Official Protocol Title:	A Phase 1/Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Trial to Evaluate the Safety, Tolerability and Immunogenicity of V591 (COVID-19 Vaccine) in Healthy Younger and Older Participants
NCT number:	NCT04498247
Document Date:	19-Feb-2021

Title Page

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Protocol Title: A Phase 1/Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Trial to Evaluate the Safety, Tolerability and Immunogenicity of V591 (COVID-19 Vaccine) in Healthy Younger and Older Participants

Protocol Number: 001-04

Compound Number: V591

Sponsor Name:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or MSD)

Legal Registered Address:

One Merck Drive

P.O. Box 100

Whitehouse Station, New Jersey, 08889-0100, U.S.A.

Regulatory Agency Identifying Number(s):

IND	24420
EudraCT	2020-003493-46

Approval Date: 19 February 2021

Sponsor Signatory

Typed Name: Title:	Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
V591-001-04	19-FEB-2021	The protocol amendment 03 is being amended to document the early study termination as permitted under flexible protocol language. Additionally, "plaque reduction neutralization test (PRNT)" is changed to "Pseudo-virus Neutralization Assay (PNA)" throughout the protocol. This change and other minor clarifications in this protocol amendment are unrelated to decision to terminate the study early.
V591-001-03	02-OCT-2020	The protocol amendment 02 is being amended to revise the derived date for the time window between the previous vaccine study to the current screening visit in exclusion criteria 25 and to revise BMI rounding criteria in order to optimize recruitment of Part 2B in the study.
V591-001-02	14-SEP-2020	The protocol amendment 01 is being amended to expand age range for Part 2B (reduce lower limit to >55 years old). Additionally, clarifications to the inclusion/exclusion criteria and the criteria that will trigger a study pause, as well corrections of typographical errors, are included in the amendment.
V591-001-01	13-AUG-2020	The original protocol is being amended to revise several exclusion criteria, add a second vaccination of 10^5 $TCID_{50}$ on Day 169 for participant receiving the lowest first dose of 10^4 $TCID_{50}$ Panel (the new Panel F) and specify sentinel dosing arrangements in Panels A, B and Panel E (the highest single dose panel).
Original Protocol (V591-001-00)	17-JUL-2020	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: [04]

Overall Rationale for the Amendments:

An evaluation of available Day 29 immunogenicity data, including both ELISA and a pseudo-neutralization assay, indicated that the immune responses elicited by V591 were inferior to those following natural infection and to those reported for other SARS-CoV-2/COVID-19 vaccines. Thus, V591 was not predicted to protect against disease caused by SARS-CoV-2. Based on these data, the Sponsor has decided to terminate the V591-001 study, thereby allowing participants to seek COVID-19 vaccinations outside of the study. V591 was generally well-tolerated, and the decision to discontinue this trial was based solely on the immunogenicity data. This amendment is intended to document the termination of the study as permitted under flexible protocol language. Participants will complete activities through at least Day 56, which includes all protocol specified safety laboratory and routine AE assessments. Participants will not be actively followed beyond end of trial activities (to occur on or after Day 56); spontaneous reporting of SAEs and other protocol-specified events may continue through the protocol specified durations. In place of an Interim Analysis of data, the final study analysis will be performed on the collected dataset through at least Day 56.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 1.3, Schedule of Activities 3, Hypotheses, Objectives, and Endpoints 4.1, Overall Design 4.2.1.2 Immunogenicity Endpoints 8.2.1, Serum Neutralizing Antibodies Measured by PNA	Changed “plaque reduction neutralization test (PRNT)” to “Pseudo-virus Neutralization Assay (PNA)” throughout the protocol. Added PNA in Abbreviation List	Pseudo-virus Neutralization Assay (PNA) will be used to measure serum neutralization antibodies against SARS-CoV-2 spike protein. Both PNA and PRNT test for the same neutralization antibodies and report an NT50 titer. There is no impact on data report for the assay change.

Section # and Name	Description of Change	Brief Rationale
8.11.5, Critical Procedures Based on Study Objectives: Timing of Procedure 9, Statistical Analysis Plan 10.8, Appendix 8: Blood Volume Table Appendix 10: Abbreviations		
6.7.1, Stopping Rules 8.3.5 Vaccine Report Card	Removed "severe" from "Severe (Grade 3 or higher) at the beginning of bullets 4 and 5. Removed "(severe)" after grade 3 in the last sentence in the 2nd paragraph.	Toxicity grade is used for the stopping rule assessment. In some case intensity may not match toxicity grade.
8.11.4, Poststudy	Added text to clarify required procedures at the final post-study visit at least 56 days post the last vaccination.	The sponsor has decided to terminate the study based on the immunogenicity results. This clarification is provisioned by the language as indicated in Section 8.11.6 Study Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters: "Modification of the immunogenicity sampling schedule, including omitting Timepoints"

Section # and Name	Description of Change	Brief Rationale
10.2, Appendix 2: Clinical Laboratory Tests	Changed "HbA1c" to "HbA1c (required at screening only)" in the table "Protocol-required Safety Laboratory Assessments".	HbA1c measurement is required at screening visit only in order to fulfill exclusion criteria #26. The inclusion of HbA1C in Appendix 2, Table 14 is not intended to indicate that it is a Protocol-required Safety Laboratory Assessment that must be regularly assessed along with hematology and chemistry assessments.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 1/Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Trial to Evaluate the Safety, Tolerability and Immunogenicity of V591 (COVID-19 Vaccine) in Healthy Younger and Older Participants

Short Title: Phase 1/Phase 2 Dose Ranging Trial to Assess Safety, Tolerability, and Immunogenicity of V591 (COVID-19 Vaccine) in Healthy Participants

Acronym: NA

Hypotheses, Objectives, and Endpoints:

Healthy male participants and female participants between the ages of 18-55 years (inclusive) of age in Parts 1 and 2A (younger adults) and > 55 years of age in Part 2B (older adults)

Primary Objectives	Primary Endpoints
To assess the safety and tolerability of V591 compared with placebo	Solicited injection site adverse events from Day 1 through Day 5 after any study intervention Solicited systemic adverse events from Day 1 through Day 14 after any study intervention Unsolicited adverse events from Day 1 through Day 28 after any study intervention SAEs from Day 1 throughout the duration of study Medical attended AEs (MAAEs) collected from Day 1 throughout the duration of study
Secondary Objectives	Secondary Endpoints
To compare the humoral immunogenicity of V591 with placebo at Day 29 (all panels) and Day 85 (Panels A, B, I, and J) or Day 197 (Panels K and L)	Anti-SARS-CoV-2 spike serum neutralizing antibody (nAb) responses, as measured by Pseudo-virus Neutralization Assay (PNA) Anti-SARS-CoV-2 spike Immunoglobulin G (IgG) responses, as measured by ELISA
To evaluate the humoral immunogenicity of V591 at all timepoints with serum collection	Anti-SARS-CoV-2 spike serum nAb responses, as measured by Pseudo-virus Neutralization Assay (PNA) Anti-SARS-CoV-2 spike IgG responses, as measured by ELISA

Overall Design:

Study Phase	Phase 1/Phase 2
Primary Purpose	Prevention
Indication	COVID-19
Population	Healthy adult participants
Study Type	Interventional
Intervention Model	Sequential This is a multi-site study.
Type of Control	Placebo
Study Blinding	Double-blind
Blinding Roles	Participants or Subjects Investigator Outcomes Assessor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 30 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 260 participants will be allocated/randomized.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Administration	Vaccination Regimen	Use
Part 1 (18 to 55 years old) Sentinel Cohort						
Panel A	V591	$1 \cdot 10^5$ $TCID_{50}$	2 doses	IM	IM injection on Day 1 and Day 57	Experimental Treatment
Panel B	V591	$1 \cdot 10^6$ $TCID_{50}$				
Panels A, B	Placebo	NA	2 doses	IM	IM injection on Day 1 and Day 57	Placebo
Part 2A (18 to 55 years old)						
Panel C	V591	$1 \cdot 10^5$ $TCID_{50}$	Single Dose	IM	Single IM injection on Day 1	Experimental Treatment
Panel D	V591	$1 \cdot 10^6$ $TCID_{50}$				
Panel E	V591	$1 \cdot 10^7$ $TCID_{50}$				
Panels C-E	Placebo	NA	Single Dose	IM	Single IM injection on Day 1	Placebo
Panels F	V591	$1 \cdot 10^4$ $TCID_{50}$ / $1 \cdot 10^5$ $TCID_{50}$	2 doses	IM	IM injection on Day 1 and Day 169	Experimental Treatment
Panel F	Placebo	NA	2 doses	IM	IM injection on Day 1 and Day 169	Placebo
Part 2B (> 55 years old)						
Panel G	V591	$1 \cdot 10^5$ $TCID_{50}$	Single Dose	IM	Single IM injection on Day 1	Experimental Treatment
Panel H	V591	$1 \cdot 10^6$ $TCID_{50}$				
Panes G and H	Placebo	NA	Single Dose	IM	Single IM injection on Day 1	Placebo
Panel I	V591	$1 \cdot 10^5$ $TCID_{50}$	2 doses	IM	IM injection on Day 1 and Day 57	Experimental Treatment
Panel J	V591	$1 \cdot 10^6$ $TCID_{50}$				
Panels I and J	Placebo	NA	2 doses	IM	IM injection on Day 1 and Day 57	Placebo
Panel K	V591	$1 \cdot 10^5$ $TCID_{50}$	2 doses	IM	IM injection on Day 1 and Day 169	Experimental Treatment
Panel L	V591	$1 \cdot 10^6$ $TCID_{50}$				
Panels K and L	Placebo	NA	2 doses	IM	IM injection on Day 1 and Day 169	Placebo

Abbreviations: IM: intramuscular; NA=not applicable; $TCID_{50}$=Median tissue culture infectious dose

Other current or former name(s) or alias(es) for study intervention(s) are as follows: NA

Total Number of Intervention Groups/ Arms

260 participants (10 in Part 1 younger sentinel cohort, 100 in Part 2A younger cohort and 150 in Part 2B older cohort) will participate in the study that will include a total of 4 dose-levels and 12 Panels. Under each panel, participants will be randomized to receive V591 or placebo in a 4:1 ratio.

Duration of Participation	Each participant will participate in the study for approximately 15 to19 months for 2-dose panels and 13 months for 1-dose panels from the time the participant provides documented informed consent through the final contact. After a screening phase of 28 days, each participant will be receiving either 2 doses of assigned intervention (Panels A, B, F, I, J, K and L) or 1 dose of assigned intervention (Panels C-E and G-H). After the last vaccination, each participant will be followed for 12 months.

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	No
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No
Insert Other Oversight Committee	No
Study governance considerations are outlined in Appendix 1.	

Study Accepts Healthy Volunteers: Yes

A list of abbreviations used in this document can be found in Appendix 10.

1.2 Schema

The study design is depicted in Table 1 and Figure 1.

Table 1 V591/Placebo Dose Scheme

Part 1 (18 to 55 years old) Sentinel Cohort		**Part 2A (18 to 55 years old)**				**Part 2B (> 55 years old)**					
Sentinel/2-dose (Day 1, Day 57)		**1-dose**			**2-dose (Day 1, Day 169)**	**1-dose**		**2-dose (Day 1, Day 57)**		**2-dose (Day 1, Day 169)**	
Panel A (n=5)	**Panel B (n=5)**	**Panel C (n=25)**	**Panel D (n=25)**	**Panel E (n=25)**	**Panel F (n=25)**	**Panel G (n=25)**	**Panel H (n=25)**	**Panel I (n=25)**	**Panel J (n=25)**	**Panel K (n=25)**	**Panel L (n=25)**
10^5 $TCID_{50}$	10^6 $TCID_{50}$										
		10^5 $TCID_{50}$	10^6 $TCID_{50}$								
				10^7 $TCID_{50}$	10^4 $TCID_{50}$ / 10^5 $TCID_{50}$						
						10^5 $TCID_{50}$	10^6 $TCID_{50}$				
								10^5 $TCID_{50}$	10^6 $TCID_{50}$	10^5 $TCID_{50}$	10^6 $TCID_{50}$

FIH=first in human: n=number of participants; siDMC= Standing Internal Data Monitoring Committee; $TCID_{50}$=median tissue culture infectious dose

a) Within each panel, participants will be randomized to receive V591 or Placebo in a 4:1 ratio according to a computer-generated allocation schedule. The suggested doses may be adjusted downward based on evaluation of safety or tolerability data observed in previous participants.
b) Part 2A and Part 2B may initiate simultaneously based upon siDMC recommendation following review of at least seven days of safety data from n = 5 participants from each panel in Part 1 after their Day 1 vaccination. The second vaccination for Panel F and Panels I-L in Part 2B may initiate based upon siDMC recommendation following review of at least seven days of safety data from n = 5 participants from each panel in Part 1 after their Day 57 vaccination.
c) If available, Part 2A and Part 2B may initiate simultaneously based upon siDMC recommendation following review of safety and tolerability data from the COVID-19-101 study (V591 FIH study sponsored by the Institut Pasteur).
d) As safety precaution, the enrollment for Panel E, the highest dose panel, will begin Day 1 vaccination with at a minimum five sentinel participants.

1.3 Schedule of Activities

1.3.1 SoA for 1-Dose Panels

1-dose Panels C-E and G-H													
	Screening	**Study Day**										**Post-Study**	**Notes**
Scheduled Hour, Day, Week, etc.	Screening -28 to -1[b]	Day 1 Pre-dose	1	2[a]	8±1	15±1	29±3	57±3	85±3	115±7	211±14	365±14	**Section 8.11.5** Details on variance in procedure collection times
Administrative Procedures													
Informed Consent	X												**Section 8.1.1.1**
Informed Consent for Future Biomedical Research	X												**Section 8.1.1.2**
Demographics	X												
Inclusion/Exclusion Criteria	X	X											**Section 5.0**
Participant ID Card	X												**Section 8.1.3**
Medical History & Vaccination History	X												**Section 8.1.4**
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	**Sections 6.6, 8.1.5** Including Non-study Vaccination Review
Assignment of Screening Numbers	X												**Section 8.1.6**
Assignment of Randomization Number		X											**Sections 5.5 and 8.1.7**
COVID-19 Symptoms Training		X				X	X	X	X	X	X		**Section 8.3.7**
V591/Placebo Administration			X										**Section 8.1.8**
Clinical Procedures/ Safety Assessment													
Full physical examination	X	X									X	X	**Section 8.3.1.1**
Symptoms driven physical exam			X		X	X	X	X	X	X			**Section 8.3.1.2** Only to be conducted if participant symptoms warrant an exam or at investigator's discretion

1-dose Panels C-E and G-H													
	Screening	**Study Day**										**Post-Study**	**Notes**
Scheduled Hour, Day, Week, etc.	Screening -28 to -1[b]	Day 1 Pre-dose	1	2[a]	8±1	15±1	29±3	57±3	85±3	115±7	211±14	365±14	**Section 8.11.5** Details on variance in procedure collection times
Targeted physical examination of injection site			X		X	X							**Section 8.3.1.3** Panel E: At ~ 8 hours after vaccination on Day 1 for the five sentinel participants. All other panels: At ~1 hour postdose on Day 1.
Height	X												**Section 8.3.1.4**
Weight	X											X	**Section 8.3.1.4**
Semi-recumbent Vital Signs (Blood Pressure [BP] and Heart Rate [HR] and Respiratory Rate [RR]	X	X	X		X	X	X	X	X	X	X	X	**Section 8.3.2** Day 1 predose measurements will be done within ~ 3 hours of dosing. Day 1 postdose measurements: Panel E: At ~ 8 hours after vaccination on Day 1 for the five sentinel participants. All other Panels: will be taken minimum ~ 1 hour after vaccination.
Body Temperature	X	X	X	X	X	X	X	X	X	X	X	X	**Section 8.3.2.2 (temperature) and Section 8.3.5 (VRC)** Days 1 to 14 will be done by participant and recorded on the VRC. All other measurements will be done by clinic staff.
12-lead ECG	X	X											**Section 8.3.3** Day 1 Predose ECG will be done within 24 hours of dosing.
Distribute Paper Vaccination Report Card (VRC)			X										**Section 8.3.5 (VRC)** Paper VRC will be provided on Day 1.

1-dose Panels C-E and G-H													
	Screening	**Study Day**										**Post-Study**	**Notes**
Scheduled Hour, Day, Week, etc.	Screening -28 to -1[b]	Day 1 Pre-dose	1	2[a]	8±1	15±1	29±3	57±3	85±3	115±7	211±14	365±14	**Section 8.11.5** Details on variance in procedure collection times
Participant Record Paper VRC			X	X	X	X							**Section 8.3.5 (VRC)** On the VRC, the participant records information, including solicited and unsolicited (local and systemic) AEs, temperature, medications, and other complaints.
Review Paper VRC Data with Participant				X	X	X	X						**Section 8.3.5**
Collect Paper VRC From Participant							X						**Section 8.3.5**.
Postvaccination Observation Period			X										**Section 8.11.2** Panel E: Participants will be observed for ~ 8 hours postdose on Day 1 for the five sentinel participants. All other panels: Participants will be observed for ~ 1 hour postdose on Day 1.
Safety Phone Call Follow-up				X									**Section 8.3.6** On non-clinic days the, safety phone calls will follow up on AEs, any associated medications and vaccinations.
AE Review		X	X	X	X	X	X						**Sections 8.4 and Appendix 3**
SAE/ECI/MAAE review		X	X	X	X	X	X	X	X	X	X	X	**Sections 8.4 and Appendix 3** Nonserious AEs are to be reported from Days 1 to 28. SAEs/ECIs/MAAE and deaths are to be reported throughout the duration of an individual's study participation.
Laboratory Procedures/Assessments													
Serum β-hCG or urine pregnancy test (WOCBP only)	X	X										X	**Appendix 2** Pregnancy test on Day 1 to be performed before vaccination.

1-dose Panels C-E and G-H													
	Screening	**Study Day**										**Post-Study**	**Notes**
Scheduled Hour, Day, Week, etc.	Screening -28 to -1[b]	Day 1 Pre-dose	1	2[a]	8±1	15±1	29±3	57±3	85±3	115±7	211±14	365±14	**Section 8.11.5** Details on variance in procedure collection times
Serum FSH - (WONCBP only)	X												**Appendix 2** Confirmatory for WONCBP who are postmenopausal or oophorectomized.
HIV, hepatitis B and C screen (per site SOP)	X												**Appendix 2**
UDS/BDS/Alcohol Breath (per site SOP)	X												Any additional UDS/BDS are conducted per site SOP
Coagulation: Prothrombin time/International Normalized Ratio	X												**Appendix 2**
Hematology	X				X	X	X	X	X			X	**Section 8.3.7 and Appendix 2**
Urinalysis	X				X	X	X	X	X			X	**Section 8.3.7 and Appendix 2**
Chemistry	X				X	X	X	X	X			X	**Section 8.3.7 and Appendix 2**
Screening and SARS-CoV-2 Test													
SARS-CoV-2 PCR	X												**Appendix 2**
Immunogenicity													
Serum Collection for Neutralizing Antibodies by PNA		X				X	X	X	X	X	X	X	Leftover main study serum samples to be stored for FBR
Serum Collection for Total Anti-spike IgG and Total Anti-N IgG Antibodies by ELISA		X				X	X	X	X	X	X	X	Leftover main study serum samples to be stored for FBR
Serum collection for Immunological Assessments (Panels C, D, G, and H only)		X			X								Leftover main study serum samples to be stored for FBR
PBMC collection for Immunological Assessments (Panels C, D, G, and H only)		X					X						Leftover main study PBMC samples to be stored for FBR
Biomarkers													
Blood (DNA) for Future Biomedical Research		X											**Section 8.9** Collect from enrolled participants only.

1-dose Panels C-E and G-H													
	Screening	**Study Day**										**Post-Study**	**Notes**
Scheduled Hour, Day, Week, etc.	Screening -28 to -1[b]	Day 1 Pre-dose	1	2[a]	8±1	15±1	29±3	57±3	85±3	115±7	211±14	365±14	**Section 8.11.5** Details on variance in procedure collection times

AE=adverse event; β-hCG=beta human chorionic gonadotropin; BDS=blood drug screen; BP=blood pressure; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECI=event(s) of clinical interest; ELISA=enzyme-linked immunosorbent assay; FBR=future biomedical research; FSH=follicle stimulating hormone; HIV=human immunodeficiency virus; HR=heart rate; ID=identification; IgG=immunoglobulin G; MAAE= Medically Attended Adverse Event; PBMC=peripheral blood mononuclear cells; PCR=polymerase chain reaction; PNA=Pseudo-virus Neutralization Assay; RR=respiratory rate; SAE=serious adverse event; SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus (novel); SOP=standard operating procedure; UDS=Urine Drug Screen; VRC=vaccine report card; WOCBP=women of childbearing potential; WONCP=women of nonchildbearing potential

a. Safety calls on Day 2 must occur on the day after Day 1 visit, approximately 18 to 30 hours postdose.
b. SARS-CoV-2 serology testing will be performed at the screening visit for participants in sentinel Panels A, B and the 5 sentinel participants in panel E only. SARS-CoV-2 seronegative participants will be enrolled in the sentinel Panels A,B and 5 sentinels participants of panel E. Part 2A (with the exception of the 5 sentinel participants in panel E) and Part 2B of the study are not affected by this modification.

1.3.2 SoA for 2-Dose Panels (Day 1, Day 57)

2-dose Day 1, Day 57-Panels A-B and I-J															
	Screening	**Study Day**												**Post-Study**	**Notes**
Scheduled Hour, Day, Week, etc.	Screening -28 to -1[b]	Day 1 Pre-dose	1	2[a]	8±1	15±1	29±3	57±3	58[a]	71±1	85±3	115±7	211±14	422±14	**Section 8.11.5** Details on variance in procedure collection times
Administrative Procedures															
Informed Consent	X														**Section 8.1.1.1**
Informed Consent for Future Biomedical Research	X														**Section 8.1.1.2**
Demographics	X														
Inclusion/Exclusion Criteria	X	X						X							**Section 5.0**
Participant ID Card	X														**Section 8.1.3**
Medical History & Vaccination History	X														**Section 8.1.4**
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	**Sections 6.6, 8.1.5** Including Non-study Vaccination Review
Assignment of Screening Numbers	X														**Section 8.1.6**
Assignment of Randomization Number		X													**Sections 5.5 and 8.1.7**
COVID-19 Symptoms Training		X				X	X	X		X	X	X	X		**Section 8.3.7**
V591/Placebo Administration			X					X							**Section 8.1.8**
Clinical Procedures/ Safety Assessment															
Full physical examination	X	X											X	X	**Section 8.3.1.1**

2-dose Day 1, Day 57-Panels A-B and I-J															
	Screening	**Study Day**												**Post-Study**	**Notes**
Scheduled Hour, Day, Week, etc.	Screening -28 to -1[b]	Day 1 Pre-dose	1	2[a]	8±1	15±1	29±3	57±3	58[a]	71±1	85±3	115±7	211±14	422±14	**Section 8.11.5** Details on variance in procedure collection times
Symptoms driven physical exam			X		X	X	X	X		X	X	X			**Section 8.3.1.2** Only to be conducted if participant symptoms warrant an exam or at investigator's discretion
Targeted physical examination of injection site			X		X	X		X		X					**Section 8.3.1.3** Panels A and B: ~ 8 hours after vaccination on Day 1 and Day 57. Panels I and J: ~ 1 hour after vaccination on Day 1 and Day 57.
Height	X														**Section 8.3.1.4**
Weight	X							X						X	**Section 8.3.1.4**
Semi-recumbent Vital Signs (Blood Pressure [BP] and Heart Rate [HR] and Respiratory Rate [RR]	X	X	X		X	X	X	X		X	X	X	X	X	**Section 8.3.2** Day 1 predose: within ~ 3 hours of dosing. Panels A and B Postdose: ~ 8 hours after vaccination on Day 1 and Day 57. Panels I and J Postdose: ~ 1 hour after vaccination on Day 1 and Day 57.
Body Temperature	X	X	X	X	X	X	X	X	X	X	X	X	X	X	**Section 8.3.2.2 (temperature) and Section 8.3.5 (VRC)** Days 1 to 14 and Days 57 to 70 will be done by participant and recorded on the VRC. All other measurements will be done by clinic staff.
12-lead ECG	X	X													**Section 8.3.3** Day 1 predose ECG will be done within 24 hours of dosing.

2-dose Day 1, Day 57-Panels A-B and I-J															
	Screening	**Study Day**												**Post-Study**	**Notes**
Scheduled Hour, Day, Week, etc.	Screening -28 to -1[b]	Day 1 Pre-dose	1	2[a]	8±1	15±1	29±3	57±3	58[a]	71±1	85±3	115±7	211±14	422±14	**Section 8.11.5** Details on variance in procedure collection times
Distribute Paper Vaccination Report Card (VRC)			X					X							
Participant Record VRC			X	X	X	X		X	X	X					**Section 8.3.5 (VRC)** Paper VRC will be provided on Day 1 and Day 57. On the VRC, the participant records information, including solicited and unsolicited (local and systemic) AEs, temperature, medications, and other complaints.
Review Paper VRC Data with Participant				X	X	X	X		X	X	X				**Section 8.3.5**
Collect Paper VRC From Participant							X				X				**Section 8.3.5**.
Postvaccination Observation Period			X					X							**Section 8.11.2** Panels A and B: ~ 8 hours after vaccination on Day 1 and Day 57. Panels I and J: ~ 1 hour after vaccination on Day 1 and Day 57.
Safety Phone Call Follow-up				X					X						**Section 8.3.6** On non-clinic days the, safety phone calls will follow up on AEs, any associated medications and vaccinations.
AE Review		X	X	X	X	X	X	X	X	X	X				**Sections 8.4 and Appendix 3**

2-dose Day 1, Day 57-Panels A-B and I-J															
	Screening	**Study Day**												**Post-Study**	**Notes**
Scheduled Hour, Day, Week, etc.	Screening -28 to -1[b]	Day 1 Pre-dose	1	2[a]	8±1	15±1	29±3	57±3	58[a]	71±1	85±3	115±7	211±14	422±14	**Section 8.11.5** Details on variance in procedure collection times
SAE/ECI/MAAE/ review		X	X	X	X	X	X	X	X	X	X	X	X	X	**Sections 8.4 and Appendix 3** Nonserious AEs are to be reported from Days 1 to 28 and Days 57 to 84. SAEs/ECIs/MAAEs and deaths are to be reported throughout the duration of an individual's study participation.
Laboratory Procedures/Assessments															
Serum β-hCG or urine pregnancy test (WOCBP only)	X	X						X						X	**Appendix 2** Pregnancy test on Day 1 and Day 57 to be performed before vaccination.
Serum FSH - (WONCBP only)	X														**Appendix 2** Confirmatory for WONCBP who are postmenopausal or oophorectomized.
HIV, hepatitis B and C screen (per site SOP)	X														**Appendix 2**
UDS/BDS/Alcohol Breath (per site SOP)	X														Any additional UDS/BDS are conducted per site SOP
Coagulation: Prothrombin time/International Normalized Ratio	X														**Appendix 2**
Hematology	X				X	X	X	X		X	X			X	**Section 8.3.7 and Appendix 2**
Urinalysis	X				X	X	X	X		X	X			X	**Section 8.3.7 and Appendix 2**
Chemistry	X				X	X	X	X		X	X			X	**Section 8.3.7 and Appendix 2**
Screening and SARS-CoV-2 Test															
SARS-CoV-2 PCR	X														**Appendix 2**
Immunogenicity															
Serum Collection for Neutralizing Antibodies by PNA		X				X	X	X		X	X	X	X	X	Leftover main study serum samples to be stored for FBR

2-dose Day 1, Day 57-Panels A-B and I-J															
	Screening	**Study Day**												**Post-Study**	**Notes**
Scheduled Hour, Day, Week, etc.	Screening -28 to -1[b]	Day 1 Pre-dose	1	2[a]	8±1	15±1	29±3	57±3	58[a]	71±1	85±3	115±7	211±14	422±14	**Section 8.11.5** Details on variance in procedure collection times
Serum Collection for Total Anti-spike IgG and Total Anti-N IgG Antibodies by ELISA		X				X	X	X		X	X	X	X	X	Leftover main study serum samples to be stored for FBR
PBMC collection for Immunological Assessments		X									X				Leftover main study PBMC samples to be stored for FBR
Biomarkers															
Blood (DNA) for Future Biomedical Research		X													**Section 8.9** Collect from enrolled participants only.

AE=adverse event; β-hCG=beta human chorionic gonadotropin; BDS=blood drug screen; BP=blood pressure; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECI=event(s) of clinical interest; ELISA=enzyme-linked immunosorbent assay; FBR=future biomedical research; FSH=follicle stimulating hormone; HIV=human immunodeficiency virus; HR=heart rate; ID=identification; IgG=immunoglobulin G; MAAE= Medically Attended Adverse Event; PBMC=peripheral blood mononuclear cells; PCR=polymerase chain reaction; PNA=Pseudo-virus Neutralization Assay; RR=respiratory rate; SAE=serious adverse event; SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus (novel); SOP=standard operating procedure; UDS=Urine Drug Screen; VRC=vaccine report card; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential

a. Safety calls on Days 2 and 58 must occur on the day after the Day 1 and Day 57 visits, respectively, approximately 18 to 30 hours postdose.
b. SARS-CoV-2 serology testing will be performed at the screening visit for participants in sentinel Panels A, B and the 5 sentinel participants in panel E Only. SARS-CoV-2 seronegative participants will be enrolled in the sentinel Panels A,B and 5 sentinels participants of panel E. Part 2A (with the exception of the 5 sentinel participants in panel E) and Part 2B of the study are not affected by this modification.

1.3.3 SoA for 2-Dose Panels (Day 1, Day 169)

2-dose Day 1, Day 169-Panels F and K-L														
	Screening	**Study Day**											**Post-Study**	**Notes**
Scheduled Hour, Day, Week, etc.	Screening -28 to -1	Day 1 Pre-dose	1	2[a]	8±1	15±1	29±3	85±3	169±3	170[a]	197±3	365±7	534±14	**Section 8.11.5** Details on variance in procedure collection times
Administrative Procedures														
Informed Consent	X													**Section 8.1.1.1**
Informed Consent for Future Biomedical Research	X													**Section 8.1.1.2**
Demographics	X													
Inclusion/Exclusion Criteria	X	X							X					**Section 5.0**
Participant ID Card	X													**Section 8.1.3**
Medical History & Vaccination History	X													**Section 8.1.4**
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	**Sections 6.6, 8.1.5** Including Non-study Vaccination Review
Assignment of Screening Numbers	X													**Section 8.1.6**
Assignment of Randomization Number		X												**Sections 5.5 and 8.1.7**
COVID-19 Symptoms Training		X				X	X	X	X		X	X		**Section 8.3.7**
V591/Placebo Administration			X						X					**Section 8.1.8**
Clinical Procedures/ Safety Assessment														
Full physical examination	X	X											X	**Section 8.3.1.1**
Symptoms driven physical exam			X		X	X	X	X	X		X			**Section 8.3.1.2** Only to be conducted if participant symptoms warrant an exam or at investigator's discretion
Targeted physical examination of injection site			X		X	X			X					**Section 8.3.1.3** At ~ 1 hour postdose on Day 1 and Day 169

2-dose Day 1, Day 169-Panels F and K-L														
	Screening	**Study Day**											**Post-Study**	**Notes**
Scheduled Hour, Day, Week, etc.	Screening -28 to -1	Day 1 Pre-dose	1	2[a]	8±1	15±1	29±3	85±3	169±3	170[a]	197±3	365±7	534±14	**Section 8.11.5** Details on variance in procedure collection times
Height	X													**Section 8.3.1.4**
Weight	X								X				X	**Section 8.3.1.4**
Semi-recumbent Vital Signs (Blood Pressure [BP] and Heart Rate [HR] and Respiratory Rate [RR]	X	X	X		X	X	X	X	X		X	X	X	**Section 8.3.2** Day 1 predose measurements will be done within ~ 3 hours of dosing. Day 1 and Day 169: Postdose measurements will be taken ~ 1 hour after vaccination.
Body Temperature	X	X	X	X	X	X	X	X	X	X	X	X	X	**Section 8.3.2.2 (temperature) and Section 8.3.5 (VRC)** Days 1 to14 and Days 169 to 182 will be done by participant and recorded on the VRC. All other measurements will be done by clinic staff.
12-lead ECG	X	X												**Section 8.3.3** Day 1 predose ECG will be done within 24 hours of dosing.
Distribute Paper Vaccination Report Card (VRC)			X						X					
Participant Record VRC			X	X	X	X			X	X				**Section 8.3.5 (VRC)** Paper VRC will be provided on Day 1 and Day 169. On the VRC, the participant records information, including solicited and unsolicited (local and systemic) AEs, temperature, medications, and other complaints.
Review Paper VRC Data with Participant				X	X	X	X		X	X	X			**Section 8.3.5**
Collect Paper VRC From Participant							X				X			**Section 8.3.5**.

2-dose Day 1, Day 169-Panels F and K-L														
	Screening	**Study Day**											**Post-Study**	**Notes**
Scheduled Hour, Day, Week, etc.	Screening -28 to -1	Day 1 Pre-dose	1	2[a]	8±1	15±1	29±3	85±3	169±3	170[a]	197±3	365±7	534±14	**Section 8.11.5** Details on variance in procedure collection times
Postvaccination Observation Period			X						X					**Section 8.11.2** Participants will be observed for minimum ~ 1 hour postdose on Day 1 and Day 169.
Safety Phone Call Follow-up				X						X				**Section 8.3.6** On non-clinic days the, safety phone calls will follow-up on AEs, any associated medications and vaccinations.
AE Review		X	X	X	X	X	X		X	X	X			**Sections 8.4 and Appendix 3**
SAE/ECI/MAAE review		X	X	X	X	X	X	X	X	X	X	X	X	**Sections 8.4 and Appendix 3** Nonserious AEs are to be reported from Days 1 to 28 and Days 169 to 196. SAEs/ECIs/MAAEs and deaths are to be reported throughout the duration of an individual's study participation.
Laboratory Procedures/Assessments														
Serum β-hCG or urine pregnancy test (WONCBP only)	X	X							X				X	**Appendix 2** Pregnancy test on Day 1 and Day 169 to be performed before vaccination.
Serum FSH - (WOCBP only)	X													**Appendix 2** Confirmatory for WONCBP who are postmenopausal or oophorectomized.
HIV, hepatitis B and C screen (per site SOP)	X													**Appendix 2**
UDS/BDS/Alcohol Breath (per site SOP)	X													Any additional UDS/BDS are conducted per site SOP
Coagulation: Prothrombin time/International Normalized Ratio	X													**Appendix 2**
Hematology	X				X	X	X		X		X	X	X	**Section 8.3.7 and Appendix 2**

2-dose Day 1, Day 169-Panels F and K-L														
	Screening	**Study Day**											**Post-Study**	**Notes**
Scheduled Hour, Day, Week, etc.	Screening -28 to -1	Day 1 Pre-dose	1	2[a]	8±1	15±1	29±3	85±3	169±3	170[a]	197±3	365±7	534±14	**Section 8.11.5** Details on variance in procedure collection times
Urinalysis	X				X	X	X		X		X	X	X	**Section 8.3.7 and Appendix 2**
Chemistry	X				X	X	X		X		X	X	X	**Section 8.3.7 and Appendix 2**
Screening and SARS-CoV-2 Test														
SARS-CoV-2 PCR	X													**Appendix 2**
Immunogenicity														
Serum Collection for Neutralizing Antibodies by PNA		X				X	X	X	X		X	X	X	Leftover main study serum samples to be stored for FBR
Serum Collection for Total Anti-spike IgG and Total Anti-N IgG Antibodies by ELISA		X				X	X	X	X		X	X	X	Leftover main study serum samples to be stored for FBR
PBMC collection for Immunological Assessments		X									X			Leftover main study PBMC samples to be stored for FBR
Biomarkers														
Blood (DNA) for Future Biomedical Research		X												**Section 8.9** Collect from enrolled participants only.

AE=adverse event; β-hCG=beta human chorionic gonadotropin; BDS=blood drug screen; BP=blood pressure; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECI=event(s) of clinical interest; ELISA=enzyme-linked immunosorbent assay; FBR=future biomedical research; FSH=follicle stimulating hormone; HIV=human immunodeficiency virus; HR=heart rate; ID=identification; IgG=immunoglobulin G; MAAE= Medically Attended Adverse Event; PBMC=peripheral blood mononuclear cells; PCR=polymerase chain reaction; PNA=Pseudo-virus Neutralization Assay; RR=respiratory rate; SAE=serious adverse event; SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus (novel); SOP=standard operating procedure; UDS=Urine Drug Screen; VRC=vaccine report card; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential

a. Safety calls on Days 2 and 170 must occur on the day after the Day 1 and Day 169 visits, respectively, approximately 18 to 30 hours postdose.

2 INTRODUCTION

2.1 Study Rationale

Coronaviruses (CoV) are a large family of viruses that can cause illness ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV). In 2019, an acute respiratory syndrome, COVID-19, caused by a novel coronavirus, SARS-CoV-2 was identified [Harapan, H., et al 2020]. The ongoing outbreak of COVID-19 was declared a pandemic on 11-MAR-2020 by the World Health Organization (WHO). Community spread has been observed in nearly all countries worldwide with over seven million confirmed cases and 400,000 deaths reported as of June 2020[COVID-19 Treatment Guidelines Panel 2020] [Dong, E., et al 2020]. More recently a multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19 has been observed in pediatric patients, who have generally not displayed severe respiratory symptoms[Dufort, E. M., et al 2020].

There is currently no marketed vaccine for SARS-CoV-2 and therapies have demonstrated limited efficacy to date. There is a pressing global need for a safe and effective vaccine. V591 is a live recombinant viral vaccine against the SARS-CoV-2 Spike protein which is based upon an attenuated measles virus measles virus (Schwarz Vaccine strain), commonly used in authorized measles vaccines.

This study is a placebo-controlled dose-ranging trial to evaluate the safety and immunogenicity of V591, also designated as TMV-083, in single and two-dose regimens in healthy younger and older adults. The primary objectives will be the safety and tolerability of the V591 vaccine. Secondary objectives will be to evaluate anti-Spike binding antibody titers as well as neutralizing antibody (nAb) titers. Exploratory objectives will include additional immunogenicity endpoints of cell mediated immunity, Th1/Th2 polarization, and serologic or clinical evidence of SARS-CoV-2 infection.

2.2 Background

Refer to the IB for detailed background information on V591.

2.2.1 Pharmaceutical and Therapeutic Background

V591 is a live attenuated recombinant viral vectored vaccine for the prevention of COVID-19 disease. The Schwarz measles vaccine strain is used as vector. The measles vaccine is a live-attenuated negative-stranded RNA virus, which induces life-long protective immunity after a single injection and has dramatically reduced childhood mortality from measles by 90% since its introduction. Frédéric Tangy and colleagues at the Institut Pasteur introduced the live attenuated measles Schwarz strain (MV-Schwarz) as a vector to express heterologous viral antigens [Combredet, C., et al 2003]. This technology has been utilized as a platform technology for the development of a wide variety of experimental vaccines against different indications, particularly against emerging infectious diseases. These experimental measles-vectored vaccines have been shown to be safe, well tolerated and immunogenic in pre-clinical and clinical studies to date. The most advanced clinical vaccine MV-CHIK has been

demonstrated to be well tolerated and immunogenic through Phase 2 studies. The MV vector is thus an appropriate platform for developing an effective COVID-19 vaccine.

The spike protein of SARS-CoV-2 was selected as target antigen to induce the development of neutralizing antibodies. Specific mutations were introduced to keep the protein in its pre-fusion conformation and to avoid cleavage into its subdomains. Nucleotide sequences encoding the modified SARS-CoV-2 surface protein Spike (S) were codon-optimized for the expression in human cells, chemically synthesized and inserted into the Schwarz vaccine strain of measles virus to produce the COVID-19 vaccine candidate on Vero cells.

The MV vector has been shown to stably express large, heterologous antigens up to 5kb long. To date, the vector has been used to generate a number of recombinant MV clones expressing heterologous viral antigens including CHIKV [Brandler, S., et al 2013], WNV [Brandler, S., et al 2012] [Despres, P., et al 2005], DENV [Brandler, S., et al 2007] [Brandler, S., et al 2010], HIV [Lorin, C., et al 2004] [Stebbings, R., et al 2012], MERS-CoV [Bodmer, B. S., et al 2018] [Malczyk, A. H., et al 2015], SARS-CoV [Escriou, N., et al 2014] and LASV [Mateo, M., et al 2019]. The constructs created for the prevention of MERS and SARS are of particular interest, because of their high degree of similarity to the COVID-19 vaccine. In both cases, the full-length nucleotide sequence encoding the respective MERS and SARS Spike genes were inserted into the MV backbone. The resulting constructs were found to induce both neutralizing antibodies as well as IFNγ-producing T cells in animal models, indicative of a Th1-type immune response [Bodmer, B. S., et al 2018] [Malczyk, A. H., et al 2015] [Escriou, N., et al 2014].

The Measles Vector platform used for V591 is well suited for the development of a SARS-CoV-2 vaccine, as both the measles virus itself and MV platform vaccines produce Th1 polarized responses, which are less likely to predispose to antibody dependent or vaccine induced disease enhancement.

Studies of SARS vaccine candidates in animal models suggested that some of them could exacerbate disease severity. Immunization with inactivated or subunit vaccine candidates in mice followed by challenge with SARS-CoV resulted in immunopathology in the lungs despite protection against viremia[Lambert, P. H., et al 2020]. The pathology was identified as a Th2-type pathology characterized by heavy eosinophil infiltration. Immunopathology was not seen with vaccine formulations known to generate a Th 1-type response, either through the use of Th1-polarizing adjuvants or viral vectors [Honda-Okubo, Y., et al 2015]. Together, the available results point to the induction of a Th1-type polarized immune response as an important safety aspect of a SARS-CoV-2 vaccine candidate[Lambert, P. H., et al 2020].

The measles vector is a replicating vector which is known to elicit strong and persistent humoral and cellular immune response [Plotkin, Stanley A. 2010]. The standard measles vaccine elicits a predominantly Th1-type directed immune response [Ovsyannikova, I. G., et al 2003] [Howe, R. C., et al 2005] [Moss, W. J. and Griffin, D. E. 2006]. Importantly, for the measles vaccine-derived vector, Th1-type directed immune responses have been confirmed in preclinical studies for several different vaccine candidates. A MV-based vaccine candidate was generated against Lassa fever, a major threat in Western Africa. A single dose of the

vaccine protected NHP against lethal challenge with Lassa virus. Analysis of the immune responses showed that complete protection was associated with robust secondary T cell and antibody responses against Lassa virus. The T cells response was Th1-driven, largely characterized by TNF-a and/or IFN-y positive CD8+ and CD4+ T cells [Mateo, M., et al 2019].

An MV-SARS vaccine candidate expressing the membrane-bound SARS-CoV spike protein (analogous to the COVID-19 vaccine candidate) was demonstrated to be efficacious in mice against challenge with SARS-CoV. The vaccine candidate elicited high titers of neutralizing antibodies as well as a predominantly Th1-type T cell response, as determined by IgG2a over IgG1 ratio [Escriou, N., et al 2014].

Collectively, there is strong evidence that vaccine candidates based on the measles vector platform induce a Th1-type oriented immune response. Particularly, the prior evidence for an MV-SARS preclinical vaccine candidate is highly promising for the development of V591 as a SARS-CoV-2 vaccine.

2.3 Benefit/Risk Assessment

Healthy participants in clinical studies may not receive direct benefit from treatment during participation as clinical studies are designed to provide information about the safety and potential effectiveness of an investigational vaccine.

V591 is intended to induce an immune response against the SARS-CoV-2 virus, and no prior clinical studies have been completed with V591 to date. There are no clinical or preclinical data to indicate whether this vaccine will induce clinically meaningful protection against SARS-CoV-2 disease or infection. The risk of disease enhancement by the vaccine has not yet been evaluated preclinically.

Additional details regarding specific benefits and risks for participants in this clinical study can be found in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Healthy male participants and female participants between the ages of 18-55 years (inclusive) of age in Parts 1 and 2A (younger adults) and > 55 years of age in Part 2B (older adults)

Objectives	Endpoints
Primary	
To assess the safety and tolerability of V591 compared with placebo	Solicited injection site adverse events from Day 1 through Day 5 after any study intervention Solicited systemic adverse events from Day 1 through Day 14 after any study intervention Unsolicited adverse events from Day 1 through Day 28 after any study intervention SAEs from Day 1 throughout the duration of study Medical attended AEs (MAAEs) collected from Day 1 throughout the duration of study
Secondary	
To compare the humoral immunogenicity of V591 with placebo at Day 29 (all panels) and Day 85 (Panels A, B, I, and J) or Day 197 (Panels K and L)	Anti-SARS-CoV-2 spike serum neutralizing antibody (nAb) responses, as measured by Pseudo-virus Neutralization Assay (PNA) Anti-SARS-CoV-2 spike Immunoglobulin G (IgG) responses, as measured by ELISA
To evaluate the humoral immunogenicity of V591 at all timepoints with serum collection	Anti-SARS-CoV-2 spike serum nAb responses, as measured by Pseudo-virus Neutralization Assay (PNA) Anti-SARS-CoV-2 spike IgG responses, as measured by ELISA
Tertiary/Exploratory	
To evaluate the immune response to of V591, including cell-mediated immunity	PBMCs stimulated with SARS-CoV-2 Spike peptides for characterization of cell mediated immunity and serum to characterize the immune response to V591

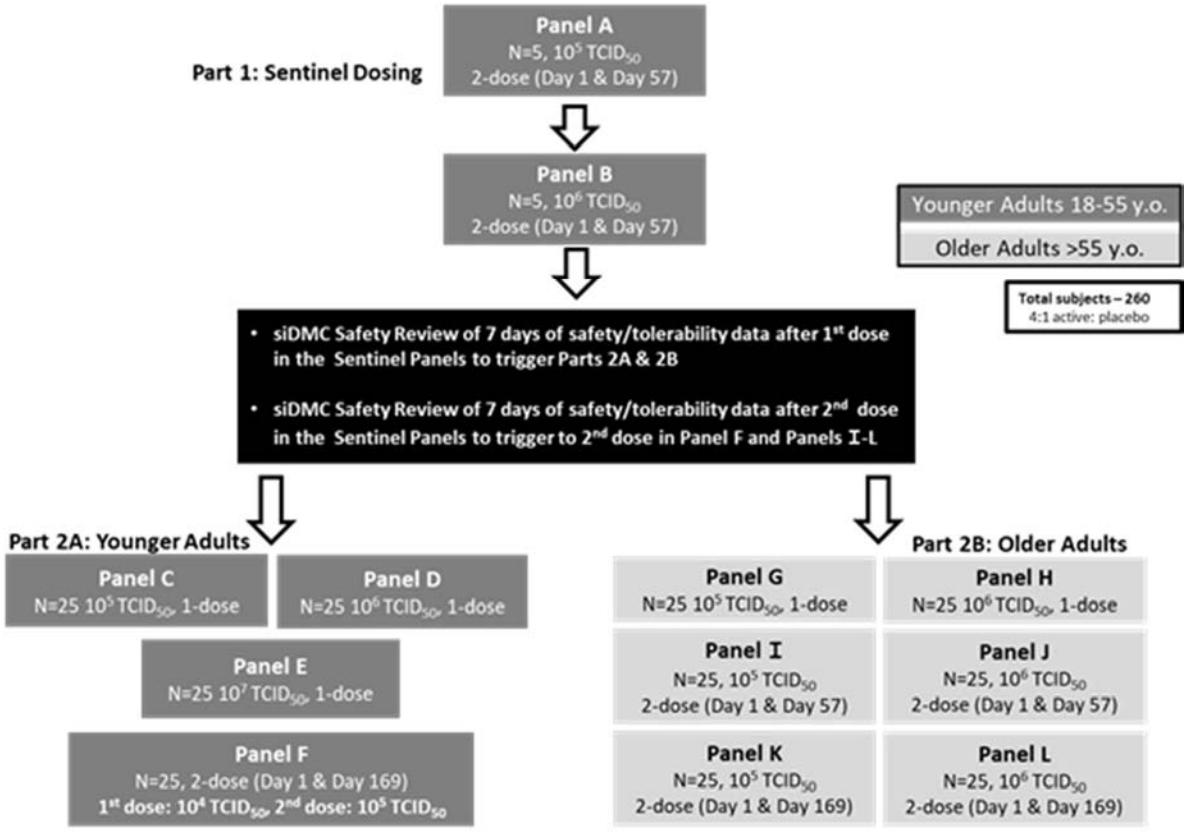
Objectives	Endpoints
To characterize SARS-CoV-2 seroconversion rates among participants	Anti-SARS-CoV-2 N-protein IgG responses, as measured by immunoassay
To document confirmed diagnoses of SARS-CoV-2 infection among study participants	Laboratory confirmed diagnosis of SARS-CoV-2 infection reported as an ECI
To document study participants' exposures to confirmed SARS-CoV-2 cases	Known exposure to a confirmed case of active SARS-CoV-2 reported as an ECI

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, placebo-controlled, two-part, multi-site, double-blind dose-ranging study of V591 in healthy younger and older adults to be conducted in conformance with Good Clinical Practice in approximately 260 participants as outlined in Figure 1.

Figure 1 Study Diagram



In this 2-part Phase 1/2 trial, two Sentinel Panels will be enrolled in Part 1 followed by the review of safety/tolerability data through 7 days following dose 1 by a standing internal Data Monitoring Committee (siDMC) prior to initiation of dosing in Parts 2A and 2B. The siDMC will also review the safety/tolerability data from the sentinel Panels through 7 days following dose 2 prior to administration of the 2nd dose in Panel F in Part 2A and Panels I-L in Part 2B. The study design is described in detail in the protocol text and the SoA.

In Part 1, approximately 10 healthy younger participants (age 18-55 years inclusive) will be enrolled in two Sentinel Panels, Panel A and Panel B, and administered two doses of either $1 \cdot 10^5$ $TCID_{50}$ or $1 \cdot 10^6$ $TCID_{50}$ V591. Five participants will be randomized into each Panel per dose to receive two vaccinations of V591 or placebo 56 days apart in a 4:1 ratio.

As safety precaution, the study will begin with the Day 1 vaccination of a small group of sentinel participants (5 participants from Panel A and 5 participants from Panel B) at one investigational site.

The first and the second participant of sentinel Panel A will receive the Day 1 vaccination on the same day, with an interval of at least 3 hours. Twenty-four hours after the injection, the participants will be called to collect safety information related to the vaccination. The clinical investigator can then decide to move on with the vaccination of the remaining 3 participants in Panel A based on the absence of related severe AEs/SAEs.

The first and the second participant of sentinel Panel B may be enrolled at least seventy-two hours after the first participant in Panel A has received the first vaccination. The first and the second participant in Panel B will receive the Day 1 vaccination on the same day, with an interval of at least 3 hours. Twenty-four hours after the injection, the participants will be called to collect safety information related to the vaccination. The clinical investigator can then decide to move on with the vaccination of the remaining 3 participants in Panel B based on the absence of related severe AEs/SAEs.

In Part 2A, approximately 100 healthy younger participants (age 18-55 years inclusive) will be enrolled in four Panels, Panel C, Panel, D, Panel E, and Panel F. Participants in Panels C-E will be administered a single dose of either $1 \cdot 10^5$ $TCID_{50}$, $1 \cdot 10^6$ $TCID_{50}$, or $1 \cdot 10^7$ $TCID_{50}$ of V591, respectively. Participant in Panel F will be administered 2 doses of V591 or placebo: 1 10^4 $TCID_{50}$ on Day 1 and $1 \cdot 10^5$ $TCID_{50}$ on Day 169. 25 participants will be randomized into each Panel per dose to receive a single vaccination of V591 or placebo in a 4:1 ratio. Part 2A may initiate based upon siDMC recommendation as outlined below and may initiate simultaneously with Part 2B. Panel C, Panel, D, Panel E and Panel F may all be enrolled in parallel.

Panel E in Part 2A: As safety precaution, the enrollment for Panel E, the highest dose panel, will begin with the Day 1 vaccination with five sentinel participants at a single investigational site. The first 5 participants in Panel E will be enrolled and receive the Day 1 vaccination with an interval of at least 3 hours between each participant. Twenty-four hours after the injection, the participants will be called to collect safety information related to the vaccination. The clinical investigator can then decide to move on with the vaccination of the remaining participants in Panel E based on the absence of related severe AEs/SAEs.

In Part 2B, approximately 150 healthy older participants (aged > 55 years) will be enrolled in six Panels. Two Panels of older participants, Panel G and Panel H, will be administered a single dose of either $1 \cdot 10^5$ $TCID_{50}$ or $1 \cdot 10^6$ $TCID_{50}$ of V591. Two Panels of older participants, Panel I and Panel J, will be administered two doses of either $1 \cdot 10^5$ $TCID_{50}$ or $1 \cdot 10^6$ $TCID_{50}$ of V591 56 days apart. Two Panels of older participants, Panel K and Panel I, will be administered two doses of either $1 \cdot 10^5$ $TCID_{50}$ or $1 \cdot 10^6$ $TCID_{50}$ of V591 168 days apart. Twenty-five participants will be randomized into each panel per dosing regimen to receive IM vaccination of V591 or placebo in a 4:1 ratio. Part 2B may initiate based upon siDMC recommendation as outlined below and may initiate simultaneously with Part 2A. Study participants in Panels I-L may receive their second dose of V591 based upon siDMC recommendation as outlined below. Panel G, Panel H, Panel I, and Panel J may be enrolled in parallel, while Panel K and Panel L will only commence recruiting study participants after Panel G, Panel H, Panel I, and Panel J are full enrolled.

In accordance with the FDA's "Development and Licensure of Vaccines to Prevent COVID-19, Guidance for Industry", the Sponsor will make efforts recruit a representative population for this Phase 1/2 study, particularly in the Panels of older adults as this is the only planned study in Phase 1 that will include this population. In order to facilitate the enrollment of diverse study population, particularly those that have been disproportional impacted by COVID-19 and historically underrepresented in vaccine trials, older adults in Part 2B will only be recruited in the United States.

The Sponsor's standing internal Data Monitoring Committee (siDMC) will review safety and tolerability data throughout this study, will evaluate safety data for the Safety Reviews following the first and second vaccinations in the sentinel Panels, and will be convened to evaluate available data if stopping rules are met. The siDMC is a standing, internal Sponsor committee established to monitor early phase clinical studies. Additional details are provided in Section 10.1.4.1 and in the siDMC charter.

The siDMC will conduct a Safety Review on at least 7 days of safety and tolerability data from 5 participants in each Panel of Part 1 after their Day 1 vaccination to decide on proceeding to Part 2A and Part 2B of the study.

The siDMC will also conduct a Safety Review on at least 7 days of safety and tolerability data from 5 participants in each Panel of Part 1 after their Day 57 vaccination to decide on proceeding to administer the second V591 dose to Panels F in Part 2A and Panels I-L in Part 2B of the study.

V591, also known as TMV-083, is planned to be introduced into a FIH clinical study, COVID-19-101, sponsored by the Institut Pasteur. In COVID-19-101 sentinel cohorts of three health young adults each are planned to be vaccinated with a two dose regimen 28 days apart at doses of $1 \cdot 10^5$ $TCID_{50}$ and $1 \cdot 10^6$ $TCID_{50}$ in the middle of August 2020, and it is anticipated that at least 7-day safety and tolerability data in three participants at each dose level may be available for review by the siDMC before the safety and tolerability data from the sentinel Panels (Panels A and B) of V591-001.

If safety and tolerability data are available for review from the COVID-19-101 study, it may be reviewed by the siDMC instead of the V591-001 safety and tolerability data from Panel A and Panel B of this study in order to make a decision to proceed to Part 2A and 2B of V591-001.

At least seven days of safety and tolerability data from the COVID-19-101 sentinel cohorts following their Day 28 vaccination may be reviewed by the siDMC instead of the V591-001 safety and tolerability data from Panel A and Panel B in order to make a decision to proceed to administer the second dose to Panel F in Part 2A and Panels I-L in Part 2B of the V591-001 study.

Up to two interim analyses may be performed on safety and immunogenicity data through at least Day 29. In order to trigger the first interim analysis at least 75% of study participants per Panel in at least 6 Panels must have completed their Day 29 visit. In order to trigger the second interim analysis at least 75% of study participants per Panel in at least 10 Panels must have completed their Day 29 visit.

An interim analysis may be performed on safety and immunogenicity data through at least Day 85 for Panels A, B, I, and J. To trigger this interim analysis at least 75% of these Panel's participants must have completed their Day 85 visit. A minimum percentage of participants from other study Panels is not required for this interim analysis, though all available data will be included.

An interim analysis may be performed on safety and immunogenicity data through at least Day 197 for Panels K and L. To trigger this interim analysis at least 75% of these Panel's participants must have completed their Day 197 visit. A minimum percentage of participants from other study Panels is not required for this interim analysis, though all available data will be included.

These interim immunogenicity analyses will include all available Pseudo-virus Neutralization Assay (PNA) data and IgG ELISA data.

Because this is a Phase 1/Phase 2 assessment of V591 in humans, the immunogenicity and safety profile of the vaccine are still being elucidated. This protocol is therefore written with flexibility to accommodate the inherent dynamic nature of Phase 1/Phase 2 clinical studies. Refer to Section 8.11.6 for examples of modifications permitted within the protocol parameters.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the SoA in Section 1.3. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

This study is being conducted to evaluate the safety, tolerability and immunogenicity of V591 in healthy younger (18-55 years of age) and older (> 55 and older) adults. It will probably commence shortly after the Institut Pasteur sponsored FIH clinical study of

V591(also known as TMV-083) in healthy young adults, COVID-19-101, plans to begin. This study is designed to maximize participant safety while permitting efficient trial conduct in the setting of the global COVID-19 pandemic. The design is supported by past clinical and preclinical experience with MV-CHIK which uses the same measles virus vector platform as V591 and has completed Phase 2 trials, as well as preclinical data for V591.

The study consists of a placebo controlled, double-blind, dose-ranging design of single or two doses regimens of V591. The study incorporates two sentinel cohorts to evaluate safety and tolerability of $1 \cdot 10^5$ $TCID_{50}$ and $1 \cdot 10^6$ $TCID_{50}$ of V591, doses selected as likely to be immunogenic and well tolerated, before proceeding to additional Panels. Based on prior experience with MV-CHIK immunogenicity, only doses of V591$\geq 1 \cdot 10^4$ $TCID_{50}$ will be administered as these are expected to be immunogenic. They have been selected for clinical dosing in order limit the possibility that study participants will being given a sub-immunogenic dose of V591.

MV vector shedding has not been observed in prior clinical study with the MV-CHIK. Vector shedding will be evaluated by PCR in the FIH COVID-19-101 study, and thus it will not be evaluated in this study.

The total sample size was selected to achieve a reasonably sized safety database for the study population exposed to V591. In addition, the sample size is considered to be reasonably sufficient to achieve adequate precision to evaluate the immunogenicity different doses and both single and two regimens of V591.

Overall, this study aims to obtain safety, tolerability and immunogenicity from a broad age range of healthy participants in order to facilitate development of this vaccine.

4.2.1 Rationale for Endpoints

4.2.1.1 Safety Endpoints

As this is a Phase 1/2 study of V591, safety and tolerability will be primary endpoints and will be closely monitored and followed. It is anticipated that IM administration of V591 at the proposed doses will be well-tolerated in humans based on preclinical studies as well as previous experience with the MV vector platform used for MV-CHIK.

The safety and tolerability of V591 will be monitored by standard means including clinical assessments of adverse experiences, physical examinations, monitoring of vital signs (VS), and standard laboratory tests (including hematology, chemistry, urinalysis and coagulation).

Assessments will occur throughout the trial, with time points optimized based on the expected timing of local and systemic reactions to vaccination (See Section 8.4.1 and Appendix 3). Specific safety endpoints to be gathered include:

- Solicited injection site AEs (pain/tenderness, swelling, redness) up to 5 days post each study intervention.

- Solicited systemic AEs [fever (oral temperature), muscle pain, joint pain, headache, fatigue, rash, nausea] up to 14 days post each study intervention.
- Unsolicited AEs up to 28 days post each study intervention.
- SAEs, MAAEs and events of clinical interest from Day 1 throughout the duration of the study. Safety laboratory tests as described in the SoA
- Vital sign measurements and physical exam findings as described in the SoA

The 2007 Center for Biologics Evaluation and Research (CBER) Guidance Document will be used as the toxicity grading scale for this study (see Appendix 3).

4.2.1.2 Immunogenicity Endpoints

As a vaccine trial, secondary and exploratory endpoints in this trial will evaluate the immunogenicity of V591 using assays to measure neutralizing antibodies by PNA, IgG antibody titers against spike protein by ELISA, cell mediated immune responses, including Th1/Th2 polarization, and additional exploratory immunogenicity assays.

For secondary endpoints serum samples will be collected as outlined in the SoA for:

- Serum neutralizing antibodies measured by PNA
- Total anti-spike IgG antibodies measured by ELISA

For exploratory endpoints PBMCs and serum will be collected as outlined in the SoA for:

- PBMCs to be stimulated with SARS-CoV-2 Spike peptides for characterization of cell mediated immunity
- Serum for further characterization of the immune response to V591

Additionally, samples including serum and PBMCs will be collected for additional exploratory immunogenicity endpoints as outlined in the objectives.

4.2.1.3 Exploratory Endpoints

In accordance with regulatory guidance, this trial will endeavor to identify potential exposures and infections by SARS-CoV-2 amongst study participants. However, this clinical trial is not intended to interfere with local health practices and regulations regarding the management of confirmed or suspected SARS-CoV-2 infections. Study participants will be tested as appropriate according to local regulations and will receive any required medical care within their existing healthcare systems, please refer to Section 8.3.7 for further details.

Additional exploratory endpoints will include the follow assessments to assess the potential exposure to and infection by SARS-CoV-2 amongst study participants without potentially disrupting medical care:

- SARS-CoV-2 N protein specific antibody up to Study Day 534 as assessed by immunoassay. As the SARS-CoV-2 N protein is not included in the vaccine, infections in study participants seroconversion will identify asymptomatic and pauci-symptomatic SARS-CoV-2 over the entire course of the study.

- Any laboratory confirmed diagnosis of SARS-CoV-2 infection (PCR or antigen based) and any resulting clinical sequelae will be reported as an ECI in study participants throughout the duration of the study.

- Known exposure to a confirmed case of active SARS-CoV-2, defined as individual who has had close contact (< 1.5 meters for ≥15 minutes), will be reported as an ECI in study participants throughout the duration of the study.

4.2.1.4 Future Biomedical Research

The Sponsor will conduct FBR on specimens for which consent was provided during this study. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma), and/or the measurement of other analytes, depending on which specimens are consented for FBR.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for FBR is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of FBR research are presented in Appendix 6.

4.2.2 Rationale for the Use of Comparator/Placebo

A placebo-controlled study will minimize bias during assessment of safety, tolerability, and immunogenicity. In addition, placebo serves as a negative control for potential environmental exposures to SARS-CoV-2 and provides a control for immunologic assays.

4.2.3 Justification for Dose

The methods and rationale for selecting the proposed doses and estimated exposures of V591 are detailed in Sections 4.2.4 and 4.2.5.

As this is a Phase 1/Phase 2 assessment of V591 in humans, and the immunogenicity and safety profiles of the vaccine are still being evaluated, modifications to the dose or dosing regimen may be required to achieve the scientific goals of the study objectives and/or to

ensure appropriate safety monitoring of the study participants. Details of allowed modifications are provided in Section 8.11.6.

4.2.4 Starting Dose for This Study

The starting V591 doses for this study are $1 \cdot 10^5$ $TCID_{50}$ and $1 \cdot 10^6$ $TCID_{50.}$ These doses of have been selected based upon prior clinical safety/tolerability and immunogenicity data with the most advanced vaccine using the MV platform, MV-CHIK, along with supportive preclinical biodistribution and GLP toxicology studies undertaken with MV platform vaccines. MV-CHIK has been administered to healthy volunteers in Phase 1 and Phase 2 studies at doses ranging from $1 \cdot 10^4$ to $1 \cdot 10^6$ $TCID_{50}$ without any significant safety findings.

Clinical safety and tolerability data from Phase 2 studies that administered MV-CHIK at the relevant dose levels of $1 \cdot 10^5$ and/or $1 \cdot 10^6$ $TCID_{50}$ are summarized below.

MV-CHIK-202

The immunogenicity and safety of the MV-CHIK vaccine was evaluated in a Phase 2 clinical trial, MV-CHIK-202, in 263 study participants[Reisinger, E. C., et al 2019]. Healthy adults aged 18-55 years of age were randomly assigned to receive intramuscular injections of either $5 \cdot 10^4$ or $5 \cdot 10^5$ 50% tissue culture infectious dose ($TCID_{50}$) per dose of MV-CHIK or a Priorix® control in two different administration regimens. Analysis of vaccine safety and tolerability during the trial revealed a comparable profile for MV-CHIK as compared to the licensed control vaccine Priorix® (Priorix® contains the attenuated vaccine Schwarz strain of the measles virus). Adverse events frequencies were similar between groups. with 73.4% of MV-CHIK and 70.6% of Priorix® recipients reporting solicited AEs, and 50.7% (116 of 229) of MV-CHIK and 50.0% (17 of 34) of Priorix® recipient reporting unsolicited AEs. No serious AEs related to the vaccine were recorded.

The most frequent related AEs amongst recipients of MV-CHIK were 52.4% of subjects with injection site tenderness, 120 of 229 subjects), 33.2% of subjects with headache (76 of 229 subjects), 32.8% of subjects with injection site pain (75 of 229 subjects), 22.7% of subjects with fatigue (52 of 229 subjects), and 16.2% of subjects with injection site induration (37 of 229 subjects).

An increased frequency of injection site tenderness (MV-CHIK: 52.4% (120 of 229), Priorix®: 20.6% (7 of 34) and induration (MV-CHIK: 16.2% (37 of 229), Priorix®: 0% (0 of 34)) were the only meaningful differences observed between the MV-CHIK and Priorix® recipients regarding safety and tolerability. The majority of solicited AEs was reported as either mild or moderate. However, 10 recipients of MV-CHIK reported at least one solicited AE classified as severe: 3 subjects reported injection site pain, 1 reported injection site induration, 4 reported fatigue, 2 reported headache, 1 reported flu-like symptoms, and 1 reported nausea and vomiting. The frequency of severe AEs was not meaningfully different between MV-CHIK (4.4% (10 of 229)) and Priorix® (0.0% (0 of 34)) recipients (P=0.3694). All solicited AEs reported as severe resolved within one week, and no unsolicited AEs were reported as being severe.

MV-CHIK-205

MV-CHIK-205 is a Phase 2 trial conducted in healthy adults aged 18-55 years of age in Northern Ireland that investigated the immunogenicity, safety and tolerability of MV-CHIK after administration of different dose levels in different formulations in five groups of 12 subjects each:

- Group A: MV-CHIK in a lyophilized formulation, ($5 \cdot 10^4$ $TCID_{50}$/dose), on day 0 and day 28
- Group B: MV-CHIK in liquid frozen formulation, ($1 \cdot 10^5$) $TCID_{50}$/dose), on day 0 and day 28
- Group C: MV-CHIK in liquid SPS® formulation, ($1 \cdot 10^5$ $TCID_{50}$/dose), on day 0 and day 28
- Group D: MV-CHIK in liquid frozen formulation, ($1 \cdot 10^6$ $TCID_{50}$/dose), on day 0 and day 28
- Group E: MV-CHIK in liquid frozen formulation, ($1 \cdot 10^6$ $TCID_{50}$/dose), on day 0 and placebo vaccination on day 28

All dose levels and formulations were generally well tolerated and no serious AEs related to the vaccine were recorded. No clinically significant safety laboratory or vital signs abnormalities were reported.

All AEs were of mild or moderate severity, with the exception of one severe solicited AE of joint pain in a subject in Group B that was considered by the Investigator to be possibly related to the investigational vaccine. Solicited and unsolicited AE were similar across all Groups with the exception of Group C, where the percentage of subjects reporting any AE was lower (58.3%) than in the other groups (83.3 to 91.7%). For solicited AEs, a lower percentage of subjects reported AEs in the low dose groups (Groups A to C, 41.7 to 58.3%) than in the high dose groups (Groups D and E, 75.0%). This difference was attributable to local AEs, which occurred in 16.7 to 33.3% of subjects in Groups A to C, and in 66.7% of subjects in Groups D and E. Systemic solicited AEs, in contrast, were reported in a similar percentage of subjects across treatment groups. The most frequently reported local solicited AE was injection site tenderness, with the majority of cases in the high dose Groups D and E (five [41.7%] subjects each). The most frequent systemic solicited AE was headache in 21 (35.0%) subjects overall, with a similar frequency across all treatment groups. For unsolicited AEs, there were no overall trends with regard to formulation or dose level.

MV-CHIK has been generally well tolerated in pre-clinical GLP toxicity studies. MV-CHIK was well tolerated in a pre-clinical repeated dose toxicity study in NHPs up to $2.5 \cdot 10^7$ $TCID_{50}$, the NOAEL. This is 50-fold higher than the planned V591 $1 \cdot 10^6$ $TCID_{50}$ clinical starting dose on an absolute basis and approximately 500-fold higher than the planned clinical starting dose on a $TCID_{50}$/kg basis.

Single and 2-dose regimens of $1 \cdot 10^5$ $TCID_{50}$ and $1 \cdot 10^6$ $TCID_{50}$ V591 will also be the only dose levels administered to older participants, as they are doses that are most likely to be both well tolerated and immunogenic in this population, and it is intended to only administer V591 doses that are anticipated to elicit an immune response against SARS-CoV-2 to these participants.

4.2.5 Maximum Dose/Exposure for This Study

The maximum dose planned for this study is $1 \cdot 10^7$ $TCID_{50}$. This is approximately 50-fold lower than the animal exposure on a $TCID_{50}$/kg basis. This maximum dose will only be administered to younger adults in this study.

4.2.6 Rationale for Dose Interval and Study Design

Both single and two dose regimens of V591 will be explored in this study. Prior clinical studies with MV-CHIK have demonstrated immunogenicity after a single dose and a boost in titers following a second vaccination, suggesting that either a single or two dose regimen of V591 may induce an effective immune response against SARS-CoV-2.

Doses of $1 \cdot 10^5$ $TCID_{50}$ and $1 \cdot 10^6$ $TCID_{50}$ will be administered for the initial sentinel Panels as they are doses that are most likely to be both well tolerated and immunogenic based on prior clinical experience with MV-CHIK, which uses the same measles virus vector platform as V591 and has been demonstrated to be immunogenic and well tolerated through Phase 2 trials. These two dose levels of V591 will also be administered in the clinical study, COVID-19-101, sponsored by the Institut Pasteur that plans to begin dosing participants in the middle of August, 2020. In the COVID-19-101 study doses of $1 \cdot 10^5$ $TCID_{50}$ and $1 \cdot 10^6$ $TCID_{50}$ will be administered as a two dose regimen 4 weeks apart, and $1 \cdot 10^6$ $TCID_{50}$ will also be administered as a single dose.

As participants in Part 1 of this study will be among the first humans to receive V591, they will be monitored closely for serious vaccine reactions and vaccinated in a staggered manner as described in Section 4.1, with Panel B following Panel A after an initial safety review by the Investigator. As serious acute-onset vaccine associated reactions often manifest within minutes and the vast majority occur within 1-4 hours of vaccination[Ruggeberg, J. U., et al 2007] [McNeil, M. M. 2018], study participants in the sentinel Panels will be conservatively monitored for at least 8 hours after both their first and second vaccinations. The first five subjects enrolled in Panel E that will be the first to receive $1 \cdot 10^7$ $TCID_{50}$ V591, the highest planned dose in the study, and will also be enrolled in a staggered approach as described in Section 4.1 and conservatively monitored for at least 8 hours after their vaccination. The rest of the participants in the study will be monitored for at least 1 hour after vaccination.

As participants in Panel A, Panel B, and the first 5 subjects in Panel E will be amongst the first to receive doses of $1 \cdot 10^5$ $TCID_{50}$, $1 \cdot 10^6$ $TCID_{50}$, and $1 \cdot 10^7$ $TCID_{50}$ V591 respectively, they will be required to be seronegative for SARS-CoV-2 as an additional precaution. Participants in the rest of the study will not be screened by serology for SARS-CoV-2 and thus will not be required to be seronegative for enrollment.

Doses of $1 \cdot 10^5$ $TCID_{50}$ and $1 \cdot 10^6$ $TCID_{50}$ will also be the only dose levels administered to older participants after they have been assessed to be well tolerated in younger adults based on data from this study or the COVID-19-101 study as outlined in Section 4.1. These are doses that are most likely to be both well tolerated and immunogenic in this population, and it is intended to only administer V591 doses that are generally well tolerated and anticipated to elicit an immune response against SARS-CoV-2 in older participants. Two dose regimens of V591 will be given either 8 or 24 weeks apart in Panels of adults > 55 years of age. As older adults have historically demonstrated weaker responses to vaccines[Weinberger, B. 2012], 2 dose regimens of V591 with wider intervals than the 4 week interval in the COVID-19-101 study will be evaluated in an effort to identify a regimen of V591 that displays enhanced immunogenicity in older adults. This design will minimize the risks to older participants while efficiently obtaining immunogenicity data in this older population that is at greatest risk for severe COVID-19 disease.

In an previous Phase 1 study, MV-CHIK 101, that explored doses ranging from $1.5 \cdot 10^4$ to $3 \cdot 10^5$ $TCID_{50}$ of MV-CHIK in healthy adults, Doses of $7.5 \cdot 10^4$ and $3 \cdot 10^5$ $TCID_{50}$ MV-CHIK were generally immunogenic after a single vaccination, while the lower dose of $1.5 \cdot 10^4$ $TCID_{50}$ required 2 doses for comparable immunogenicity. Based on this clinical data, it is anticipated that a single dose of V591 greater than $7.5 \cdot 10^4$ $TCID_{50}$ may provide adequate immunogenicity after a single dose. Thus a single dose of $1 \cdot 10^5$ $TCID_{50}$ will be the lowest dose administered as a single dose regimen in this trial.

Doses of $1 \cdot 10^4$ $TCID_{50}$ is the minimum dose level that demonstrated immunogenicity with the MV platform in prior clinical studies of MV-CHIK. As noted previously, doses of $1.5 \cdot 10^4$ $TCID_{50}$ MV-CHIK required both a prime and boost regimen in younger adults to display comparable immunogenicity to the response of single doses of $7.5 \cdot 10^4$ and $3 \cdot 10^5$ $TCID_{50}$ in the MV-CHIK 101 study. Younger adults administered a dose of $1 \cdot 10^4$ $TCID_{50}$ V591 in Panel F will also receive a second dose of $1 \cdot 10^5$ $TCID_{50}$ V591 at 169 days. This design will ensure that every study participant will receive at least one dose of $1 \cdot 10^5$ $TCID_{50}$V591, the minimum dose anticipated to be immunogenic. The $1 \cdot 10^4$ $TCID_{50}$ dose is intended to provide a lower margin of immunogenicity to support further clinical development of the V591 vaccine.

The dose of $1 \cdot 10^7$ $TCID_{50}$ V591 is the maximum dose level planned in the study and is intended to provide a safety margin to support the further development of V591. A single dose regimen of $1 \cdot 10^7$ $TCID_{50}$ V591 will only be administered to younger adult participants after doses of $1 \cdot 10^5$ $TCID_{50}$ and $1 \cdot 10^6$ $TCID_{50}$ have been assessed to be well tolerated in younger adults based on data from this study or the COVID-19-101 study. For added safety precaution at this highest planned dose, the enrollment for Panel E, the $1 \cdot 10^7$ $TCID_{50}$ Panel, will commence with vaccination of a small group of sentinel participants as described above.

4.3 Beginning and End of Study Definition

The overall study begins when the first participant signs (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

A study may be paused during review of newly available preclinical/clinical safety, PK, pharmacodynamic, efficacy, or biologic data or other items of interest, prior to a final decision on continuation or termination of the study. It may be necessary to keep the study open for gathering/reviewing of additional supportive data to optimally complete the objective(s) of the study. If necessary, the appropriate amendment(s) to the protocol and/or appropriate communication(s) will be generated. If the decision has been made to end the study following this review period, the study end will be defined as the date of the Sponsor decision, and this end of study date supersedes the definitions outlined above. The Competent Authority(ies) and IRB(s)/IEC(s) will be apprised of the maximum duration of the study beyond the last participant out and the justification for keeping the study open.

4.3.1 Clinical Criteria for Early Study Termination

There are no prespecified criteria for terminating the study early.

A primary objective of this early Phase 1 study is to identify the V591 dose that achieves the target immune response in humans based on preclinical or early clinical data. Therefore, it is possible that not all dose levels specified in the protocol will be evaluated if this objective is achieved at lesser dose levels in this study. This would not be defined as early termination of the study, but rather an earlier than anticipated achievement of the study objective(s). If a finding from another preclinical or clinical study using the study intervention(s), agent of the same or similar class, or methodology(ies) used in this study results in the study(ies) or program being stopped for nonsafety reasons, this also does not meet the definition of early study termination.

Early study termination is defined as a permanent discontinuation of the study due to unanticipated concerns of safety to the study participants arising from clinical or preclinical studies with the study intervention(s), comparator(s), drug(s) of the same class, or methodology(ies) used in this study.

5 STUDY POPULATION

Healthy male participants and female participants between the ages of 18-55 years (inclusive) of age in Parts 1 and 2A (younger adults) and > 55years of age in Part 2B (older adults) will be enrolled in this study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant:

Type of Participant and Disease Characteristics

1. Is in overall good health based on medical history, physical examination, ECG and VS measurements performed prior to randomization.

2. Is in overall good health based on laboratory safety tests obtained at the screening visit. Appendix 2 provides a table of laboratory safety tests to be performed. Appendix 9 provides an algorithm for the assessment of out of range laboratory values.

3. Have a BMI < 30 kg/m^2 inclusive. See Section 8.3.1 for criteria on rounding to a single decimal place. On this basis a rounded BMI of 29.9 is acceptable to satisfy the inclusion criteria. BMI = weight (kg)/height $(m)^2$.

4. Has been practicing social distancing for at least two weeks prior to planned Day 1 vaccination and has no close contacts with known active SARS-CoV-2 infection in that time period.

5. Sentinel trial participants ONLY (Panel A, Panel B, and the first 5 subjects of Panel E): Seronegative for SARS-COV-2.

Demographics

6. Is male or female, from 18 years to 55 years of age (inclusive) (Parts 1 and 2A) or > 55 years of age (Part 2B), at the time of providing documented informed consent.

Male Participants

7. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 6 months after the last dose of study intervention:

- Refrain from donating sperm during the intervention period and for at least 6 months after the last dose of study intervention.

Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

OR

Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause [Appendix 5]) as detailed below:

- Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.

Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Female Participants

8. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

   - Is not a WOCBP

     OR

   - Is a WOCBP and using an acceptable contraceptive method, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis), as described in Appendix 5 during the intervention period and for at least 6 months after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

     - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) before the first dose of study intervention.

     - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

     - Refrain from donating oocyte during the intervention period and for at least 6 months after the last dose of study intervention.

     - Additional requirements for pregnancy testing during and after study intervention are located in Section 8.4.5.

     - The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

     - Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Informed Consent

9. The participant (or legally acceptable representative) has provided documented informed consent/assent for the study, including for future biomedical research.

Additional Categories

10. Is willing to comply with the study restrictions (see Section 5.3 for a complete summary of study restrictions), including social distancing between screening and randomization).

11. Is willing to abstain from donating whole blood or blood derivatives, tissue or organ all along the study.

12. Agrees to provide study personnel with a primary telephone number as well as an alternate means of contact, if available (such as an alternate telephone number or email) for follow-up purposes.

13. Can read, understand, and complete the Vaccination Report Card.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant:

Medical Conditions

1. Is currently actively infected with SARS-CoV-2 (confirmed by PCR).

2. Has prior medical history of confirmed SARS-CoV-2 infection or known exposure to an individual with confirmed COVID-19 disease or SARS-CoV-2 infection within the past 2 weeks. With the exception of the sentinel participants (Panel A, Panel B, and the first 5 subjects of Panel E), study participants will not be screened for enrollment by SARS-CoV-2 serology, allowing those who may have had a prior asymptomatic SARS-CoV-2 infection to be enrolled.

3. Has a history of severe adverse reactions to vaccine administration, including anaphylaxis and related symptoms, such as urticaria, respiratory difficulty, angioedema and abdominal pain to vaccines, or history of known or suspected allergic reaction likely to be exacerbated by any component of the COVID-19 vaccine.

4. Is currently (or highly suspected to be) immunocompromised, including anticipating the need for systemic immunosuppressive treatment within the next 6 months or 12 months for 2-dose Day 1 Day 169 panels or has been diagnosed or highly suspected as having a congenital or acquired immunodeficiency, HIV infection, lymphoma, leukemia, systemic lupus erythematosus (SLE), rheumatoid arthritis, juvenile rheumatoid arthritis (JRA), inflammatory bowel disease, or other autoimmune condition that could impact the immune response or the safety of the study vaccine.

5. Has clinically significant thrombocytopenia or other coagulation disorder contraindicating intramuscular vaccination or repeated venipuncture.

6. *Had a recent febrile illness (defined as oral or tympanic temperature ≥100.4°F [≥38.0°C] within a week before receiving the first study vaccination.

7. Has history or current evidence of any condition, therapy, laboratory abnormality, or other circumstance that might expose the participant to risk by participating in the study, confound the results of the study or interfere with the participant's participation for the full duration of the study.

8. Has a history or presence of clinically significant pulmonary disorders (e.g. COPD, etc.), or asthma.

9. Has a history of confirmed SARS-CoV-1 or MERS.

10. Has a history of or a current clinically significant medical condition that puts or may put a participant at increased risk for severe SARS-CoV-2 disease.

    These include the following conditions associated with or which might be associated with increased risk of severe illness from COVID-19 as currently defined by the CDC:

    i. Conditions that are associated with increased risk of severe illness from COVID-19 (first list by CDC: 'People with the following conditions are at increased risk of severe illness from COVID-19')

    - Cancer
    - Chronic kidney disease
    - COPD (chronic obstructive pulmonary disease)
    - Immunocompromised state (weakened immune system) from solid organ transplant
    - Obesity (BMI of 30 or higher)
    - Serious heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies
    - Sickle cell disease
    - Type 2 diabetes mellitus

    ii. Conditions that might be associated with increased risk of severe illness from COVID-19 (second list by CDC: 'People with the following conditions might be at an increased risk for severe illness from COVID-19').

    - Asthma (moderate-to-severe)
    - Cerebrovascular disease (affects blood vessels and blood supply to the brain)
    - Cystic fibrosis
    - Hypertension or high blood pressure
    - Immunocompromised state (weakened immune system) from blood or bone marrow transplant, immune deficiencies, HIV, use of corticosteroids, or use of other immune weakening medicines

- Neurologic conditions, such as dementia
- Liver disease
- Pregnancy
- Pulmonary fibrosis (having damaged or scarred lung tissues)
- Smoking
- Thalassemia (a type of blood disorder)
- Type 1 diabetes mellitus

Note: Refer to the most updated risk factors as defined by the CDC for people of any age with the following conditions are or might be at increased risk of severe illness from COVID-19: (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html).

11. Part 2B ONLY: Older adult participants having mild, well controlled hypertension as is widely characteristic of aging are allowed if their medication regimens have not substantively changed for the past 6 months, hypertension has not led to hospitalization or currently increased rate of clinic visits over the past year, and hypertension has not been confirmed as putting subjects at increased risk of severe illness from COVID-19 by the CDC (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/groups-at-higher-risk.html).

12. Is mentally or legally incapacitated, has significant emotional problems at the time of prestudy (screening) visit or expected during the conduct of the study or has a history of clinically significant psychiatric disorder of the last 5 years. Participants who have had situational depression may be enrolled in the study at the discretion of the investigator.

13. Has a history of any clinically significant major neurological disorders or seizures (including Guillain-Barré syndrome), with the exception of febrile seizures during childhood.

14. Has a history of cancer (malignancy).

    Exceptions: (1) Adequately treated nonmelanomatous skin carcinoma or carcinoma in situ of the cervix or; (2) Other malignancies which have been successfully treated with appropriate follow up and therefore unlikely to recur for the duration of the study, in the opinion of the investigator and with agreement of the Sponsor (eg, malignancies which have been successfully treated ≥10 years prior to the prestudy [screening] visit).

15. Has a known or suspected history of significant multiple and/or severe allergies (eg, food, drug, latex allergy), or has had an anaphylactic reaction or significant intolerability (ie, systemic allergic reaction) to prescription or non-prescription drugs or food.

16. Is positive for HBsAg, hepatitis C antibodies or HIV-1 or 2 antibodies. Individuals with antibodies to hepatitis C may be enrolled if hepatitis C viral load is undetectable and there is no evidence of or history of liver disease.

17. Had major surgery, donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the prestudy (screening) visit.

Prior/Concomitant Therapy

18. Has received immunosuppressive drugs like e.g. systemic corticosteroids (excluding topical preparations and inhalers) within 3 months prior to the first vaccination or 6 months for chemotherapies.

19. *Has received vaccination within 4 weeks prior to first vaccination or is planning to receive a licensed vaccine 4 weeks before or after each study vaccination (e.g. Inactivated influenza vaccine).

20. *Has received measles-containing vaccine within 3 months prior to the first vaccination.

21. Has received a blood transfusion or blood products, including immunoglobulin, starting from 3 months before the first study vaccination or is scheduled to receive a blood transfusion or blood product through study completion. Autologous blood transfusions are not considered an exclusion criterion.

22. Is unable to meet the concomitant medication restrictions (see Section 6.6).

23. Is using antiviral medications or any investigational agents for prophylaxis of SARS-CoV-2 within 4 weeks prior to the first vaccination

Prior/Concurrent Clinical Study Experience

24. Has ever participated in an investigational study of a SARS-CoV-2 vaccine, or an antiviral or other biologic product intended for the treatment of COVID-19.

25. Is currently participating in any study of a vaccine or IMP, or has recently completed participation in another study of a vaccine or IMP and received a vaccine within 3 months prior to screening or an IMP within 4 weeks (or 5 half-lives of the IMP, whichever is longer) prior to the prestudy (screening) visit. The window will be derived from the date of the last study intervention (e.g., receiving a vaccine or IMP) in the previous study to the date of the prestudy (screening) visit for this study. In addition, a participant cannot participate in another investigational trial up to the post-trial visit of this study (approximately 12 months after the last study vaccination).

Diagnostic Assessments

26. Hemoglobin A1C $\geq$ 6.5% at screening.

Other Exclusions

27. A history of alcohol, cocaine, or opioid abuse during the previous 3 years.

28. Participants who currently smoke or used nicotine or nicotine-containing products (e.g., nicotine patch) within last 3 months. Former smokers that have less than a 10 pack-year history of smoking and have not smoker in the last 12 months are eligible to be enrolled.

29. Has a tattoo, scar or other physical finding at the area of the vaccination site that would interfere with intramuscular injection or a local tolerability assessment.

30. Presents any concern by the investigator regarding safe participation in the study or for any other reason the investigator considers the participant inappropriate for participation in the study.

31. Lives in a nursing home or long-term care facility. (Other age-restricted residences, such as over-55 communities, are permissible so long as the participant is capable of independently performing their activities of daily living including social distancing and mask usage as recommended by local public health authorities, and following recommendations regarding mask use and social distancing).

32. Is currently working in occupations with high risk of exposure to SARS-CoV-2 (e.g., health care worker with direct patient contact, emergency response personnel), or , at the investigator's discretion to be at increased risk to acquire SARS-CoV-2 for any other reason.

33. Individuals who are living and/or working with severely immunocompromised people, pregnant women, lactating women, children under 12 months old, or any other individual that, in the judgment of the investigator, might be at increased risk.

34. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

For items with an asterisk (*), if the participant meets these exclusion criteria, the Day 1 Visit may be rescheduled for a time when these criteria are not met.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

5.3.1.1 Diet Restrictions

Dietary restrictions are not required.

5.3.1.2 Fruit Juice Restrictions

Fruit juice restrictions are not required.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

5.3.2.1 Caffeine Restrictions

Participants will refrain from consumption of caffeinated beverages or xanthine-containing products from 12 hours prior to the screening and poststudy visits and from 12 hours prior to and after study intervention.

5.3.2.2 Alcohol Restrictions

Participants will refrain from consumption of alcohol 24 hours prior to each laboratory safety evaluation.

5.3.2.3 Tobacco Restrictions

Smoking (and/or the use of nicotine/nicotine-containing products) is not permitted during the study.

5.3.3 Activity Restrictions

Participants will avoid unaccustomed strenuous physical activity (ie, weight lifting, running, bicycling, etc.) for 48 hours prior to each laboratory safety evaluation.

5.3.4 Other Restriction

Participants should be advised to avoid contacts with vulnerable individuals as listed in exclusion #33 for the duration of the study.

5.3.5 Contraceptive Requirements

Participants will follow the contraceptive guidance indicated in Appendix 5.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized in the study. A minimal set of screen failure information may be included, as outlined in the eCRF entry guidelines. Minimal information may include demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements.

5.5 Participant Replacement Strategy

If a participant discontinues from study intervention OR withdraws from the study a replacement participant may be enrolled if deemed appropriate by the investigator and Sponsor. The replacement participant will generally receive the same intervention or intervention sequence (as appropriate) as the participant being replaced. The replacement participant will be assigned a unique treatment/randomization number. The study site should contact the Sponsor for the replacement participant's treatment/randomization number.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies provided by the Sponsor (Themis Bioscience GmbH) will be packaged to support enrollment and replacement participants as required. When a replacement participant is required, the Sponsor or designee needs to be contacted prior to dosing the replacement participant. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study are outlined in Table 2.

Table 2 Study Interventions

Arm Name	Arm Type	Inter-vention Name	Inter-vention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Admin-istration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP/ NIMP	Sourcing
Active	Experimental	V591	Biological/ Vaccine	Sterile Solution	0.5 ml	10^4 $TCID_{50}$ 10^5 $TCID_{50}$ 10^6 $TCID_{50}$ 10^7 $TCID_{50}$	IM	Day 1 Day 1, Day 57 Day 1, Day 169	Experimental	IMP	Provided Centrally by the Sponsor
Placebo	Placebo Comparator	Placebo	Other	Sterile Solution	NA	NA	IM	Day 1 Day 1, Day 57 Day 1 Day 169	Placebo	IMP	Provided Centrally by the Sponsor or sourced locally
The classification of Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) in this table is based on guidance issued by the European Commission and applies to countries in the European Economic Area (EEA). Country differences with respect to the definition/classification of IMP/NIMP may exist. In these circumstances, local legislation is followed.											

All supplies indicated in Table 2 will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

Refer to Section 8.1.8 for details regarding administration of the study intervention.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Specific calculations or evaluations required to be performed in order to administer the proper dose to each participant are outlined in a separate document provided by the Sponsor. The rationale for selection of doses to be used in this study is provided in Section 4.2.

V591 and placebo (0.9% sodium chloride, USP or BP sterile saline) will be prepared by an unblinded pharmacist or medically qualified study personnel (see Section 6.3.3 and the Pharmacy Manual). The syringe for IM injection should be prepared shortly before administration, per the instructions. Refer to the Pharmacy Manual for detailed instructions.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Participants will be assigned randomly according to a computer-generated allocation schedule.

A sample allocation schedule is shown below in Table 3 for Part 1 and Part 2A, and Table 4 for Part 2B respectively.

Table 3 Sample Allocation Schedule for Part 1 and Part 2A

Participants	Dose[a]
Part 1 (18 to 55 years old) Sentinel Cohort	
Panel A	
n=4	Day 1: 10^5 $TCID_{50}$ / Day 57: 10^5 $TCID_{50}$
n=1	PBO
Panel B	
n=4	Day 1: 10^6 $TCID_{50}$ / Day 57: 10^6 $TCID_{50}$
n=1	PBO
Part 2A (18 to 55 years old)	
Panel C	
n=20	Day 1: 10^5 $TCID_{50}$
n=5	PBO
Panel D	
n=20	Day 1: 10^6 $TCID_{50}$
n=5	PBO
Panel E	
n=20	Day 1: 10^7 $TCID_{50}$
n=5	PBO
Panel F	
n=20	Day 1: 10^4 $TCID_{50}$ / Day 169: 10^5 $TCID_{50}$
n=5	PBO

n=number of participants; PBO=placebo; $TCID_{50}$=median tissue culture infectious dose
[a] The suggested doses may be adjusted downward based on evaluation of safety or tolerability data observed in previous participants.

Table 4 Sample Allocation Schedule for Part 2B

Participants	Dose[a]
Part 2B (> 55 years old)	
Panel G	
n=**20**	Day 1: 10^5 $TCID_{50}$
n=**5**	PBO
Panel H	
n=**20**	Day 1: 10^6 $TCID_{50}$
n=**5**	PBO
Panel I	
n=**20**	Day 1: 10^5 $TCID_{50}$ / Day 57: 10^5 $TCID_{50}$
n=**5**	PBO
Panel J	
n=**20**	Day 1: 10^6 $TCID_{50}$ / Day 57: 10^6 $TCID_{50}$
n=**5**	PBO
Panel K	
n=**20**	Day 1: 10^5 $TCID_{50}$ / Day 169: 10^5 $TCID_{50}$
n=**5**	PBO
Panel L	
n=**20**	Day 1: 10^6 $TCID_{50}$ / Day 169: 10^6 $TCID_{50}$
n=**5**	PBO

n-number; **PBO=placebo**; $TCID_{50}$=median tissue culture infectious dose
[a] **The suggested doses may be adjusted downward based on evaluation of safety or tolerability data observed in previous participants.**

6.3.2 Stratification

No stratification based on age, sex, or other characteristics will be used in this study. Based on the study design, intervention allocation/randomization will automatically be stratified according to participant's age at time of randomization (18 to 55 and > 55 years of age).

6.3.3 Blinding

A double-blinding technique will be used. V591 and placebo will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified study site personnel. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

6.4 Study Intervention Compliance

Interruptions from the protocol-specified vaccination plan require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Management of GMO

V591 is a GMO requiring BSL1 standards. Needles and syringes that have been in contact with the COVID-19 vaccine, as well as all other potentially contaminated materials, will be collected in dedicated containers and will be destroyed in a safe manner. This study will be conducted under regulations for contained use of a GMO.

6.6 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during time periods specified by this protocol for that medication or vaccination. If there is a clinical indication for any medications or vaccinations specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

Listed below are specific restrictions for prior/concomitant therapy or vaccination:

- Any administration of a nonstudy COVID-19 vaccine is prohibited during the study.
- Any administration of a nonstudy live and non-live vaccines is prohibited within four weeks (within 3 months for measles-containing vaccine) prior to or after each study vaccination.
- Any use of immunosuppressive drugs like corticosteroids (excluding topical preparations and inhalers) is prohibited within 3 months prior to the first vaccination or 6 months for chemotherapies and throughout the study.
- Any scheduled administration of antipyretic or analgesic medication on a daily or every other day basis from the day of vaccination through Day 5 after receiving each study vaccination is prohibited.
- Receipt of blood products or immunoglobulins is prohibited within 3 months prior to enrollment or anticipated receipt of any blood product or immunoglobulin before completion of study participation (365 days after the last vaccination).

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the participant is

receiving at the time of enrollment or receives through 28 days after each study vaccination must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Clinical Director should be contacted if there are any questions regarding concomitant or prior therapy.

6.6.1 Rescue Medications and Supportive Care

CRUs will be staffed with medically trained personnel with appropriate access to full service acute-care hospitals to facilitate rapid institution of medical intervention.

6.7 Dose Modification (Escalation/Titration/Other)

At least 7 days of safety and tolerability data after the first dose from n = 5 participants from each sentinel cohort (Panels A and B) will be reviewed by the siDMC prior to dosing of Parts 2A and 2B, which may initiate simultaneously. At least 7 days of safety and tolerability data after the second dose from n = 5 participants from each sentinel cohort (Panels A and B) will be reviewed by the siDMC prior to dosing of Panels F, I-L. The suggested doses may be adjusted downward based on evaluation of safety or tolerability data observed in previous participants.

If safety and tolerability data are available for review from the COVID-19-101 study, it may be reviewed by the siDMC instead of the V591-001 safety and tolerability data from Panel A and Panel B of this study in order to make a decision to proceed to Part 2A and 2B of V591-001.

At least seven days of safety and tolerability data from the FIH clinical study sponsored by the Institut Pasteur (COVID-19-101) sentinel cohorts following their Day 28 vaccination may be reviewed by the siDMC instead of the V591-001 safety and tolerability data from Panel A and Panel B in order to make a decision to proceed to administer the second dose to Panels F, I-L in Part 2B of the V591-001 study.

6.7.1 Stopping Rules

The following stopping rules will be employed during the conduct of this study.

If any of the following stopping rules are met, the study will be paused and no further dosing will occur until the siDMC has reviewed the totality of data available.

1. Any participant dies or requires ICU admission due to SARS-CoV-2 infection.

2. Any participant experiences a serious adverse (SAE) considered related to the vaccine.

3. Any participant experiences any of the following ECIs that are considered as related to the vaccine administration: acute respiratory distress syndrome (ARDS), pneumonitis, acute cardiac injury, arrhythmias, septic shock-like syndrome, acute kidney injury, vasculitis, new onset autoimmune disease, meningitis, atypical measles, encephalitis, or encephalopathy.

If any of the following stopping rules are met, dosing will be paused in the affected Panel, and any other Panels employing the same or higher dose levels, until the siDMC has reviewed the totality of data available. Dosing may continue in Panels receiving lower dose levels while data is reviewed by the siDMC.

4. Grade 3 or higher solicited local AE, considered as related to the vaccine administration reported on 2 or more days within the 5 day post-vaccination period in ≥2 participants per panel

5. Grade 3 or higher solicited systemic AE, considered as related to the vaccine administration reported on 2 or more days within the 14 day post-vaccination period in ≥2 participants per panel

6. Severe unsolicited AE, considered as related to the vaccine administration within the 28 day post-vaccination period in ≥2 participants per panel

6.7.2 Delaying Scheduled Study Vaccinations

Study vaccination should be delayed for the following reasons:

- Clinically significant acute illness at the time of vaccination
- Fever (body temperature ≥38.0°C [100.4°F]) within 24 hours prior to the planned time of vaccination.

6.8 Intervention After the End of the Study

There is no study-specified intervention following the end of the study.

6.9 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention allocation/randomization schedule for the study to unblind participants and to unmask study intervention identity . The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.10). The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

This study is blinded but supplies are provided open label; therefore, an unblinded pharmacist or qualified study site personnel will be used to blind supplies. Study intervention identity (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

See Section 8.1.10 for a description of the method of unblinding a participant during the study should such action be warranted.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

In clinical trials with a single intervention, discontinuation of study intervention can only occur prior to the intervention and generally represents withdrawal from the study. In this study, participants who receive a single-dose intervention cannot discontinue study intervention.

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified vaccination regimen will still continue to participate in the study as specified in Section 1.3 and Section 8.1.9, or if available, a protocol clarification letter.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Sections 8.1.9.

A participant must be discontinued from study intervention but continue to be monitored in the study for any of the following reasons:

The participant or participant's legally acceptable representative requests to discontinue study intervention.

The participant's treatment assignment has been unblinded by the investigator, the Sponsor, or through the emergency unblinding call center.

The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.

The participant has a confirmed positive serum pregnancy test.

Participant who experiences any of the following events assessed to be related to the product will not receive further vaccination:

- Solicited grade 3 adverse event (AE) for more than 24 hours;

- Unsolicited grade 3 or higher AE;
- Any grade 4 or higher AE; OR
- Serious adverse event (SAE).

For all participants enrolled in 2-dose panels, the inclusion and exclusion criteria should be reviewed prior to the second vaccination. Participants who no longer meet inclusion and exclusion criteria as specified in Section 5.2 will not receive their second scheduled vaccination. If a subject does not receive their second study vaccination, they should still continue all scheduled visits for appropriate safety follow up.

For participants who are discontinued from study intervention but continue to be monitored in the study, see Section 1.3 and Section 8.11.3 for those procedures to be completed at each specified visit.

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from future biomedical research, are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).

All study-related medical decisions must be made by an investigator who is a qualified physician.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

Procedures conducted as part of a site generic screening (with an ERC/IRB approved site generic screening consent) on potential participants (eg, blood count, vital signs, ECG, etc.) and obtained before signing of study ICF may be utilized for screening or baseline purposes provided the procedures met the protocol specified criteria and were performed within the screening window defined in this protocol.

The maximum amount of blood collected from each participant over the duration of the study will not exceed 288 to 441 mL depending on each panel (Appendix 8).

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant (or their legally acceptable representative) prior to participating in this clinical study or future biomedical research. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

8.1.1.1 General Informed Consent

Informed consent given by the participant or legally acceptable representative must be documented on a consent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent form should be given to the participant (or their legally acceptable representative) before participation in the study.

The initial ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's or by the participant's legally acceptable representative's dated signature.

Specifics about the study and the study population are to be included in the study informed consent form.

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the future biomedical research consent to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to future biomedical research. A copy of the informed consent will be given to the participant before performing any procedure related to future biomedical research.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent. At the time of intervention randomization, site personnel will add the treatment/randomization number to the participant identification card.

The participant identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 4 weeks before the first dose of study vaccination.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study. New and/or concomitant medications and nonstudy vaccines taken after study vaccination through 28 days after each study vaccination will be recorded with the paper VRC as specified in Section 8.3.5.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening visit. Specific details on the screening/rescreening visit requirements are provided in Section 8.11.1.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the

participant for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

A single participant cannot be assigned more than 1 treatment/randomization number.

8.1.8 Study Intervention Administration

Study vaccines should be prepared and administered by appropriately qualified members of the study personnel (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local/state, country, and institutional guidance.

Study intervention on Day 1 should begin on the day of treatment allocation/randomization or as close as possible to the date on which the participant is allocated/assigned.

8.1.8.1 Timing of Dose Administration

The first dose of study vaccine will be administered on Day 1, which should be the day of randomization. For 2-dose Day 1, Day 57 panels, the second vaccination will be administered on Day 57. For 2-dose Day 1, Day 169 panels, the second vaccination will be administered on Day 169. Vaccinations may be administered in the morning and without regard to timing of meals.

Each participant's body temperature must be taken before vaccine administration. After randomization, the dosing for individuals who present with fever (oral ≥100.4°F [≥38.0°C]) may be rescheduled when the fever has resolved. In addition, the second vaccination will be administered after predose procedures are executed as per SOA and adherence to study restrictions has been confirmed.

The predose collection of blood samples must be performed before vaccine administration.

As described in section 4.2.6, all participants will be observed for at least 8 hours for sentinel panels (Panel A and B) after the first and the second vaccination. At a minimum the first 5 participants enrolled in Panel E that will be conservatively monitored for at least 8 hours after their vaccination as well. The rest of the participants in the study will be monitored for at least 1 hour after vaccination.

8.1.9 Discontinuation and Withdrawal

The investigator or study coordinator must notify the Sponsor when a participant has been discontinued/withdrawn from the study and/or intervention. If a participant discontinues for any reason at any time during the course of the study and/or intervention, the participant may be asked to return to the clinic (or be contacted) for a poststudy visit as per the number of days described in Section 8.11.4 to have the applicable procedures conducted. However, the investigator may decide to perform the poststudy procedures at the time of discontinuation or as soon as possible after discontinuation. If the poststudy visit occurs prior to the safety

follow-up time frame as specified in Section 8.4.1, the investigator should perform a follow-up telephone call at the end of the follow-up period (Section 8.4.1) to confirm if any AEs have occurred since the poststudy clinic visit. Any AEs that are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.9.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's consent for future biomedical research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the participant’s personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

8.1.10 Participant Blinding/Unblinding

STUDY INTERVENTION IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND.

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a participant’s intervention assignment, the investigator who is qualified physician should make reasonable attempts to enter the toxicity grade of the AEs observed, the relation to study drug, the reason thereof, etc., in the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

In the event that unblinding has occurred, the circumstances around the unblinding (eg, date, reason, and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible.

Once an emergency unblinding has taken place, the investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician must be discontinued from study intervention, but should continue to be monitored in the study.

8.1.11 Domiciling

Not applicable for this study.

8.1.12 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Immunogenicity Assessments

8.2.1 Serum Neutralizing Antibodies Measured by PNA

The presence of serum neutralization antibodies against SARS-CoV-2 spike protein will be assessed using Pseudo-virus Neutralization Assay using a pseudovirus expressing SARS-CoV-2 spike protein on a VSV-backbone. This pseudovirus also contains a luciferase-reporter gene and the amount of luciferase produced after overnight incubation with Vero cells is negatively correlated with the amount of spike-protein neutralizing antibodies in testing serum samples. This reporter assay reduces the assay time from a typical 2 to 3 days plaque assay to overnight.

Serum sample processing, storage, and shipment specifics will be described in more detail in the Study Operations Manual (SOM).

8.2.2 Total Anti-Spike IgG Antibodies Measured by ELISA

An ELISA for immunoglobulin G (IgG) will be used to quantify the serum antibody responses against the S protein. The ELISA will use target antigen a recombinant, purified, stabilized extracellular domain (ectodomain) of the S protein, which was trimerized using a fold-on motif (ELISA tri- S; Grzelak, preprint). Specificity against circulating coronavirus such as 229E, NL63, OC43, and HKU1 will be tested during assay qualification.

Other exploratory assays to characterize the immune response to V591 may be performed with excess serum at the discretion of the Sponsor.

Serum sample processing, storage, and shipment specifics will be described in more detail in the Study Operations Manual (SOM).

8.2.3 Immune Responses Including Cell-mediated Immunity

T cell responses, including Th1/Th2 polarization, to V591 may be evaluated by stimulating PBMCs with Spike derived peptides and measuring responses by intracellular cytokine staining and flow cytometry or ELISPOT. Exploratory assays to characterize the immune response to the vaccine may be performed with excess PBMCs and serum collected in this study.

Detailed instructions on requirements for collection of PBMCs, handling and preparation of the samples for analysis, and storage requirements will be provided in the SOM.

8.2.4 Exploratory Immunogenicity Assays

Exploratory immunogenicity assays will be performed on collected samples in order to characterize the immune response elicited by V591. This may include assays performed on serum, and PBMCs.

These exploratory immunology endpoints may include the following:

- PBMCs stimulated with SARS-CoV-2 Spike peptides for characterization of cell mediated immunity and serum to characterize the immune response to V591
- Anti-SARS-CoV-2 N-protein IgG responses, as measured by immunoassay

These exploratory immunology assays, if performed, may be reported in a separate results memo outside of the CSR.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood/tissue to be drawn/collected over the course of the study (from screening to poststudy visits (Day 422 or Day 534 for 2-dose panels and Day 365 for 1-dose panels), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in Appendix 8.

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

8.3.1.1 Full Physical Examination

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard and timepoints as specified in the SoA.

Height and weight will also be measured and recorded per SoA.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.1.2 Symptoms Driven Physical Examination

A symptom driven physical examination will be conducted only if participant symptoms warrant an exam or at the investigator's discretion. The symptom driven physical should be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard, specifically targeted at the V591/placebo injection site (e.g. deltoid) and/or any areas for which there are symptoms of concern.

8.3.1.3 Targeted Physical Examinations

A targeted physical examination of the injection site will be conducted by the investigator or medical qualified designee (consistent with local requirements) per institutional standard on vaccination day as outlined in Section 1.3 SoA.

8.3.1.4 Height and Weight

Body weight and height will be obtained with the participant's shoes off and jacket or coat removed.

BMI

Body Mass Index equals a person's weight in kilograms divided by height in meters squared (BMI=kg/m^2). Body Mass Index will be rounded to a single decimal place according to the standard convention of 0.01 to 0.04 round down and 0.05 to 0.09 round up.

8.3.2 Vital Signs

Vital signs (i.e. body temperature, pulse or heart rate, respiratory rate, and blood pressure) will be assessed.

8.3.2.1 Semi-recumbent Heart Rate and Blood Pressure

Blood pressure and heart rate measurements should be preceded by at least 10 minutes of rest for the participant in a quiet setting without distractions. Blood pressure and heart rate measurements will be assessed in the semi-recumbent position with a completely automated device. Manual techniques will be used only if an automated device is not available.

The correct size of the BP cuff and the correct positioning on the participants' arm is essential to increase the accuracy of BP measurements.

All vital signs will be measured and recorded as single measurements.

8.3.2.2 Body Temperature

Body temperature should be measured orally and recorded as single measurements per timepoint. The same method must be used for all measurements for each individual participant and should be the same for all participants.

Oral temperature will be assessed before study vaccine is administered on Day 1. If the participant has a fever (defined as an oral temperature of ≥100.4°F or ≥38.0°C) within the 1 week period prior to receiving a study vaccination, the participant should not receive the study vaccine. The Day 1 vaccination may be rescheduled for a time when fever is resolved.

Postvaccination, if an oral temperature indicates a fever (defined as an oral temperature of ≥38.0°C or 100.4°F), then an AE of "fever" must be documented in the eCRF.

For measurements to be collected on the VRC on Days 1-14 and Days 57-70 or Days 169-182 (2-dose panels only), participants will be provided an oral thermometer. For sentinel panels (Panels A and B), Day 1 and Day 57 postdose measurements will be done approximately 8 hours (± 15 min). For Panel E, Day 1 postdose measurements will be done approximately 8 hours (± 15 min) for at a minimum the first 5 subjects in the Panel. The rest of the participants in panel E will be monitored for at least 1 hour (± 15 min) after vaccination. The Day 1, and Day 57 or Day 169 (2-dose panels only) postdose measurement for all other panels will be done approximately 1 hour (± 15 min). The Day 1, and Day 57 or Day 169 (2-dose panels only) postdose measurement will be measured and recorded by the participants on the VRC, under observation by the clinic staff. All the other measurements on the VRC and will be done by the participant without supervision. See Section 8.3.5.

All other temperature measurements listed on the SoA that are not on the VRC will be done by clinic staff on the CRU source documents.

8.3.3 Electrocardiograms

Single 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals.

Special care must be taken for proper lead placement by qualified personnel. Skin should be clean and dry prior to lead placement. Participants may need to be shaved to ensure proper lead placement. Female participants may need to remove interfering garments.

Participants should be resting in the semi-recumbent for at least 10 minutes prior to each ECG measurement.

The correction formula to be used for QTc is Fridericia.

If repeat ECGs are required, the clinical site will decide whether to leave the electrodes in place or mark the position of the electrodes for subsequent ECGs. To mark the position of the

electrodes, 12-lead electrode sites will be marked on the skin of each participant with an ECG skin marker pen to ensure reproducible electrode placement.

Pre-dose ECGs should be obtained on Day 1 within 24 hours prior to dosing V591/placebo. All ECG measurements will be single measurements.

Post-dose ECG may be performed if clinically indicated, as a single measurement, according to the judgement of the investigator.

8.3.4 Study Intervention Administration

Instructions on how to prepare and administer the proper dose to each participant are outlined in a separate document provided by the Sponsor. Study intervention will be administered and witnessed by unblinded study staff and recorded in the source documents. Study site staff will confirm that the participant has received the entire dose of study intervention. On Day 1, the time of V591/Placebo administration is considered time= 0.

8.3.5 Vaccine Report Card

Participants will be provided with a VRC to fill out on a daily basis from Day 1 to Day 28 post each vaccination. The VRC will be used to collect and grade injection site and systemic AEs, using both specific questions for solicited AEs and a space to record unsolicited AEs as "other complaints."

On Day 1 and/or as needed, the study staff should review the VRC instructions (including AE severity grading) and each page of the VRC carefully with the participant to ensure participant comprehension of their requirements. The study staff should instruct participants to inform them if there is a grade 3 event recorded on the VRC as soon as possible.

Participants will use the VRC to document the following information:

- AEs as outlined in Section 8.4.8
- Concomitant medications and nonstudy vaccinations for the first 28 days after each study intervention.

The VRC will be reviewed during the Day 2 and Day 58 or Day 170 (2-dose panels only) safety phone calls and during the Day 8, Day 15, Day 29, and Day 71, Day 85 or Day 197 (for 2-dose panels only) in-person visit for the purposes of early detection of safety concerns. The safety calls on Day 2 and Day 58 or 170 (for 2-dose panels only) must occur on the day after the Day 1, Day 57 or Day 169 visits, respectively, approximately 18 to 30 hours post-dose.

During the Day 1, Day 8, Day 57 and Day 169 visit, the study staff should observe the participant taking their temperature and measuring any injection site redness or swelling in order to confirm that the participant is documenting this on the VRC correctly.

The VRC will be reviewed with the participant as outlined in the SoA to ensure understanding of instructions. Participants will be reminded to complete the VRC at their scheduled visits on Day 8, Day 15 and Day 71 (2-dose Day 1 Day 57 panels only) and during safety phone calls on Day 2 and Day 58 or Day 170 (2-dose panels only). As noted above, study staff should observe the temperature, swelling, and redness assessments (if any) on Day 1 and Day 57 or Day 169 (2-dose panels only). Any AEs recorded in the VRC should be reviewed by the investigator and entered into the Sponsor database in a timely manner as per the Data Entry Guidelines.

8.3.6 Safety Phone Call Follow Up

Safety follow-up phone calls will be performed at the timepoints indicated in the SoA (Section 1.3). Safety calls on Days 2 and 58 or 170 must occur after the Day 1, Day 57 or Day 169 visits, respectively approximately 18 to 30 hours postdose.

Safety calls must be done by appropriately trained study site staff. If the initial call is unsuccessful, the study site staff should make a total of 3 attempts for each scheduled safety call. All attempts to contact the participants will be recorded in the source documents.

These calls will facilitate the collection of relevant safety information (see Section 8.4). The participant will be interviewed to obtain information relating to unsolicited AEs including SAEs and other significant medical events. In addition, associated concomitant medications and all vaccinations will be recorded. All safety information described by the participant must be documented in the source documents.

8.3.7 Monitoring for SARS Cov-2 Exposure and COVID-19 Disease

As outlined in Section 4.2.1.3, this trial intends to identify potential exposures and confirmed infections by SARS-CoV-2 amongst study participants.

Study participants will be educated to recognize and report symptoms that may be related to SARS-CoV-2 infection and will be instructed to contact the site via phone in case of suspected SARS-CoV-2 infection (if severe symptoms are reported the participant will be instructed to seek urgent medical attention). The Investigator will facilitate the study participant receiving medical care as appropriate based on their clinical judgement, including arranging a nasopharyngeal PCR testing for acute disease. No more than 3 days should transpire between the subject contacting the clinical site and the arrangement of a medical care visit by the investigator.

Trial participants will be educated at regular intervals during in person visit to recognize and report the following potential SARS-CoV-2 symptoms based on current CDC guidance (https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html).

- Fever or chills
- Cough

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

The Investigator will endeavor to collect detailed data on confirmed COVID-19 cases including the onset of specific symptoms, duration of symptoms, hospitalization (if any), and COVID-19 will be classified as severe or non-severe based on the FDA's "Development and Licensure of Vaccines to Prevent COVID-19, Guidance for Industry"

For the purposes of this study, a virologically confirmed SARS-CoV-2 infection is defined as any study participant with positive SARS-CoV-2 PCR test.

Severe COVID-19 is defined as:

Virologically confirmed SARS-CoV-2 infection with any of the following:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300 mm Hg)
- Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or ECMO)
- Evidence of shock (SBP < 90 mm Hg, DBP < 60 mm Hg, or requiring vasopressors)
- Significant acute renal, hepatic, or neurologic dysfunction
- Admission to an ICU
- Death

This clinical trial is not intended to interfere with local health practices and regulations regarding the management of confirmed or suspected SARS-CoV-2 infections or COVID-19 disease. The main role of the Investigator to help study participants to receive all appropriate

medical care according to local health practices and regulations. Study participants may be tested as appropriate according to local regulations and will receive any required medical care within their existing healthcare systems. However if a subject is not administered a nasopharyngeal PCR test for SARS-CoV-2 according to local regulations and the Investigator feels it is warranted, then they may directly arrange for SARS-CoV-2 PCR testing as available by nasopharyngeal swab.

If a subject is suspected/diagnosed with an actual COVID-19 infection they will not receive any subsequent study vaccination but should endeavor to perform all visits for safety follow-up that they are safely able to attend in person as allowed according to local regulations.

Exposure to known SARS CoV-2 infected patients and SARS-CoV-2 infection, and COVID-19 disease, will be captured as ECIs as documented in Section 8.4.7.

8.3.8 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

If laboratory values from nonprotocol-specified laboratory assessments performed at the institution’s local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.4 Adverse Events, Serious Adverse Events, Medically-Attended Adverse Events and Other Reportable Safety Events

The definitions of an AE, SAE, or MAAE as well as the method of recording, evaluating, and assessing causality of AE, SAE and MAAE and the procedures for completing and transmitting AE, SAE, MAAE and other reportable safety event reports can be found in Appendix 3.

Adverse events, SAEs, MAAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE, SAE or MAAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, MAAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE, SAE or MAAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

8.4.1 Time Period and Frequency for Collecting AE, SAE, MAAE, and Other Reportable Safety Event Information

AEs, SAEs, MAAEs, and other reportable safety events that occur after the participant provides documented informed consent form, but before intervention allocation/randomization, must be reported by the investigator for randomized participants only if the event is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo, or a procedure.

From the time of vaccination all AEs must be reported by the investigator up to 28 days after any study vaccination. SAEs, MAAEs, ECIs, arthralgia of any grade and other reportable safety events must be reported by the investigator from the time of vaccination through the end of study visit.

Additionally, any SAE brought to the attention of an investigator any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor if the event is considered related to study intervention.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, MAAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 5.

Table 5 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation (Randomized participants only)	Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period	Reporting Time Period: After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
NSAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
MAAEs	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 days of learning of event
Pregnancy/ Lactation Exposure	Report if: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in)	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
ECI (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report all - require regulatory reporting	Not required	Within 24 hours of learning of event
ECI (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless serious)
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 24 hours of learning of event

DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse event

8.4.2 Method of Detecting AEs, SAEs, MAAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, MAAE, and Other Reportable Safety Event Information

After the initial AE/SAE/MAAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, MAAEs and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as

serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

This is not applicable.

8.4.7 Events of Clinical Interest

Selected serious and nonserious AEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

1. An overdose of Sponsor's product, as defined in Section 8.5.

2. Any laboratory confirmed diagnosis of SARS-CoV-2 infection (virologically confirmed by PCR) and any resulting clinical sequelae will be reported as an ECI in study participants throughout the duration of the study. See Section 8.3.7 for further details.

3. Known exposure to a confirmed case of active SARS-CoV-2, defined as individual who has had close contact (< 1.5 meters for ≥15 minutes), will be reported as an ECI in study participants throughout the duration of the study

4. AEs≥ Grade 3 reported as a solicited AE on the VRC

5. Acute respiratory distress syndrome (ARDS)

6. Pneumonitis

7. Acute cardiac injury

8. Arrhythmias

9. Septic shock-like syndrome

10. Acute kidney injury

11. Vasculitis

12. New onset Autoimmune disease (AID)

13. Meningitis

14. Atypical measles

15. Anosmia

16. Dysgeusia
17. Encephalitis
18. Encephalopathy
19. Clinically significant arthralgias

The investigator should report all ECIs for the whole period of the study.

8.4.8 Adverse Events Reported on the VRC

Participants will use a VRC to report solicited and unsolicited AEs.

The definitions of solicited and unsolicited AEs can be found in Appendix 3.

8.4.8.1 Solicited Adverse Event

Solicited AEs for this study are summarized in Table 6.

Table 6 Solicited Adverse Events for Protocol

Type of Solicited Adverse Event	Predefined Solicited Adverse Events	Solicited Time Period
Injection site	○ Injection-site pain/tenderness ○ Injection-site swelling ○ Injection-site redness/erythema	For the first 5 days after each study intervention ○ For 1-dose panels: Day 1 to Day 5 ○ For 2-dose Day 1 Day 57 panels: Day 1 to Day 5 and Day 57 to Day 61 ○ For 2-dose Day 1 Day 169 panels: Day 1 to Day 5 and Day 169 to Day 173
Systemic	○ Muscle pain/myalgia ○ Joint pain/arthralgia ○ Headache ○ Fatigue/Tiredness ○ Rash ○ Nausea ○ Fever	For the first 14 days after each study intervention ○ For 1-dose panels: Day 1 to Day 14 ○ For 2-dose Day 1 Day 57 panels: Day 1 to Day 14 and Day 57 to Day 71 ○ For 2-dose Day 1 Day 169 panels: Day 1 to Day 14 and Day 169 to Day 183

All solicited injection-site AEs will be considered related to study intervention. The investigator will assess all solicited injection-site AEs for toxicity, and all solicited systemic AEs for both toxicity and causality (Appendix 3).

In addition, the investigator will review all solicited AEs for the following:

- Is the event a symptom of another diagnosis?
- Is the event ongoing at the end of the solicited period?
- Does the event meet serious criteria?

A solicited AE that meets any of the above criteria must also be reported on the appropriate eCRF as specified in the data entry guidelines.

8.4.8.2 Unsolicited Adverse Events

Unsolicited AEs will be followed up for 28 days. All adverse events with Grade > 3 will be followed up throughout the study.

As detailed in Section 8.4, the investigator will assess unsolicited AEs that meet the definition of an AE or SAE with respect to seriousness, intensity/toxicity, and causality.

8.5 Treatment of Overdose

In this study, an overdose is defined as more than 1 dose of study vaccine in a 24-hour period or more than 2 doses of study vaccine throughout the study. Sponsor does not recommend specific treatment for an overdose. Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Sponsor Clinical Director based on the clinical evaluation of the participant.

8.6 Pharmacokinetics

Pharmacokinetic parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.8.1 Planned Genetic Analysis Sample Collection

Planned genetic analysis samples will not be evaluated in this study.

8.9 Future Biomedical Research Sample Collection

The following specimens will be obtained as part of future biomedical research:

- DNA for future research
- Leftover main study serum from neutralizing antibodies by PNA stored for future research
- Leftover main study serum from total anti-spike IgG antibodies by ELISA stored for future research
- Leftover main study serum from immunological assessments stored for future research (Panels C, D, G, and H only)
- Leftover main study PBMCs from immunological assessments stored for future research

8.10 Health Economics Medical Resource Utilization and Health Economics

Health Economics OR Medical Resource Utilization and Health Economics are not evaluated in this study.

8.11 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

8.11.1 Screening

Within 28 days prior to allocation/randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.

Participants may be rescreened after consultation with the Sponsor. Rescreening should include all screening procedures listed in the SoA, including consent review. Rescreen procedures cannot be conducted the day prior to intervention allocation/randomization if there are Day -1 procedures planned per protocol.

8.11.2 Vaccination Visit

Refer to the SoA (Section 1.3) and Administrative General Procedures (Section 8.1).

<u>Day 1</u>

Participants will be randomized and vaccinated at the study site on Day 1, as set forth in the SoA and Section 6.

If all criteria are fulfilled, no significant change in the participant's health, participants will be assigned a study randomization number to receive V591 or placebo. The assigned study intervention (V591 or placebo) will be administered via IM (left or right deltoid) injection. The time and the arm (left or right) in which the vaccine was injected will be recorded in the participant's source data and in the eCRF.

After injection, the participants will remain in the clinical sites for medical supervision and monitoring as the following:

- Panels A and B: for a minimum of 8 hours after the first and the second injection.
- Panel E: at a minimum for the first 5 subjects for a minimum of 8 hours post-injection. The rest of the participants for a minimum of 1 hour post-injection.
- All other panels: for a minimum of 1 hour post-injection.

Post vaccination safety assessments (VS and local reaction of the injection site and general reaction) on Day 1 will be performed as set forth in the SoA.

Participant will be provided with a VRC, a ruler and a thermometer and they will receive instructions on how to measure temperature and record adverse events during the subsequent 28 days after the injection. The VRC will be returned on the next visit at the clinical sites.

Subject will be given an emergency card with a phone number to call in case of questions or upon occurrence of any AE.

At the end of the visit, which lasts approximately 9 hours in Panels A, B and for the sentinel participants of panel E, and approximately 2 hours in other panels and remaining participants of panel E, once the study physician has determined that a participant is fit to be released, the participant will be discharged from the clinical site. The appointment for the phone call (24 hours ± 6 hours) and for the next clinical visit will be scheduled and confirmed with the participant.

Day 57 (the second vaccination for 2-dose Day 1, Day 57 panels)

On Day 57 of the study, participants in the 2-dose Day 1, Day 57 panels (Panels A, B, I and J) will receive the second intramuscular injection of V591 or placebo into the deltoid muscle accordingly to protocol randomization schedule. Predose and post vaccination safety and immunogenicity assessments will be performed as set forth in the SoA. After injection, the participants will remain in the clinical sites for medical supervision and monitoring for a minimum of 8 hours after injection. (Panels A and B) and for a minimum of 1 hour after injection (Panels I and J).

Participant will be provided with a new VRC for the 28 following days. At the end of the visit, which lasts approximately 9 hours in Panels A and B , 2 hours for Panels I and J, once the study physician has determined that participant is fit to be released, the participant will be

discharged from the clinical site. The appointment for the phone call (24 hours ±6 hours) and for the next clinical visit will be scheduled and confirmed with the participant.

Day 169 (the second vaccination for 2-dose Day 1, Day 169 panels)

On Day 169 of the study participants in the 2-dose Day 1, Day 169 panels (Panels F, K and L) will receive the second intramuscular injection of V591 or placebo into the deltoid muscle accordingly to protocol randomization schedule. Predose and post vaccination safety and immunogenicity assessments will be performed as set forth in the SoA. After injection, the participants will remain in the clinical sites for medical supervision and monitoring for a minimum of 1 hour after injection.

Participant will be provided with a new VRC for the 28 following days. At the end of the visit, which lasts approximately 2 hours, once the study physician has determined that participant is fit to be released, the participant will be discharged from the clinical site. The appointment for the phone call (24 hours ± 6 hours) and for the next clinical visit will be scheduled and confirmed with the participant.

8.11.3 Discontinued Participants Continuing to be Monitored in the Study

At any point if a participant discontinues from treatment but continues to be monitored in the study, study procedures specified in the SoA may be completed at the discretion of the investigator and with Sponsor agreement. The subset of study procedures completed will be communicated in a PCL.

8.11.4 Poststudy

The investigator or study coordinator must notify the Sponsor when a participant has been discontinued/withdrawn from the study. If a participant discontinues for any reason at any time during the course of the study, the participant may be asked to return to the study site (or be contacted) for a post-study visit (approximately 365 days after the last vaccination) to have the applicable procedures conducted. However, the investigator may decide to perform the post-study procedures at the time of discontinuation or as soon as possible after discontinuation. If the poststudy visit occurs less than 365 days after the last study intervention, a subsequent follow-up telephone call should be made at 365 days or after (within the protocol-specified variance) of the last study intervention to determine if any SAEs, ECIs or MAAEs have occurred since the poststudy clinic visit (as well as AEs through Day 28 if not already collected).

Amendment 04:

The sponsor has decided to terminate the study based on the immunogenicity results. All participants should be asked to return to the study site (or be contacted by phone) for a final post-study visit at least 56 days post the last vaccination to have the applicable procedures conducted. The post-study procedures as outlined Section 1.3.1, 1.3.2 and 1.3.3 (Schedule of Activities for all panels) should be followed for the final post-study visit, except for the serum sample collection for immunogenicity assessments. Serum sample for neutralizing

antibodies and serum sample for total anti-spike IgG and total anti-N IgG antibodies will not be collected.

8.11.5 Critical Procedures Based on Study Objectives: Timing of Procedure

For this study, the timely and accurate collection and recording of AEs, along with blood samples for anti-SARS-CoV-2 spike serum neutralizing antibody titers (PNA) and anti-SARS-CoV-2 spike IgG titers (ELISA) are the critical procedures.

At any postdose time point, the blood sample for PNA and ELISA titers needs to be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible. Study procedures can be performed prior or after the prescribed/scheduled time.

The order of priority can be changed during the study with joint agreement of the investigator and the Sponsor Clinical Director.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

The following variance in procedure collection times will be permitted.

Vaccination Day Postdose procedure of panels A and B may be obtained within approximately 8 hours [±15 min] for Day 1 and Day 57. Vaccination Day Postdose procedure for the sentinel participants in Panel E may be obtained within approximately 8 hours [±15 min] for Day 1. Vaccination day (D1, D57, D169) postdose procedure may be obtained within approximately 1 hour [±15 min] for all other panels and remaining participants of panel E. Day 2, Day 58 and Day 170 (for 2-dose panels only) evaluations can occur any time the day after dosing (approximately 18 to 30 hours post-dose)

Day 8 evaluations can occur ± 24 hours (approximately Day 7 to Day 9 postdose)

Site visit windows as outlined for Two dose Panels in Table 7 and Single dose Panels Table 8.

Table 7 Two Dose Panels (Panels A-B, F and I-J) Site Visit Windows

Site Visit	Visit Window
Day 1	No variance
Day 2	On the day after Day 1 visit
Day 8	± 1 day
Day 15	± 1 day
Day 29	± 3 days
Day 57/Day 169	± 3 days
Day 58, Day 170	On the day after Day 57 or Day 169
Day 71	± 1 day
Day 85, Day 197	± 3 days
Day 115, Day 365	± 7 days
Day 211	± 14 days
Day 422, Day 534	± 14 days

Table 8 Single Dose Panels (Panels C-E, G-H) Site Visit Windows

Site Visit	Visit Window
Day 1	No variance
Day 2	On the day after Day 1 visit
Day 8	± 1 day
Day 15	± 1 day
Day 29	± 3 days
Day 57	± 3 days
Day 85	± 3 days
Day 115	± 7 days
Day 211	± 14 days
Day 365	± 14 days

8.11.6 Study Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters

This is a Phase 1/Phase 2 assessment of V591 in humans, and the safety profile of the vaccine is still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of early phase clinical studies. Modifications to the dose, dosing regimen, and/or clinical or laboratory procedures currently outlined may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants. As such, some alterations from the currently outlined dose and/or dosing regimen may be permitted based on newly available data, but the maximum doses may not exceed those currently outlined in the protocol.

- Repeat of or decrease in the dose of the study intervention administered in any given panel
- Interchange of doses between panels
- Entire panel(s) may be omitted, or the number of participants in each panel may be decreased
- Modification of the vaccination interval between the 1st and 2nd vaccination (for 2-dose panels only)
- Modification of the sample processing and shipping details based on newly available data
- Modification of the immunogenicity sampling schedule, including omitting timepoints
- Addition of a siDMC review
- Addition of Safety Phone Call Follow-ups
- Clinic in-person visit may be replaced by telephone, video or home visit using a site staff or a nursing service if circumstance do not support an in-person site visit.

The safety and immunogenicity sampling scheme currently outlined in the protocol may be modified during the study based on newly available data. If indicated, these collected samples may also be assayed in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

Up to additional 50 mL of blood may be drawn for safety and/or immunogenicity analyses. The total blood volume withdrawn from any single participant will not exceed the maximum allowable volume during his/her participation in the entire study (Appendix 8).

The timing of procedures for assessment of safety procedures (eg, vital signs, ECG, safety laboratory tests, etc.) may be modified during the study based on newly available data.

Additional laboratory safety tests may be added to blood samples previously drawn to obtain additional safety information. These changes will not increase the number of study procedures for a given participant during his/her participation in the entire study.

It is understood that the current study may employ some or none of the alterations described above. Any non-substantial alteration made to this protocol to meet the study objectives must be detailed by the Sponsor in a letter to the Study File and forwarded to the investigator for retention. All substantial changes to the protocol will be submitted to the regulatory authorities and ethics committees accordingly for evaluation and approval before implementation. .

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to unblinding, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 9.2-9.9.

Study Design Overview	A Phase 1/Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Trial to Evaluate the Safety, Tolerability and Immunogenicity of V591 in Healthy Younger and Older Participants
Treatment Assignment	260 participants (10 in Part 1 younger sentinel cohort, 100 in Part 2A younger cohort and 150 in Part 2B older cohort) will participate in the study that will include a total of 4 dose-levels and 12 Panels. Under each panel, participants will be randomized to receive V591 or placebo in a 4:1 ratio.
Analysis Populations	Safety: All Participants as Treated (APaT) Immunogenicity: Per-Protocol (PP)
Primary Endpoint(s)	• Solicited injection site AEs from Day 1 through Day 5 after any study intervention • Solicited systemic AEs from Day 1 through Day 14 after any study intervention • Unsolicited AEs from Day 1 through Day 28 after any study intervention • SAEs and MAAEs from Day 1 throughout the duration of study
Key Secondary Endpoints	• Anti-SARS-CoV-2 spike serum nAb as measured by PNA • Anti-SARS-CoV-2 spike IgG as measured by ELISA

Statistical Methods for Key Safety Analyses	For the Tier 2 endpoints, 95% CIs will be provided for between-treatment differences in the percentage of participants with events; these analyses will be performed using the Miettinen and Nurminen method (1985) [Miettinen, O. and Nurminen, M. 1985].
Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses	The geometric mean ratios and 95% CIs of the anti-SARS-CoV-2 spike serum nAb GMTs will be calculated using a cLDA method proposed by Liang and Zeger (2000) [Liang, K-Y and Zeger, S. L. 2000]. In this model, the response vector consists of the log-transformed prevaccination and postvaccination antibody titers. The repeated measures model will include terms for time, the interaction of time-by-vaccination group (with a restriction of the same baseline mean across groups). The treatment difference in terms of a geometric mean ratio at a given post-vaccination time point will be estimated and tested from this model. The term for time will be treated as a categorical variable. An unstructured covariance matrix will be used to model the correlation among repeated measurements. This model allows the inclusion of participants who are missing either the baseline or postbaseline measurements, thereby increasing efficiency. A similar statistical approach will be used to evaluate the anti-SARS-CoV-2 spike IgG responses.
Interim Analyses	Up to two interim analyses may be performed on safety and immunogenicity data through at least Day 29. In order to trigger the first interim analysis at least 75% of study participants per Panel in at least 6 Panels must have completed their Day 29 visit. In order to trigger the second interim analysis at least 75% of study participants per Panel in at least 10 Panels must have completed their Day 29 visit. An interim analysis may be performed on safety and immunogenicity data through at least Day 85 for Panels A, B, I, and J. To trigger this interim analysis at least 75% of these Panel's participants must have completed their Day 85 visit. A minimum percentage of participants from other study Panels is not required for this interim analysis, though all available data will be included. An interim analysis may be performed on safety and immunogenicity data through at least Day 197 for Panels K and L. To trigger this interim analysis at least 75% of these Panel's participants must have completed their Day 197 visit. A minimum percentage of participants from other study Panels is not required for this interim analysis, though all available data will be included. These interim immunogenicity analyses will include all available nAb PNA and IgG ELISA data. Results of the interim analysis will be provided to the unblinded siDMC.
Multiplicity	No multiplicity adjustment is planned.
Sample Size and Power	**Safety:** Section 9.9.1 provides information about the ability of this study to estimate the incidence of AEs within the V591 group as well as differences between V591 and Placebo. **Immunogenicity:** This is a descriptive study and there are no hypotheses to be evaluated. This study will randomize approximately a total of 208 participants into 4 different dose-levels of the V591 group and 52 participants into the placebo group. Section 9.9.2 provides information about the expected variability of the GMT ratios given the sample size.

9.2 Responsibility for Analyses

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

This study will be conducted as a double-blind study. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete. Section 6.3.3 specifies the roles and responsibilities of the site and Sponsor personnel who will be unblinded during the study.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study treatment assignment.

Blinding details related to the planned interim analyses are described in Section 9.7.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

9.4 Analysis Endpoints

Analysis endpoints of safety and immunogenicity are listed below.

9.4.1 Safety Endpoints

The safety analysis endpoints include:

Solicited injection-site AEs from Day 1 through Day 5 after study intervention

Solicited systemic AEs from Day 1 through Day 14 after study intervention

Unsolicited AEs from Day 1 through Day 28 after study intervention

The broad AE categories consisting of any AE and any vaccine-related AE from Day 1 through Day 28 after study intervention

The broad AE categories consisting of any SAE, any vaccine related SAEs, and death from Day 1 through the duration of participation in the study

The broad AE categories consisting of any MAAE and any ECI (event of clinical interest) from Day 1 throughout the duration of the study.

Maximum temperature measurements meeting the Brighton Collaboration cut points from Day 1 through Day 14 after study intervention

Safety laboratory results, vital signs, and physical exam findings as described in the SoA

9.4.2 Immunogenicity Endpoints

The immunogenicity analysis endpoints include:

Anti-SARS-CoV-2 spike serum nAb as measured by PNA

Anti-SARS-CoV-2 spike IgG as measured by ELISA

PBMCs stimulated with SARS-CoV-2 Spike peptides for characterization of cell mediated immunity and serum to characterize the immune response to V591

Anti-SARS-CoV-2 N-protein IgG responses as measured by immunoassay

9.5 Analysis Populations

9.5.1 Safety Analysis Populations

Safety analyses will be conducted in the All Participants as Treated (APaT) population, which consists of all randomized participants who received at least one dose of study intervention. Participants will be included in the treatment group corresponding to the study intervention they received for the analysis of safety data using the APaT population. This will be the treatment group to which they are randomized except for participants who receive an incorrect dose of study vaccine or placebo; such participants will be included in the treatment group corresponding to the study treatment actually received. In the 2-dose panels, safety parameters for cross-treated participants (ie, those who received vaccinations of both V591 and Placebo) will be summarized separately.

9.5.2 Immunogenicity Analysis Populations

The Per-Protocol (PP) population will be used for the analysis of immunogenicity data in this study. The PP population consists of all randomized participants without deviations from the protocol that may substantially affect the results of the immunogenicity endpoint. Potential deviations that may result in the exclusion of a participant from the PP population for all immunogenicity analyses include:

- Failure to receive any study vaccine at Day 1
- Failure to receive the correct dose of study vaccine at Day 1
- Receipt of prohibited medication or prohibited vaccine prior to the Day 1 blood sample collection

Additional deviations that may result in the exclusion of a participant from the PP population for specific immunogenicity analyses at a particular timepoint include:

- Collection of blood sample outside of the pre-specified window (as described in Section 1.3)

- Receipt of prohibited medication or prohibited vaccine prior to a blood sample collection

- Failure to receive the second dose of V591 or placebo according to vaccination schedule (for 2-dose panels only)

The final determination on protocol deviations, and thereby the composition of the PP population, will be made prior to the final unblinding of the database. Participants will be included in the vaccination group to which they are randomized for the analysis of immunogenicity data using the PP population. Determinations on protocol deviations will be made by blinded study team members prior to the planned interim analyses (Section 9.7) and prior to the final unblinding of the database. Participants will be included in the vaccination group to which they are randomized for the analysis of immunogenicity data using the PP population.

A supportive analysis using the Full Analysis Set (FAS) population will also be performed for the key secondary immunogenicity analysis endpoints. The FAS population consists of all randomized participants who received at least 1 vaccination and have at least 1 serology result. Participants will be included in the vaccination group to which they are randomized for the analysis of immunogenicity data using the FAS population.

9.6 Statistical Methods

Statistical testing and inference for safety and immunogenicity analyses are described in Section 9.6.1 and Section 9.6.2, respectively. Section 9.6.3 describes how demographic and baseline characteristics will be summarized.

9.6.1 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters, including AEs, postvaccination temperatures, laboratory measurements, ECGs, and vital signs. For the 2-dose panels, summary of safety parameters following each dose separately will also be provided.

The analysis of AEs and postvaccination temperature measurements will follow a tiered approach (Table 9). The tiers differ with respect to the analyses that will be performed. Events (specific preferred terms as well as system organ classes) are either pre-specified as “Tier 1” endpoints, or will be classified as belonging to “Tier 2” or “Tier 3” based on the number of events observed.

Tier 1 Events

Safety events or AEs of special interest that are pre-identified constitute Tier 1 safety endpoints which will be subject to inferential testing for statistical significance with 95% CIs and corresponding p-values provided for the between-treatment differences in the proportion of participants with events.

No Tier 1 events are defined for this study.

This study will solicit for predefined injection-site and systemic AEs. However, as this is the first clinical study of V591, no data exists around which a comparative, data-driven safety hypothesis can be formulated and tested. As a result, the solicited injection-site and systemic AE reported in this study will be analyzed as Tier 2 events.

Tier 2 Events

Tier 2 parameters will be assessed via point estimates with 95% CIs provided for differences in the proportion of participants with events using the Miettinen and Nurminen method (1985) [Miettinen, O. and Nurminen, M. 1985].

Tier 2 events for this study include solicited injection-site AEs from Day 1 through Day 5 postvaccination, solicited systemic AEs from Day 1 through Day 14 postvaccination (Section 8.4.8.1). In addition, the broad AE categories consisting of the percentage of participants with any AE, any vaccine-related AE, any SAE, any vaccine-related SAE, any MAAEs, any ECI, and death will be considered Tier 2 events. Nonserious AEs will be followed for 28 days postvaccination, while SAEs will be followed through the duration of participation in the study. The proportion of participants with maximum temperature measurements meeting the Brighton Collaboration cut points (Days 1 to 14) will also be considered Tier 2 endpoints.

Adverse events (specific PTs as well as SOCs) will be classified as belonging to Tier 2 if at least 4 participants in any vaccination group exhibit the event. The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when vaccination groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% CIs for Tier 2 events may be provided without adjustment for multiplicity, the CIs should be regarded as a descriptive measure supportive of safety review, not a formal method assessing the statistical significance of the between-group differences in AEs.

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. Only point estimates by vaccination group are provided for Tier 3 safety parameters.

Table 9 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Between-Group Comparison [a]	Descriptive Statistics
Tier 2	Solicited injection site AE (Days 1 to 5 after study intervention)	X	X
	Solicited systemic AE (Days 1 to 14 after study intervention)	X	X
	Any AE[b]	X	X
	Any Vaccine-Related AE[b]	X	X
	Any SAE[b]	X	X
	Any Vaccine-Related SAE	X	X
	Any MAAE	X	X
	Any ECI	X	X
	Death[b]	X	X
	Maximum temperature measurements meeting the Brighton Collaboration cut points (Days 1 to 14 after study intervention)	X	X
	Specific AEs by SOC or PT (incidence ≥4 participants in at least one of the vaccination groups)	X	X
Tier 3	Specific AEs by SOC and PT[c] (incidence <4 participants in one of the vaccination groups)		X

AE = adverse event; CI = confidence interval; M&N = Miettinen and Nurminen; PT = preferred term; SAE = serious adverse event; SOC = system organ class; X = results will be provided.

[a] These analyses will be performed using the M&N method.

[b] These endpoints are broad AE categories. For example, descriptive statistics for the safety endpoint of "Any AE" will provide the number and percentage of participants with at least 1 AE.

[c] Includes only those endpoints not prespecified as Tier 2 endpoints.

9.6.2 Statistical Methods for Immunogenicity Analyses

This section describes the statistical methods that address the secondary immunogenicity objectives. Methods related to exploratory objectives will be further described in the supplemental statistical analysis plan.

The geometric mean ratios and 95% CIs of the anti-SARS-CoV-2 spike serum nAb GMTs will be calculated using a cLDA method proposed by Liang and Zeger (2000) [Liang, K-Y and Zeger, S. L. 2000]. In this model, the response vector consists of the log-transformed prevaccination and postvaccination antibody titers. The repeated measures model will include terms for time, the interaction of time-by-vaccination group (with a restriction of the same baseline mean across groups). The treatment difference in terms of a geometric mean ratio at a given postvaccination time point will be estimated and tested from this model. The term for time will be treated as a categorical variable. An unstructured covariance matrix will be used to model the correlation among repeated measurements. This model allows the inclusion of participants who are missing either the baseline or postbaseline measurements, thereby increasing efficiency.

The observed nAb GMTs at each timepoint with serum collection and GMFRs from prevaccination to postvaccination will be performed within each vaccination group separately. Descriptive statistics with point estimates and within-group 95% CIs will be provided. The point estimates will be calculated by exponentiating the estimates of the mean of the natural log values and the within-group CIs will be derived by exponentiating the bounds of CIs of the mean of the natural log values based on the t-distribution.

A similar statistical approach will be used to evaluate the anti-SARS-CoV-2 spike serum IgG responses.

For responses smaller than the lower limit of quantitation (LLOQ), half of the LLOQ will be used for analysis when calculating the nAb GMTs and IgG GMCs.

A detailed analysis strategy for key immunogenicity endpoints is listed in Table 10.

Table 10 Analysis Strategy for Immunogenicity Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach[a]	Statistical Method	Analysis Population	Missing Data Approach
Secondary Endpoint				
nAb GMT ratio and IgG GMC ratio at Day 29 (all panels) and Day 85 (2-dose panels only)	P/S	cLDA model[b] (estimate and 95% CI)	PP/FAS	Model-based
nAb GMT and IgG GMC at all timepoint with serum collection	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed
GMFR from baseline to postvaccination for nAb and IgG	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed

CI = confidence interval; FAS = Full Analysis Set; GMC = geometric mean concentration; GMFR=geometric mean foldrise; GMT = geometric mean titer; IgG = Immunoglobulin G; nAb = neutralizing antibody; PP = Per-Protocol.

[a] P = Primary approach; S = Supportive approach.

[b] Estimation of the GMT ratios and computation of the corresponding 95% CIs will be calculated using t-distribution with the variance estimate from a constraint longitudinal data model (cLDA) utilizing the log-transformed antibody titers as the response and a single term for vaccination group.

9.6.3 Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant demographic and baseline characteristic will be assessed by using summary tables. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables (e.g., age, race, and gender), baseline characteristics, and prior and concomitant therapies will be summarized by treatment group either by descriptive statistics or categorical tables.

9.7 Interim Analyses

Up to two interim analyses may be performed on safety and immunogenicity data through at least Day 29. In order to trigger the first interim analysis at least 75% of study participants per Panel in at least 6 Panels must have completed their Day 29 visit. In order to trigger the second interim analysis at least 75% of study participants per Panel in at least 10 Panels must have completed their Day 29 visit.

An interim analysis may be performed on safety and immunogenicity data through at least Day 85 for Panels A, B, I, and J. To trigger this interim analysis at least 75% of these Panel's participants must have completed their Day 85 visit. A minimum percentage of participants from other study Panels is not required for this interim analysis, though all available data will be included.

An interim analysis may be performed on safety and immunogenicity data through at least Day 197 for Panels K and L. To trigger this interim analysis at least 75% of these Panel's participants must have completed their Day 197 visit. A minimum percentage of participants from other study Panels is not required for this interim analysis, though all available data will be included.

These interim immunogenicity analyses will include all available nAb PNA and IgG ELISA data.

For this early phase study, an internal statistician, statistical programmer, and modelers assigned to the protocol will be unblinded throughout the duration of the study to facilitate the interim reviews and analyses of the safety and immunogenicity data. Analyses of immunogenicity data may also be conducted at the discretion of the sponsor when data are available.

Results of the interim analysis will be provided to the unblinded siDMC. The siDMC will make a recommendation for further clinical development. Group summaries will be reviewed by the Sponsor's study team. Sponsor's study team (except for the unblinded statistician and programmer) will be blinded to the V591 treatment information at the participant level.

9.8 Multiplicity

No adjustment will be made for multiplicity.

9.9 Sample Size and Power Calculations

9.9.1 Sample Size and Power for Safety Analyses

The probability of observing at least 1 SAE in this study depends on the number of participants vaccinated and the underlying incidence of participants with a SAE in the study population. Calculations below assume that 100% of the randomized participants will be evaluable for safety analyses. There is an 80% chance of observing at least 1 SAE among 228 participants receive a vaccination of V591 if the underlying incidence of a SAE is 0.70%

(1 of every 143 participants receiving the vaccine). There is a 50% chance of observing at least 1 SAE among 228 participants receive a vaccination of V591 if the underlying incidence of a SAE is 0.30% (1 of every 329 participants receiving the vaccine). If no SAEs are observed among the 228 participants receive a vaccination of V591, this study will provide 97.5% confidence that the underlying percentage of participants with a SAE is <1.61% (1 in every 63 participants) in the V591 group.

Table 11 summarizes the percentage point differences between the 2 vaccination groups that could be detected with 80% probability for a variety of hypothetical underlying incidences of an adverse event. These calculations assume 228 participants receive a vaccination of V591 and 57 participants receive placebo and are based on a 2-sided 5% alpha level. The calculations are based on an asymptotic method proposed by Farrington and Manning (1990) [Farrington, C. P. 1990]; no multiplicity adjustments were made.

Table 11 Differences in Incidence of AE Rates between the 2 Vaccination Groups That can be Detected With an ~80% Probability (Assuming 2-sided 5% Alpha Level With 228 Participants in the V591 Group and 57 Participants in the Placebo Group)

Incidence of Adverse Event		**Risk Difference**
V591 (%)	**Placebo (%)**	**Percentage Points**
6.0	0.1	5.9
11.2	2	9.2
16.9	5	11.9
24.9	10	14.9
31.8	15	16.8
38.2	20	18.2
49.9	30	19.9
Incidences presented here are hypothetical and do not represent actual adverse experiences in either group. Based on an asymptotic method [Farrington, C. P. 1990]		

9.9.2 Sample Size and Power for Immunogenicity Analyses

This is a descriptive study and there are no hypotheses to be evaluated. This study will randomize approximately a total of 228 participants into 4 different dose-levels of the V591 group and 57 participants into the placebo group. Table 12 displays the numbers of participants scheduled to receive each study intervention.

Table 12 Numbers of Participants Scheduled to Receive Each Study Intervention

Treatment Group	Number of Participants		
	Day 1 (Dose 1 for all panels)	Day 57 (Dose 2 for Panels A, B, I, and J)	Day 169 (Dose 2 for Panels F[†], K, and L)
V591-10^4/10^5 $TCID_{50}$	20	0	20
V591-10^5 $TCID_{50}$	84	24	20
V591-10^6 $TCID_{50}$	84	24	20
V591-10^7 $TCID_{50}$	20	0	0
125-fold dilution of V591-10^7 $TCID_{50}$	20	0	0
Placebo	57	12	15

$TCID_{50}$=median tissue culture infectious dose

[†]Participant in Panel F will be administered V591-10^4 $TCID_{50}$ or placebo on Day 1, and V591-10^5 $TCID_{50}$ or placebo on Day 169.

The width of the 95% CIs for the GMT/GMC ratios depend on the sample size, variability of the natural log concentrations, and the magnitude of the ratio. In Table 13, 95% CIs for various hypothetical GMT/GMC ratios at Day 29 and various hypothetical standard deviation estimates for the natural log titers are displayed. It is assumed that approximately 85% participants will be evaluable for immunogenicity analyses based on PP population at Day 29.

Table 13 95% CIs for Varying Hypothetical GMT/GMC Ratios (V591/Placebo) and Varying Standard Deviations

Standard Deviation of Natural Log Titers/Concentration	GMT/GMC Ratios (V591/Placebo)			
	1.5	2.0	2.5	3.0
1.0	(1.04, 2.17)	(1.38, 2.90)	(1.73, 3.62)	(2.07, 4.34)
1.5	(0.86, 2.61)	(1.15, 3.48)	(1.44, 4.36)	(1.72, 5.23)
2.0	(0.72, 3.14)	(0.95, 4.19)	(1.19, 5.24)	(1.43, 6.29)

CI=confidence interval; GMC=geometric mean concentration; GMT= geometric mean titer.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus

source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

10.1.2 Financial Disclosure

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

10.1.4.1 Stand Internal Data Monitoring Committee

To supplement the routine monitoring outlined in this protocol, a separate siDMC will monitor the interim data from this study. The siDMC is comprised of members of Sponsor Senior Management, none of whom are directly associated with the conduct of this study. The siDMC will monitor the study at an appropriate frequency for evidence of adverse effects of study intervention. The siDMC will determine whether the study should continue (or other modifications, prespecified or otherwise, should be made) according to the protocol, considering the overall risk and benefit to study participants. The siDMC will also make recommendations to the Sponsor protocol team regarding steps to ensure both participant safety and the continued ethical integrity of the study.

Specific details regarding responsibilities of the siDMC will be described in a separate charter that is reviewed and approved by the siDMC.

10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive, or other locally mandated registries are that of the

Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.10 Study and Site Closure

The Sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 14 will be performed by the local laboratory.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and 5.2 of the protocol.

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

Table 14 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH MCHC Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
	HbA1c (required at screening only)			
Coagulation	Prothrombin time/International Normalized Ratio (PT/INR)			
Chemistry	BUN	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the ULN)
	Albumin	LDH	GGT	Serum Ferritin
	Creatinine	Sodium	ALT/SGPT	Total Protein
		CPK	Alkaline phosphatase	
Routine Urinalysis	Specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte by dipstick Microscopic examination (if blood or protein is abnormal)			
Pregnancy Testing	Highly sensitive serum or urine hCG pregnancy test (as needed for WOCBP) Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.			
Other Screening Tests	FSH (as needed in WONCBP only) Alcohol breath test and drug screen (to include at minimum: cocaine and opiates), sample to be determined by site SOP Serology (HIV antibody, HBsAg, and hepatitis C virus antibody) SARS-CoV-2 serology testing: at the screening visit for participants in sentinel Panels A, B and the 5 sentinel participants in panel E Only. COVID-19 PCR test Additional tests may be done per site SOP with Sponsor agreement.			

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CPK=creatine phosphokinase; FSH=follicle-stimulating hormone; GGT= gamma-glutamyl transpeptidase; HBsAg=hepatitis B surface antigen; hCG=human chorionic gonadotropin; HIV= human immunodeficiency virus; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean cell hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; SOP=standard operating procedure; ULN=upper limit of normal; WBC=white blood cell; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

- Any new cancer or progression of existing cancer.

- Medically Attended Adverse Events (MAAEs): defined as adverse events in which medical attention is received during an unscheduled, non-routine outpatient visit, such as an emergency room visit, office visit, or an urgent care visit with any medical personnel for any reason. Routine visits are not considered MAAEs. Examples of routine visits include: physical examinations, wellness visits or vaccinations.

- Note: Determination of MAAEs is the responsibility of the investigator or a qualified designee. Once identified, MAAEs should be reported to the Sponsor within 5 calendar days of learning of the event.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.

- Refer to Section 8.4.6 for protocol-specific exceptions.

Definition of Unsolicited and Solicited AE

- An unsolicited AE is an AE that was not solicited using a VRC and that is communicated by a participant who has provided documented informed consent. Unsolicited AEs include serious and nonserious AEs.

- Solicited AEs are predefined local (at the injection site) and systemic events for which the participant is specifically questioned, and which are noted by the participant in their VRC.

10.3.2 Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:

a. **Results in death**

b. **Is life-threatening**

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE.) A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. **Results in persistent or significant disability/incapacity**

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. **Is a congenital anomaly/birth defect**

In offspring of participant taking the product regardless of time to diagnosis.

f. **Other important medical events**

Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Additional Events Reported

Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

Is a cancer

Is associated with an overdose

10.3.4 Recording AE, SAE, and MAAE

AE, SAE and MAAE recording

- When an AE/SAE/MAAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE/MAAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE/MAAE.
- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

Participant assessment of intensity/severity

The study participants will make a self-assessment of intensity/severity for each AE, SAE and MAAE (and other reportable safety event) reported during the study. The study participant will assign an intensity or severity of mild, moderate, or severe, as defined in the VRC.

Injection site erythema/redness or swelling from Day 1 (the day of vaccination) through Day 5 postvaccination will be evaluated for maximum size by the study participant and will not be assigned an intensity/severity rating.

Values self-assessed by the study participants (of intensity/severity and/or daily maximum size) should be entered into the database without investigator modification.

Investigator assessment of toxicity

The investigator will make an assessment of toxicity (ie, Grades 1, 2, 3, or 4) for each AE, SAE, and MAAE (and other reportable event) reported during the study. A toxicity grade will be assigned to injection-site AEs, specific systemic AEs, other systemic AEs, and vital sign (temperature) AEs as shown in Table 15 through Table 18. The laboratory values in Table 19, Table 20 and Table 21 should serve as approximate guidelines for defining toxicities due to variations in established normal ranges. Local laboratory ranges and investigator discretion should be used for defining [Grade 1] toxicities. Local laboratory ranges and investigator discretion may be used for defining [Grade 2] toxicities with Sponsor Consultation. the following tables. The toxicity grading scales used in this study are adapted from the "FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007."

Table 15 Injection-Site AE Toxicity Grading Scale

Injection Site Reaction to Study Vaccine/Placebo[a]	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Injection-site AEs occurring Days 1 through 5 following receipt of study vaccine/placebo				
Pain/Tenderness	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	ER visit or hospitalization
Erythema/Redness	Size measured as B	Size measured as C or D	Size measured as E→	Necrosis or exfoliative dermatitis or results in ER visit or hospitalization
Induration/Swelling	Size measured as B	Size measured as C or D	Size measured as E→	Necrosis or ER visit or hospitalization
Other	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	ER visit or hospitalization

Injection Site Reaction to Study Vaccine/Placebo[a]	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Any injection-site reaction that begins ≥6 days after receipt of study vaccine/placebo				
Pain/tenderness Erythema/Redness Induration/Swelling Other	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	ER visit or hospitalization

Abbreviations: AE = adverse event; ER = emergency room; VRC =Vaccine Report Card; SAE = serious adverse event

[a] Based upon information provided by the participant on the VRC and verbally during VRC review. Erythema/Redness and Induration/Swelling are specific injection-site AEs with size designations of letters A through E→, based upon a graphic in the VRC. Size A is not assigned a toxicity grade; however, injection-site AEs that measure size A should be reported as adverse experiences. If the participant has an ER visit or is hospitalized for any injection-site AE, that AE is to be assigned a toxicity grade of 4, regardless of the size measured.

Table 16 Specific Systemic AE Toxicity Grading Scale

Systemic (General)	**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 daily activity	ER visit or hospitalization

Abbreviations: ER = emergency room

Table 17 Other Systemic AE Toxicity Grading Scale

Systemic Illness[a]	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)[b]**
Illness or clinical AE (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and required medical intervention	ER visit or hospitalization

Abbreviations: ER = emergency room; VRC = Vaccine Report Card; SAE = serious adverse event

[a] Based upon information provided by the patient on the VRC and verbally during the VRC review during the primary safety follow-up period. For SAEs reported beyond the primary safety follow-up period, grading will be based upon the initial report and/or follow-up of the event.

[b] AEs resulting in death will be assessed as Grade 4.

Table 18 Vital Sign (Temperature) Toxicity Grading Scale

Vital Signs[a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C)[b]	38.0 to 38.4	38.5 to 38.9	39.0 to 40.0	>40.0
(°F)[b]	100.4 to 101.1	101.2 to 102.0	102.1 to 104.0	>104.0

[a] Participant should be at rest for all vital sign requirements.

[b] Oral temperature; no recent hot or cold beverages or smoking.

Table 19 Laboratory Abnormalities - Serum

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

***ULN" is the upper limit of the normal range.

Table 20 Laboratory Abnormalities - Hematology

Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.
** "ULN" is the upper limit of the normal range.

Table 21 Laboratory Abnormalities – Urine

Urine *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Assessment of causality

Did the Sponsor's product cause the AE?

The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initial document must be retained for the required regulatory time frame. The criteria below are

intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

The following components are to be used to assess the relationship between the Sponsor's product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:

- **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (diary, etc.), seroconversion or identification of vaccine virus in bodily specimen?

- **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a vaccine-induced effect?

- **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors?

- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in the study?

    - If yes, did the AE recur or worsen?

    - If yes, this is a positive rechallenge.

    - If no, this is a negative rechallenge.

    (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose vaccine study; or (3) Sponsor's product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

Consistency with study intervention profile: Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

The assessment of relationship will be reported on the CRFs/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.

Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).

- Yes, there is a reasonable possibility of Sponsor's product relationship:
    - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
- No, there is not a reasonable possibility of Sponsor's product relationship:
    - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE, SAE and MAAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.5 Reporting of AEs, SAEs, MAAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, MAAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
    - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
    - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
        - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Medical Device and Drug-device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

This appendix is not applicable to this study.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

Premenarchal

Premenopausal female with 1 of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only contraceptive implant[c,d] • IUS[c,e] • Non-hormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. **Highly Effective Contraceptive Methods That Are User Dependent[b]** *Failure rate of <1% per year when used consistently and correctly.* • Combined (estrogen- and progesterone-containing) hormonal contraception[c,d]   • Oral   • Intravaginal   • Transdermal   • Injectable • Progestogen-only hormonal contraception[c,d]   • Oral   • Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant. [a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. [c] Male condoms must be used in addition to female participant hormonal contraception. [d] IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this study as outlined in Section 8.9 will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways with which drugs/vaccines may interact
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research

a. Participants for Enrollment

All participants enrolled in the clinical study will be considered for enrollment in future biomedical research.

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

4. Confidential Participant Information for Future Biomedical Research

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participants' clinical information with future test results. In fact, little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like sex, age, medical history and intervention outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in future biomedical research protocol and consent. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for future biomedical research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which

operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include: Lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@merck.com.

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618

2. International Council on Harmonisation [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html

3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.7 Appendix 7: Country-specific Requirements

As noted in Section 4, Study Design, older adults in Part 2B will only be recruited in the United States in order to facilitate the enrollment of minority groups that have been disproportional impacted by COVID-19 and historical underrepresented in vaccine trials.

10.8 Appendix 8: Blood Volume Table

Panels C-E and G-H (1-dose Panels)	**Screening**	**Treatment Periods**	**Poststudy**	**Total Collections**	**mL Per Collection**	**Total mL/ Test**
Laboratory Safety Tests	1	5	1	7	12.5	87.5
Blood for HIV/Hepatitis screen (at the discretion of the investigator)	1			1	9	9
Blood (DNA) for Future Biomedical Research		1		1	8.5	8.5
Blood for Drug Screen	1			1	10	10
Prothrombin Time	1			1	3	3
Serum β-hCG pregnancy test (Females only)	1		1	2	3.5	7
FSH (Females only)	1			1	3.5	3.5
Serum Collection for PNA and ELISA Assays		7	1	8	20	160
Serum collection for Immunological Assessments (Panels C, D, G, and H only)		2		2	5	10
Blood for PBMCs Assays (for Panels C, D, G and H only)		2		2	60	120
Total Blood Volume per Male Participant for Panels C, D, G and H[a]						408 mL
Total Blood Volume per Female Participant for Panels C, D, G and H[a]						418.5 mL
Total Blood Volume per Male Participant for Panels E[a]						288 mL
Total Blood Volume per Female Participant for Panels E[a]						298.5 mL

[a] If additional immunogenicity assessments and/or safety analysis is necessary, additional blood (up to 50 mL) may be obtained. Note: never to exceed 50 mL.

Panels A, B, I and J (2-dose Day 1, Day 57 panels)	**Screening**	**Treatment Periods**	**Poststudy**	**Total Collections**	**mL Per Collection**	**Total mL/ Test**
Laboratory Safety Tests	1	6	1	8	12.5	100
HIV/Hepatitis Screen (at the discretion of the investigator)	1			1	9	9
Blood (DNA) for Future Biomedical Research		1		1	8.5	8.5
Blood for Drug Screen	1			1	10	10
Prothrombin Time	1			1	3	3
Serum β-hCG pregnancy test (Females only)	1		1	2	3.5	7
FSH (Females only)	1			1	3.5	3.5
Serum Collection for PNA and ELISA Assays		8	1	9	20	180
Blood for PBMCs Assays		2		2	60	120
					Total Blood Volume per Male Participant[a]	430.5 mL
					Total Blood Volume per Female Participant[a]	441 mL
[a] If additional immunogenicity assessments and/or safety analysis is necessary, additional blood (up to 50 mL) may be obtained. Note: never to exceed 50 mL.						

Panels F, K and L (2-dose Day 1, Day 169 panels)	**Screening**	**Treatment Periods**	**Poststudy**	**Total Collections**	**mL Per Collection**	**Total mL/ Test**
Laboratory Safety Tests	1	6	1	8	12.5	100
HIV/Hepatitis Screen (at the discretion of the investigator)	1			1	9	9
Blood (DNA) for Future Biomedical Research		1		1	8.5	8.5
Blood for Drug Screen	1			1	10	10
Prothrombin Time	1			1	3	3
Serum β-hCG pregnancy test (Females only)	1		1	2	3.5	7
FSH (Females only)	1			1	3.5	3.5
Serum Collection for PNA and ELISA Assays		7	1	8	20	160
Blood for PBMCs Assays		2		2	60	120
					Total Blood Volume per Male Participant[a]	410.5 mL
					Total Blood Volume per Female Participant[a]	421 mL
[a] If additional immunogenicity assessments and/or safety analysis is necessary, additional blood (up to 50 mL) may be obtained. Note: never to exceed 50 mL.						

10.9 Appendix 9: Algorithm for Assessing Out of Range Laboratory Values

For all laboratory values obtained at prestudy (screening) visit and/or predose evaluation:

A. If all protocol-specified laboratory values are normal, the participant may enter the study.

B. If a protocol specified laboratory value is outside of the parameter(s) outlined in the inclusion/exclusion criteria (including a repeat if performed), the participant will be excluded from the study.

C. If ≥1 protocol-specified laboratory value not specified in the inclusion/exclusion criteria is outside the normal range, the following choices are available:

    1. The participant may be excluded from the study;

    2. The participant may be included in the study if the abnormal value(s) is NCS (the investigator must annotate the laboratory value "NCS" on the laboratory safety test source document).

    3. The participant may be included in the study if the abnormality is consistent with a pre-existing medical condition which is not excluded per protocol (eg, elevated eosinophil count in a participant with asthma or seasonal allergies), the medical condition should be annotated on the laboratory report.

    OR

    4. The abnormal test may be repeated (refer items a. and b. below for continuation of algorithm for repeated values).

        a. If the repeat test value is within the normal range, the participant may enter the study.

        b. If the repeat test value is still abnormal, the study investigator will evaluate the potential participant with a complete history and physical examination, looking especially for diseases that could result in the abnormal laboratory value in question. If such diseases can be ruled out, and if the abnormal laboratory value is not clinically relevant, then the participant may enter the study.

D. If there is any clinical uncertainty regarding the significance of an abnormal value, the participant will be excluded from the study.

10.10 Appendix 10: Abbreviations

Abbreviation	Expanded Term
AE	adverse event
APaT	All-Participants-as-Treated
AR	adverse reaction
BMI	body mass index
BP	blood pressure
BSL 1	Biosafety Level 1
CHIKV	Chikungunqa virus
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CoV	coronaviruses
CrCl	creatinine clearance
CRF	Case Report Form
CRU	clinical research unit
CSR	Clinical Study Report
DENV	Dengue virus
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
FDAAA	Food and Drug Administration Amendments Act
FAS	Full Analysis Set
FIH	first in human
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practice
GMO	genetically-modified organism
HBV	Hepatitis B virus
hCG	human chorionic gonadotropin
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG	immunoglobulin G
IFNγ	interferon gamma
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
LAM	lactational amenorrhoea method
LASV	Lassa Fever virus

Abbreviation	Expanded Term
LLOQ	lower limit of quantitation
MAAE	Medically-attended adverse event
MERS	Middle Eastern Respiratory Syndrome
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
MIS-C	Multisystem Inflammatory Syndrome in Children
MV	Measles virus
MV-CHIK	Measles vector-Chikungunya
MV-SARS	Measles vector-Severe Acute Respiratory Syndrome
nAb	neutralizing antibody
NCS	not clinically significant
NOAEL	no observed adverse effect level
PK	pharmacokinetic
PP	per-protocol
PNA	Pseudo-virus Neutralization Assay
PRNT	plaque reduction neutralization test
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
siDMC	Standing Internal Data Monitoring Committee
SoA	schedule of activities
sSAP	supplemental Statistical Analysis Plan
TNF-a	tumor necrosis factor alpha
UDS	urine drug screen
USP	United States Pharmacopeia
VRC	vaccination report card
VS	vital sign
WHO	World Health Organization
WNV	West Nile virus
WOCBP	woman/women of childbearing potential

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