enhancement and vaccine-associated enhanced respiratory disease, unscheduled visits should occur in the case of SARS-CoV-2 infection or vaccination against COVID-19 with a vaccine as standard-of-care outside the study. After an unscheduled visit, the regular scheduled study visits must continue according to the planned visit and assessment schedule.

9.4.7.5 Early termination

All enrolled participants who complete the study or discontinue early from the study will have the follow-up assessments and procedures completed for their safety as outlined in Table 1 and Table 2. Participants who discontinue early or withdraw from the phase Ib study will be replaced as outlined in section 9.4.7.2.

In some cases, it may be necessary for participants to return to the study ward for additional care, confinement, and/or follow-up. Circumstances in which this may be necessary are:

- Follow-up on abnormal laboratory evaluations
- Follow-up on an ongoing AE at the final visit

All additional safety follow-up visits will be at the discretion of the PI/deputy and the sponsor.

9.4.7.6 End of trial

A participant is considered to have completed the study if he/she has completed the last follow-up visit (end of study visit). Last participant last visit is defined as end of trial.

9.5 Protocol deviations (PD)

All PDs will be tracked and actions will be defined, as feasible. All PDs classified as major will be reviewed in Data Review Meetings for the interim analysis and the final analysis for assessment of their influence on the quality of the study analysis. Classification of PDs by the study site will be reviewed before the Data Review Meeting by the sponsor.

Protocol deviations due to COVID-19 will be tracked and reported together with the other protocol deviations in the CSR.

Major PD are defined as follows:

- Informed consent procedure: ICF not signed and dated by participant/investigator
- Violation of an in- or exclusion criterion
- Incorrect use of vaccine (storage, preparation and administration)
- Use of forbidden concomitant medication
- Delayed reporting of serious adverse events
- Unauthorized unblinding
- Other deviations which might compromise the quality of the study analysis

9.6 Methods and timing of safety measurement

Details regarding scheduled assessments and procedures to be conducted in this study are provided below. For detailed assessment of schedules refer to Table 1, Table 2, and Table 3.

All relevant laboratories involved in this trial are accredited for the assays performed and copies of the accreditation certificates are to be filed in the TMF. Continuous compliance with legal requirements throughout the trial will be assured.

9.7 Appropriateness of measurements

9.7.1 Screening procedures

Written, signed, and dated informed consent from the participant prior to the performance of any study related procedures must be obtained by an investigator. Participants will first have ample time to read the participant information before an investigator will start the information and informed consent process. The participant information/informed consent process will be performed according to the study site's processes.

A copy of the signed informed consent form must be given to the participants for their records.

Screening procedures must be completed between 28 days and 1 day prior to receiving the first dose of study medication. See section 9.4.7.3.1 for a complete list of screening procedures to be performed. Re-checks may be performed for individual events as long as they are within the screening window.

Only an authorized and trained investigator may decide on the eligibility of the participant.

9.7.1.1 Screening failure

A screening failure is defined as a participant who has given informed consent and failed to meet at least one inclusion criterion or met at least one exclusion criterion or has not been enrolled. Enrollment is defined as first vaccination received.

Eligible participants who meet all inclusion criteria and no exclusion criterion but are unable to participate in the study due to scheduling conflicts will not be considered screening failures.

9.7.1.2 Re-screening of participants

Screening failures will not be enrolled into the study or vaccinated but may be re-screened based on investigator's discretion and sponsor's approval. In these cases, a new screening number must be assigned for each participant to be re-screened and a new informed consent form must be signed to confirm consent for study participation.

9.7.2 Study examinations

Assessments are to be performed according to the schedule shown in Table 1 and Table 2 and depend on timepoint of vaccination.

9.7.2.1 Safety

Safety will be evaluated by collecting reported adverse events at regular intervals throughout the study and by the assessment of physical examination findings, vital signs, and clinical laboratory parameters.

9.7.2.2 Medical and medication history

A complete medical and medication history as well as demographic information will be assessed at the time points indicated in Table 1 and Table 2.

The medical history will be reviewed and recorded, including:

Medical and Medication History

- Recent ingestion of medication (30 days prior to entering the screening period)
- History of respiratory, cardiovascular, renal, gastrointestinal, hepatic, endocrine, hematological, neurological, psychiatric, musculoskeletal and other diseases.

Demographic information

- Year of birth
- Sex

9.7.2.3 Physical examination

A complete physical examination will be performed at the timepoints described in Table 1 and Table 2.

The physical examination will include a review of the following body systems:

- General appearance
- Skin
- Head, eyes, ears, nose and throat
- Spine/Neck/Thyroid
- Musculoskeletal
- Respiratory
- Cardiovascular
- Neurological
- Abdomen (including liver and kidneys).

Any abnormalities or changes in intensity from the screening visit noted during the review of body systems have to be documented in the source documents. Clinically significant abnormal findings discovered during a physical examination after screening will be documented either as part of medical history (participant forgot to mention an intermittent medical condition at screening) or documented as an adverse event or part of an adverse event (up from the time after dose administration), if the discovered symptom is leading to a diagnosis.

9.7.2.4 Electrocardiogram

A 12-lead ECG will be performed at the timepoints described in Table 1 and Table 2. Actual ECG assessment times will be documented.

Participants must be resting in a supine position for at least 5 minutes prior to performing the ECG. At a minimum, the date and time of when the event was performed, the investigator's assessment and the heart rate, RR, PR, QT, and QRS intervals are to be collected. All clinically significant abnormalities will be recorded on the appropriate source documents.

9.7.2.5 Vital signs

Blood pressure should be determined by cuff (using the same method and in the same position throughout the study). Measurements of vital signs (systolic and diastolic blood pressure as well as pulse rate) will be performed after the participant has been in a sitting position for at least 5 minutes at the time points specified in Table 1 and Table 2. Actual vital sign assessment times will be recorded.

All measurements of vital signs must be recorded in the appropriate source documents.

9.7.2.6 Temperature

Temperature will be measured using a digital thermometer (orally at the timepoints specified in Table 1 and Table 2.

9.7.2.7 Height and weight

Measurements of height and weight will be performed according to the schedule in Table 1 and Table 2.

Height is measured in centimeters (cm) and weight is measured in kilograms (kg). Measurements are to be taken in light clothing and socks (without shoes) with pockets emptied. The participant's height is recorded to the nearest cm and weight is recorded to the nearest 0.1 kg.

Height and weight will be measured and used to calculate the BMI using the following formula:

$$\text{BMI} = \frac{weight\,[kg]}{(height\,[m])^2}$$

9.7.2.8 Patient diary

Participants must complete a patient diary on the timepoints specified in Table 1 and Table 2. Participants are asked to document local and systemic reactions, temperature, medication and other reactions or disease for 28 days after each vaccination. The diary must be reviewed by an investigator during the ambulatory study visits.

9.7.2.9 Clinical laboratory evaluations

All laboratory tests will be performed according to the normal procedures in the local laboratory. Reference ranges must be supplied by the laboratory and used to assess the laboratory data for clinical significance and out-of-range pathological changes. The investigator should assess out-of-range laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant (NCS) or clinically significant (CS). Abnormal laboratory values that are unexpected or not explained by the participant's clinical condition may be, at the discretion of the physician, investigator or sponsor, repeated until confirmed, explained, or resolved as soon as possible. Additional laboratory tests may be performed for assessment of AEs or other medical events based on the investigator's judgment.

The following laboratory assessments will be performed:

Clinical chemistry

Blood samples for biochemistry will be collected at the time points described in Table 1 and Table 2. The following parameters will be assessed:

Sodium	Aspartate transaminase (AST)
Potassium	Alanine transaminase (ALT)
Calcium	Alkaline phosphatase (ALP)
Urea	Gamma-glutamyl transferase (GGT)
Creatine kinase (total)	Total bilirubin
Albumin	Glucose
Total protein	Pancreas-specific amylase
Creatinine	Lactate dehydrogenase (LDH)
Creatinine clearance (MDRD) (only at Screening)	C-reactive protein (CRP)

Hematology

Blood will be drawn at the timepoints described in Table 1 and Table 2. The following parameters will be assessed:

Hemoglobin	Mean corpuscular hemoglobin concentration (MCHC)
Hematocrit	White blood cell (WBC) count; total and differential
Red blood cells (RBC)	Neutrophils
Mean corpuscular volume (MCV)	Lymphocytes

	Monocytes
Platelet count	Eosinophils
Mean corpuscular hemoglobin (MCH)	Basophils

Urine pregnancy test

In all female participants a urine ß-HCG test will be performed on fresh midstream urine at the time points described in Table 1 and Table 2.

Safety urinalysis

The following parameters will be analyzed in fresh midstream urine at the timepoints described in Table 1 and Table 2.

pH	Ketones	Specific gravity
Bilirubin	Protein	Blood
Glucose		

Microscopic examination will be conducted if blood is detected during urinalysis. The microscopic examination will comprise of RBC, WBC, casts, and bacteria.

Serology

During the screening period only, blood sample(s) will be drawn to test for the presence of HIV, HBsAg, HCV, and SARS-CoV-2 antibody.

HIV testing (HIV I and HIV II)	HCV antibody screen
HBV testing (HBsAg)	SARS-CoV antibody testing (not applicable for Phase Ib Part B)

PCR for SARS-CoV-2

For PCR for SARS-CoV-2 samples are taken from the nose, nose and throat or throat at timepoints described in Table 1 and Table 2.

COVID-19 antigen test

For COVID-19 antigen testing samples are taken from the nose, nose and throat or throat at timepoints described in Table 1 and Table 2.

9.7.2.10 Alternative measures with respect to the COVID-19 pandemic

In case trial participants may not be able to come to the site for protocol-specified visits (e.g. due to the public health emergency related to COVID-19 or quarantine), 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 4.0 [10] which states that "in case the trial participant cannot reach the site to have these performed, it is acceptable that laboratory, imaging or other diagnostics test are done at local laboratory or relevant clinical facility authorized/certified (as legally required nationally) to perform such test routinely, if this can be done within local restrictions on social distancing". 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.

All efforts should be made to collect blood samples for safety and humoral immune response assessment via a home visit within the protocol-specified time window.

Any participant with clinical suspicion of SARS-CoV-2 infection will undergo appropriate testing and referral within the local health care system as appropriate.

The WHO/European Centre for Disease Prevention and Control case definition for a suspected case requiring diagnostic testing will be used.

9.7.2.11 Procedures in case of occurrence of COVID-19 symptoms

Participants will be instructed to report clinical evidence of COVID-19-like symptoms to the study site.

The investigator decides on the strategy to secure a diagnosis according to the current recommendations of the Robert Koch-Institut (RKI) and local guidelines.

Reporting of COVID-19-like symptoms might be facilitated by providing diary-like instructions indicating start and stop dates of specific symptoms, diagnostic information outside the study site, or information related to health care service contacts or hospitalizations.

Diagnostic procedures to detect or rule out COVID-19 disease will be performed according to established procedures at each study site but will be based for all cases on PCR diagnostics. Swabs for antigen tests might be performed using self-sampling devices or by health care provider (or both). Participants will be provided with antigen self-test kits and instructions for handling and shipment after enrolment. In addition, participants will be asked to contact a test facility according to local requirements in case of COVID-19 symptoms. At least one antigen or test result shall be performed at each occurrence in case of suspected of COVID-19-like symptoms, a second swab following a first negative result is encouraged for suspected cases based on the investigator's decision.

If the result of the test is positive the participant has to follow local quarantine requirements. If applicable, upcoming on-site study visits will be replaced by phone visits. Additional phone visits for follow-up until resolution of all COVID-19 symptoms may be scheduled.

9.7.2.12 Reactogenicity

To assess reactogenicity after each immunization, body temperature and reaction are recorded once daily for at least 7 days after vaccination by the participant in the diary or longer in case of systemic adverse events until they have subsided. Fever is defined as at least one measured body temperature of ≥ 38 °C. If fever is detected, temperature should be measured twice a day (in the morning and evening) until two consecutive measurements are < 38 °C. According to the defined time frames in the study schedules, recording might be shortened to less days. During the ambulatory visits at the study ward temperature, solicited injection site and systemic reactions will be assessed and recorded by a designated member of the study team. After dismissal participants are asked to maintain a diary to record daily temperature and injection site and systemic reactions for 7 days after each dosing and to record medical events for 28 days after each dosing. Participants will be trained on the thermometer and diary use.

The following items will be recorded:

- Daily temperature (oral);
- Daily measurement of intensity grade of all other injection site and systemic reactions;
- Action taken for each recorded event (none, medication taken, physician consulted, hospitalization).

9.7.2.13 Local reaction assessments

A local reaction is defined as any morphological or physiological change at or near the reaction site, not resulting from a generalized systemic reaction, i.e. urticaria or other distinct clinical entities, i.e. lymphadenopathy. Local reactions include, but are not limited to: pain, erythema, hematoma maculopapular eruptions, induration, pruritus, blistering, ulceration, cellulitis, phlebitis, necrosis or abscesses.

Local reactions, occurring after vaccination, will be graded using the toxicity grading scale in section 9.8.1.

9.7.2.14 Adverse events assessments

Participants will be questioned in a general way to ascertain if AEs have occurred (e.g. "Have you had any health problems since the last time you came to the clinic/since you were last questioned?"). This open, standardized questioning should be done discretely in order to prevent participants from influencing each other. Spontaneous reports of AEs will also be recorded as well as AEs that are observed by an investigator or a staff member.

All AEs will be reviewed, confirmed, and classified by a qualified, designated investigator.

9.7.2.15 Immunology measurements

Detailed information on blood sampling and exact volume of blood are defined in the Laboratory Manual. Details of sample processing are defined in the SOPs and manuals of respective laboratories.

9.7.2.15.1 Immunogenicity assays

Serum blood samples will be collected for assessment of humoral immune responses in all participants. In a subgroup, we additionally collect whole blood for RNA isolation and EDTA & heparin blood for analysis of innate and cellular immune responses.

Details on the exact blood volume, processing and storage are specified in the Laboratory Manual.

Qualified assays that evaluate binding and neutralizing SARS-CoV-2-specific antibodies are used within the phase I and II trials investigating MVA-SARS-2-ST. We will include the WHO Reference Panel for anti-SARS-CoV-2 antibodies and will use the 1st WHO International Standard for anti-SARS-CoV-2 antibody (National Institute for Biological Standards and Control [NIBSC]) for calibration as soon as both reagents are available.

Humoral and cellular immunogenicity assays may include, but are not limited to, those summarized in the Table below:

Assay	Purpose
Humoral Immunogenicity	
Secondary endpoints	
SARS-CoV-2 Spike ELISA/In-house ELISA (UMR)	Investigation of vaccine-induced binding antibodies (IgG) to SARS-CoV-2-spike protein (S1 domain)
SARS-CoV-2 VNT_{100} assay (UMR) Testing neutralizing capacity against SARS-CoV-2 (German Isolate: GISAID ID EPI_ISL 406862)	Investigation of vaccine-induced neutralizing antibodies against SARS-CoV-2
Humoral Immunogenicity	
Exploratory Endpoints	
SARS-CoV-2 neutralizing antibodies via VNT_{100} & pseudovirus-neutralization assay	Investigation of vaccine-induced neutralizing antibodies against SARS-CoV-2
(German isolate BavPat1/2020; European Virus Archive Global # 026V-03883; and selected emerging virus variants of concern)	Evaluation of the ratio between binding (Elecsys® Anti-SARS-CoV-2 S) and neutralizing antibodies
SARS-CoV-2 neutralizing antibodies via plaque peduction peutralization test (PRNT) 50, pseudovirus-neutralization assay and surrogate assay. Investigation of vaccine-induced neutralizing antibodies against SARS-CoV-2.	Characterization of humoral responses induced by vaccination
Various assays (Elecsys® Anti-SARS-CoV-2 S, in house ELISA, multiplex ELISA, VNT100, PRNT50, surrogate assays, flowcytometry, ELISpot, ELISA, Sequencing	
Cellular Immunogenicity and Innate Immune Responses	
Exploratory Endpoints	
ELISpot	Analysis of antigen-specific T-cell responses (IFNg)
ELISpot/Flowcytometry	Analysis of antigen-specific T-cell responses (IL4)
Flowcytometry	Analyses of CD4/CD8 responses, polyfunctionality of T-cell responses and TH1 and TH2 skewed responses

Variety of techniques like e.g. flowcytometry, ELISA, Sequencing	Characterization of innate and adaptive responses induced by vaccination

9.7.2.16 Shipment of samples

After processing and aliquoting sera, samples will be stored at a minimum of -20°C. Analyses for secondary endpoints will be performed at the Philipps University Marburg (Prof. Stephan Becker):

Prof. Stephan Becker
Institute for Virology
Philipps University Marburg
Hans Meerweinstr. 2
35043 Marburg, Germany

Samples will be shipped to the collaborators named in section 6 (Immunogenicity Laboratories).

9.7.2.17 Future use of stored samples

Left over blood samples may be used in the further evaluation of an adverse event or for the subsequent evaluation of additional parameters that are identified as important to the evaluation of an individual participant or to the study, or for further research regarding the immune response to the MVA-SARS-2-ST vaccine. Any unused part of the blood samples will be securely stored at the sponsor Institution for 15 years for analyses of exploratory objectives. Parts of the pseudonymized blood samples may be shipped to collaborators for further evaluation.

9.7.3 Safety variables

Assessment of safety is performed for the safety collective.

Safety data include:

- Adverse events (including changes from baseline in physical examination findings)
- Clinical laboratory results
- Vital signs
- Physical examination

The safety evaluation will be based upon the review of the individual values (potentially clinically important abnormalities) and descriptive statistics (summary Tables, graphics).

9.7.3.1 Adverse events

The adverse events will be listed per participant using MedDRA (Medical Dictionary for Regulatory Activities) terminology (and will be reported in Tables summarizing the frequency of participants with adverse events and adverse events by treatment and body system, the number of adverse events and participants with adverse events by treatments and the characteristics of adverse events.

For hematology, clinical laboratory and urine analysis, deviations from the reference ranges will be summarized in frequency Tables.

9.7.3.2 Clinical laboratory

All relevant clinical laboratory variables obtained during screening, final examination or the clinical trial periods will be reported in appropriate Tables together with descriptive statistics. Clinical laboratory findings outside of the reference range will be flagged.

9.7.3.3 Vital signs

For blood pressure and pulse rate descriptive statistics will be listed by sampling times (screening and follow-up) according to the data captured in the eCRF.

9.7.3.4 ECG

The results (normal or abnormal, and clinical significance) of the 12-lead ECG will be listed by sampling times (screening) according to the data captured in the eCRF.

9.8 Definition of adverse events, period of observation, recording of adverse events

An Adverse Event (AE) is any untoward medical occurrence in a clinical investigation participant administered an IMP and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, disease or exacerbation of a pre-existing condition temporally associated with the use of a medicinal (test) product, whether or not considered related to the medicinal product (ICH Guidance E2A 1995).

In this clinical trial AEs will be collected from the time of first administration of the IMP until the last follow-up visit, regardless of the relationship to the investigational medicinal product. Following these specifications all AEs in this clinical trial fulfil the WHO's definition of an ***Adverse Event Following Immunization*** (AEFI): An ***AEFI*** is any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom or disease.

Thus, the terms AE and AEFI are interchangeable. For better readability the common term AE will be used.

All AEs will be recorded on the appropriate source documents and subsequently will be entered into the AE module of the eCRF. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made each symptom should be entered as a separate AE.

CAVE: Solicited AEs have to be documented separately as described below. Those must not be summarized in a diagnosis.

If an event fulfils the criteria for an AE and occurs after a study participant signed the informed consent but before the administration of the first vaccination it will be documented in the medical history. If the event occurs after the first immunization the event fulfils the definition AE. An AE will also be documented in case of a worsening of severity of a pre-dose event from the medical history.

All AEs have to be recorded until the last trial visit of the participant according to the clinical trial protocol.

A **solicited AE** is a predetermined event occurring within 7 days after application of vaccine, which may reflect safety concerns related to the investigational product. The solicited AEs for this study only include:

- Local reaction (swelling, redness/ erythema, itching, warmth, induration, hematoma or pain at site of injection, tenderness)
- Fever
- Chills
- Myalgia (described to the participant as generalized muscle aches)
- Arthralgia (described to the participant as generalized joint aches)
- Fatigue
- Headache
- Gastrointestinal symptoms (nausea, vomiting, abdominal pain, loose stool and/or diarrhea)
- Malaise

Any of the following events will be classified as an adverse event of special interest (AESI) (according to SPEAC, 25-MAY-2020):

Adverse events of special interest applicable to COVID-19 vaccines			
AESIS relevant to vaccination in general	**Body System**	**AESI Type**	**Rationale for inclusion as an AESI (see footnote)**
	Neurologic	Generalized convulsion	1, 2, 4
		Guillain-Barré Syndrome (GBS)	2
		Acute disseminated encephalomyelitis (ADEM)	3
	Hematologic	Thrombocytopenia	1, 2
	Immunological	Anaphylaxis	1, 2
		Vasculitides	3, 4
	Other	Serious local/systemic AEFI	1, 2
	Body System	**Vaccine platform specific AESIs***	**Known/possible association with**
AESIs relevant to specific vaccine platforms for	Neurologic	Aseptic meningitis Encephalitis/Encephalomyelitis	Live viral vaccines including measles
	Immunologic	Arthritis	r-VSV platform
	Other	Myocarditis	MVA platform

*Review of nucleic acid platforms, and protein platforms has not been conducted since these are novel

1.Proven association with immunization encompassing several different vaccines.

2.Proven association with vaccine that could theoretically be true for CEPI vaccines under development.

3.Theoretical concern based on immunopathogenesis.

4.Theoretical concern related to viral replication during wild type disease.

5.Theoretical concern because it has been demonstrated in an animal model with one or more candidate vaccine platforms.

AESIs related to specific target disease of COVID-19			
	Body system	**COVID-19 (red font identifies AESI with existing published Brighton Case Definitions)**	**Rationale for inclusion as an AESI (see footnote)**
AESI relevant to COVID-19	Immunological	Enhanced disease following immunization	1 formalin-inactivated measles/RSV vaccines; HIV vaccine 2 Chimeric Yellow Fever Dengue vaccine 5 mouse models SARS/MERS-CoVs
		Multisystem inflammatory syndrome in children	3, 4
	Respiratory	Acute respiratory distress syndrome (ARDS)	3, 4
	Cardiac	Acute cardiac injury including: o Microangiopathy o Heart failure and cardiogenic shock o Stress cardiomyopathy o Coronary artery disease o Arrhythmia o Myocarditis, pericarditis	3, 4
	Hematologic	Coagulation disorder o Deep vein thrombosis o Pulmonary embolus o Cerebrovascular stroke o Limb ischemia o Hemorrhagic disease	3, 4
	Renal	Acute kindney injury	3, 4
	Gastrointestinal	Liver injury	3, 4
	Neurologic	Guillain Barré Syndrome	4
		Anosmia, ageusia	3, 4
		Meningoencephalitis	1, 4
	Dermatologic	Chilblain-like lesions	3, 4
		Single organ cutaneous vasculitis	3, 4
		Erythema multiforme	3, 4

1.Proven association with immunization encompassing several different vaccines.

2.Proven association with vaccine that could theoretically be true for CEPI vaccines under development.

3.Theoretical concern based on immunopathogenesis.

4.Theoretical concern related to viral replication during wild type disease.

5.Theoretical concern because it has been demonstrated in an animal model with one or more candidate vaccine platforms.

For AESIs with severe condition further information will be requested by the sponsor according to the recommendations of the Brighton Collaboration (https://brightoncollaboration.us/wp-content/uploads/2020/06/SPEAC_D2.3_V2.0_COVID-19_20200525_public.pdf) and must be provided by the study site. This information should be captured in the safety database.

Reporting procedure for AESIs for investigators are the same as for SAEs (section 9.9.1).

All AEs must be followed to closure (i.e. the participant's health has returned to his/her baseline status or all variables have returned to normal), an outcome is reached, stabilization (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained, or until the end of the trial. All related SAEs must be followed to closure (i.e. the participant's health has returned to his/her baseline status or all variables have returned to normal), an outcome is reached, stabilization (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained, regardless of whether the participant is still participating in the clinical trial and clinical judgment indicates that further follow-up is not warranted. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

9.8.1 Severity categorization

The severity of AEs must be recorded. If the severity of an AE/SAE changes, or if there are any other changes then these must be made within the same AE record. Also, only the highest severity needs to be recorded. Worsening of pre-treatment events from the medical history, after initiation of IMP, must be recorded as new AEs.

The medical assessment of severity for AEs not identified in the grading Tables the following definitions will apply:

Grade 1	mild	A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living (No interference with activity).
Grade 2	moderate	A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant (Some interference with activity not requiring medical Intervention).
Grade 3	severe	A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention (Prevents daily activity and requires medical Intervention).
Grade 4	Potentially life threatening	A type of AE causing inability to perform basic self-care functions OR medical or operative intervention indicated to prevent permanent impairment, persistent disability OR ER visit or hospitalization (ER visit or hospitalization).
Grade 5	Death	A type of AE that results in death.

The term “severe” is here used to describe the severity/intensity of the specific event; it is not the same as “serious”, which is based on participant/event outcome or action criteria.

Toxicity grading scale for local adverse events

Table 4 Toxicity grading scale for local adverse events

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness*	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling**	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

*In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
**Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement. From the FDA’s 2007 voluntary guidance: https://www.fda.gov/media/73679/download

Toxicity Grading scale for physical observations

Table 5 Toxicity grading scale for physical observations and vascular disorders

Observation	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Fever (orally)	38.0 °C - 39.0 °C	> 39.0 °C - 40.0 °C	> 40.0 °C for ≥ 24 hours	> 40.0 °C for ≥ 24 hours	Death
Tachycardia (bpm)*	Asymptomatic, intervention not indicated	Symptomatic, non-urgent medical intervention indicated	Urgent medical intervention indicated	Life-threatening consequences, urgent intervention indicated	Death
Bradycardia (bpm)**	Asymptomatic, intervention not indicated	Symptomatic, medical intervention indicated	Severe, medically significant, urgent medical intervention indicated	Life-threatening consequences, urgent intervention indicated	Death
Hypertension	**Adult:** Systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg	**Adult:** Systolic BP 140 - 159 mmHg or diastolic BP 90 - 99 mmHg if previously WNL; change in baseline medical intervention indicated; recurrent or persistent (≥24 hrs); symptomatic increase by >20 mmHg (diastolic) or to >140/90 mmHg; monotherapy indicated initiated	**Adult:** Systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated	**Adult and Pediatric:** Life-threatening consequences (e.g. malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated	Death
Hypotension	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention indicated; hospitalization indicated	Life-threatening consequences and urgent intervention indicated	Death

Definitions	
Fever	Fever is defined as the endogenous elevation of at least one measured body temperature of ≥38 °C.
Tachycardia	A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute.
Bradycardia	A disorder characterized by a dysrhythmia with a heart rate less than 60 beats per minute.
Hypertension	A disorder characterized by a pathological increase in blood pressure; a repeatedly elevation in the blood pressure exceeding 140 over 90 mmHg.
Hypotension	A disorder characterized by a blood pressure that is below the normal expected for an individual in a given environment.

Source: CTCAE Version 5.0
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

Toxicity grading scale for systemic AEs excluding the physical observations listed above

Table 6 Toxicity grading scale for systemic AEs

Systemic sign/symptom	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents dailyactivity	ER visit or hospitalization
Nausea/vomitting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization

Systemic Illness	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

From the FDA's 2007 voluntary guidance: (https://www.fda.gov/media/73679/download)

Systemic sign/symptom	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Arthralgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Chills	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Abdominal Pain	No interference with activity	Some interference with activity not required medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

Analogous to the FDA's 2007 voluntary guidance.

9.8.2 Relationship categorization

An investigator assesses each AE for its relationship to the IMP.

The assessment of the relationship of an AE to the administration of IMP is a clinical decision based on all available information at the time of and after the occurrence of the event. The factors which may be considered when evaluating the relationship of an AE to the IMP include: time from exposure to IMP until onset of the event; recovery or improvement on discontinuation of IMP; availability of alternative explanations such as underlying or intercurrent diseases; concomitant medications or treatments; pharmacology and pharmacokinetic of the IMP; known response pattern for this class of drug; recurrence on reintroduction of the IMP.

The AE should be classified as related if a reasonable possibility of a causal relationship between the AE and IMP exists. This means that there are facts (evidence) or arguments to suggest a causal relationship.

If there is no reasonable possibility for suggesting a relationship, then the AE should be classified as 'not related'. The causality must be documented in the source document.

The following additional guidance may be helpful:

Term	Relationship	Description
Related – reasonable possibility	Yes	The temporal relationship between the event and the administration of the IMP is compelling or follows a known or suspected response pattern to that product, and the event cannot be explained by the participant's medical condition, other therapies, or accident.
Not Related – no reasonable possibility	No	The event can be readily explained by other factors such as the participant's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the IMP and the event.

If the investigator decides there is a reasonable causal relationship, they should further assess the relationship of an AE to the IMP according to the following categories:

Levels	Definition
Very likely/ certain	Clinical event with a **proximal, biologically plausible, time** relationship to vaccine administration and which **cannot be explained** by concurrent disease or other drugs or chemicals.
Probable	Clinical event with a **relatively brief interval between vaccination and the event** and which is **unlikely to be attributed** to concurrent disease or other drugs or chemicals.
Possible	Clinical event with a **relatively brief interval between vaccination and the event** but which **could also be explained** by concurrent disease or other drugs or chemicals.

9.8.3 Outcome categorization

The outcome of AEs must be recorded during the course of the study in the eCRF. Outcomes are as follows:

- Recovered/resolved
- Recovering/resolving
- Resolved with sequelae
- Not recovered/not resolved/ongoing
- Fatal
- Unknown

9.8.4 Clinical laboratory evaluations

A change in the value of a safety laboratory investigation can represent an AE if the change is clinically relevant or if, during treatment with the IMP, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the IMP, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are abnormal laboratory values which were not present at baseline, further clinical or laboratory investigations should be performed until the values return to within reference range or until a plausible explanation (e.g., concomitant disease) is found for the pathological laboratory values.

The investigator should decide, based on the above criteria and the clinical condition of a participant, whether a change in a laboratory parameter is clinically significant and therefore represents an AE.

9.8.5 Procedures in case of pregnancy

All pregnancies that occur during the trial in female trial participants should be followed up. Although pregnancy is not an SAE, information about any pregnancy should be reported promptly to CTC North Safety Department on the same timeline as an SAE (without undue delay but not later than within 24 hours of the first awareness of the event) using the pregnancy form filed in the investigator site file. In case the pregnant woman gives her informed consent regarding the data collection, monitoring of the pregnant participant shall continue until the conclusion of the pregnancy. Study vaccination will be discontinued for the pregnant participant. Should pregnancy result in a congenital abnormality, birth defect, miscarriage, or medically indicated abortion an SAE must be submitted to sponsor using the SAE reporting procedures described in section 9.9.1.

9.8.6 Abuse, misuse, overdose, and medication error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor within 24 hours after first awareness by sending an e-mail to pharmacovigilance@ctc-north.com and reporting a PD (please refer to section 9.5) whether or not they result in an AE/SAE.

Misuse - Intentional or unintentional use of a study medication other than as directed or indicated at any dose, which is at or below the dose defined for overdose. (Note: this includes a situation where the study medication is not used as directed at the dose prescribed by the protocol.)

Overdose - Intentional or unintentional intake of a dose of study medication higher than the protocol prescribed dose for each participant.

Medication Error - A mistake made in prescribing, dispensing, administration, and/or use of the study medication.

Administration of an expired product should be considered as a reportable medication error.

Cases of participants missing doses of product are not considered reportable as medication errors.

9.9 Serious adverse event (SAE) and AESI procedures

9.9.1 Reporting procedures

All initial SAE and AESIs from the time of first administration of the IMP until the last follow-up visit of the participant must be reported by the investigator to the CTC North Safety Department without undue delay but not later than within 24 hours of the first awareness of the event. All SAE follow-up reports must be reported in a timely manner. If the investigator becomes aware of a SAE considered related to the IMP after last visit of the participant, the investigator must report this event to the sponsor. This event has to be documented in the safety database and if this event fulfils the criteria of a SUSAR, the event must be reported accordingly.

The investigator must complete, sign, and date the SAE Form or AESI Form provided in the eCRF and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: source documents are not to be sent unless requested) and send the form via the eCRF form to the sponsor delegated responsible Safety Department. The report will be sent by the eCRF system after an investigator signs the form by clicking the Review A button in the eCRF. All events should be followed up until closure via detailed follow-up reports that must be sent to the sponsor in a timely manner using the appropriate eCRF forms.

In case the reporting via eCRF is not possible due to technical issues with the eCRF reporting system, reporting may be handled via E-mail (pharmacovigilance@ctc-north.com) or fax (+49 (0) 40 524719 222). As soon as the technical issues are resolved all data has to recorded and transmitted additionally via eCRF.

CTC North forwards all SAEs for review to the medical monitor of the sponsor. The medical monitor assesses SAEs causality and expectedness and returns the SAE documentation to the CTC North Safety Department.

Additional information according to the Brighton Collaboration for severe AESIs only need to be captured in the safety database, not in the eCRF.

In case an SAE is considered to be a SUSAR, on behalf of the sponsor CTC North has to inform the CA, the ECs and the PIs about the SUSAR according to the applicable law and within the appropriate timelines.

9.9.2 Serious adverse event (SAE) definition

A serious adverse event (SAE) is any untoward medical occurrence (whether considered to be related to IMP or not) that follows immunization and at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event, i.e. an event that may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Hospitalizations which are the result of elective or previously scheduled surgery for pre-existing conditions which have not worsened after initiation of treatment should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE.

However, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meets serious criteria must be reported as SAE(s).

9.9.3 AE/ SAE onset and stop dates

The AE onset date is defined as the date on which an adverse event begins. The SAE onset date is defined as the date the event meets serious criteria. SAE stop date is defined as the date the event no longer meets serious criteria. The AE stop date is the date the symptoms are resolved or resolved with sequelae/event is no longer present. In the case of hospitalizations, the hospital admission and discharge dates are considered the SAE onset and SAE stop dates, respectively.

9.9.4 Fatal outcome

Any SAE that results in the participant's death (i.e. the SAE was noted as the primary cause of death) should have fatal checked as an outcome and the date of death recorded as the stop date. For all other events ongoing at time of death that did not contribute to the participant's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAEs that results in the participant's death or any ongoing events at the time of death, the action taken with the IMP should be recorded as "dose not changed" or "not applicable" (if the participant never received IMP).

9.9.5 Serious adverse reaction (SAR)

An AE (expected or unexpected) that is both serious and, in the opinion of the reporting investigator or sponsor, believed that there is a reasonable possibility that the IMP caused the event, based on the information provided.

9.9.6 Suspected unexpected serious adverse reaction (SUSAR)

Adverse events are SUSARs if the following three conditions are met:

- The event must be serious;
- There must be a reasonable possibility that one IMP caused the event, regardless of the administered dose;
- The adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the safety information as recorded in the reference safety information of the IMPs.

9.9.7 Regulatory agency, independent Ethics Committee, and investigative site reporting

The sponsor is responsible for SUSAR reporting to the relevant Regulatory Authorities/European Union (EU) central Independent ECs and investigators participating in the clinical trial.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life-threatening cases, the term will be maximally 7 days for a preliminary report with another 8 days for completion of the report.

9.10 Data quality assurance

9.10.1 Quality assurance system

Protocol development, case report form and trial master file, investigator site file, content of participant information and consent, application for Ethics approval, monitoring and data processing will follow the Standard Operating Procedures (SOP) of the CTC North. Statistics will follow sponsor SOPs.

The quality management system of CTC North has been repeatedly audited by sponsors as well as by local authorities.

Standard phases of the study may be subject to audits by the quality assurance unit (QAU) of the sponsor or the CTC North.

9.10.2 Monitoring

During the study, the monitor/clinical research associate will visit the investigational site regularly to check the completeness of participant records, the accuracy of entries in the eCRF, the adherence to the protocol and to ICH-GCP, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key trial personnel must be available to assist the monitor during these visits. The investigator must maintain source documents for each participant in the study, consisting of case and visit notes containing demographic and medical information, laboratory data and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the participant's file. Data not requiring a written or electronic record will be defined before study start and will be recorded directly in the eCRFs, which will be documented as being the source data. The investigator must also keep the original of the signed informed consent form. The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables.

A combination of remote monitoring and regular on-site visits will be performed depending on the possibility for on-site visits due to the current COVID-19 pandemic. Close-out visits are planned as on-site visits. The frequency and kind of monitoring visits will depend on the current situation. The detailed extent of the monitoring and the risk-based approach considering the COVID-19 pandemic situation and its influence on the daily life and the health system will be defined in the monitoring plan.

9.10.3 Documentation and data collection

An eCRF will be prepared to report all data required by the protocol.

Site staff will transfer the study data from the source documents into the eCRF and will check eCRF entries for completeness. Completed eCRF modules will be electronically signed by an investigator in order to ensure data entry accuracy.

Corrections to source data documents will be dated and initialed. Reasons for the corrections should be given. Corrections to eCRF entries must be electronically signed and reasons for the corrections must be provided. The date on which the correction was performed is automatically recorded by the system's audit trail.

A study monitor will review source data and the eCRF data for consistency, completeness and accuracy during the monitoring visits (source data verification). The study monitor will point out discrepancies between source data and the data captured in the eCRF. The monitor will issue electronic queries to site staff in order to initiate discrepancy resolution. Discrepancies which require eCRF data corrections have to be resolved by authorized site personnel by answering the queries and changing the respective eCRF entries. These query management and query resolution activities are also automatically recorded by the system's audit trail.

If a participant is a screening failure (according to section 9.7.1.1), only baseline characteristic data of this participant may be entered in the eCRF and will not be analyzed in the CSR.

Data generated by this study must be available for inspection and audits by representatives of other national and local Health Authorities and the sponsor, if appropriate.

Participants will be identified on eCRFs and other documents submitted to the sponsor or organizations working on behalf of the sponsor only by participant number, not by name or initials. Documents not to be submitted to the sponsor or organizations working on behalf of the sponsor that identify the participant (e.g., the signed informed consent) must be maintained in confidence at the study site.

9.10.4 Data management

Data management will double check all eCRF entries as defined in the data management plan (DMP) and the data validation plan (DVP).

Quality control and data validation procedures such as programmed automatic edit and consistency checks ensure data validity and accuracy immediately at the point of entry into the clinical database. The database application which is used to capture electronic study data is fully 21 CFR part 11 compliant. Thus, it is access restricted, demands electronic signatures, maintains an electronic audit trail and provides appropriate backup functionalities. Details of the application and eCRF configuration and all further data management procedures will be described in the DMP.

The database will only be locked after all queries and discrepancies that may occur during data entry are resolved.

Upon request safety reports and interim analysis will be generated and provided to the respective members of the SSC.

After database lock, the data in the study database will be exported and SPSS datasets will be compiled for statistical analysis. The data will be exported in SPSS transport files or other SPSS-compatible format and transferred electronically to the responsible biometrician for statistical analysis. The locked SPSS database will be used to generate the participant listings, tabulations, and analyses.

9.10.5 Archival of documents

The study site will maintain the trial documents and take measures to prevent accidental or premature destruction of these documents according to the respective SOPs.

All documents related to the study will be retained by the sponsor until at least 15 years after the end of the study.

The sponsor will receive an electronic copy of the eCRF for archival and study sites will receive and electronic copy of the site eCRF data for archival

If documents shall be retained for a longer period, it is the responsibility of the sponsor to inform the study site when these documents no longer need to be retained.

In case of any change concerning the archiving modalities the study site has to inform the sponsor immediately.

9.11 Statistical methods planned in the protocol and determination of sample size

9.11.1 Statistical and analytical plan

Details for the statistical evaluation of the results will be given in a separate statistical analysis plan (SAP).

9.11.1.1 Software to be used

The data will be analyzed using SAS 9.4 or later, Stata 16.0 or later, or R 3.6.3 or later by a biometrician of the Institute of Medical Biometry and Epidemiology.

9.11.1.2 Analysis populations

Eligibility of participants will be determined within the data review meeting (DRM). The following populations will be investigated.

- Safety population: All participants who received at least one vaccination will be part of the safety population.
- Per-protocol population: All participants who received one vaccination (Part B) or two vaccinations (Part A), respectively, and for whom no major protocol deviation was reported will be part of the per-protocol population.

All safety endpoints will be investigated in the safety population. Immune response endpoints will be investigated in the per-protocol population only.

9.11.1.3 Statistical analyses

All analyses will be conducted separately for the two study parts Part A and Part B.

The primary objective of the study will be the assessment of safety, tolerability and reactogenicity following injection.

All safety information will be listed by participant and by treatment group.

Data will be summarized with respect to demographic and baseline characteristics, immune response, and safety data. Safety data comprises AEs, laboratory tests, vital signs, and physical examination. AE data will be reported tabulated by system organ class and preferred term using MedDRA coding.

Exposure to study medication will be summarized by number of injections and dose intensity using descriptive statistics. Reasons for not giving all protocol required injections will be presented.

Immunogenicity will be determined by levels of anti-SARS-CoV-2-S antibodies in response to vaccination.

For continuous variables, mean, standard deviation (SD), coefficient of variation (CV), or geometric mean (GeoM) and geometric coefficient of variation (GeoCV), as appropriate, as well as minimum, maximum and median will be reported per treatment group.

Unless otherwise specified, baseline is defined as the time point closest but prior to the first administration of the vaccine.

Categorical variables will be summarized by treatment group in frequency tables (absolute and relative (%) frequencies).

Number of related AEs between groups will be compared using descriptive statistics. For the total frequency of adverse events by treatment group 95% Miettinen-Nurminen confidence intervals will be presented. Furthermore, humoral response based on number of responders, mean, and median of ELISA and virus neutralization assays will be compared between groups using descriptive statistics.

Furthermore group comparisons might be performed using Student's t-tests, ANOVA or baseline adjusted ANCOVA models for continuous variables and chi square tests for categorical variables. All p-values resulting from statistical tests will be interpreted as descriptive measures only and hence, adjustments for multiplicity are not considered. Log transformation is applied before evaluation if required.

If deemed necessary, 95% Wald confidence intervals will be provided for means (metric variables) and proportions (categorical variables).

The results will be summarized in a report according to the ICH E3 guideline.

Further details regarding the analyses will be provided in the SAP.

9.11.1.3.1 Missing data

Subjects who withdraw or are withdrawn from the study prior to the first vaccine injection (Parts A and B), or subjects who received the first injection but are withdrawn without medical reasons prior to the second injection (Part A only), will be replaced. When a subject withdraws or needs to be withdrawn from the study after the first vaccine injection and before the planned end of the study period, all efforts will be made to complete the end-of-study evaluation at the time of the subject's withdrawal and to receive complete data regarding adverse events. For safety data (i.e. SAEs) we therefore do not expect a substantial amount of missing data (namely in more than 5% of participants) which justify any imputation methods. If there are missing values related to adverse events of subjects not lost to follow-up, they are considered as absence of the same.
However, if there will be isolated missing values, the outcome of the SSC review of safety and immunogenicity data after day 42, on which the decision to move to Phase II of the study will be based, should not be affected. Therefore, no imputation or sensitivity analyses are planned in case of missing data.

9.11.1.3.2 Determination of sample size

For the FIH study, no formal criteria are available in order to determine the sample size. Nevertheless, most FIH trials involve a small number of healthy subjects (n<20 per arm) [11]. The MVA vaccine is licensed and has been tested in various clinical trials as listed in table 10 of the IB [8].

With 8 subjects the 95% confidence interval can be estimated with a precision of at least 0.69 (in case of a rate of 50%) or 0.52 for the rarest events (1 event in 8 subjects) (Confidence Intervals for One Proportion, PASS 2008).

With 12 subjects the 95% confidence interval can be estimated with a precision of at least 0.58 (in case of a rate of 50%) or 0.38 for the rarest events (1 event in 12 subjects) (Confidence Intervals for One Proportion, PASS 2008).

10 CHANGES IN THE CONDUCT OF THE CLINICAL TRIAL OR PLANNED ANALYSIS

Modifications of the protocol are permitted only if they are authorized by the sponsor and the Coordinating investigator in writing.

Deviations and changes to the study protocol will be classified by the sponsor and the study center as:

Note-to-File: This refers to clarifications which are not considered changes of the protocol.

Study protocol amendment: This refers to changes of the protocol. If they fulfill the criteria as set out in applicable law for definition as substantial amendment they need to be approved by the EC, the CA or both. Changes to the study protocol may also induce revision of the participant informed consent form. Accordingly, participants undergoing trial assessment procedures at the time of implementation of the change have to be given the amended version and have to be asked for consent to continue on this amended trial.

A “substantial amendment” is defined as an amendment to the terms of the applicable regulations.

All substantial amendments will be notified to the relevant authorities.

11 SAFETY STEERING COMMITTEE (SSC)

During the trial a SSC will be established.The SSC will review and judge the safety, tolerability, and immunogenicity after 50% of the subjects have been completed the first 2 weeks of the study.

In addition, an SSC meeting will be conducted whenever safety relevant data occur that might have an influence on the trial.

At a minimum the holding rules (criteria for termination of the study) specified in the protocol will automatically apply (if activated) for not proceeding with a higher dose.

The decisions of the SSCmeeting will be briefly summarized by CTC North and signed by all members involved in the meeting and the decision. Relevant findings will be reported to the responsible authorities.

12 REPORTS

All reports to the sponsor will be in English. The sponsor will receive the original CSR.

The CSR is the property of the sponsor. Publication of the report or of part of it may only be allowed when authorized by the sponsor.

12.1 Clinical study report

All clinical, analytical and statistical results will be presented in a CSR. The outline of this report will accord to the ICH-GCP E3 document "Structure and Content of Clinical Study Reports" in its current version. Within a year upon completion of the clinical trial, a summary of the CSR will be sent to the ECs and CAs uploaded in the EU database as required by appropriate law(s).

12.2 Additional reports

Upon completion of the study, a short report will be sent to the ECs, stating any undesired event and indicating whether study objectives have been attained. Short reports to the authorities after study termination will be provided as required by law. An interims analysis may be performed.

13 REFERENCES

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ANNEX I INVESTIGATOR PROTOCOL ACKNOWLEDGMENT

I have read this protocol and hereby acknowledged the protocol and I agree to conduct the study in compliance with the protocol. I confirm that I will provide the study team with a copy of the protocol and will forward any protocol amendments that I acknowledge to any team members involved in the conduct of the trial.

Name investigator

Institution

Date and Signature

ANNEX II DEFINITION OF COVID-19 DISEASE IN THE STUDY

COVID-19-like symptoms include: fever[1], cough, dyspnea, anosmia/ageusia, sore throat, diarrhea[1], nausea/vomiting[1], headache[1], congested/runny nose.

[1] These symptoms will not be considered COVID-19 like within 7 days post vaccinations.

Fever, chills, cough and dyspnea will be considered of any duration, all other symptoms should be present of at least 48 hours.

1. **Symptomatic COVID-19:** Positive SARS-CoV-2 PCR result and at least 1 COVID-19-like symptom.
2. **Asymptomatic COVID-19**: Positive SARS-CoV-2 PCR result without clinical symptoms, or evidence of SARS-CoV-2 infection as documented by N-antigen seroconversion.
3. **SARS-CoV-2 infection:** N-antigen seroconversion in an at baseline N-antibody negative participant.