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Title Page

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Protocol Title: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Trial to Evaluate the Safety and Immunogenicity of V590 in Healthy Adults

Protocol Number: 001-03

Compound Number: V590

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	26583

Approval Date: 17 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
Amendment 03	17-FEB-2021	Documentation of early study termination
Amendment 02	23-OCT-2020	Inclusion of safety reviews in Part 1
Amendment 01	17-SEP-2020	Modification of doses
Original Protocol	10-SEP-2020	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: [001-03]

Overall Rationale for the Amendments:

Rationale for Amendment 001-03: An evaluation of available Day 28 immunogenicity data, including both ELISA and PRNT, indicated that V590 was not predicted to protect against disease caused by SARS-CoV-2. Based on these data the Sponsor made the decision not to enroll further participants in the study, to bring the study to a close, and to discontinue development of intramuscularly administered V590. V590 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.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
1 Protocol Summary 1.1 Protocol Synopsis	Updated Estimated Study Duration section Updated Duration of Participation section	Modified to reflect planned study conduct.
1.3 Schedule of Activities	Added the following in the schedule details Notes section: **Amendment 001-03:** Study visits on Days 90, 180, 270, and 365 will not be performed. A poststudy visit/phone call will be performed, which may be combined with the Day 28 visit. .	Modified to reflect planned study conduct.
2 Introduction 2.1 Study Rationale	Updated background to be current.	Updated to reflect current SARS-CoV-2 epidemiology.

Section # and Name	Description of Change	Brief Rationale
3 Hypotheses, Objectives, and Endpoints	Updated primary endpoints Updated secondary endpoints	Modified to reflect planned study conduct. Modified for flexibility for stool shedding assessment.
4.1 Overall Design	Added the following: **Amendment 001-03**: Enrolled participants in all parts will be followed through Day 28 for safety, tolerability, immunogenicity, shedding and viremia. A final study analysis will be performed on all available data through Day 28, in place of an Interim Analysis.	Modified to reflect planned study conduct.
4.2 Scientific Rationale for Study Design	Added Rationale for Amendment 001-03	Provides background and rationale for this amendment.
4.2.1.2 Safety Endpoints	Added the following: **Amendment 001-03**: Active monitoring of AEs, ECIs, and MAAEs will occur through Day 28. Spontaneously reported SAEs will be collected per protocol (up to 365 Days for all SAEs, and indefinitely if considered related to intervention).	Modified to reflect planned study conduct.

Section # and Name	Description of Change	Brief Rationale
5.3.2.1 Caffeine Restrictions 8 Study Assessments and Procedures 8.3 Safety Assessment 8.11.4 Poststudy	Deleted "(Day 365)" as it relates to the poststudy.	Modified to reflect planned study conduct.
8 Study Assessments and Procedures	Added the following: **Amendment 001-03:** Blood will be collected through Day 28.	Modified to reflect planned study conduct.
8.4.1 Time Period and Frequency for Collecting AE, SAE, MAAE and Other Reportable Safety Event Information	Added the following: **Amendment 001-03:** All AEs, ECIs, and MAAEs must be reported by the investigator up to Day 28. Spontaneously reported SAEs will be collected per protocol (up to 365 Days for all SAEs, and indefinitely if considered related to intervention).	Modified to reflect planned study conduct.
8.11.4 Poststudy	Added the following: **Amendment 001-03**: A poststudy visit/phone call will be performed for safety assessment. This may be combined with the Day 28 visit. Active monitoring of AEs, ECIs, and MAAEs will occur through Day 28. Spontaneously reported SAEs will be collected per protocol.	Modified to reflect planned study conduct.

Section # and Name	Description of Change	Brief Rationale
9 Statistical Analysis Plan 9.1 Statistical Analysis Plan Summary	Added the following: For primary safety endpoint: **Amendment 001-03**: MAAEs from Day 1 through Day 28. SAEs from Day 1 through the duration of the study until the final database lock. For secondary immunogenicity endpoint: **Amendment 001-03**: Immunogenicity analyses will include all available data through Day 28. **Amendment 001-03**: Active monitoring and immunogenicity assessments in the study will occur through Day 28. Spontaneous safety reporting is permitted beyond Day 28 for the protocol specified durations. Immunogenicity analyses will include all available data through Day 28. Safety analyses will include all collected safety data through the duration of the study until the final database lock. A final analysis of study data will occur instead of an interim analysis.	Modified to reflect planned study analysis.
9.4.1 Safety Endpoints	Added the following: **Amendment 001-03**: MAAEs from Day 1 post-dose through Day 28. SAEs from Day 1 through the duration of the study until the final database lock.	Modified to reflect planned study analysis.

Section # and Name	Description of Change	Brief Rationale
9.4.2 Immunogenicity Endpoints	Added the following: **Amendment 001-03**: Immunogenicity analyses will include all available data through Day 28.	Modified to reflect planned study analysis.
9.4.3 Viremia and Viral Shedding Endpoints	Added the following: **Amendment 001-03**: Viremia and viral shedding samples will be assayed with the intention of testing until negative for viremia/viral shedding. Viremia and viral shedding analyses will include all available data through Day 28.	Modified to reflect planned study analysis.
9.4.4 Efficacy Endpoints	Added the following: **Amendment 001-03**: Efficacy analyses will include all available data through Day 28.	Modified to reflect planned study analysis.
9.6.1 Statistical Methods for Safety Analyses	Added the following: **Amendment 001-03**: MAAEs from Day 1 post-dose through Day 28. SAEs from Day 1 through the duration of the study until the final database lock.	Modified to reflect planned study analysis.

Section # and Name	Description of Change	Brief Rationale
9.6.2 Statistical Methods of Immunogenicity Analyses	Added the following: **Amendment 001-03**: Immunogenicity analyses will include all available data through Day 28.	Modified to reflect planned study analysis.
9.6.3 Statistical Methods for Viremia and Viral Shedding Analyses	Added the following: **Amendment 001-03**: Viremia and viral shedding samples will be assayed with the intention of testing until negative for viremia/viral shedding. Viremia and viral shedding analyses will include all available data through Day 28.	Modified to reflect planned study analysis.
9.6.4 Statistical Methods for Efficacy Analyses	Added the following: **Amendment 001-03**: Efficacy analyses will include all available data through Day 28.	Modified to reflect planned study analysis.
9.7 Interim Analyses	Added the following: **Amendment 001-03:** Participants in all parts will be followed through Day 28 for safety, tolerability, immunogenicity, viremia and viral shedding. A final study analysis will be performed on all available data through Day 28, in place of an Interim Analysis.	Modified to reflect planned study analysis.

Section # and Name	Description of Change	Brief Rationale
10.8 Appendix 8: Approximate Blood Volume Table	Added the following: **Amendment 001-03:** Blood will be collected through Day 28. Study visits on Days 90, 180, 270, and 365 will not be performed.	Modified to reflect planned study conduct.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Trial to Evaluate the Safety and Immunogenicity of V590 in Healthy Adults

Short Title: Phase 1 Dose Ranging Trial to Assess Safety and Immunogenicity of V590 in Healthy Adults

Acronym:

Hypotheses, Objectives, and Endpoints:

Primary Objectives	**Primary Endpoints**
All Parts: - To assess the safety and tolerability of V590 versus placebo	- Solicited injection site AEs from Day 1 through Day 5 after study intervention - Solicited systemic AEs from Day 1 through Day 28 after study intervention - Unsolicited AEs from Day 1 through Day 28 after study intervention - Medically attended AEs (MAAEs) collected from Day 1 through Day 180 after study intervention - SAEs collected from Day 1 through Day 365 after study intervention **Amendment 001-03**: AEs/MAAEs/SAEs collected through at least Day 28. Spontaneous reporting of SAEs after Day 28 will be recorded through Day 365 for unrelated SAEs and indefinitely for SAEs considered related to study intervention.
Parts 1 and 2 only: - To assess the immunogenicity of V590 on Day 28 - Hypothesis: At least one well-tolerated dose of V590 increases the GMTs of Anti-SARS-CoV-2 spike serum neutralizing antibody, as measured by PRNT, compared to placebo.	- Anti-SARS-CoV-2 spike serum neutralizing antibody responses, as measured by plaque reduction neutralization test (PRNT), at Day 28

Secondary Objectives	**Secondary Endpoints**
Parts 1 and 2 only: - To assess the immunogenicity of V590 using assays to measure immune responses	- Anti-SARS-CoV-2 spike serum neutralizing antibody responses, as measured by PRNT (all timepoints except Day 28) - Anti-SARS-CoV-2 spike IgG responses, as measured by ELISA
All Parts: - To assess V590 viral shedding and viremia	- V590 plasma viremia, as measured by RT-PCR - V590 viral shedding in saliva, urine, and stool (if assayed), as measured by RT-PCR

Overall Design:

Study Phase	Phase 1
Primary Purpose	Prevention
Indication	Prevention of 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	Participant Investigator Monitor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 13 months from the time the first participant provides documented informed consent until the last participant's last study-related contact. **Amendment 001-03:** Study duration will be approximately 3.5 months.

Number of Participants:

Approximately 252 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 54 years old SARS-CoV-2 seronegative)						
Panel A	V590	$5.00 \cdot 10^5$ pfu	Single Dose	IM	Single IM injection on Day 1	Experimental Treatment
Panel B	V590	$2.40 \cdot 10^6$ pfu				
Panel C	V590	$1.15 \cdot 10^7$ pfu				
Panel D	V590	$5.55 \cdot 10^7$ pfu				
Panels A-D	Placebo	NA				Placebo
Part 2 (≥ 55 years old SARS-CoV-2 seronegative)						
Panel E	V590	$5.00 \cdot 10^5$ pfu	Single Dose	IM	Single IM injection on Day 1	Experimental Treatment
Panel F	V590	$2.40 \cdot 10^6$ pfu				
Panel G	V590	$1.15 \cdot 10^7$ pfu				
Panel H	V590	$5.55 \cdot 10^7$ pfu				
Panels E-H	Placebo	NA				Placebo
Part 3 (18 to 54 years old SARS-CoV-2 seropositive)						
Panel I	V590	$5.55 \cdot 10^7$ pfu	Single Dose	IM	Single IM injection on Day 1	Experimental Treatment
Panel I	Placebo	NA				Placebo

Abbreviations: IM: intramuscular

Total Number of Intervention Groups/ Arms	252 participants (112 participants in Part 1, 112 participants in Part 2, and 28 participants in Part 3) will participate in the study that will include a total of 4 dose-levels and 9 Panels.
Duration of Participation	Each participant will participate in the study for approximately 13 months from the time the participant provides documented informed consent through the final contact. Each participant will be receiving a single dose of study intervention on Day 1. After administration of the study intervention, each participant will be followed for 12 months. **Amendment 001-03:** Participants will be followed for a minimum of approximately 28 days after study intervention.

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	No
Data Monitoring Committee	Yes
Clinical Adjudication 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 11.

1.2 Schema

The study design is depicted in Table 1.

Table 1 Study Design

Part 1 (18 to 54 years old SARS-CoV-2 seronegative) [a, b, c]			
Panel A (n = 28)	Panel B (n = 28)	Panel C (n = 28)	Panel D (n = 28)
V590 $5.00 \cdot 10^5$ pfu or pbo	V590 $2.40 \cdot 10^6$ pfu or pbo	V590 $1.15 \cdot 10^7$ pfu or pbo	V590 $5.55 \cdot 10^7$ pfu or pbo
Part 2 (≥ 55 years old SARS-CoV-2 seronegative) [a, b, c]			
Panel E (n = 28)	Panel F (n = 28)	Panel G (n = 28)	Panel H (n = 28)
V590 $5.00 \cdot 10^5$ pfu or pbo	V590 $2.40 \cdot 10^6$ pfu or pbo	V590 $1.15 \cdot 10^7$ pfu or pbo	V590 $5.55 \cdot 10^7$ pfu or pbo
Part 3 (18 to 54 years old SARS-CoV-2 seropositive) [a, c]			
			Panel I (n = 28)
			V590 $5.55 \cdot 10^7$ pfu or pbo

a. Within each panel of Parts 1, 2, and 3, participants will be randomized to receive V590 or matching Placebo in a 3:1 ratio according to a computer-generated, permuted-block allocation schedule (i.e., in each panel 21 participants to receive V590 and 7 participants to receive matching placebo).

b. Within Part 1, safety data through Day 7 must be reviewed for at least 6 participants prior to administration of the next higher dose level. At least 6 participants from an equal or greater dose level in Part 1 must be dosed with either V590 or placebo and safety reviewed through Day 7 prior to dosing in Parts 2 or 3.

c. The suggested doses may be adjusted downward based on evaluation of safety and tolerability data observed from a subset of participants in previous Parts or based upon emerging preclinical data. Part 3 may initiate in parallel with Part 2 Panel H. Refer to Section 6.6 (Dose Modification) for the safety data that will be reviewed prior to dosing in Parts 2 and 3.

1.3 Schedule of Activities

All Parts/Panels																	
Study Period:	Screening	Study Day		Study Day												Post-study	Notes
Scheduled Hour, Day, Week, etc.	Screening	Days -3 to -1	Day 1 Pre-dose	1	2	3	4	5	6	7	14	28	90	180	270	365	**Section 8.11.5** Details on variance in procedure collection times. **Amendment 001-03:** Study visits on Days 90, 180, 270, and 365 will not be performed. A poststudy visit/phone call will be performed, which may be combined with the Day 28 visit.
Administrative Procedures																	
Informed Consent	X																**Sections 8.1.1.1 and 8.11.1** Separate Screening protocol and informed consent form may be utilized in advance of main consent availability to perform assessments at Screening. In this event, the main informed consent should be obtained on or before Days -3 to -1.
Informed Consent for Future Biomedical Research		X															**Section 8.1.1.2**
Participant Identification Card		X															**Section 8.1.3**
Inclusion/Exclusion Criteria	X	X															**Section 5.0** Prior to admission on Days -3 to -1 and Day 1 randomization, confirm participant still meets all eligibility criteria (except laboratory assessment, which will be based on screening)
Medical History	X	X															**Section 8.1.4**

All Parts/Panels																	
Study Period:	Screening	Study Day		Study Day												Post-study	Notes
Scheduled Hour, Day, Week, etc.	Screening	Days -3 to -1	Day 1 Pre-dose	1	2	3	4	5	6	7	14	28	90	180	270	365	**Section 8.11.5** Details on variance in procedure collection times. **Amendment 001-03:** Study visits on Days 90, 180, 270, and 365 will not be performed. A poststudy visit/phone call will be performed, which may be combined with the Day 28 visit.
Prior/Concomitant Medication Review	X	X	X								X	X	X	X	X	X	**Sections 6.5, 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**
Domiciling (including meals)		X----------X															**Section 8.1.11** The first day of admission is flexible and may be between Days -3 and -1 based upon the time required to obtain SARS-CoV-2 testing results to confirm eligibility.
Clinical Procedures/ Safety Assessment																	
Full physical examination	X		X														**Section 8.3.1** Day 1 predose will be done within 24 hours prior to dosing.
Symptoms driven physical exam				X	X	X	X	X	X	X	X	X	X	X	X	X	**Section 8.3.2** Only to be conducted if participant symptoms warrant an exam or at investigator's discretion.

All Parts/Panels																	
Study Period:	Screening	Study Day		Study Day												Post-study	Notes
Scheduled Hour, Day, Week, etc.	Screening	Days -3 to -1	Day 1 Pre-dose	1	2	3	4	5	6	7	14	28	90	180	270	365	**Section 8.11.5** Details on variance in procedure collection times. **Amendment 001-03:** Study visits on Days 90, 180, 270, and 365 will not be performed. A poststudy visit/phone call will be performed, which may be combined with the Day 28 visit.
Targeted physical examination of injection site				X	X	X	X	X									**Section 8.3.3** Day 1 (post-dose) exam should occur ~ 1-2 hours postdose.
Height	X																**Section 8.3.4**
Weight	X																**Section 8.3.4**
Semi-recumbent Vital Signs (Blood Pressure [BP] and Heart Rate [HR] and Respiratory Rate [RR] and pulse oximetry [SaO2])	X		X	X	X	X	X	X	X	X							**Section 8.3.6** All measurements of HR and BP will be preceded by at least 10 minutes of quiet semi-recumbent rest. Days 1 predose measurements will be done within ~3 hours of dosing. Day 1: Post-dose measurements will be taken approximately 2 and 4 hours after vaccination. Days 2 to 7 measurements will be taken around the same time as Day 1 dosing.

All Parts/Panels																	
Study Period:	Screening	Study Day		Study Day												Post-study	Notes
Scheduled Hour, Day, Week, etc.	Screening	Days -3 to -1	Day 1 Pre-dose	1	2	3	4	5	6	7	14	28	90	180	270	365	**Section 8.11.5** Details on variance in procedure collection times. **<u>Amendment 001-03:</u>** Study visits on Days 90, 180, 270, and 365 will not be performed. A poststudy visit/phone call will be performed, which may be combined with the Day 28 visit.
Body Temperature	X	X	X	X----------X													**Section 8.3.5 and Section 8.3.8** While domiciled, clinic staff will observe the participant temperature measurement at Screening, Day -3 to Day-1, Day 1 predose and 2-hour postdose to done by clinic staff. Day 1 (4-hour postdose) and daily Days 2-28 temperatures are done and noted on the VRC by the participant.
12-lead ECG	X		X														**Section 8.3.7** Predose ECG will be done within 24 hours of dosing. Postdose ECG may be done at the investigator discretion (e.g., to further assess new symptoms, VS, or PE findings).

All Parts/Panels																	
Study Period:	Screening	Study Day		Study Day												Post-study	Notes
Scheduled Hour, Day, Week, etc.	Screening	Days -3 to -1	Day 1 Pre-dose	1	2	3	4	5	6	7	14	28	90	180	270	365	**Section 8.11.5** Details on variance in procedure collection times. **<u>Amendment 001-03:</u>** Study visits on Days 90, 180, 270, and 365 will not be performed. A poststudy visit/phone call will be performed, which may be combined with the Day 28 visit.
Paper Vaccination Report Card (VRC)			X----------X														**Section 8.3.8** Paper VRC will be provided on Day 1. 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	X	X					**Section 8.3.8**
Collect Paper VRC From Participant												X					**Section 8.3.8**
V590/Placebo Administration				X													**Section 8.1.8**
Postvaccination Observation Period				X													**Section 8.3.9** Participants will be observed for ~4 hours postdose on Day 1.
AE/ECI Review				X----------X													**Sections 8.4 and 10.3**
MAAE Review				X----------X													**Sections 8.4 and 10.3**

All Parts/Panels																	
Study Period:	Screening	Study Day		Study Day												Post-study	Notes
Scheduled Hour, Day, Week, etc.	Screening	Days -3 to -1	Day 1 Pre-dose	1	2	3	4	5	6	7	14	28	90	180	270	365	**Section 8.11.5** Details on variance in procedure collection times. **<u>Amendment 001-03:</u>** Study visits on Days 90, 180, 270, and 365 will not be performed. A poststudy visit/phone call will be performed, which may be combined with the Day 28 visit.
SAE review				X----------X													**Sections 8.4 and 10.3** Nonserious AEs and ECIs are to be reported from Days 1 through 28 following vaccination. SAEs and deaths are to be reported throughout the duration of an individual's study participation.
Laboratory Procedures/ Assessments																	
Serum for VSV Antibodies		X															Test will be read at the central laboratory. Test results not required for dosing.
Serum β-hCG or urine pregnancy test (WOCBP only)	X	X										X					**Sections 10.2 and 10.5.3**
Serum FSH – (WONCBP only)	X																**Section 10.2** Confirmatory for WONCP who are postmenopausal or oophorectomized.
HIV, hepatitis B and C screen (per site SOP)	X																**Section 10.2**
UDS/BDS (per site SOP)	X	X															Any additional UDS/BDS are conducted per site SOP
Hematology / Chemistry / Coagulation	X	X				X				X		X					

All Parts/Panels																	
Study Period:	Screening	Study Day		Study Day												Post-study	Notes
Scheduled Hour, Day, Week, etc.	Screening	Days -3 to -1	Day 1 Pre-dose	1	2	3	4	5	6	7	14	28	90	180	270	365	**Section 8.11.5** Details on variance in procedure collection times. **Amendment 001-03:** Study visits on Days 90, 180, 270, and 365 will not be performed. A poststudy visit/phone call will be performed, which may be combined with the Day 28 visit.
Urinalysis	X	X				X				X		X					
Screening and SARS-CoV-2 Tests																	
Swab for SARS-CoV-2 Virus by RT-PCR	X	X															Screening and Admission (Days -3 to -1) tests will be done with the Abbott RealTime SARS-CoV-2 test, supplied by and read at the central laboratory. Alternate tests for active SARS-CoV-2 (including nasal/oral swabs in place of nasopharyngeal swabs, and/or antigen tests) at both Screening and Admission (Days -3 to -1) may be permitted with agreement by the Sponsor. Additional testing may be performed based on participant symptoms and/or SARS-CoV-2 exposures, as described in Sections 4.2.1.1 and 8.3.10. Additional testing may be done at the discretion of the investigator and per site SOP.

All Parts/Panels																	
Study Period:	Screening	Study Day		Study Day												Post-study	Notes
Scheduled Hour, Day, Week, etc.	Screening	Days -3 to -1	Day 1 Pre-dose	1	2	3	4	5	6	7	14	28	90	180	270	365	**Section 8.11.5** Details on variance in procedure collection times. **Amendment 001-03:** Study visits on Days 90, 180, 270, and 365 will not be performed. A poststudy visit/phone call will be performed, which may be combined with the Day 28 visit.
Serum for Anti-SARS-CoV-2 Nucleocapsid Antibodies	X	X								X	X	X	X	X	X	X	Tests at all timepoints will be done with the Roche Elecsys Anti-SARS-CoV-2 test, supplied by and measured at the central laboratory. Alternate tests during the Days -3 to -1 assessment, including anti-spike antibody tests, may be permissible with agreement from the Sponsor. Post-vaccination samples are only collected for Parts 1 and 2 (not Part 3).
Immunogenicity and Shedding																	
Serum for Anti-SARS-CoV-2 Spike Neutralizing Antibodies (PRNT)			X							X	X	X	X	X	X	X	Leftover main study serum will be stored for FBR.
Serum for Anti-SARS-CoV-2 Spike IgG (ELISA)			X							X	X	X	X	X	X	X	Leftover main study serum will be stored for FBR.

All Parts/Panels																	
Study Period:	Screening	Study Day		Study Day												Post-study	Notes
Scheduled Hour, Day, Week, etc.	Screening	Days -3 to -1	Day 1 Pre-dose	1	2	3	4	5	6	7	14	28	90	180	270	365	**Section 8.11.5** Details on variance in procedure collection times. **Amendment 001-03:** Study visits on Days 90, 180, 270, and 365 will not be performed. A poststudy visit/phone call will be performed, which may be combined with the Day 28 visit.
Plasma for V590 Viremia				X	X	X	X	X	X	X	X	X					Day 1 postdose will be done at ~6 hours. Other days will be done at approximately the same time of day as the Day 1 dosing. Leftover main study plasma will be stored for FBR.
Saliva for V590 Shedding				X	X	X	X	X	X	X	X	X					Day 1 postdose will be done at ~6 hours. Other days will be done at approximately the same time of day as the Day 1 dosing. Leftover main study saliva will be stored for FBR.
Urine for V590 Shedding				X	X	X	X	X	X	X	X	X					Day 1 postdose will be done at ~6 hours. Other days will be done at approximately the same time of day as the Day 1 dosing. Leftover main study urine will be stored for FBR.
Stool for V590 Shedding					-----X-----			------X------									Total of 2 stool samples collected if produced: one sample on Days 2 to 4; one sample on Days 5 to 7. Leftover main study stool will be stored for FBR.

All Parts/Panels																	
Study Period:	Screening	Study Day		Study Day												Post-study	Notes
Scheduled Hour, Day, Week, etc.	Screening	Days -3 to -1	Day 1 Pre-dose	1	2	3	4	5	6	7	14	28	90	180	270	365	**Section 8.11.5** Details on variance in procedure collection times. **Amendment 001-03:** Study visits on Days 90, 180, 270, and 365 will not be performed. A poststudy visit/phone call will be performed, which may be combined with the Day 28 visit.
Serum for Cytokines			X	X			X										Day 1 postdose will be done at ~6 hours. Tests at all timepoints will be done with a kit to be supplied by and measured at the central laboratory.
Biomarkers																	
Blood for Genetic Analysis			X														Collect predose from enrolled participants only. See section 8.8.1.
Blood (RNA) for Future Biomedical Research			X	X			X										Collect predose from enrolled participants only.
Blood for PBMCs and Plasma for Future Biomedical Research			X									X					PBMCs and plasma will be taken at selected sites only.
Serum for Future Biomedical Research			X							X	X	X	X	X	X	X	
Mucosal Samples for Future Biomedical Research			X							X	X	X					
AE=adverse event; β-hCG=beta human chorionic gonadotropin; BDS=blood drug screen; ELISA= enzyme-linked immunosorbent assay; FBR=future biomedical research; FSH=follicle stimulating hormone; ID=identification; MAAE=medically attended adverse event, SAE=serious adverse event; SOP=standard operating procedure; UDS=Urine Drug Screen; PRNT=plaque reduction neutralization test; PBMC=peripheral blood mononuclear cells																	

2 INTRODUCTION

2.1 Study Rationale

SARS-CoV-2 is the virus responsible for the ongoing global COVID-19 pandemic with over 106 million confirmed cases and 2.3 million deaths as of February 2021 (https://coronavirus.jhu.edu/map.html). There is a pressing global need for safe and effective vaccines. V590 is a live recombinant viral vaccine against SARS-CoV-2 that is based upon the same platform as ERVEBO, a licensed vaccine against Zaire Ebola virus.

This study is a placebo-controlled dose-ranging trial to evaluate the safety and immunogenicity of V590 in healthy younger and older seronegative adults and will additionally include a single dose level panel of seropositive younger adults. The primary objectives will be safety and tolerability, as well as neutralizing antibodies as measured by plaque reduction neutralization test (PRNT) at Day 28. Secondary and Exploratory objectives will include vaccine viremia and shedding, anti-Spike antibodies measured by ELISA and other immunogenicity endpoints, and serologic evidence of SARS-CoV-2 infection.

2.2 Background

Refer to the IB for detailed background information on V590.

2.2.1 Pharmaceutical and Therapeutic Background

V590 is a live recombinant viral vaccine consisting of a vesicular stomatitis virus (VSV) in which the gene for the VSV envelope glycoprotein (G) has been deleted and replaced with coding sequence for the spike glycoprotein of the coronavirus SARS-CoV-2.

This recombinant VSV-vectored replication competent chimeric virus platform technology enables delivery of native glycoprotein immunogens in the context of a VSV vaccine infection. VSV-vectored live chimeric virus vaccines exchange the VSV G gene (VSVΔG vectors or chimeras) with sequence encoding heterologous glycoproteins from other pathogens. The VSVΔG chimera avoids the potential negative associations with the VSV glycoprotein including the strong anti-G humoral response and neurotropism in animal models. Benefits of the platform include: 1) fast production of high titers and propagation in almost all mammalian cells; 2) lack of reassortment and corresponding potential to undergo genetic shift *in vivo*; 3) inability of the vector's viral RNA to integrate into the host genome; 4) simple genetic modification with the possibility to accommodate one or multiple antigenic inserts; 5) the low anti-VSV seroprevalence in the human population; 6) mild pathogenicity in humans; 7) induction of innate, humoral and cellular immune responses irrespective of VSV seropositivity [Clarke, D. K., et al 2016].

Preclinical vaccines based on the VSVΔG platform have been developed for diseases resulting from coronavirus infection including the 2002 Severe Acute Respiratory Syndrome (SARS) agent and Middle Eastern Respiratory Syndrome (MERS) [Kapadia, S. U., et al 2005] [Kapadia, S. U., et al 2008] [Liu, R., et al 2018]. These SARS and MERS constructs,

each expressing the spike protein, demonstrated efficacy in mouse models of infection, and immunogenicity in NHPs, respectively.

VSVΔG chimeras expressing glycoproteins from multiple other viruses have also been derived and studied, including ERVEBO, a licensed vaccine against Zaire ebolavirus. ERVEBO was approved based on a clinical program that included immunization of approximately 16,000 subjects in 12 Phase 1, 2, and 3 trials. The clinical benefit of the vaccine was demonstrated in the ring vaccination trial conducted in Guinea, with vaccine efficacy (VE) reported as 100% (95% CI: 63.5 to 100%, p=0.0471) at least 10 days after vaccination [Camacho, A., et al 2015] [Henao-Restrepo, A. M., et al 2015] [Henao-Restrepo, A. M., et al 2017].

ERVEBO was generally well-tolerated in healthy adult subjects, and injection-site AEs were generally mild to moderate in intensity and of limited duration. Systemic AEs were more commonly reported in vaccinated subjects than placebo subjects and were generally mild to moderate in intensity and of short duration. The typical onset of systemic AEs was 12 to 24 hours after vaccination [Regules, J. A., et al 2017]. AEs of arthritis and vesicular lesions occurred in 4.7 and 1.5 percent of subjects who received ERVEBO respectively, and most occurrences were reported within the first few weeks following vaccination.

ERVEBO viremia and shedding were assessed by RT-PCR in the Phase 1 program. Viremia was common among V920 recipients and generally resolved by Day 14 postvaccination, with a median duration of 2 to 3 days. Vaccine virus RNA was found in saliva and urine from adult vaccines by RT-PCR at low incidence and low copy number (<270 copies/mL), and transmission risk was considered low based upon low magnitude of shedding. Transmission was not evaluated in clinical trials with ERVEBO. Higher rates of shedding were observed in children and adolescents.

The rVSVΔG-SARS-CoV-2 chimera was constructed using an approach similar to ERVEBO (rVSVΔG ZEBOV-GP), except for replacing the ZEBOV-GP insert with the gene encoding the SARS-CoV-2 spike glycoprotein as outlined in the IB. The SARS-CoV-2 spike protein has been adapted for efficient chimeric virus growth by natural selection in the manufacturing cell line.

CCI

[redacted]

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.

V590 is being developed with the intention of protecting against SARS-CoV-2 disease, and no prior clinical studies have been performed with V590. There are no clinical or preclinical data to indicate whether this vaccine will protect 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 participating in this clinical study may be found in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Objectives	Endpoints
Primary	
All Parts: • To assess the safety and tolerability of V590 versus placebo	• Solicited injection site AEs from Day 1 through Day 5 after study intervention • Solicited systemic AEs from Day 1 through Day 28 after study intervention • Unsolicited AEs from Day 1 through Day 28 after study intervention • Medically attended AEs (MAAEs) collected from Day 1 through Day 180 after study intervention • SAEs collected from Day 1 through Day 365 after study intervention • **Amendment 001-03**: AEs/MAAEs/SAEs collected through at least Day 28. Spontaneous reporting of SAEs after Day 28 will be recorded through Day 365 for unrelated SAEs and indefinitely for SAEs considered related to study intervention.
Parts 1 and 2 only: • To assess the immunogenicity of V590 on Day 28 • Hypothesis: At least one well-tolerated dose of V590 increases the GMTs of Anti-SARS-CoV-2 spike serum neutralizing antibody, as measured by PRNT, compared to placebo.	• Anti-SARS-CoV-2 spike serum neutralizing antibody responses, as measured by plaque reduction neutralization test (PRNT), at Day 28

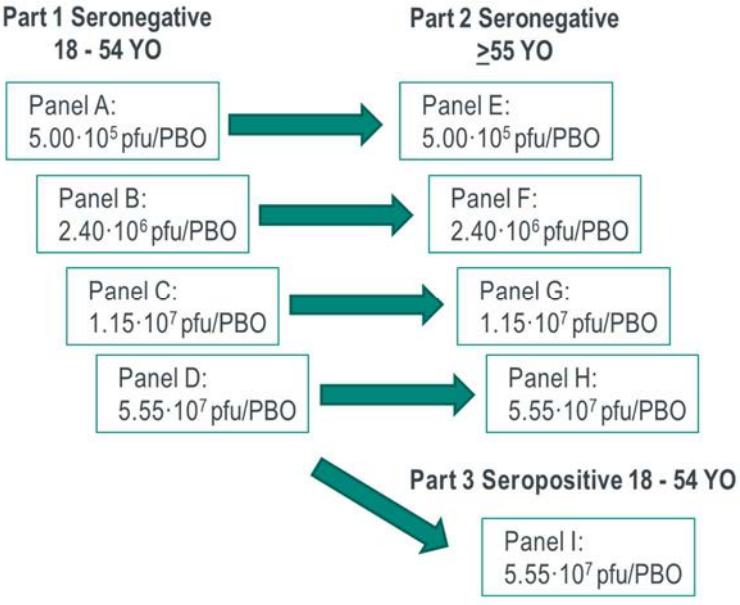
Objectives	Endpoints
Secondary	
Parts 1 and 2 only: • To assess the immunogenicity of V590 using assays to measure immune responses	• Anti-SARS-CoV-2 spike serum neutralizing antibody responses, as measured by PRNT (all timepoints except Day 28) • Anti-SARS-CoV-2 spike IgG responses, as measured by ELISA
All Parts: • To assess V590 viral shedding and viremia	• V590 plasma viremia, as measured by RT-PCR • V590 viral shedding in saliva, urine, and stool (if assayed), as measured by RT-PCR
Exploratory	
Parts 1 and 2 only: • To characterize SARS-CoV-2 seroconversion rates among participants	• Serum anti-SARS-CoV-2 nucleocapsid antibodies
Part 3 only: • To assess the immunogenicity of V590 in seropositive subjects using assays to measure immune responses	• Anti-SARS-CoV-2 spike serum neutralizing antibody responses, as measured by PRNT • Anti-SARS-CoV-2 spike IgG responses, as measured by ELISA
All Parts: • To characterize the immune response from participants vaccinated with V590 or placebo	• Enzyme-linked immunospot assay (ELISPOT) and intracellular cytokine staining (ICS) of peripheral blood mononuclear cells (PBMCs) • Anti-SARS-CoV-2 spike antibodies in mucosal samples • Serum cytokines/chemokines

Objectives	Endpoints
All Pa rts: • To characterize the incidence of SARS-CoV-2 infection among participants	• SARS-CoV-2 infection as assessed by PCR in participants with either symptoms potentially consistent with COVID-19 or with potential exposures to SARS-CoV-2
All Parts: • To explore the relationship between genetic variation and response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in the study.	• Germline genetic variation and association to clinical data collected in this study.

4 STUDY DESIGN

4.1 Overall Design

Figure 1 Study Schematic



In this 3-part dose-ranging trial, in Part 1 doses will be ranged in a rolling fashion starting from the lowest dose. The arrows indicate review of safety data through Day 7 from n ≥ 6 participants prior to initiation of administration of that dose level in Part 2 or 3. There will additionally be a review of safety data from n ≥ 6 participants through Day 7 before initiating dosing of higher dose levels in Part 1. The study design is described in detail in the protocol text.

This is a randomized, placebo-controlled, three-part, multi-site, double-blind dose-ranging study of V590 in healthy younger and older adult participants to be conducted in conformance with Good Clinical Practice. In Parts 1 and 2 (younger and older SARS-CoV-2 seronegative participants, respectively), four dose levels of V590 will be administered: $5.00 \cdot 10^5$ pfu/PBO, $2.40 \cdot 10^6$ pfu/PBO, $1.15 \cdot 10^7$ pfu/PBO and $5.55 \cdot 10^7$ pfu/PBO. Dose-ranging in Parts 1 and 2 will initiate with the lowest dose level and will be followed by administration of the next higher dose level in a rolling fashion. In Part 1 initiation of dosing of Panels B, C, and D will follow review of blinded safety data through Day 7 for at least six participants from the prior panel by the Sponsor safety review team (described further below). Higher dose levels may be administered before completion of dosing of lower levels. Part 2 entails dosing of older participants; 7 days of blinded safety data from at least six participants from an equal or higher dose level from the younger participants in Part 1 will be reviewed by the Sponsor safety review team (described further below) prior to administration in Part 2. Clinical conduct of Parts 1 and 2 may run concurrently provided the formal reviews of safety data have been performed before initiation of dosing Panels B, C, and D and before dosing each dose level to the older participants. Part 3 is comprised of SARS-CoV-2 seropositive participants who will receive a single dose level of $5.55 \cdot 10^7$ pfu/PBO and may start concurrently to the same dose level in Part 2.

In Part 1, approximately 112 seronegative healthy young participants (age 18-54 years inclusive) will be enrolled. Twenty-eight (28) participants will be randomized in each dose level to receive a single IM dose of V590 or placebo in a 3:1 ratio. Dosing of each subsequent panels at a higher dose will occur after the Sponsor safety review team (as described immediately below) evaluates safety data through Day 7 for at least six participants from the preceding panel.

In Part 2, approximately 112 seronegative healthy older participants (age $\geq$ 55 years) will be enrolled. Twenty-eight (28) participants will be randomized in each dose level to receive a single IM dose of V590 or placebo in a 3:1 ratio. Prior to dosing each dose level in Part 2, the Sponsor safety review team will evaluate blinded data through Day 7 for at least six participants from the corresponding dose level in Part 1. The Sponsor safety review team will evaluate these data at formal meetings, and this team consists of a Therapeutic Area Head and/or Department Vice President, a Clinical Director, Clinical Scientist(s), Biostatistician, as well as input from the Investigator(s). Available blinded safety data from lower doses from both Parts 1 and 2 will also be evaluated.

In Part 3, approximately 28 seropositive healthy participants (age 18-54 years inclusive) will be enrolled and randomized to receive a single IM dose ($5.55 \cdot 10^7$ pfu/PBO) of V590 or placebo in a 3:1 ratio. Part 3 may initiate based upon review of seven days of safety data from $n \geq 6$ participants at this dose level in Part 1 by the Sponsor safety review team (as described immediately above) and may initiate simultaneously to administration of this dose level in Part 2.

In all parts participants will be domiciled for 7 days from vaccination to facilitate close monitoring and specimen acquisition. Participants will have visits as outlined in the SoA over the following 12 months to monitor safety and to obtain samples for immunogenicity assessments. An Interim Analysis will be performed on safety through at least Day 28 as

well as PRNT and IgG ELISA immunogenicity from Day 1 Predose and Day 28 postvaccination for participants from Parts 1 and 2, as well as the available data from Part 3 (Part 3 is not required for this interim analysis, but available data will be included). Upon completion of Day 28 by enrolled participants in Parts 1 and 2, analyses will be performed to summarize the safety and immunogenicity data in order to inform potential subsequent clinical studies.

An siDMC will evaluate safety data and immunogenicity for the Day 28 Interim Analysis and will additionally be convened to evaluate available data if stopping rules are met. The siDMC is a standing, internal Sponsor committee established to monitor clinical studies. Additional details are provided in Section 10.1.4.1 and in the siDMC Charter.

Triggering of Parts 2 and 3 dosing will be based on the Sponsor safety review team's assessment of blinded safety data.

Because this is a Phase 1 assessment of V590 in humans, the viral dynamics, 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 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.

Amendment 001-03: Enrolled participants in all parts will be followed through Day 28 for safety, tolerability, immunogenicity, shedding and viremia. A final study analysis will be performed on all available data through Day 28, in place of an Interim Analysis.

4.2 Scientific Rationale for Study Design

This study is being conducted to evaluate the safety, tolerability and immunogenicity in healthy younger (18-54 years of age) and older (55 and older) SARS-CoV-2 seronegative participants, and in healthy younger (18-54 years of age) seropositive participants.

This study is designed to ensure participant safety while permitting efficient study conduct in the setting of a global pandemic. This accelerated design is supported by past clinical and preclinical experience with ERVEBO, which shares a platform technology with V590, as well as preclinical data for V590. For each dose level younger participants will be dosed first with safety evaluated up to Day 7 before administration of that dose level to older participants in Part 2. This is designed to minimize risk to older participants in the context of a replication competent chimeric virus, while efficiently obtaining immunogenicity data in this older population which is at greatest risk for severe COVID-19 disease. Within Part 1 safety data from at least six individuals through Day 7 from the preceding dose level will be reviewed prior to administration of the next higher dose level.

Parts 1 and 2 will provide safety data for seronegative individuals and will inform on immunogenicity of V590. Part 3 will assess safety and immunogenicity in seropositive individuals to inform on whether prior exposure to the SARS-CoV-2 spike protein, the common antigen shared between V590 and SARS-CoV-2, results in a different safety or tolerability profile.

Clinical conduct will occur in individuals who are not considered to be at high risk for severe SARS-CoV-2 disease, with the exception those considered at high risk based solely on age (as it is critical to assess immunogenicity in this population). Exclusion criteria are based on CDC guidance regarding those at high risk for disease (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/groups-at-higher-risk.html) and are further informed by available literature [Petrilli, C. M., et al 2020] [Docherty, A. B., et al 2020]. Such risk factors for severe disease include chronic obstructive pulmonary disease, immunocompromised state, serious heart conditions (such as heart failure, coronary artery disease, cardiomyopathies, and pulmonary hypertension), sickle cell disease, obesity and type 2 diabetes mellitus.

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.

Rationale for Amendment 001-03: The evaluation of available Day 28 immunogenicity data, including both ELISA and PRNT, indicated that V590 was not predicted to protect against disease caused by SARS-CoV-2. Based on these data the Sponsor made the decision not to enroll further participants in the study, to bring the study to a close, and to discontinue development of intramuscularly administered V590. V590 was generally well-tolerated, and the decision to discontinue development 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 Day 28, which includes all protocol specified safety laboratory and routine AE assessments. Spontaneous reporting of SAEs and other protocol-specified events may continue through the protocol specified durations (one year for all SAEs, indefinitely for SAEs considered related to intervention). In place of an Interim Analysis of data through Day 28, the final study analysis will be performed on the collected dataset through Day 28.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

This study includes two exploratory efficacy endpoints.

Seroconversion to the SARS-CoV-2 nucleocapsid antigen, a SARS-CoV-2 antigen that is not present in V590, will be assessed through 12 months post-vaccination in order to determine the rate of SARS-CoV-2 infection (irrespective of symptoms and occurrence of clinical COVID-19 disease).

Additionally, participants with either symptoms potentially consistent with COVID-19, or with potential exposures to SARS-CoV-2 (defined by having close contacts with testing

positive for acute SARS-CoV-2 [i.e. not an antibody test]), will be tested for SARS-CoV-2 by RT-PCR. This endpoint will assess the incidence of acute SARS-CoV-2 infection in participants during the study.

As the epidemiology of SARS-CoV-2 is both highly dynamic and geographically heterogeneous, it is not possible to make predictions of infection rates during study conduct. Given the small sample size it is unlikely that the study will provide sufficient data for vaccine efficacy assessment.

4.2.1.2 Safety Endpoints

As this is the first clinical investigation of V590, safety and tolerability will be primary endpoints and will be carefully monitored. It is anticipated that IM administration of V590 at the proposed doses will be well-tolerated in humans based on preclinical studies as well as previous experience with the VSV-ΔG vector platform from ERVEBO.

The safety and tolerability of V590 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). Additionally, as this is a replication-competent live attenuated vaccine, viral shedding and vaccine strain viremia will be assessed in this study.

Assessments will occur throughout the trial, with time points optimized based on the expected timing of local and systemic reactions to vaccination (See Section 8.3). Specific safety endpoints to be gathered include:

- Solicited local reactogenicity AEs (injection site pain/tenderness, swelling, redness) will be collected through Day 5. Solicited systemic reactogenicity AEs (muscle pain, joint pain, headache, fatigue, rash, nausea, joint swelling, oral lesions, sweating more than usual) will be collected through Day 28. These will be recorded by the participant in a VRC.

- Unsolicited AEs and events of clinical interest (ECIs; overdose, vesicular rashes, arthritis) will be collected and analyzed through Day 28 following study intervention.

- After Day 28, and up to 180 days after study intervention, only SAEs and MAAEs will be analyzed.

- After Day 180, and up to 365 days after study intervention, only SAEs will be analyzed.

- Safety laboratory tests will be collected as described in the SoA

Vital sign measurements and physical exam findings will be collected at scheduled times through Day 7 (See Section 1.3)

All arthritis and/or vesicular lesions will be followed to resolution (or the end of the study, provided stable). Additionally, subjects will be instructed to report any recurrence of symptoms corresponding to these events at any time postvaccination through the end of the study and any recurrence will also be followed to resolution (or the end of study, if stable). Evaluations by the investigator and/or by a rheumatologist/dermatologist may be conducted as outlined in the separate guidance document covering arthritis, rashes, and oral lesions, see Guidance for Assessment and Work-up of Specific Postvaccination Adverse Effects (Appendix 10.4).

The 2007 Center for Biologics Evaluation and Research (CBER) Guidance Document will be used as guidance for the toxicity grading scale for this study (see Appendix 10.3).

Amendment 001-03: Active monitoring of AEs, ECIs, and MAAEs will occur through Day 28. Spontaneously reported SAEs will be collected per protocol (up to 365 Days for all SAEs, and indefinitely if considered related to intervention).

4.2.1.3 Immunogenicity Endpoints

Primary, secondary and exploratory endpoints in this trial will address the immunogenicity of V590 using assays to measure neutralizing antibodies by PRNT, IgG antibody titers against spike protein by ELISA, and exploratory immunogenicity assays.

Serum samples will be collected as outlined in the SoA for:

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

Additionally, samples (including serum, PBMCs, nasal swabs and saliva) will be collected for exploratory immunogenicity endpoints as outlined in the objectives.

4.2.1.4 Viremia and Viral Shedding Endpoints

As V590 is a replication-competent chimeric virus, secondary objectives will include assessing vaccine viremia and viral shedding.

The following samples will be collected as outlined in the SoA at the timepoints through Day 28 and will be assessed by RT-PCR for the presence of V590:

- Blood for V590 viremia
- Saliva, urine and stool for shedding

If RT-PCR assays are positive, V590 viremia and shedding samples may additionally be measured by plaque assay in order to assess whether replication-competent virus is present.

If samples are positive at Day 28 additional samples may be collected until testing is negative as a part of the safety evaluation.

Stool collection is only included during the domiciled portion of this study based on operational considerations including requirements for sample collection and preparation.

4.2.1.5 Planned Exploratory Biomarker Research

4.2.1.5.1 Planned Genetic Analysis

Genetic variation may impact a participant's response to therapy, susceptibility to, severity, and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis from consenting participants.

DNA samples may be used for research related to the study intervention(s), the disease under study, or related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases, and study intervention(s). Genetic research may consist of the analysis of 1 or more candidate genes, the analysis of genetic markers throughout the genome, or analysis of the entire genome. Analysis may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to understand study disease or related conditions.

4.2.1.6 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 Placebo

A primary objective of this study is to evaluate the safety and tolerability of V590. A placebo-controlled trial will facilitate an unbiased assessment of safety and tolerability. Secondary and exploratory endpoints also support the use of placebo, as this serves as a negative control for potential environmental exposures to SARS-CoV-2 and provides a control for immunologic assays.

4.3 Justification for Dose

The methods used in calculating doses and estimated exposures are detailed in Sections 4.3.1 and 4.3.2.

As this is a Phase 1 assessment of V590 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.

4.3.1 Starting Dose for This Study

The starting dose for this study is $5 \cdot 10^5$ pfu and is based on the non-GLP NHP biodistribution study and non-GLP NHP pharmacology study with toxicity endpoints, as well as prior preclinical and clinical experience with ERVEBO. The non-GLP NHP pharmacology study with toxicity endpoints identified the NOAEL as the highest dose tested ($5.94 \cdot 10^7$ pfu/animal). This is 119-fold higher than the planned clinical starting dose on an absolute basis and approximately 742-fold higher than the planned clinical starting dose on a pfu/kg basis.

Immunogenicity was observed in the non-GLP NHP pharmacology study with toxicity endpoints at $5.94 \cdot 10^7$ pfu and was not observed at $1.00 \cdot 10^5$ pfu. Immunogenicity was observed in the non-GLP NHP biodistribution study at the single dose level tested of $5.94 \cdot 10^7$ pfu.

4.3.2 Maximum Dose/Exposure for This Study

The maximum dose for this study is $5.55 \cdot 10^7$ pfu, which is similar to the highest dose tested in the supporting non-GLP NHP pharmacology study with toxicity endpoints and biodistribution study ($5.94 \cdot 10^7$ pfu). There were no adverse V590-related findings observed. This dose is also similar to the highest dose tested in the ERVEBO clinical program. This is approximately 7- to 13-fold lower than the animal exposure on a pfu/kg basis.

4.3.3 Rationale for Dose Interval and Study Design

ERVEBO, which uses the same VSVΔG platform as V590, was studied in multiple Phase 1 studies in which dose steps of approximately 1 log pfu (i.e. tenfold changes in pfu between dose levels) were tested. Based on the shared platform technology and the safety/tolerability profile observed with ERVEBO, dose intervals of up to approximately 1 log pfu would be considered reasonable for V590. With a planned starting dose of $5 \cdot 10^5$ and a highest planned dose of $5.55 \cdot 10^7$ pfu, and with four dose levels total in this study, evenly spaced dose intervals on a log scale are planned which results in approximately five-fold differences between dose levels.

Based on the clinical and preclinical experience with ERVEBO, and the preclinical experience with V590, a dose-ranging design is employed in Parts 1 and 2.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws from the study, 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.

4.4.1 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 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.

5 STUDY POPULATION

Healthy male and female participants between the ages of 18 to 54 years (Parts 1 and 3) or ≥ 55 years (Part 2) will be enrolled in this study.

The minimum age for Parts 1 and 3 may be adjusted up based upon the legal age of majority based upon CRU location (for example, in Nebraska Parts 1 and 3 may enroll from ages 19-54, based on an age of majority of 19).

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, and VS measurements performed prior to randomization, as assessed by the investigator.

2. Is in overall good health based on laboratory safety tests obtained at the screening visit. When available, predose safety labs will additionally be reviewed prior to dosing. Appendix 2 provides a table of laboratory safety tests to be performed. Appendix 10 provides an algorithm for the assessment of out of range laboratory values.

3. Has a BMI ≤30 kg/m2 inclusive (after rounding to the nearest whole number). See Section 8.3.4 for criteria on rounding to the nearest whole number. BMI = weight (kg)/height (m)2.

4. **Parts 1 and 2 only**: Has negative testing for SARS-CoV-2 based on both antibody and RT-PCR, at screening and upon start of domiciling.

   Part 3 only: Has positive serology (antibody) testing for SARS-CoV-2, also with negative SARS CoV-2 RT-PCR testing at screening and upon start of domiciling, and without symptoms of respiratory infection for at minimum 3 weeks preceding screening.

5. Has been practicing social distancing for at least two weeks prior to planned start of domiciling and has had no close contacts with known active SARS-CoV-2 infection in that time period.

Demographics

6. Is male or female, from 18 years to 54 years of age inclusive (Parts 1 and 3) or ≥ 55 years of age (Part 2) at the time of signing the informed consent.

   For Parts 1 and 3, if the age of majority at the location of the CRU is older than 18, this legal age of majority must be used as the minimum for enrollment.

7. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 2 months after administration 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.

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 2 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 (e.g., 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.

  - Additional requirements for pregnancy testing during and after study intervention are located in Section 8.4.5 and Section 10.5.3.

  - 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 provides written informed consent 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 domiciling).

11. 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.

12. 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

Is currently known or suspected to be infected with SARS-CoV-2.

1. Has a known hypersensitivity to any component of V590 or placebo (including Tris, rHSA, rice protein, and benzonase).

2. Has any known or suspected active clinically significant autoimmune disease or immunosuppressive condition, acquired or congenital, as determined by medical history and/or physical examination. (Note that medical history that does not constitute an active clinically significant autoimmune/immunosuppressive condition, such as longstanding hypothyroidism on stable thyroid hormone replacement, is permitted.)

3. Has thrombocytopenia or other coagulation disorder contraindicating intramuscular vaccination or repeated venipuncture.

4. *Had a recent febrile illness (defined as oral or tympanic temperature ≥100.4°F [≥38.0°C] or axillary or temporal temperature ≥99.4°F [≥37.4°C]) or received antibiotic therapy for any acute illness occurring within 7 days before receipt of study vaccine.

5. 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.

6. Has a history of ongoing liver disease or, at the time of screening, has any one of the following:

   -Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 1.5 × Upper Limit of Normal (ULN)

   -Alkaline phosphatase and direct bilirubin > ULN. Total bilirubin may be up to 2 × ULN as long as direct bilirubin is equal to or below the ULN.

-Prothrombin time (PT) international normalized ratio (INR) > 1.25

Investigator discretion may be used to determine significance based on local laboratory reference ranges.

7. Has a history of asthma or allergic asthma that required systemic corticosteroids in the previous year.

8. Has a history of Guillain-Barré syndrome.

9. Has a history of diabetes mellitus, requiring medication at the time of assessment, OR has a hemoglobin A1c ≥ 6.5.

10. Has a history of any medical condition that would put the participant at risk for severe SARS-CoV-2 disease as judged by the investigator, including uncontrolled hypertension (defined as resting systolic ≥140 mmHg and/or diastolic ≥90 mmHg at screening and allowing stable antihypertensive use), significant ischemic or structural heart disease, diabetes, liver disease, chronic pulmonary disease, pulmonary hypertension, sickle cell disease, clinically significant thalassemia, is immunocompromised, or anticipates the need for immunosuppressive treatment within the next 6 months.

11. Has any ongoing, symptomatic, acute or chronic illness requiring medical or surgical care or any condition that is immunosuppressive. Asymptomatic conditions and conditions with no evidence of end-organ involvement (e.g., stable hypothyroidism on thyroid hormone replacement, dyslipidemia, mild well-controlled hypertension) are not exclusionary provided that they are being appropriately managed and are clinically stable (i.e., unlikely to result in symptomatic illness within the time-course of this study) in the opinion of the Investigator, and are not considered to put the participant at risk for severe SARS-CoV-2 disease (with the exception of the age category of over 55). Symptomatic osteoarthritis is permitted if surgery and/or intra-articular injections are not anticipated during the study, but rheumatoid arthritis and other autoimmune inflammatory arthritides such as ankylosing spondylitis, psoriatic arthritis, and lupus are prohibited. Note that illnesses or conditions may be exclusionary, even if otherwise stable, due to therapies used to treat them, at the discretion of the investigator.

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 with a more recent history of situational depression may be enrolled in the study at the discretion of the investigator.

13. 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 (e.g., malignancies which have been successfully treated ≥10 years prior to the prestudy [screening] visit).

14. Participant has an estimated eGFR ≤60 mL/min/1.73 m^2] based on either the MDRD or the CKD-EPI equation. The selection of equation is at discretion of the investigator.

MDRD Equation:

eGFR (mL/min/1.73 m^2) =
175 x (serum creat)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 [if female]) x (1.212 [if African American])

At the discretion of the investigator a measured creatinine clearance, as determined by a 24-hour urine collection, may be used in place of, or in conjunction with, the estimate of the eGFR.

Participants who have an eGFR or measured creatinine clearance of up to 10% below of either 60 mL/min (for creatinine clearance) or 60 mL/min/1.73m2 (for eGFR) may be enrolled in the study at the discretion of the investigator.

OR

CKD-EPI Equation:

eGFR = 141 × min (S_{cr} /κ, 1)$^{\alpha}$ × max(S_{cr} /κ, 1)$^{-1.209}$ × 0.993^{Age} × 1.018 [if female] × 1.159 [if African American]

At the discretion of the investigator a measured creatinine clearance, as determined by a 24-hour urine collection, may be used in place of, or in conjunction with, the estimate of the eGFR.

Participants who have an eGFR or measured creatinine clearance of up to 10% below of either 60 mL/min (for creatinine clearance) or 60 mL/min/1.73m^2 (for eGFR) may be enrolled in the study at the discretion of the investigator.

15. Has a history of significant multiple and/or severe allergies (e.g., food, drug, latex allergy), or has had an anaphylactic reaction or significant intolerability (i.e., systemic allergic reaction) to a vaccine or prescription or non-prescription drugs or food as judged by the investigator.

16. Is positive for hepatitis B surface antigen, hepatitis C antibodies or HIV-1 or 2 antibodies. Individuals with antibodies to hepatitis C may be enrolled if hepatitis C viral load is negative 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.

18. A WOCBP who has a positive urine or serum pregnancy test before vaccination.

19. A WOCBP who is breastfeeding.

20. Has any unstable chronic medical condition, including one that has resulted in change in therapy (medication or other) in the 30 days prior to randomization or hospitalization in the previous year or might be predicted to result in hospitalization in the year after enrollment. Participants with severe, untreated, or uncontrolled underlying medical disease that might either compromise participant safety or affect the ability to assess safety of the investigational product are excluded.

Prior/Concomitant Therapy

21. Has received or is expected to receive any SARS-CoV-2 vaccine or other coronavirus vaccine during the study (except V590), is using investigational agents for prophylaxis of SARS-CoV-2 or is taking any systemic antiviral medications.

22. *Has received systemic corticosteroids (equivalent ≥20 mg/day of prednisone for persons weighing >10 kg) for ≥14 consecutive days and has not completed intervention at least 30 days prior to study vaccination.

23. *Has received systemic corticosteroids exceeding physiologic replacement doses (approximately 5 mg/day prednisone equivalent) starting from 14 days prior to study vaccination. (**Note**: Topical, ophthalmic, and inhaled/nebulized steroids are permitted upon joint agreement with the Sponsor.)

24. Has received any intra-articular steroid injections within the 3 months prior to study vaccination or is expected to require intra-articular steroid injection during the study.

25. Is receiving immunosuppressive therapy or has received immunosuppressive therapy within 6 months of enrollment, including but not limited to chemotherapeutic agents used to treat cancer or other conditions, and interventions associated with organ or bone marrow transplantation, or autoimmune disease. This exclusion criterion does not include corticosteroids, which are covered in separate dedicated exclusion criteria.

26. *Has received any non-live vaccine starting from 14 days prior to study vaccination or is scheduled to receive any non-live vaccine through 30 days following study vaccination. **Exception**: Inactivated influenza vaccine may be administered but must be given at least 7 days before receipt of study vaccine or at least 15 days after receipt of study vaccine.

27. *Has received any live vaccine starting from 30 days before study vaccination or is scheduled to receive any live vaccine through 30 days following study vaccination.

28. Has received a blood transfusion or blood products, including immunoglobulin, in the 3 months before anticipated study vaccination. Autologous blood transfusions are not considered an exclusion criterion.

29. Is expected to be receiving or is currently receiving antipyretic or analgesic medication on a daily or every other day basis from randomization through Day 7 (a daily dose of ≤150 mg of aspirin given under the guidance of a physician is not considered exclusionary for enrollment).

30. Is unable to meet the concomitant medication restrictions (see Section 6.5).

Prior/Concurrent Clinical Study Experience

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

32. Has participated in another vaccine study within 3 months prior to screening or has participated in an investigational study within 4 weeks prior to the prestudy (screening) visit. The window will be derived from the date of the last visit in the previous study. In addition, participant cannot participate in another investigational trial up to the post-trial visit (approximately 12 months after the study vaccination). Participation in the separate screening protocol is not exclusionary.

33. Has ever received a vaccine based on VSV.

Diagnostic Assessments

34. Has a QTcF interval >470 msec (male) or >480 msec (female), has a history of risk factors for Torsades de Pointes (eg, heart failure/cardiomyopathy or family history of long QT syndrome), has uncorrected hypokalemia or hypomagnesemia.

Other Exclusions

35. Is under the age of legal consent.

36. Is smoking or vaping and/or has a history of chronic smoking or vaping within approximately six months prior to planned vaccination.

37. Does not agree to follow the alcohol restrictions (e.g., refrain from consumption of alcohol 24 hours prior to each laboratory safety evaluation as well as 24 hours prior to treatment vaccination and while domiciled.)

38. 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.

39. Is a regular user of any illicit drugs or has a history of drug (including alcohol) abuse within approximately 1 year. Smoking of cannabis within approximately six months is excluded, but oral consumption of cannabis is not prohibited. Participants must have a negative UDS prior to randomization (except for cannabis if non-inhaled per participant history).

40. 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.

41. 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.)

42. Is currently working in an occupation with high risk of exposure to SARS-CoV-2 (e.g., health care worker with direct patient contact, emergency response personnel).

43. Has a house-hold contact (HHC) who is immunodeficient, on immunosuppressive medications (e.g., parenteral immunosuppressants, >10 mg prednisone equivalent daily), human immunodeficiency virus (HIV)-positive with CD4 count <500, pregnant, or has an unstable medical condition.

44. Has an HHC 5 years of age or younger or is a childcare worker who has direct contact with children 5 years of age or younger.

45. Has direct hands-on job preparing food in the food industry.

46. Has a history of employment in an industry involved in contact with ruminant animals, veterinary sciences, or other potential exposure to VSV.

47. 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

Fasting requirements for study procedures, such as but not limited to laboratory safety evaluations are specified in Appendix 2.

Otherwise, 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 as well as 24 hours prior to study vaccination and while domiciled.

5.3.2.3 Tobacco Restrictions

Smoking or vaping is not permitted during the study.

5.3.3 Activity Restrictions

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

5.3.4 Blood Donation Restrictions

Blood donation is prohibited during the first 4 months following vaccination due to blood volume requirements of this study. Routine blood draws for medical care are acceptable. Blood donation is not recommended during the remainder 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 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

Panel Name	Panel Type	Inter-vention Name	Intervention 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	V590	Biological/ Vaccine	Sterile Solution	Titer ≥ 1E6pfu/ml	$5.00X10^5$ pfu/mL $2.40X10^6$ pfu/mL $1.15X10^7$ pfu/mL $5.55X10^7$ pfu/mL	IM	Day 1	Experimental	IMP	Provided Centrally by the Sponsor
Placebo	Placebo Comparator	Placebo	Other	Sterile Solution	N/A	N/A	IM	Day 1	Placebo	IMP	Provided Centrally by the Sponsor
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. In this protocol, placebo for V590 is diluent (10mM Tris 2.5mg/mL rHSA, 10% w/v Sucrose pH 7.5); diluent is used for blinding purposes and does not contain active ingredients.											

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 (e.g., not applicable in the case where multiple lots or batches may be required due to the length of the study,).

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

All placebos were created by the Sponsor to match the active product.

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 4.3. V590 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.

Table 3 Sample Allocation Schedule

	Part 1 (18 to 54 years old SARS-CoV-2 seronegative) [a]			
Subjects Per Panel	**Panel A** (N = 28)	**Panel B** (N = 28)	**Panel C** (N = 28)	**Panel D** (N = 28)
N = 21	V590 $5.00 \cdot 10^5$ pfu	V590 $2.40 \cdot 10^6$ pfu	V590 $1.15 \cdot 10^7$ pfu	V590 $5.55 \cdot 10^7$ pfu
N = 7	Placebo	Placebo	Placebo	Placebo
	Part 2 (≥ 55 years old SARS-CoV-2 seronegative) [a]			
Subjects Per Panel	**Panel E** (N = 28)	**Panel F** (N = 28)	**Panel G** (N = 28)	**Panel H** (N = 28)
N = 21	V590 $5.00 \cdot 10^5$ pfu	V590 $2.40 \cdot 10^6$ pfu	V590 $1.15 \cdot 10^7$ pfu	V590 $5.55 \cdot 10^7$ pfu
N = 7	Placebo	Placebo	Placebo	Placebo
	Part 3 (18 to 54 years old SARS-CoV-2 seropositive) [a]			
Subjects Per Panel				**Panel I** (N = 28)
N = 21				V590 $5.55 \cdot 10^7$ pfu
N = 7				Placebo

a. Within each panel of Parts 1, 2, and 3, participants will be randomized to receive V590 or matching Placebo in a 3:1 ratio according to a computer-generated, permuted-block allocation schedule (i.e., in each panel 21 participants to receive V590 and 7 participants to receive matching placebo).

6.3.2 Stratification

No stratification based on age, sex, or other characteristics will be used in this study.

6.3.3 Blinding

A double-blinding technique will be used. V590 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 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.
- Live and non-live vaccines may only be administered prior to or following the receipt of study vaccine according to the time frames specified in Exclusion Criteria (Section 5.2).

  Exception: Inactivated influenza vaccine may be administered but must be given at least 7 days before receipt of study intervention or at least 15 days after receipt of study intervention.
- Participants should not receive systemic corticosteroids (prednisone equivalent of ≥20 mg/day for ≥14 consecutive days) starting from 30 days prior to vaccination through 60 days following vaccination.
- Participants should not receive systemic corticosteroids exceeding physiologic replacement doses (prednisone equivalent dose >5 mg/day) starting from 14 days prior to vaccination through 60 days following vaccination.

Note: Topical, ophthalmic, or soft-tissue (e.g., tendon steroid injections) and inhaled/nebulized steroids are permitted. Intra-articular steroid injections should be avoided.

- Scheduled antipyretic or analgesic medication on a daily or every other day basis from randomization through Day 7 after receiving study vaccination are not permitted.

  - A daily dose of ≤150 mg of aspirin given under the guidance of a physician is not considered exclusionary for enrollment or a contraindication for enrolled participants.

  - For enrolled participants, occasional administration of anti-pyretic or analgesic medication to control pain is allowed and not considered a contraindication.

  -Antipyretics/analgesics may be administered on an as needed basis following vaccination.

- Immunoglobulins and/or any blood products within 3 months preceding the study intervention or at any time during the study.

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 the first 3 months of the study must be recorded along with:

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

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 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.

6.6 Stopping Rules

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

If any of the below stopping rules are met, no further enrollment or dosing will occur (unless permitted at lower dose levels as specified under criteria #2) until the Sponsor has reviewed the totality of data available. This review will include formal assessment by the siDMC. For stopping rules #1 and #2 any further dosing will additionally require joint agreement with the Sponsor and the investigator at the involved site(s).

1. Any participant experiences a serious adverse event (SAE) considered at least possibly related to the vaccine; laryngospasm, bronchospasm, or anaphylaxis after vaccine administration considered related to the vaccine; ulceration, abscess, or necrosis at the injection site that is considered related to vaccine; or generalized urticaria after vaccine administration considered related to the vaccine.

2. Any two or more participants at a given dose level experience the same Grade 3 AE with the same Preferred Term based on MedDRA coding and is considered related to vaccine. If this criterion is met dosing of lower dose panels may continue upon joint agreement between the Sponsor and the investigator(s).

3. Any participant has severe COVID-19 as defined in the FDA Guidance on the Development and Licensure of Vaccines to Prevent COVID-19 (https://www.fda.gov/media/139638/download). Severe COVID-19 is defined as virologically confirmed SARS-CoV-2 infection with any of the following: a) 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) b) Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or ECMO) c) Evidence of shock (SBP < 90 mm Hg, DBP < 60 mm Hg, or requiring vasopressors) d) Significant acute renal, hepatic, or neurologic dysfunction e) Admission to an ICU or f) Death. If this stopping rule is met, the siDMC will evaluate available preclinical data in addition to the clinical data in order to evaluate for vaccine-enhanced disease.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

This study is blinded but supplies are provided as 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.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

In clinical studies with a single intervention, discontinuation of study intervention can only occur prior to the intervention and generally represents withdrawal from the study.

Participants who receive a single-dose intervention cannot discontinue study intervention.

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant 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.

Up to ~627.5 mL of blood may be drawn during the study (up to ~457.5 mL of blood may be drawn before Day 90 for safety, viremia or immunologic assessments and up to ~168 mL of blood may be drawn from Day 90 to Day 365 for safety, viremia or immunologic assessments). The total blood volume withdrawn from any single participant will not exceed the maximum allowable volume before and after Day 90. (Appendix 8 or operations/laboratory manual).

Amendment 001-03: Blood will be collected through Day 28.

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 prior to participating in a 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 must be documented on a consent form. The form must include the trial protocol number, trial protocol title, dated signature, andalong with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated informed consent form should be given to the participant 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 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 dated signature.

If the investigator recommends continuation of study intervention beyond disease progression, the participant will be asked to provide documented informed consent.

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, 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 before vaccination at Day 1.

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 (see Section 5.2 and Section 6.5 for Exclusion Criteria and Study Restrictions pertaining to prior medications and vaccines.)

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 Day 28 will be recorded with the paper VRC as specified in Section 8.3.8.

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.

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.

Procedures for handling, preparing, and administering the unblinded vaccines are provided in the Pharmacy Manual provided by the Sponsor. Study intervention will be administered into the deltoid muscle and witnessed by study staff and recorded in the source documents. The deltoid muscle of the non-dominant arm is the preferred site of administration.

Study site staff will confirm that the participant has received the entire dose of study intervention. On Day 1, the time of V590/Placebo administration is considered Time 0. Care will be taken to maintain the study blinding.

Adequate treatment provision, including epinephrine and equipment for maintaining an airway should be available for immediate use should an anaphylactic or anaphylactoid reaction occur [Centers for Disease Control and Prevention 2015].

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.

Vaccinations may be administered at any time (although morning administration is suggested based upon study design), and without regard to timing of meals.

Each participant's body temperature must be taken before vaccine administration. Individuals who present with fever (oral ≥100.4°F [≥38.0°C]) may be replaced.

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

All participants will be observed for at least 4 hours after vaccination for any immediate reactions.

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. 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 protocol-specified procedures conducted 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

Participants will report to the CRU between Day -3 and Day -1 prior to the scheduled day of study intervention administration on Day 1 and remain in the unit until all procedures have been completed on Day 7. At the discretion of the investigator, participants may be requested to remain in the CRU longer. Participants may be permitted to leave the unit, for emergency situations only, during the domiciling period at the discretion of the investigator after discussion with the Sponsor. The decision how to monitor the participant will be at the discretion of the investigator after discussion with the Sponsor.

The pre-vaccination domiciling period may be shortened at the discretion of the site provided results for the SARS-CoV-2 RT-PCR (or antigen test) and serology tests can be available and reviewed by the investigator prior to vaccine administration.

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 and Efficacy Assessments

8.2.1 Neutralizing Antibody

Neutralizing antibody titers are a measure of antibody levels capable of neutralizing infectivity of the vaccine strain V590, which bears the functional SARS-CoV-2 spike protein on its surface. This vaccine strain neutralization assay is anticipated to correspond to levels antibodies capable of neutralizing wild type SARS-CoV-2 virus. Neutralizing antibody titers will be assessed by a plaque reduction neutralization assay (PRNT), which is a standard functional assay for quantitating the neutralizing antibody response elicited by the vaccine.

8.2.2 ELISA Antibody Titers

ELISA-based analysis will be used to quantify serum total IgG titers to the SARS-CoV-2 spike protein. This will serve as a measure of the magnitude of the IgG antibody response against spike protein.

8.2.3 Anti-Nucleocapsid Antibody Assay (Evidence of Infection)

V590 encodes for SARS-CoV-2 spike protein but does not contain any other SARS-CoV-2 sequences. Thus, development of an immune response to a SARS-CoV-2 protein other than spike is indicative of infection (but does not differentiate between symptomatic and asymptomatic infection). Anti-nucleocapsid antibodies will be measured using an assay currently available under emergency use authorization (EUA) as outlined in the SoA. This will be performed using an EUA authorized qualitative test yielding a positive vs negative result for anti-nucleocapsid antibodies.

8.2.4 SARS-CoV-2 RT-PCR (Evidence of Active Infection)

Participants with symptoms suggestive of potential COVID-19, or with close contacts who test positive for active SARS-CoV-2 infection, will be tested for active infection with a SARS-CoV-2 RT-PCR assay. The preferred assay is the Abbott RealTime SARS-CoV-2 test performed on a nasopharyngeal swab and run by the central laboratory. This test is available under an EUA and is a dual target assay for SARS-CoV-2 RdRp and N-genes. Other EUA approved acute SARS-CoV-2 tests are also acceptable but not preferred; sites should obtain the Abbott RealTime SARS-CoV-2 test when possible.

8.2.5 Exploratory Immunogenicity Assays

Exploratory immunogenicity assays will be performed on collected samples in order to characterize the immune response elicited by V590. This may include assays performed on serum, saliva, and PBMCs (for sites with PBMC-processing capabilities).

These exploratory immunology endpoints **may** include the following:

- ELISPOT assay against spike protein and ICS
- Anti-spike antibodies in mucosal samples
- Serum cytokines/chemokines
- Wild type SARS-CoV-2 neutralization assays

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

Additionally, VSV serologies will be obtained predose for all participants. It is anticipated that these serologies will be negative based on exclusion criteria; if positive VSV serologies

are observed the relationship between positive VSV serology and immune response to V590 may be evaluated.

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), 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 Complete Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard at screening and within a 24-hour window prior to dosing.

8.3.2 Symptom Driven Physical Examinations

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 any areas for which there are symptoms of concern.

8.3.3 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 at Day 1 (approximately 1-2 hours after dosing) and as outlined in the SoA Section 1.3. Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.4 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 the nearest whole number according to the standard convention of 0.1 to 0.4 round down and 0.5 to 0.9 round up.

8.3.5 Oral Temperature Measurements

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.

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.

Screening, Days -3 to -1, and Day 1 predose and 2 hours postdose will be done by clinic staff and noted on the source document. Screening and admission temperatures will use the clinic's thermometer; the Day 1 predose, the 2 hour postdose, and all later timepoints will use the thermometer provided to the participant.

For measurements to be collected on the VRC on Days 1-28, participants will be provided an oral thermometer. The Day 1 postdose measurements will be done approximately 4 hours after dosing. The Day 1 to Day 7 temperature will be measured and recorded by the participants on the VRC, under observation by the clinic staff (see Section 8.3.8). All the other measurements will be done by the participant without supervision.

8.3.6 Heart Rate, Blood Pressure, Respiratory Rate, and Pulse Oximetry

Participants should be resting in a quiet setting without distractions in a semi-recumbent position for at least 10 minutes prior to having VS measurements obtained. Semi-recumbent VS will include HR, systolic and diastolic BP, respiratory rate, and pulse oximetry at timepoints indicated in the SoA. The correct size of the BP cuff and the correct positioning on the participants' arm is essential to increase the accuracy of BP measurements. Measurements will be taken with a completely automated device. Manual techniques will be used only if an automated device is not available.

The predose (baseline) HR and BP will be triplicate measurements, obtained approximately 1-2 minutes apart] within 3 hours of dosing V590/placebo. The mean of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed). Postdose VS measurements will be single measurements.

Participants will be encouraged to rest semi-recumbent from dosing until 4 hours postdose except to stand for other study-related procedure; sitting is also permitted during this window except as otherwise required (such as at least 10 minutes semi-recumbent prior to VS).

8.3.7 Electrocardiograms

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 heart rate and measures PR, QRS, QT, and [QTc] intervals. Refer to Appendix 9 for evaluation and withdrawal criteria and additional [QTc] readings that may be necessary.

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 or supine position 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.

A cardiologist will be consulted by the investigator as needed to review ECG tracings with significant abnormalities.

8.3.8 Vaccine Report Card

Participants will be provided with a VRC to fill out on a daily basis from Day 1 (~4 hours postdose) to Day 28. 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." The VRC will be reviewed daily with the participants while domiciled for the purposes of early detection of safety concerns.

Participants will use the VRC to document the following information:

- Oral body temperatures measured from Day 1 (~4 hours postdose) to Day 28.
- Solicited injection-site AEs (swelling, redness, pain or tenderness) from Day 1 to Day 5.
- Solicited systemic AEs (muscle pain, joint pain, headache, tiredness, rash, nausea, joint swelling, oral lesions, sweating more than usual) from Day 1 to Day 28.
- Any other unsolicited AEs from Day 1 to Day 28 (as "other complaints").
- Concomitant medications and non-study vaccinations Day 1 to Day 28.

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.

During the domiciled period, the study staff should observe and confirm the participant's proper use of the VRC as instructed, including the measurement of temperature and any injection site redness or swelling. On Day 14, the study staff should confirm the participant's proper use of the VRC as instructed.

The VRC entries will be reviewed with the participant at each CRU visit (i.e., Day 14 and Day 28) to ensure the instructions were correctly understood and the VRC completed properly. Participants will be reminded to complete the VRC daily. As noted above, study staff should observe the temperature, swelling, and redness assessments (if any) on Days 1 through 7. Any AEs recorded in the VRC should be reviewed and fully assessed by the investigator as described in Section 8.4 and entered into the Sponsor database in a timely manner as per the Data Entry Guidelines.

8.3.9 Postvaccination Observation Period (4 Hours)

All participants will be observed for 4 hours after the vaccination for any immediate reactions (injection site and systemic reactions, solicited and unsolicited AEs). If any immediate AEs (including allergic reactions) are observed during this period, the time at which the event occurred within this timeframe, as well as the event itself, any concomitant medications that were administered, and resolution of the event, must be recorded on the appropriate eCRF.

8.3.10 Monitoring for SARS-CoV-2 Infection

During the 12 months post-vaccination, participants will be instructed to contact the clinical site if they either have 1) a close contact who tests positive for SARS-CoV-2 or 2) symptoms potentially consistent with SARS-CoV-2 as outlined by the CDC (https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html). If participants have any emergency warning signs as outlined by the CDC, they should seek emergent medical care. Clinical sites will solicit participant symptoms and exposure histories, and if the investigator considers the participant to meet one of these two conditions (or both conditions) the participant will be requested to have SARS-CoV-2 RT-PCR testing performed by the clinical site. Central laboratory PCR testing is preferred, but other EUA authorized (or, if available, FDA-licensed) PCR tests are permissible. PCR tests are preferred over antigen tests, but EUA authorized (or FDA-licensed) antigen tests are also acceptable. The CRU will additionally make every effort to follow up on any testing performed that was not ordered by the investigator.

Those with positive tests will be followed up weekly by phone for two weeks or until resolution of acute symptoms if present, whichever is longer. These individuals will be referred for medical treatment if the investigator considers this medically indicated and will additionally be encouraged to follow local public health department guidelines.

8.3.11 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 but before intervention allocation, 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 intervention allocation, all AEs and ECIs must be reported by the investigator up to Day 28. MAAEs must be reported by the investigator from the time of intervention to Day 180. SAEs, and other reportable safety events, must be reported by the investigator from the time of intervention allocation to Day 365.

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 4.

Amendment 001-03: All AEs, ECIs, and MAAEs must be reported by the investigator up to Day 28. Spontaneously reported SAEs will be collected per protocol (up to 365 Days for all SAEs, and indefinitely if considered related to intervention).

Table 4 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
MAAE	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. Rashes assessed as vesicular in nature.

3. Any new or worsening arthritis (i.e., that is not consistent with a participant’s chronic osteoarthritis if present).

Further guidance on the evaluation of these ECIs is provided in the Guidance for Assessment and Work-up of Specific Postvaccination Adverse Effects (Appendix 4).

8.5 Treatment of Overdose

In this study, an overdose is defined as a participant receiving either more than 1 dose of study vaccine or a higher dose than intended in a 24-hour period. 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

PK parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants as specified in the SoA:

- Blood for genetic analysis

8.8.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the participant provides documented informed consent for future biomedical research. If the planned genetic analysis is not approved, but future biomedical research is approved, this sample will be collected for the purpose of future biomedical research.

Sample collection, storage, and shipment instruction for planned genetic analysis samples will be provided in the operations/laboratory manual.

8.9 Future Biomedical Research Sample Collection

If the participant provides documented informed consent for future biomedical research, the following specimens will be obtained as part of future biomedical research:

- RNA for future research
- Serum for future research
- Mucosal samples for future research
- PBMCs and Plasma for future research
- Leftover DNA for future research
- Leftover main study serum from anti-SARS-CoV-2 spike neutralizing antibodies (PRNT) stored for future research
- Leftover main study serum from anti-SARS-CoV-2 spike IgG (ELISA) stored for future research
- Leftover main study plasma from V590 viremia stored for future research
- Leftover main study saliva from V590 shedding stored for future research
- Leftover main study urine from V590 shedding stored for future research
- Leftover main study stool from V590 shedding stored for future research

8.10 Health Economics Medical Resource Utilization and Health Economics

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

The Screening period will be up to 6 weeks before Admission (Day -3 to Day -1 on SoA), and at minimum 7 days prior to vaccine administration. A separate Screening Protocol with its own informed consent may be utilized by sites in advance of main consent availability to perform tests at Screening as indicated on the study SoA. Screening Protocol assessments/ activities will allow potential participants to be evaluated to determine if they may be eligible to enroll in the study based on the requirements described in Section 5; those considered potentially eligible may subsequently consider enrolling in this protocol.

The participant data collected under the Screening Protocol and informed consent will be captured on the site study participant source per site SOP. These participant data may be applied for screening in this study after the participant has provided main informed consent. The Screening data will be reviewed with the Sponsor. The Screening data entry into the main study database will not be rate-limiting to the study start and the timing and procedures of post hoc data entry will be outlined in the supportive data management and monitoring documentation.

All assessments/activities starting at and during Day -3 to Day -1 (beginning with participant admission to the clinical unit to begin domiciling) will be performed after the participants sign the main study informed consent, per SoA and Section 5. Data entry will be per study process and supporting documentation.

A screening SARS-CoV-2 RT-PCR and serology test should be performed in the screening window per SoA.

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 (Admission, Vaccination, and Postdose)

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

8.11.3 Discontinued Participants Continuing to be Monitored in the Study

This section is not applicable to this study.

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 12 months after study vaccination) 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 less than 12 months after study intervention (and not within protocol-specified variance), a subsequent follow-up telephone call should be made at 12 months postdose of study intervention to determine if any SAEs have occurred since the poststudy clinic visit (as well as AEs/ECIs through Day 28 or MAAEs through Day 180, if not already collected).

Amendment 001-03: A poststudy visit/phone call will be performed for safety assessment. This may be combined with the Day 28 visit. Active monitoring of AEs, ECIs, and MAAEs will occur through Day 28. Spontaneously reported SAEs will be collected per protocol.

8.11.5 Critical Procedures Based on Study Objectives: Timing of Procedure

For this study, the timely and accurate collection and recording of AEs, and blood samples for immunogenicity (specifically PRNT and ELISA), are the critical procedures.

At any postdose time point, the blood sample for PRNT and ELISA anti-spike 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.

- Site visit windows as outlined in Table 5
- Samples collection windows as outlined in Table 6

Table 5 Site Visit Windows

Site Visit	Visit Window
Day 1	N/A
Day 14	± 2 days (~ Day 12 to Day 16 postdose)
Day 28	± 2 days (~ Day 26 to Day 30 postdose)
Day 90	± 7 days (~ Day 83 to Day 97 postdose)
Day 180	± 7 days (~ Day 173 to Day 187 postdose)
Day 270	± 14 days (~ Day 256 to Day 284 postdose)
Day 365	± 14 days (~ Day 351 to Day 379 postdose)

Table 6 Sample Collection Windows

Sample Collection	Sample Collection Window
0 - <24 hr	1 hour
Days 2-7	2 hours
Days 14 and 28	2 days
Days 90 and 180	7 days
Days 270 and 365	14 days

- Day 1 postdose will be done at ~6 hours. Other days will be done at approximately the same time of day as the Day 1 dosing, flexibly according to site SOP.
- Predose standard safety procedures: vital signs (BP, HR, RR, and temperature), and laboratory safety tests up to 3 hours before vaccine administration
- Predose physical exams up to 24 hours before vaccine administration
- Postdose standard safety evaluations: vital signs (BP, HR, RR, and temperature), laboratory safety tests, and physical exam
    - Day 1 (postdose) procedures may be obtained within approximately 60 minutes of the theoretical sampling time
    - Days 2 to 7 evaluations can occur within approximately 2 hours of theoretical sampling time

- Postdose evaluations (other):

  - For the Roche Elecsys Anti-SARS-CoV-2 (central laboratory) test postdose timpoints, samples are only collected for Parts 1 and 2 (not Part 3).

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

This is a Phase 1 assessment of V590 in humans, and the viral dynamics, immunogenicity and safety profiles of the vaccine are still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of Phase 1 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 dose may not exceed those currently outlined in the protocol.

- Repeat of or decrease in the dose of the study intervention administered in any given part/panel
- Interchange of doses between panels
- Entire panel(s) may be omitted
- Modification of the viremia/viral shedding/immunogenicity sample collection, processing, and shipping details based on newly available data
- Exploratory immunology endpoints may be removed or modified

The viremia/viral shedding/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 additional virologic and/or immunologic markers.

SARS-CoV-2 serology and RT-PCR testing may be modified based upon evolving understanding of the epidemic, development of novel tests, availability of testing, and other factors. Local testing may be permissible for serology testing with Sponsor agreement. Anti-spike serology testing (instead of anti-nucleocapsid testing) may be permitted on Admission with Sponsor agreement. Antigen tests may be permitted with Sponsor agreement in place of RT-PCR tests; RT-PCR and/or antigen tests which are at present planned to be performed with nasopharngyeal swabs may be modified to generally better tolerated collection procedures such as those sampling from nasal midturbinate, anterior nares, oral mucosa, or saliva. Additional testing per site SOP is permitted.

Up to ~627.5 mL of blood may be drawn during the study (up to ~457.5 mL of blood may be drawn before Day 90 for safety, viremia or immunologic assessments and up to ~168 mL of

blood may be drawn from Day 90 to Day 365 for safety, viremia or immunologic assessments). The total blood volume withdrawn from any single participant will not exceed the maximum allowable volume before and after Day 90. (Appendix 8).

The timing of procedures for assessment of safety procedures (e.g., vital signs, 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.

The interim analysis to summarize the safety and immunogenicity data may be performed if and when at least 80% of participants from Parts 1 and 2 have the following data available: Safety through at least Day 28 and PRNT and ELISA immunogenicity from Day 1 Predose and Day 28 postvaccination for participants from Parts 1 and 2 (and will also include as the available safety data from Part 3, which is not required for this interim analysis).

An additional interim analysis, using the same analysis plan, may be performed at the discretion of the study team when at least 80% of the above described data are available for anyone, two or three dose levels of Parts 1 and 2.

It is understood that the current study may employ some or none of the alterations described above. Any 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. The letter may be forwarded to the IRB/IEC at the discretion of the investigator.

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 International Council for Harmonisation [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 Statistical Analysis Plan 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

This section contains a brief summary of the statistical analyses for this study; the comprehensive plan is provided in Sections 9.2 through 9.9.

Study Design Overview	A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Trial to Evaluate the Safety and Immunogenicity of V590 in Healthy Adults
Intervention Assignment	Within each panel of Parts 1, 2, and 3, healthy adult participants will be assigned randomly in a 3:1 ratio to receive V590 or matching placebo: • Panel A and E: V590 $5.00 \cdot 10^5$ pfu or Placebo • Panel B and F: V590 $2.40 \cdot 10^6$ pfu or Placebo • Panel C and G: V590 $1.15 \cdot 10^7$ pfu or Placebo • Panel D, H, and I: V590 $5.55 \cdot 10^7$ pfu or Placebo All participants will receive study intervention administered via IM injection(s) on Day 1.
Analysis Populations	Safety: All Participants as Treated (APaT) Viremia and Viral Shedding: All Participants as Treated (APaT) Immunogenicity: Per-Protocol (PP) Efficacy: Per-Protocol (PP)
Primary Endpoint	Safety: • Solicited injection site AEs from Day 1 through Day 5 • Solicited systemic AEs from Day 1 through Day 28 • Unsolicited AEs from Day 1 through Day 28 • MAAEs from Day 1 through Day 180 • SAEs from Day 1 through Day 365 **Amendment 001-03**: MAAEs from Day 1 through Day 28. SAEs from Day 1 through the duration of the study until the final database lock. Immunogenicity: • Anti-SARS-CoV-2 spike serum neutralizing antibody (SNA) responses, as measured by plaque reduction neutralization test (PRNT), at Day 28 (Parts 1 and 2)

Key Secondary Endpoints	Immunogenicity: • Anti-SARS-CoV-2 spike SNA responses, as measured by PRNT, at Days 7, 14, 90, 180, 270, and 365 (Parts 1 and 2) • Anti-SARS-CoV-2 spike IgG responses, as measured by enzyme-linked immunosorbent assay (ELISA), at Days 7, 14, 28, 90, 180, 270, and 365 (Parts 1 and 2) **Amendment 001-03**: Immunogenicity analyses will include all available data through Day 28.
Statistical Methods for Key Immunogenicity Analyses	Separately for each primary and secondary immunogenicity parameter, the geometric mean titers (GMT) with 95% confidence interval (CI), GMT ratios with 90% CI, and the hypothesis test (i.e., 2-sided p-value) if applicable, will be estimated using a longitudinal data analysis (LDA) method utilizing data from all vaccination and combining placebo groups. The primary hypothesis that at least one well-tolerated dose level of a single dose administration of V590 increases the GMTs of anti-SARS-CoV-2 spike SNA, as measured by PRNT, compared to placebo, will be tested using a stepwise procedure with an assumption that there is an increasing relationship between anti-SARS-CoV-2 spike SNAs and V590 doses.
Statistical Methods for Key Safety Analyses	The analysis of safety results will follow a tiered approach. No Tier 1 events are defined in this study. For Tier 2 events, 95% CIs will be provided for between-vaccination group differences in the percentage of participants with events; these analyses will be performed using the M&N method [Miettinen, O. and Nurminen, M. 1985] [Miettinen, O. 1985]. All safety parameters will also be summarized via descriptive statistics.
Interim Analyses	An interim analysis of safety and immunogenicity data to inform further clinical development will be performed, when at minimum 80% participants in Parts 1 and 2 have completed at least 28-day follow-up post-vaccination and immunogenicity data are available.
Multiplicity	The study has only 1 primary hypothesis which will be addressed using a closed step-wise testing procedure that preserves the overall alpha level at 0.05 1-sided (assuming a monotonic dose-response).
Sample Size and Power	Section 9.9 provides information about the ability of this study to estimate the incidence of AEs in recipients of a dose of V590; and the power to demonstrate an increase in anti-SARS-CoV-2 SNAs elicited by V590, compared to placebo.

Amendment 001-03: Active monitoring and immunogenicity assessments in the study will occur through Day 28. Spontaneous safety reporting is permitted beyond Day 28 for the protocol specified durations. Immunogenicity analyses will include all available data through Day 28. Safety analyses will include all collected safety data through the duration of the study until the final database lock. A final analysis of study data will occur instead of an interim analysis.

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, immunogenicity, viremia and viral shredding, and efficacy are listed below.

9.4.1 Safety Endpoints

Safety and tolerability will be assessed by clinical review of all relevant parameters, including AEs, postvaccination body temperature measurements, physical examinations, laboratory safety tests, and vital signs following any vaccination with V590 or Placebo.

The safety analysis endpoints that address the primary objective include:

- Solicited injection-site AEs (redness, swelling, and tenderness/pain) from Day 1 post-dose through Day 5 after study intervention
- Solicited systemic AEs (muscle pain, joint pain, headache, tiredness, fatigue, rash, nausea, joint swelling, oral lesions, sweating more than usual) from Day 1 post-dose through Day 28 after study intervention
- Unsolicited AEs from Day 1 post-dose through Day 28 after study intervention

- The broad AE categories consisting of any AE, vaccine-related AE, ECIs, and vaccine-related ECIs from Day 1 post-dose through Day 28 after study intervention
- The broad AE categories consisting of any MAAE and vaccine related MAAE from Day 1 post-dose through Day 180 after study intervention
- The broad AE categories consisting of any SAE, vaccine related SAEs, and death from Day 1 post-dose through the duration of participation in the study after study intervention
- Maximum temperature measurements meeting the Brighton Collaboration cut points from Day 1 through Day 28 after study intervention

Additional Safety analysis endpoints include:

- Safety laboratory results collected at Day 1 predose, Days 3, 7, and 28
- Vital signs collected at scheduled (see Section 1.3) and unscheduled visits.

Amendment 001-03: MAAEs from Day 1 post-dose through Day 28. SAEs from Day 1 through the duration of the study until the final database lock.

9.4.2 Immunogenicity Endpoints

The primary immunogenicity analysis endpoints include:

- Anti-SARS-CoV-2 spike SNA at Day 28, as measured by plaque reduction neutralization test (PRNT), in Parts 1 and 2 participants

The secondary immunogenicity analysis endpoints include:

- Anti-SARS-CoV-2 spike SNA at Day 1 Predose, Days 7, 14, 90, 180, 270, and 365, as measured by PRNT, in Parts 1 and 2 participants
- Anti-SARS-CoV-2 spike IgG at Day 1 Predose, Days 7, 14, 28, 90, 180, 270, and 365, as measured by enzyme-linked immunosorbent assay (ELISA), in Parts 1 and 2 participants

The exploratory immunogenicity analysis endpoints include:

- Anti-SARS-CoV-2 spike SNA at Day 1 Predose, Days 7, 14, 28, 90, 180, 270, and 365, as measured by PRNT, in Part 3 participants
- Anti-SARS-CoV-2 spike IgG at Day 1 Predose, Days 7, 14, 28, 90, 180, 270, and 365, as measured by ELISA, in Part 3 participants

Additional exploratory immunogenicity analysis endpoints may include:

- Enzyme-linked immunospot assay (ELISPOT) and intracellular cytokine staining (ICS) of peripheral blood mononuclear cells (PBMC)
- Anti-SARS-CoV-2 spike antibodies in mucosal samples
- Serum cytokines/chemokines

Exploratory immunogenicity endpoints may be summarized and reported separately.

Amendment 001-03: Immunogenicity analyses will include all available data through Day 28.

9.4.3 Viremia and Viral Shedding Endpoints

There is no primary analysis endpoint for V590 viremia and viral shedding.

The secondary V590 viremia and viral shedding analysis endpoints include:

- V590 plasma viremia, as detected by RT-PCR at Day 1 post-dose, Days 2, 3, 4, 5, 6, 7, 14, and 28
- V590 viral shedding in urine and saliva, as detected by RT-PCR at Day 1 post-dose, Days 2, 3, 4, 5, 6, 7, 14, and 28

V590 viral shedding in stool, as detected by RT-PCR at Days 2-4, and 5-7 (if assayed)
Exploratory viremia and viral shedding analysis endpoints include:

- V590 plasma viremia, as detected by Plaque Assay
- V590 viral shedding in urine, saliva, and stool as detected by Plaque Assay

Amendment 001-03: Viremia and viral shedding samples will be assayed with the intention of testing until negative for viremia/viral shedding. Viremia and viral shedding analyses will include all available data through Day 28.

9.4.4 Efficacy Endpoints

The exploratory efficacy analysis endpoint includes:

- Number and proportion of participants in Parts 1 and 2 experiencing seroconversion, which is determined by anti-SARS-CoV-2 nucleocapsid antibody titers at Days 7, 14, 28, 90, 180, 270, and 365, compared to baseline (Screening).

Amendment 001-03: Efficacy analyses will include all available data through Day 28.

9.5 Analysis Populations

The following analysis populations are defined for the analysis and reporting of data.

All Participants as Treated (APaT): The All Participants as Treated population consists of all randomized participants who received at least one dose of study vaccination. Participants will be included in the vaccination group corresponding to the study intervention they received for the analysis using the APaT population. This will be the vaccination 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 vaccination group corresponding to the study vaccine actually received.

FAS (Full Analysis Set): The Full Analysis Set population consists of all randomized participants who received at least one dose of study vaccination and have at least 1 result of the analysis endpoints. Participants will be included in the vaccination group to which they are randomized for the analysis using the FAS population.

Per-Protocol (PP): The Per-Protocol population consists of all randomized participants with exclusions for important deviations from the protocol that may substantially affect the results of the analysis endpoints. Participants will be included in the vaccination group to which they are randomized for the analysis using the PP population.

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 vaccination.

At least one laboratory, vital sign, or ECG measurement obtained subsequent to at least one study treatment is required for inclusion in the analysis of the respective safety parameter. To assess change from baseline, a baseline measurement is also required.

9.5.2 Immunogenicity Analysis Populations

The Per-Protocol (PP) population will be used for the analysis of immunogenicity data. The PP population consists of all randomized participants with exclusions for important deviations from the protocol that may substantially affect the results of the immunogenicity endpoints. Deviations that may result in the exclusion of a participant from the PP population include:

- Failure to receive the correct dose of study vaccination at Day 1
- Receipt of prohibited medication or prohibited vaccine prior to a blood sample collection
- Collection of blood sample outside of the pre-specified window

The final determination on important protocol deviations, and thereby the composition of the Per-Protocol population, will be made by blinded study team members prior to the final unblinding of the database.

A supplementary analysis using the Full Analysis Set (FAS) population will also be performed for the primary and secondary immunogenicity endpoints.

Details on the approach to handle missing data are provided in Section 9.6.

9.5.3 Viremia and Viral Shedding Analysis Populations

The All Participants as Treated (APaT) population will be used for the analysis of viremia and viral shedding data. The APaT population consists of all randomized participants who received at least one dose of study vaccination. At least one viremia or viral shedding measurement obtained subsequent to at least one study vaccination is required for inclusion in the analysis of the respective parameter.

A supplementary analysis using the Per-Protocol (PP) population may also be performed for the viremia and viral shedding endpoints.

9.5.4 Efficacy Analysis Population

The Per-Protocol (PP) population will be used for the analysis of efficacy data. The PP population consists of all randomized participants with exclusions for important deviations from the protocol that may substantially affect the results of the anti-SARS-CoV-2 nucleocapsid antibody titers.

A supplementary analysis using the Full Analysis Set (FAS) population will also be performed for the efficacy endpoint.

9.6 Statistical Methods

Statistical methods for safety, immunogenicity, and viremia and viral shedding analyses are described in Section 9.6.1, Section 9.6.2, and Section 9.6.3, respectively. Section 9.6.4 describes how demographic and baseline characteristics will be summarized.

For all analyses, data will be examined for departures from the assumptions of the statistical model(s) as appropriate; e.g., heteroscedasticity, non-normality of the error terms. Distribution-free methods may be used if a serious departure from the assumptions of the models(s) is observed, or suitable data transformations may be applied.

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.

The analysis of AEs and postvaccination temperature measurements will follow a tiered approach [Table 7]. The tiers differ with respect to the analyses that will be performed. Events (specific preferred terms (PT) as well as system organ classes (SOC)) 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.

Laboratory measurements, ECGs, and vital signs will be summarized separately. Summary statistics and plots will be generated for raw laboratory safety tests, ECGs, and/or vital signs as well as for change from baseline, as deemed clinically appropriate. Depending on the safety parameter, the difference from baseline will either be computed on the original scale (raw change from baseline) or on the log scale and back-transformed for reporting (percent change from baseline). Baseline is defined as the pre-dose measurement.

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 V590, 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 events will be assessed via point estimates and risk differences with 95% CIs provided for differences in the proportion of participants with events. Analyses will be performed using the Miettinen and Nurminen (M&N) method [Miettinen, O. 1985], an unconditional, asymptotic method.

Tier 2 events for this study include solicited injection-site AEs (redness/erythema, swelling, and tenderness/pain) from Day 1 through Day 5 postvaccination, solicited systemic AEs (muscle pain, joint pain, headache, tiredness, rash, nausea, joint swelling, oral lesions, sweating more than usual) from Day 1 through Day 28 postvaccination, and ECIs from Day 1 through Day 28 postvaccination. In addition, the broad AE categories consisting of the percentage of participants with any AE, any vaccine-related AE, any ECI, any vaccine-related ECI, any MAAE, any vaccine-related MAAE, any SAE, any vaccine-related SAE, and death will be considered Tier 2 events. Nonserious AEs will be followed for 28 days postvaccination, while MAAEs will be followed through Day 180 and SAEs will be followed through the duration of participation in the study. The proportion of participants with maximum temperature measurements meeting the Brighton Collaboration [Marcy, S. M., et al 2004] cut points (Days 1 to 28) 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% CI 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 7 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint[†]	95% CI for Between-Group Comparison [a]	Descriptive Statistics
Tier 2	Injection-site redness/erythema (Days 1 to 5)	X	X
	Injection-site swelling (Days 1 to 5)	X	X
	Injection-site tenderness/pain (Days 1 to 5)	X	X
	Muscle pain/myalgia (Days 1 to 28)	X	X
	Joint pain/arthralgia (Days 1 to 28)	X	X
	Joint swelling (Days 1 to 28)	X	X
	Rash (Days 1 to 28)	X	X
	Oral lesion (Days 1 to 28)	X	X
	Nausea (Days 1 to 28)	X	X
	Headache (Days 1 to 28)	X	X
	Tiredness/fatigue (Days 1 to 28)	X	X
	Sweating more than usual/abnormal sweating (Days 1 to 28)	X	X
	Any AE[b]	X	X
	Any Vaccine-Related AE[b]	X	X
	Any ECI[b]	X	X
	Any Vaccine-Related ECI[b]	X	X
	Any MAAE[b]	X	X
	Any Vaccine-Related MAAE[b]	X	X
	Any SAE[b]	X	X
	Any Vaccine-Related SAE[b]	X	X
	Death[b]	X	X
	Maximum temperature measurements meeting the Brighton Collaboration cut points (Days 1 to 28)	X	X
	Specific AEs by SOC and 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

Safety Tier	Safety Endpoint[†]	95% CI for Between-Group Comparison [a]	Descriptive Statistics
AE = adverse event; CI = confidence interval; MAAE = medically attended adverse event; 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 [Miettinen, O. and Nurminen, M. 1985]. [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.			

Amendment 001-03: MAAEs from Day 1 post-dose through Day 28. SAEs from Day 1 through the duration of the study until the final database lock.

9.6.2 Statistical Methods for Immunogenicity Analyses

This section describes the statistical methods that address the primary, secondary, and exploratory immunogenicity objectives. The immunogenicity analyses will be conducted for each endpoint separately [Table 8].

Primary Hypothesis

At least one well-tolerated dose level of a single dose administration of V590 increases the GMTs of anti-SARS-CoV-2 spike SNA, as measured by PRNT, compared to placebo.

The primary endpoint, anti-SARS-CoV-2 spike SNA GMTs at Day 28 will be assessed via the following hypotheses:

H0: GMT1/GMT2 ≤1 versus

H1: GMT1/GMT2 >1,

where GMT1 is the anti-SARS-CoV-2 spike SNA GMT for a V590 dose level and GMT2 is the anti-SARS-CoV-2 spike SNA GMT for the placebo. Estimation of the GMT ratio and the corresponding 90% CI will be calculated using a LDA model utilizing the log-transformed antibody titers as the response.

A Stepwise Procedure

The primary hypothesis will be tested using the following stepwise procedure with an assumption that there is an increasing relationship between anti-SARS-CoV-2 spike SNAs and V590 doses. The primary hypothesis will be supported if the lower limit of the 90% CI (equivalent to the lower bound of a one-sided 95% CI) for the GMT ratio between the highest V590 dose and placebo is >1 (indicating an increase). If the hypothesis is supported in the previous step, then the same procedure will be applied to the next lowest dose. The procedure continues in this stepwise fashion until the lower limit of the 90% CI at a particular dose is ≤1.

LDA Model

Separately for each primary and secondary immunogenicity parameter, the GMTs with 95% CI, GMT ratios with 90% CI, and the hypothesis test (i.e., 2-sided p-value) if applicable, will be estimated using an LDA method utilizing data from all vaccination and placebo groups. The response vector consists of the natural log-transformed prevaccination (Day 1) and postvaccination (Days 7, 14, 28, 90, 180, 270, and 365) antibody titers. The linear mixed-effects model will include fixed effects of dose (4 dose levels of V590 and placebo), time (Days 1, 7, 14, 28, 90, 180, 270, and 365), age stratum (i.e., 18 to 54 years, and ≥ 55 years), the dose-by-time interaction, and age-by-time interaction. 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. The Kenward-Roger adjustment will be used with REML to make proper statistical inference. This model allows the inclusion of participants who are missing either the baseline or postbaseline measurements, thereby increasing efficiency.

Exponentiating the least squares means and the lower and upper limits of CIs will yield estimates for the population GMTs and corresponding 95% CIs by dose, time, and/or age stratum on the original scale. To assess the treatment difference between 1 of the 4 dose levels of V590 relative to the placebo, the least squares mean differences (V590 – placebo) and 90% CIs from this model will be back-transformed to obtain the GMT ratios (V590/placebo) and 90% CIs.

Secondary and Exploratory Endpoints

The evaluations of secondary and exploratory objectives will be performed within each vaccination group separately. Descriptive statistics with point estimates and within-group 95% CIs will be provided by dose, time, and/or age stratum. For the continuous endpoints, 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. For the dichotomous endpoints, if any, the within-group CIs will be calculated based on the exact method proposed by Clopper and Pearson [Clopper, C. J. 1934].

Additionally, SNA GMTs and IgG GMTs and corresponding 95% CIs may be calculated using the same LDA model as for the primary endpoint.

Miscellaneous

The relationship between anti-SARS-CoV-2 spike SNAs and V590 doses will be displayed graphically. Reverse Cumulative Distribution Curves for postvaccination SNA GMTs and IgG GMTs will be graphically displayed by time points.

For titer measurements that are smaller than the lower bound of the assay detectable range, half of the lower bound may be used as the value of the titer.

Table 8 Analysis Strategy for Immunogenicity Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach†	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoint (H1)				
GMTs of anti-SARS-CoV-2 spike SNA, as measured by PRNT, at Day 28 (Parts 1 and 2)	P	t-distribution with the variance estimate from an LDA model‡ (estimate, 95% CI, p-value)	PP	Missing data will not be imputed
	S		FAS	
Secondary Endpoint				
GMTs of anti-SARS-CoV-2 spike SNA, as measured by PRNT, at Days 7, 14, 90, 180, 270, and 365 (Parts 1 and 2)	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed
	S		FAS	
GMTs of anti-SARS-CoV-2 spike serum IgG, as measured by ELISA, at Days 7, 14, 28, 90, 180, 270, and 365 (Parts 1 and 2)	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed
	S		FAS	
Exploratory Endpoints				
GMTs of anti-SARS-CoV-2 spike SNA, as measured by PRNT, at Days 7, 14, 28, 90, 180, 270, and 365 (Part 3)	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed
	S		FAS	
GMTs of anti-SARS-CoV-2 spike serum IgG, as measured by ELISA, at Days 7, 14, 28, 90, 180, 270, and 365 (Part 3)	P	Descriptive Statistics (estimate, 95% CI)	PP	Missing data will not be imputed
	S		FAS	

CI = confidence interval; FAS = Full Analysis Set; GMT = geometric mean titer; H = hypothesis; IgG = Immunoglobulin G; SNA = serum neutralizing antibody; PP = Per-Protocol.

† P = Primary approach using PP population; S = Supportive approach using FAS population.

‡ Estimation of the SNA 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 (LDA) utilizing the log-transformed antibody titers as the response and a single term for vaccination group.

Amendment 001-03: Immunogenicity analyses will include all available data through Day 28.

9.6.3 Statistical Methods for Viremia and Viral Shedding Analyses

The viremia and viral shedding analyses will be conducted for each endpoint separately.

Numbers and proportions of participants with positive V590 plasma viremia and positive viral shedding in urine, saliva, and stool (if assayed), as detected by RT-PCR, will be calculated by dose, time, and/or age stratum.

GMs with 95% CIs of positive V590 plasma viremia and positive viral shedding in urine, saliva, and stool (if assayed), will be estimated by dose, time, and/or age stratum. Descriptive statistics including n, median, minimum, and maximum will also be provided.

Area under the curve (AUC) of each viremia and viral shedding endpoints between Day 1 and Day 7 will be calculated and analyzed using a linear model with dose as a fixed categorial effect. The mean AUC in each dose group and 95% CIs will be computed based on the model. Descriptive statistics of AUC including n, median, minimum, and maximum will be provided.

Median, minimum, and maximum durations of positive V590 plasma viremia and viral shedding in urine, saliva, and stool (if assayed), will be reported.

The longitudinal patterns of each viremia and viral shedding endpoints after vaccination from Day 1 through Day 7 will be displayed graphically by dose group.

Positive viremia and viral shedding are defined as a detectable RT-PCR results greater than or equal to lower limit of detection [≥ LLOD]. Results are deemed quantifiable if the result is greater than or equal to the lower limit of quantification [≥ LLOQ].

Amendment 001-03: Viremia and viral shedding samples will be assayed with the intention of testing until negative for viremia/viral shedding. Viremia and viral shedding analyses will include all available data through Day 28.

9.6.4 Statistical Methods for Efficacy Analyses

The exploratory efficacy analysis will assess the efficacy of V590 to prevent seroconversion to anti-SARS-Cov-2 nucleocapsid antibody positivity, an evidence of infection.

GMTs of anti-SARS-CoV-2 nucleocapsid antibody will be calculated by dose, time and/or age stratum. Numbers and proportions of participants in the PP population of Parts 1 and 2, who meet seroconversion criteria, will be estimated by dose, time, and/or age stratum. Corresponding within-group 95% CIs will be calculated based on the exact method proposed by Clopper and Pearson [Clopper, C. J. 1934].

Amendment 001-03: Efficacy analyses will include all available data through Day 28.

9.6.5 Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant demographic and baseline characteristic will be assessed by the use of tables and/or graphs. 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) and baseline characteristics will be summarized by treatment group either by descriptive statistics or categorical tables.

9.7 Interim Analyses

An interim analysis of safety and immunogenicity data to inform further clinical development will be performed, when at minimum 80% participants in Parts 1 and 2 have completed at least 28-day follow-up post-vaccination and immunogenicity data are available. All available safety data will be evaluated. Serum samples collected on Day 1 prior to vaccination and on Day 28 postvaccination will be assayed for vaccine-induced immune responses to V590. Anti-SARS-CoV-2 spike SNA titers measured by PRNT are the primary outcome measure. Anti-SARS-CoV-2 spike IgG titers measured using ELISA will be analyzed as a secondary objective. The study enrollment, conduct, and ongoing safety monitoring will continue.

An additional interim analysis may be conducted earlier at the discretion of the sponsor when at minimum 80% participants in one, two, or three dosing levels in Parts 1 and 2 have completed at least 28-day follow-up post-vaccination and immunogenicity data are available.

Analyses of immunogenicity data from Day 90, Day 180, and/or 270 may also be conducted at the discretion of the sponsor when data are available, to inform future study designs.

<u>siDMC</u>

An unblinded siDMC will receive the unblinded IA safety and immunogenicity data. The siDMC will make a recommendation for further clinical development based on review of: (1) available safety data through at least Day 28 for all participants enrolled in Parts 1 and 2; (2) available immunogenicity data for all evaluable participants enrolled in Parts 1 and 2; and (3) any available safety data from Part 3. The primary immunogenicity hypothesis will be evaluated to inform the decision.

A description of the structure and function of the siDMC, along with the timing and content of the safety review, will be outlined in the siDMC charter. Information regarding the composition of the siDMC is provided in Section 10.1.4.1.

Blinding

Regardless of the outcome of the IA, blinding to treatment assignment will be maintained at all investigational sites. The results of IAs will not be shared with the investigators prior to the completion of the study.

For this Phase I study, an internal statistician, statistical programmers, 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.

Treatment-level safety and immunogenicity results from the IA will be provided by the unblinded statistician to the siDMC. Aggregate safety data and treatment-level immunogenicity results will be provided by the unblinded statistician to the sponsor study team. The extent to which individuals are unblinded with respect to the results of IAs will be documented by the unblinded statistician.

Amendment 001-03: Participants in all parts will be followed through Day 28 for safety, tolerability, immunogenicity, viremia and viral shedding. A final study analysis will be performed on all available data through Day 28, in place of an Interim Analysis.

9.8 Multiplicity

The study has only 1 primary hypothesis which will be addressed using a closed step-wise testing procedure that preserves the overall alpha level at 0.05 1-sided (assuming a monotonic dose-response).

9.9 Sample Size and Power Calculations

9.9.1 Sample Size and Power for Safety Analyses

The probability of observing at least one SAE in this study depends on the number of participants dosed and the underlying percentage 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 90% chance of observing at least 1 SAE among 189 participants receiving V590 if the underlying incidence of a SAE is 1.2% (1 out of every 84 vaccine recipients). There is a 60% chance of observing at least one SAE among 189 participants receiving V590 if the underlying incidence of a SAE is 0.5% (1 out of every 189 vaccine recipients). If no SAEs are observed in the approximately 189 participants receiving V590, this study provides 97.5% confidence that the true SAE rate is <1.93% (1 out of every 51 vaccine recipients).

9.9.2 Sample Size and Power for Immunogenicity Analyses

An estimate of variability was obtained from the available data from V920-009, V920-011, and V920-012. The largest variability computed for any PRNT parameter in that studies was 1.2 (standard deviation on natural log scale).

The study achieves 90% power at a 1-sided 5% alpha-level to demonstrate V590 increases anti-SARS-CoV-2 SNA GMTs, compared to placebo, based on a true GMT ratio of V590 vs. placebo ≥ 2.17, assuming (1) an 85% evaluability rate at Day 28 in Parts 1 and 2 (i.e., 36 evaluable participants out of 42 V590 recipients in each dose level, and 48 evaluable participants out of 56 placebo recipients); and (2) a comparable variability as observed in V920 (i.e., natural log scale standard deviation to be 1.2).

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 Internal Data Monitoring Committee

To supplement the monitoring outlined in this protocol, and in addition to the Sponsor safety review team, a separate siDMC will monitor the interim data from this study and will be convened if stopping rules are met. 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 the Interim Analysis (Section 9.7) to evaluate available safety and immunogenicity data for consideration of further development, as described in the detailed monitoring guidelines. The siDMC will review all available relevant data if stopping rules are met in this 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 9 will be performed by the local laboratory. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 8.1.2 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 9 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose [Indicate if fasting, or nonfasting]	Calcium	Alkaline phosphatase	
	Creatinine Kinase (CPK)	C-reactive protein (CRP) (high-sensitivity)		
Coagulation	Prothrombin time/International Normalized Ratio (PT/INR)	Activated Partial thromboplastin time (aPTT)	Fibrinogen	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			

Laboratory Assessments	Parameters
Other Tests (per SoA)	• Follicle-stimulating hormone (as needed in women of nonchildbearing potential only) • Serum β-hCG or urine pregnancy test (as needed in women of childbearing potential only) • Serum or urine [alcohol and drug screen (specific panel at the site's discretion, but at least including cocaine and opiates)] • Serology [(HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)] • Hemoglobin A1c • All study-required laboratory assessments will be performed by a local laboratory, with the exception of SARS-CoV-2 Tests (PCR and antibody tests) that will be measured by a Central laboratory (per the SoA) • Additional tests may be done per site SOP with Sponsor agreement

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.

- MAAE: 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.

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 and SAE (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 and SAE (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 10, Table 11, Table 12, and Table 13. The laboratory values in Table 14, Table 15, and Table 16 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 used for defining [Grade 2] toxicities with Sponsor Consultation. 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 10 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
Any injection-site reaction that begin on Day 6 following 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 11 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 12 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 13 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 14 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 15 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 16 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 initialled 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?

(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.)

- **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 and SAE

- 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: Guidance for Assessment and Work-up of Specific Postvaccination Adverse Effects

The following is the 'Guidance for Assessment and Work-up of Specific Postvaccination Adverse Effects' that the primary investigator should follow.

1. INTRODUCTION

One of the primary objectives of the V590-001 trial is to evaluate the safety of the recombinant vesicular stomatitis virus with SARS-CoV spike protein, hereafter referred to as V590). V590 shares the same vesicular stomatitis virus vector as the Ebola vaccine ERVEBO; in the ERVEBO Phase 1/1b clinical development program some subjects reported arthritis and/or peripheral clusters of vesicular lesions. V590-001 is the first study of V590 in humans, and it is unknown whether similar findings might be observed with this vaccine. The V590-001 trial will prospectively monitor and assess these events in order to characterize the safety profile of the V590 study vaccine.

Subjects who develop AEs potentially suggestive of arthritis, rashes and oral lesions (specifically, joint pain, joint swelling, rash and/or oral lesions) will be instructed to contact the investigator site immediately for possible evaluation.

This appendix outlines the criteria for subjects to return to the investigator site (if not already domiciled) for examination, and the assessments and work-ups that should be performed. Briefly, subjects will inform the site if they have joint pain/swelling, rash or oral lesions. The investigator will evaluate these complaints; this document provides guidance for the evaluation and workup, including potentially referrals to rheumatology and/or dermatology for consideration of synovial fluid aspiration and/or skin biopsy, respectively. Recommendations are additionally provided to test vesicular fluid and oral ulcers for the presence of V590 RNA by RT-PCR. Guidance is provided separately for evaluation of arthritis, for rashes/oral lesions, and for vesicular lesions. The rash/oral lesion evaluation can direct the investigator to the vesicular lesion section, if the rash/oral lesion is vesicular in nature. Of note, if the participant is already domiciled at the time of onset the investigator will directly assess promptly through a targeted physical exam and history and as outlined in this document.

Additional questions from the investigator or consulting rheumatologist/dermatologist that are not addressed in this document should be directed to the site's Clinical Research Associate (CRA) or the Sponsor Clinical team.

2. ADVERSE EVENTS OF ARTHRITIS

What is the definition of arthritis for the purposes of postvaccination AE evaluation in this study?

For the purposes of this trial, **arthritis** is defined as joint pain along with two or more of the following symptoms: Joint swelling, stiffness, erythema, warmth, tenderness, limitation of range of motion and/or effusions occurring at any time from study vaccination through Day 28 postvaccination.

What is the estimated incidence of postvaccination arthritis in this trial?

It is unknown whether arthritis may be observed as an AE with V590. With ERVEBO under 5% of subjects reported an AE of arthritis postvaccination.

When and how should a subject monitor and report AEs of arthritis?

Subjects will be instructed to actively self-assess for events potentially suggestive of arthritis (specifically “joint pain” and “joint swelling”) from the time of study vaccination through Day 28 postvaccination on a paper Vaccination Report Card (VRC). Subjects will be prompted for the events of joint pain and joint swelling in the “Vaccine Specific Complaints” section of the study VRC. Subjects will be asked to record the onset and stop dates, severity (mild, moderate, or severe), and urgent medical attention required (if any). Subjects will also be instructed at the time of enrollment to contact the study staff immediately if they experience arthritis/joint swelling/joint pain at any time from vaccination through Day 28 postvaccination. Any arthritis that occurs during the domiciled period (through Day 7) will be evaluated during the domiciled period, and participants may leave domiciling for rheumatology consultation.

When should the subject be brought in for a physical examination and work-up for a potential AE of arthritis?

Subjects will report symptoms potentially suggestive of arthritis occurring from the time of study vaccination through Day 28 postvaccination via phone call to the study site if not domiciled at time of onset. The study staff should instruct the subject to return to the investigator site for a directed physical examination. If these symptoms develop during the domiciled period, joint pain and/or joint swelling will be evaluated as soon as possible after onset.

What should the physical examination for potential AEs of arthritis include?

When the subject returns to the study site with an AE potentially consistent with arthritis, the investigator should conduct a directed physical examination of the affected joint(s) and record the findings, as indicated in the Data Entry and Handling Guidelines (DEGs).

What is the threshold for collecting diagnostic specimens after the determination of an AE of arthritis, and what specimens should be collected by the investigator?

If the subject's arthritis is not considered to be due to another obvious explanation, then the investigator should collect the following specimens for testing:

(1) **Blood:** To be tested for complete blood count (CBC), blood chemistry, blood urea nitrogen (BUN), creatinine, and C-reactive protein (CRP).

(2) **Urine:** To be tested for urinalysis and microscopy (with analysis of sediment).

These tests do not need to be repeated if they have otherwise been collected as outlined in the protocol SoA while these symptoms were present. These labs should be repeated if there is significant worsening of these symptoms.

What are the procedures for collection of specimens by the investigator?

The blood and urine specimens should be collected per the site's local procedures. Supplies for the collection and transport of these specimens will be provided by the site.

Where should the specimens collected by the investigator be tested?

The blood and urine specimens collected by the investigator should be tested at the site's local laboratory. Upon receipt, the study staff should manually enter the test results and the local lab's normal ranges into the Supplemental Laboratory (SLAB) eCRF.

When should the subject be referred to the rheumatologist associated with this study for additional evaluation?

The subject should be referred to the consulting rheumatologist for further evaluation if:

(1) There are objective findings of arthritis based on the investigator's directed physical examination, and/or

(2) The subject's blood and/or urine tests return any clinically significant abnormal results.

The rheumatologist consultation should occur as soon as possible, but no later than one week following the initial assessment by the investigator.

NOTE: The investigator may decide to refer the subject for a rheumatology consultation at any time based on clinical judgment and/or the severity of the subject's clinical symptoms.

What is the threshold for collecting additional specimens during the rheumatology visit and what specimens should be collected by the rheumatologist?

A consulting rheumatologist should conduct a directed physical examination of the affected joint(s). A synovial fluid specimen should be collected via arthrocentesis based on the following criteria:

(1) Based on evaluation by the consulting rheumatologist, detailed assessment of the involved joint(s)indicates that joint aspiration is clinically indicated and likely to yield fluid for further analysis, and

(2) When feasible and acceptable to the subject

Synovial fluid specimens may only be collected once the subject has signed an additional consent form for the collection of invasive specimens in accordance with site SOPs and the rheumatologist's standard of practice.

In addition to the standard clinical evaluation by the rheumatologist of this fluid which will be the priority, if any additional fluid is available it will be analyzed for the presence of V590 RNA by RT-PCR.

What is the guidance for follow-up examinations and repeated specimen collection and testing?

After lab tests are collected (and results are pending), the site should continue to follow the subject through the following tiered approach:

(1) Day 1 to 7 Post-Onset: After the initial examination and collection of lab specimens, the site should contact the subject every 1 to 2 days via telephone for the first 7 days to check on the status of the symptoms if the subject is not domiciled at the time. If domiciled, the participant should be evaluated at least daily, as per protocol. If the subject's lab results return clinically significantly abnormal, the investigator should ensure that the consulting rheumatologist is aware of the results either in advance of the initial consultation or for follow-up.

(2) Beyond Day 7 Post-Onset: The site should continue to contact the subject every 7 days via telephone (or via in person visit if scheduled or otherwise indicated, allowing for +/- 3 days) until the symptoms have resolved. Repeat lab tests are not required at this time. The site should instruct the subject to contact the site immediately if the symptoms worsen. Worsening of symptoms (e.g., increase in number of joints involved, increase in severity of pain or other symptoms, return of swelling/effusion in the joint(s) undergoing arthrocentesis, other new joint symptoms consistent with arthritis) should be communicated immediately to the consulting rheumatologist for further evaluation.

If the subject's symptoms have not fully resolved by Day 28 post-onset, then the subject should return to the study site for a follow-up examination at ~6-8 weeks

post-onset and be referred to the consulting rheumatologist for further evaluation. The site should continue to follow up with the subject approximately every 2-4 weeks by telephone until resolution of symptoms.

NOTE: The investigator may decide to conduct repeat assessments and collect repeat specimens more frequently if considered clinically indicated. The investigator may also refer the subject for a rheumatology consultation at any time based on clinical judgment, severity of symptoms, and/or the results of bloodwork/urinalysis testing.

What should be done for reported AEs of arthritis that occur after Day 28 postvaccination?

New events of arthritis reported after Day 28 postvaccination do not require unscheduled follow-up visits, directed physical examinations, or specimen collection. However, if a previous event of arthritis initially reported between Days 1 to 28 postvaccination recurs after Day 28 postvaccination, then the above-outlined procedures for assessment and work-up of arthritis should be followed.

Additionally, all serious adverse events (SAEs) are to be reported at any time during the trial (through Day 365).

How long should AEs of arthritis be followed?

All AEs of arthritis should be followed to resolution (or until the end of the study, provided stable).

3. ADVERSE EVENTS OF RASH OR ORAL LESION

What is the definition of rash for the purposes of postvaccination AE evaluation in this study?

For the purposes of this trial, all **rashes** (including but not limited to maculopapular, petechial, purpuric, localized or disseminated vesicular rashes, etc.) and/or **oral lesions** occurring at any time from study vaccination through Day 28 postvaccination should be reported to the study site. This rash will be assessed by the site. If vesicles are present as assessed by the investigator, the guidance in Section 4 should be followed on vesicular lesions. If there is also a rash or other lesion present (including oral ulceration) in addition to vesicles the instructions in this Section should be followed as well.

This approach is designed to ensure that vesicles are assessed and diagnosed by the investigator, as they may be difficult for participants to identify (especially if in the oral cavity). All rashes will be assessed, and it will be determined whether vesicles are present, in which case the vesicle guidance in Section 4 is to be followed.

When and how should a subject monitor and report AEs of rash and/or oral lesion?

Subjects will be instructed to actively self-assess for events of rash of any kind, or oral lesions, from the time of study vaccination through Day 28 postvaccination on a paper Vaccination Report Card (VRC). Subjects will be prompted for events of rash and oral lesions on the VRC. Subjects will be asked to record the onset and stop dates, severity (mild, moderate or severe), and urgent medical attention required (if any). Subjects will not be expected to characterize the rash; this characterization will be performed by the investigator. Subjects will be instructed at the time of enrollment to contact the study staff immediately if they develop a rash or oral lesion at any time from vaccination through Day 28 postvaccination, during which time the VRC is being utilized.

When should the subject be brought in for a physical examination and work-up for an AE of rash or oral lesion?

Subjects will report all AEs of rash and/or oral lesions occurring from the time of study vaccination through Day 28 postvaccination via phone call to the study site. The study staff should instruct the subject to return to the investigator site for a directed physical examination and work-up if:

(1) The rash and/or oral lesion is not due to another obvious explanation.

When the subject returns to the study site with a rash, the investigator should conduct a directed physical examination of the affected area(s) and record the findings, as indicated in the Data Entry and Handling Guidelines (DEGs).

NOTE: If the subject's rash/oral lesion is also associated with joint pain and/or swelling or includes vesicular lesions, then the procedures for the assessment and work-up of arthritis (Section 2) and/or vesicular lesions (Section 4) should also be followed.

What is the threshold for collecting diagnostic specimens for an AE of rash and/or oral lesion, and what specimens should be collected by the investigator?

All vesicular lesions should follow the guidance in Section 4, including oral vesicular lesions.

If there is an oral lesion and it is an ulceration, this should be swabbed and submitted for RT-PCR for V590.

For lesions that are not vesicular and not oral ulcerations the investigator may decide to refer the subject for a dermatology consultation at any time based on clinical judgment and/or the severity of the subject's clinical symptoms. It is expected that disseminated rashes, including disseminated vesicles, or otherwise concerning rashes, would merit consideration of referral to dermatology and consideration of collection of diagnostic specimens. The Sponsor is available to discuss individual cases if/when they arise.

If the participant is referred to a dermatologist, what is the threshold for collecting additional specimens during the dermatology visit and what specimens should be collected by the dermatologist?

The consulting dermatologist should conduct a directed physical examination of the rash. One or two tissue specimens should be collected via punch biopsy based on the following criteria:

(1) Based on clinical judgment of the consulting dermatologist, the skin lesions are maculopapular, petechial, purpuric, or disseminated vesicular in nature, or another type of skin lesion of clinical interest (such as a severe or disseminated rash), which based on the dermatologist's clinical judgment would merit biopsy, and

(2) When feasible and acceptable to the subject

Tissue biopsy specimens may only be collected once the subject has signed an additional consent form for the collection of invasive specimens in accordance with site SOPs and the dermatologist's standard of practice.

In addition to the standard pathological evaluation of this tissue biopsy which will be the priority, if any additional tissue is available it will be analyzed for the presence of V590 RNA by RT-PCR.

4. ADVERSE EVENTS OF VESICULAR LESIONS

What is the definition of vesicular lesions for the purposes of postvaccination AE evaluation in this study?

For the purposes of this trial, any **rash** or **oral lesion** occurring at any time from study vaccination through Day 28 postvaccination should be reported to the study site, as described in Section 3. The general approach to non-vesicular rashes is described in Section 3. If the investigator assesses the lesion to be a **vesicular lesion** (including vesicles in the mouth), the guidance included in this Section 4 should be followed. Please note that disseminated vesicular lesions would generally warrant a separate dermatologic consultation in addition to following the instructions in Section 4.

What is the estimated incidence of postvaccination vesicular lesions in this trial?

It is unknown whether vesicular lesions may be observed as an AE with V590. In the ERVEBO program under 2% of subjects report an AE of vesicular lesions postvaccination.

When and how should a subject monitor and report AEs of vesicular lesions?

Subjects will be instructed to actively self-assess for rashes and oral lesions from the time of study vaccination through Day 28 on a paper Vaccination Report Card (VRC). Subjects will also be instructed at the time of enrollment to contact the study staff

immediately if they develop a rash or oral lesion at any time from vaccination through Day 28 postvaccination, and this rash/oral lesion will be assessed by the investigator. If it is vesicular in nature this will be captured in the investigator assessment as described in Section 3.

When should the subject be brought in for a physical examination and work-up for an AE of vesicular lesions?

As described in Section 3, subjects will report all AEs of rash or oral lesion occurring from the time of study vaccination through Day 28 postvaccination via phone call to the study site. The study staff should instruct the subject to return to the investigator site for a directed physical examination and work-up if:

(2) The rash is not due to another obvious explanation.

What should the physical examination for potential AEs of vesicular lesions include?

When the subject returns to the study site with an AE of rash or oral lesions, the investigator should conduct a directed physical examination of the affected area(s) to characterize the lesion and determine whether a vesicular lesion is present, and record the findings, as indicated in the Data Entry and Handling Guidelines (DEGs).

NOTE: If the subject's vesicular lesions are also associated with joint pain, joint swelling and/or a rash then the procedures for the assessment and work-up of, arthritis (Section 2), and/or rash (Section 3) should also be followed.

What is the threshold for collecting diagnostic specimens for an AE of vesicular lesions and what specimens should be collected by the Primary Investigator?

If the subject's vesicular lesions: (1) Occurred at any time from study vaccination through Day 28 postvaccination, and (2) are not considered to be due to another obvious explanation, then the investigator should collect the following specimens for testing:

(1) **Blood:** To be tested for complete blood count (CBC), blood chemistry, blood urea nitrogen (BUN), creatinine, and C-reactive protein (CRP).

(2) **Urine:** To be tested for urinalysis and microscopy (with analysis of sediment).

(3) **Swabs of Vesicular Fluid:** To be tested for the presence of V590 RNA by RT-PCR.

The above listed tests do not need to be repeated if they have otherwise been collected as outlined in the protocol SoA while these symptoms were present. These labs should be repeated if there is significant worsening of these symptoms.

When should the subject be referred to the dermatologist associated with this study for additional evaluation?

Provided that the subject's vesicular lesions are isolated in nature (not disseminated) and are not associated with other dermatologic lesions, then a referral to the consulting dermatologist for further evaluation is not necessary. If the subject's vesicular lesions are associated with a rash, referral to a dermatologist should be considered by the investigator. If the vesicular lesions are widely disseminated over a large area then dermatologist evaluation is recommended.

What is the guidance for follow-up evaluations and repeat specimen collection and testing?

After lab tests are collected (and results are pending), the site should continue to follow the subject through the following tiered approach:

(1) Day 1 to 7 Post-Onset: After the initial examination and collection of lab specimens, the site should contact the subject every 1 to 2 days via telephone for the first 7 days to check on the status of the symptoms. If domiciled, the participant should be evaluated at least daily as per protocol. If the subject's lab results come back clinically significantly abnormal, the investigator should refer the subject to a consulting dermatologist for further evaluation.

(2) Beyond Day 7 Post-Onset: The site should continue to contact the subject every 7 days via telephone (or via in person visit if scheduled or otherwise indicated, allowing for +/- 3 days) until the symptoms have resolved. Repeat lab tests are not required at this time. The site should instruct the subject to contact the site immediately if the symptoms worsen. An increase in number of vesicles should prompt increased frequency of follow-up to every 1 to 2 days via telephone for the first week following worsening, as well as a prompt in person visit to re-sample for the presence of V590 by RT-PCR. The follow-up may then decrease to every 7 days in frequency. Clinically significant worsening of symptoms (e.g., excessive or persistent weeping from lesions, evidence of infection, or evidence of dissemination) should be evaluated in person as soon as possible, and referred to the consulting dermatologist as appropriate.

If the subject's symptoms have not fully resolved by Day 28 post-onset, then the subject should return to the study site for a follow-up examination at ~6-8 weeks and be referred to the consulting dermatologist for further evaluation if still present. The site should continue to follow up with the subject approximately every 2-4 weeks by telephone until resolution of symptoms.

Additional information regarding the subject's symptoms collected during follow-up phone calls should be entered, as indicated in the Data Entry and Handling Guidelines (DEGs).

NOTE: The investigator may decide to conduct repeat assessments and collect repeat specimens more frequently if considered clinically indicated in the investigator's judgement. The investigator also reserves the right to refer the subject for a dermatologist consultation at any time based on clinical judgment, severity of symptoms, and/or the results of bloodwork/urinalysis testing.

What should be done for reported AEs of vesicular lesions that occur after Day 28 postvaccination?

New events of vesicular lesions reported after Day 28 postvaccination do not require unscheduled follow-up visits, directed physical examinations, or specimen collection. However, if a previous event of vesicular lesions initially reported between Days 1 to 28 postvaccination recurs after Day 28 postvaccination, then the above-outlined procedures for assessment and work-up of vesicular lesions should be followed. New events of vesicular lesions reported after Day 28 may be further evaluated by the investigator based on the investigator's judgement.

Additionally, all serious adverse events (SAEs) are to be reported at any time during the trial (through Day 365).

How long should AEs of vesicular lesions be followed?

All AEs of vesicular lesions should be followed to resolution (or until the end of the study, provided stable).

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

Females **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 progestogen- 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.
Methods That Are Not Considered Highly Effective *Failure rate of >1% per year when used consistently and correctly.*
• Progesterone-only hormonal contraception where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide • Cervical cap, diaphragm, or sponge with spermicide • A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double barrier methods)[f]
[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] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). [If hormonal contraception efficacy for a female participant is potentially decreased due to interaction(s) with study intervention(s), add the following footnote. If hormonal contraception is prohibited, or if hormonal contraception efficacy is NOT decreased due to interaction with study intervention(s), delete the following footnote:] [c] Male condoms must be used in addition to female participant hormonal contraception. [d] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. [e] IUS is a progestin releasing IUD. [f] A combination of male condom with either cap, diaphragm, or sponge with spermicide are considered acceptable, but not highly effective, birth control methods. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male and female condom should not be used together (due to risk of failure with friction).

Male Participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to 1 of the following terms during the protocol defined time frame in Section 5.1:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.
- 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.
  - The following are not acceptable methods of contraception:
    - Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM.
    - Male and female condom cannot be used together.
  - A combination of male condom with either cap, diaphragm, or sponge with spermicide are considered acceptable, but not highly effective, birth control methods.

10.5.3 Pregnancy Testing (WOCBP)

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test and in accordance with local requirements. This test should be repeated within 24 hours before the first vaccination administration (after start of domiciling).

Following administration of treatment, additional pregnancy testing will be performed at Day 28 following dosing of study intervention, and as required locally.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

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

This appendix is not applicable to this study.

10.8 Appendix 8: Approximate Blood Volume Table

Parts 1, 2, and 3	Screening	Days -3 to -1	Vaccination Period (Day 1 to Day 270)	Poststudy (Day 365)	Total Collections	mL Per Collection	Total mL/ Test
Laboratory Safety Tests	1	1	3	0	5	8.5	42.5
Hemoglobin A1c	1	0	0	0	1	1	1
Coagulation	1	1	3	0	5	3.5	17.5
HIV/Hepatitis Screen (at the discretion of the investigator)	1	0	0	0	1	3.5	3.5
Blood for Drug Screen	1	1	0	0	2	10	20
FSH (WONCBP only)	1	0	0	0	1	3.5	3.5
Serum Pregnancy Test (WOCBP only)	1	1	1	0	2	3.5	10.5
Serum for VSV antibodies	0	1	0	0	1	3	3
Serum for anti-SARS-CoV-2 nucleocapsid antibodies	1	1	6 (Parts 1 and 2 only)	1 (Parts 1 and 2 only)	9	3	27
Serum for anti-SARS-CoV-2 spike neutralizing antibodies (PRNT)	0	0	7	1	8	10	80
Serum for anti-SARS-CoV-2 spike IgG (ELISA)	0	0	7	1	8	10	80
Plasma for V590 viremia	0	0	9	0	9	6	54
Blood for PBMCs and Plasma for Future Biomedical Research (selected sites only)	0	0	2	0	2	50	100
Serum for Cytokines	0	0	3	0	3	3	9
Blood for Genetic Analysis	0	0	1	0	1	8.5	8.5
Blood (RNA) for Future Biomedical Research	0	0	3	0	3	2.5	7.5
Serum for Future Biomedical Research	0	0	7	1	8	20	160

Total Blood Volume per Female Participants		
	Parts 1 and 2[a]	627.5 mL
	Parts 1 and 2[a] without PBMC	527.5 mL
	Parts 1 and 2 Total Blood Volume up to Day 90	457.5 mL
	Parts 1 and 2 Total Blood Volume from Days 90 to 365	168 mL
	Part 3[a]	610.5 mL
	Part 3[a] without PBMC	510.5 mL
	Parts 3 Total Blood Volume up to Day 90	450.5 mL
	Parts 3 Total Blood Volume from Days 90 to 365	160 mL

Parts 1, 2, and 3	Screening	Days -3 to -1	Vaccination Period (Day 1 to Day 270)	Poststudy (Day 365)	Total Collections	mL Per Collection	Total mL/ Test
Total Blood Volume per Male Participants							
	Parts 1 and 2[a]						613.5 mL
	Parts 1 and 2[a] without PBMC						515.5 mL
	Parts 1 and 2 Total Blood Volume up to Day 90						447.5 mL
	Parts 1 and 2 Total Blood Volume from Days 90 to 365						168 mL
	Part 3[a]						598.5 mL
	Part 3[a] without PBMC						498.5 mL
	Parts 3 Total Blood Volume up to Day 90						4438.5 mL
	Parts 3 Total Blood Volume from Days 90 to 365						160 mL
[a] If additional immunogenicity and/or safety analysis is necessary, additional blood (up to 50mL) may be obtained. Note: never to exceed 50 mL							

Amendment 001-03: Blood will be collected through Day 28. Study visits on Days 90, 180, 270, and 365 will not be performed.

10.9 Appendix 9: 12-Lead Electrocardiogram Abnormality Criteria

12-Lead Electrocardiogram Abnormality Criteria		
	Screen Failure Criteria	Potentially Significant Postrandomization Findings (clarification on action to take)
RHYTHM		
Sinus Tachycardia	>110 bpm	HR >110 bpm and HR increase of ≥25 bpm from baseline
Sinus Bradycardia	<40 bpm	HR <40 bpm and HR decrease of ≥5 bpm from baseline
Sinus Pause/Arrest	>2.0 seconds	>2.0 seconds
Atrial Premature Complex	> 1 beat	≥ 3 beats
Ventricular Premature Complex	All	≥ 3 beats
Ectopic Atrial Rhythm	None	None
Junctional Rhythm	Junctional Rhythm with HR <40 bpm	Junctional Rhythm with HR <40 bpm
Idioventricular Rhythm	All	All
Atrial Fibrillation	All	All
Atrial Flutter	All	All
Supraventricular Tachycardia	All	All
Ventricular Tachycardia	All	All
AXIS		
Left Axis Deviation	RBBB With Left Anterior Hemiblock (LAHB)	New Onset LAHB
Right Axis Deviation	RBBB With Left Posterior Hemiblock (LPHB)	New Onset LPHB
CONDUCTION		
1st Degree AV Block	PR ≥230 ms	PR ≥ 230 ms + Increase of >15 ms; or PR Increase of >25%
2nd Degree AV Block	Mobitz Type II	Mobitz Type II
3rd Degree AV Block	All	All
LBBB	All	All
RBBB	RBBB With LAHB/LPHB as Defined Above	New Onset RBBB (Not Including Rate-related)
Incomplete Right BBB (ICRBBB) (QRS <120 ms)	No Exclusion	Nothing
Short PR/ Preexcitation Syndrome	Delta Wave + PR <120 ms	Delta Wave + PR <120 ms
Other Intra-Ventricular Conduction Delay	QRS ≥130 ms	QRS ≥130 ms + Increase of ≥10 ms
QTcF		
Male	QTc ≥470 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline
Female	QTc ≥480 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline
HYPERTROPHY		
Atrial Abnormalities	Definite Evidence of P Mitrale or P Pulmonale	Definite Evidence of P Mitrale or P Pulmonale
Ventricular Abnormalities	Voltage Criteria for LVH Plus Strain Pattern	Voltage Criteria for LVH Plus Strain Pattern

12-Lead Electrocardiogram Abnormality Criteria		
	Screen Failure Criteria	Potentially Significant Postrandomization Findings (clarification on action to take)
MYOCARDIAL INFARCTION		
Acute or Recent	All	All
Old	All	All
ST/T MORPHOLOGY		
ST Elevation Suggestive of Myocardial Injury	In 2 or more contiguous leads	In 2 or more contiguous leads
ST Depression Suggestive of Myocardial Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
T-wave Inversions Suggestive of Myocardial Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
Non-specific ST-T Changes (In 2 or More Leads)	No exclusion	In 2 or more contiguous leads
PACEMAKER	All	All
Baseline is defined as Predose Day 1; ms=milliseconds, mm=millimeter		

10.10 Appendix 10: Algorithm for Assessing Out of Range Laboratory Values

For all laboratory values obtained at screening visit and/or admission day 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 (e.g., 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.

10.11 Appendix 11: Abbreviations

Abbreviation	Expanded Term
ACCP	American College of Chest Physicians
ADA	anti-drug antibodies
ADL	activities of daily living
AE	adverse event
APaT	All-Participants-as-Treated
AR	adverse reaction
ART	anti-retroviral therapy
ATD	accelerated titration design
ATP	adenosine triphosphate
BCG	Bacillus Calmette–Guérin
BDS	blood drug screen
β-hCG	β-human chorionic gonadotropin
BICR	blinded independent central review
BID	twice daily
BMI	body mass index
BP	blood pressure
CAC	Clinical Adjudication Committee
CBER	Center for Biologics Evaluation and Research
CD28	cluster of differentiation 28
CD3ζ	CD3 zeta
CF	compact flash
CG	Cockcroft-Gault
CHS	cough hypersensitivity syndrome
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	clearance
CrCl	creatinine clearance
CR	complete response
CRF	Case Report Form
CRU	clinical research unit
CSD	Cough Severity Diary
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCAE 5.0	Common Terminology Criteria for Adverse Events, Version 5.0
CTFG	Clinical Trial Facilitation Group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DAIDS	Division of AIDS
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
eCTA	exploratory Clinical Trial Application
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data collection
eGFR	estimated glomerular filtration rate

Abbreviation	Expanded Term
ECMO	Extracorporeal membrane oxygenation
ELISA	enzyme-linked immunosorbent assay
ELISPOT	Enzyme-linked immunospot assay
EMA	European Medicines Agency
EOC	Executive Oversight Committee
ePROs	electronic patient-reported outcomes
EQ-5D	EuroQoL-5D
FAS	Full Analysis Set
FBR	Future Biomedical Research
FDAAA	Food and Drug Administration Amendments Act
FEV1	forced expiratory volume in 1 second
FFPE	formalin-fixed, paraffin embedded
FIH	first in human
FSH	follicle stimulating hormone
FVC	forced vital capacity
G	glycooprotein
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
GERD	gastroesophageal reflux disease
GI	gastrointestinal
GLP	Good Laboratory Practice
GM-CSF	Granulocyte Macrophage Colony-Stimulating Factor
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HHC	house-hold contact
HIV	human immunodeficiency virus
HR	heart rate
HRQoL	health-related quality of life
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
iCRO	imaging CRO
ICU	Intensive Care Unit
ID	identification
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG4	immunoglobulin G4
IgV	immunoglobulin-variable
IHC	immunohistochemistry
IMP	Investigational medicinal product
IND	Investigational New Drug
IO	immunooncology
irAEs	immune-related AEs
IRB	Institutional Review Board
iRECIST	Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics
IRT	interactive response technology
ITP	idiopathic thrombocytopenic purpura
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IVD	in vitro diagnostic

Abbreviation	Expanded Term
IVRS	interactive voice response system
IWRS	integrated web response system
KPS	Karnofsky performance status
LAM	lactational amenorrhoea method
LCQ	Leicester Cough Questionnaire
MAAE	Medically-attended adverse event
mAb	monoclonal antibody
MAD	maximum administered dose
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle Eastern Respiratory Syndrome
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability
MTD	maximum tolerated dose
mTPI	modified Toxicity Probability Interval
NCI	National Cancer Institute
NCS	not clinically significant
NEAB	non-eosinophilic bronchitis
NIMP	Non-investigational medicinal product
NHP	non-human primate
NSCLC	non-small cell lung cancer
NDA	New Drug Application
NP	nasopharyngeal
NOAEL	no observed adverse effect level
OR	objective response
ORR	objective response rate
OS	overall survival
OSF	on-site formulation
OTC	over-the-counter
PBMC	peripheral blood mononuclear cells
PBPK	physiologically-based PK
PCR	polymerase chain reaction
PD-1	programmed cell-death 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PET	positron emission tomography
PFS	progression free survival
PGIC	Patient Global Impression Change
PK	pharmacokinetic
PKCθ	protein kinase C-theta
PO	orally
PP	per-protocol
PQC	product quality complaint
PR	partial response
PRNT	plaque reduction neutralization test
PRO	patient-reported outcome
Q2W	every 2 weeks
Q3W	every 3 weeks
QOL	quality of life
QP2	department of quantitative pharmacology and pharmacometrics
RCC	refractory chronic cough

Abbreviation	Expanded Term
rHSA	Recombinant human serum albumin
RNA	ribonucleic acid
rP2D	recommended Phase 2 dose
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS	Severe Acute Respiratory Syndrome
siDMC	Standing Internal Data Monitoring Committee
SIM	Site Imaging Manual
SNA	Serum neutralizing antibody
SoA	schedule of activities
SOP	standard operating procedure
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
TMDD	target-mediated drug disposition
UACS	upper airway cough syndrome
UCC	unexplained chronic cough
UDS	urine drug screen
URTI	upper respiratory tract infection
V	volume of distribution
VAS	Visual Analog Scale
VE	Vaccine efficacy
VS	vital sign
VSV	vesicular stomatitis virus
WBC	white blood cell
WPAI	Work Productivity and Activity Impairment
WOCBP	woman/women of childbearing potential
ZAP70	zeta-chain-associated protein kinase
ZEBOV	Zaire ebolavirus

11 REFERENCES

[Camacho, A., et al 2015]	Camacho A, Carroll MW, Dean NE, Doumbia M, Edmunds WJ, Egger M, et al. The ring vaccination trial: a novel cluster randomised controlled trial design to evaluate vaccine efficacy and effectiveness during outbreaks, with special reference to Ebola. BMJ. 2015 Jul 27;351:h3740.	[05JHRV]
[Centers for Disease Control and Prevention 2015]	Centers for Disease Control and Prevention. Epidemiology and prevention of vaccine-preventable diseases. 13th ed. Hamborsky J, Kroger A, Wolfe S, editors. Washington (DC): Department of Health and Human Services (HHS); c2015. Chapter 6, Vaccine administration; p. 79-106.	[0508PV]
[Clarke, D. K., et al 2016]	Clarke DK, Hendry RM, Singh V, Rose JK, Seligman SJ, Klug B, et al. Live virus vaccines based on a vesicular stomatitis virus (VSV) backbone: Standardized template with key considerations for a risk/benefit assessment. Vaccine. Forthcoming 2016.	[04JHYJ]
[Clopper, C. J. 1934]	Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26(4):404-13.	[03Y75Y]
[Docherty, A. B., et al 2020]	Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, et al. Features of 20133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ. 2020;369:m1985.	[05JQSM]
[Henao-Restrepo, A. M., et al 2015]	Henao-Restrepo AM, Longini IM, Egger M, Dean NE, Edmunds WJ, Camacho A, et al. Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial. Lancet. 2015 Aug 29;386:857-66.	[055B0S]
[Henao-Restrepo, A. M., et al 2017]	Henao-Restrepo AM, Camacho A, Longini IM, Watson CH, Edmunds WJ, Egger M, et al. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ca Suffit!) (including supplement appendix). Lancet. 2017 Feb 4;389(10068):505-18.	[04T4FX]

[Kapadia, S. U., et al 2005]	Kapadia SU, Rose JK, Lamirande E, Vogel L, Subbarao K, Roberts A. Long-term protection from SARS coronavirus infection conferred by a single immunization with an attenuated VSV-based vaccine. Virology. 2005;340:174-82.	[05JHSJ]
[Kapadia, S. U., et al 2008]	Kapadia SU, Simon ID, Rose JK. SARS vaccine based on a replication-defective recombinant vesicular stomatitis virus is more potent than one based on a replication-competent vector. Virology. 2008;376:165-72.	[05JHSK]
[Liu, R., et al 2018]	Liu R, Wang J, Shao Y, Wang X, Zhang H, Shuai L, et al. A recombinant VSV-vectored MERS-CoV vaccine induces neutralizing antibody and T cell responses in rhesus monkeys after single dose immunization. Antiviral Res. 2018;150:30-8.	[05JHSL]
[Marcy, S. M., et al 2004]	Marcy SM, Kohl KS, Dagan R, Nalin D, Blum M, Jones MC, et al. Fever as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. Vaccine 2004;22:551-6.	[03QPWY]
[Miettinen, O. 1985]	Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med. 1985 Apr-Jun;4(2):213-26.	[04J96G]
[Miettinen, O. and Nurminen, M. 1985]	Miettinen O, Nurminen M. Comparative Analysis of Two Rates. Stat Med 1985;4:213-26.	[03QCDT]
[Petrilli, C. M., et al 2020]	Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ. 2020;369:m1966.	[05JQG8]
[Regules, J. A., et al 2017]	Regules JA, Beigel JH, Paolino KM, Voell J, Castellano AR, Hu Z, et al. A recombinant vesicular stomatitis virus ebola vaccine. N Engl J Med. 2017 Jan 26;376(4):330-41. Supplemental material; 16 p.	[05D22Z]