NCT04537208

Immunogenicity and Safety of SARS-CoV-2 Recombinant Protein Vaccine Formulations (with or without adjuvant) in Healthy Adults 18 Years of Age and Older

A Phase I/II, Randomized, double-blind, placebo-controlled, multi-center study evaluating the safety and immunogenicity of SARS-CoV-2 recombinant protein vaccine formulations (with or without adjuvant) in healthy adults aged at least 18 years with a negative SARS-CoV-2 antibody test at time of enrollment conducted in the United States.

Statistical Analysis Plan (SAP) - Core Body Part

Trial Code:	VAT00001
Development Phase:	Phase I/II
Sponsor:	Sanofi Pasteur Inc.
Investigational Product(s):	SARS-CoV2 prefusion Spike delta TM, AF03, AS03
Form / Route:	IM injection
Indication For This Study:	Active immunization for the prevention of SARS-CoV-2 infection or disease
Version and Date of the SAP core body part:	Version 4.0, 18Aug2022

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List of Abbreviations

Ab	antibody
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
BL	blood sample
CDM	Clinical Data Management
CI	confidence interval
CMI	cellular-mediated immune
COVID	coronavirus disease 2019
CSR	clinical study report
D	day
DC	diary card
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme linked immunosorbent assay
ESDR	Early Safety Data Review
FAS	full analysis set
GM	geometric mean
GM-CSF	Granulocyte-macrophage-colony-stimulating Factor
TH1	Helper T cell type 1
TH2	Helper T cell type 2
TH17	Helper T cell type 17
THGM	Granulocyte-macrophage-colony-stimulating Factor-producing T Helper
IL	Interleukin
LLOQ	lower limit of quantification
NAAT	Nucleic Acid Amplification Test
MC	Mononuclear cell
MD	missing data
MedDRA	Medical Dictionary for Regulatory Activities
ULOQ	upper limit of quantification
PP	per-protocol analysis set
PT	preferred term
Q1; Q2; Q3	first quartile; second quartile (median); third quartile
RCDC	reverse cumulative distribution curve
SAE	serious adverse event

SafAS	safety analysis set
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SOC	system organ class (primary)
TC	telephone call
TLF	table(s), listing(s), and figure(s)
TNFα	Tumor Necrosis Factor alpha
V	Visit
VAC	Vaccination
WB	whole blood
WHO	World Health Organization

1 Introduction

An outbreak of severe respiratory illnesses in Wuhan City, Hubei Province, China in December 2019 heralded the appearance of a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in the human population. The rapid escalation of the outbreak led to a declaration by the World Health Organization on 20 January 2020 of a Public Health Emergency of International Concern, followed by declaration on 11 March 2020 of a pandemic (1). As of 22 July 2020, the virus has been detected in 188 countries/regions and infected over 15 million individuals (2).

The clinical profile of COVID-19, the illness caused by SARS-CoV-2, is variable (3). In the majority of cases, the manifestations are mild, or individuals may be asymptomatic. Among those with symptoms, typical presentations include fever, cough, and shortness of breath. More severe manifestations include acute hypoxemic respiratory failure requiring intubation and mechanical ventilation, in some cases resulting in death. Based on early data, adults over 50 years of age and individuals with chronic medical conditions are at a higher risk of severe outcomes and death. At present, no licensed vaccine exists for this strain nor any other coronaviruses.

To address the urgent medical need caused by this outbreak, Sanofi Pasteur is developing a candidate vaccine consisting of a stabilized prefusion trimer of the SARS-CoV-2 Spike (S) protein based on the work by Wrapp et al (4). Sanofi Pasteur will apply the manufacturing technology that is used to produce commercialized recombinant hemagglutinin (HA) vaccine, Flublok®. It is anticipated that the recombinant protein vaccine will require an adjuvant to optimize the immune response and for dose sparing potential. While Sanofi Pasteur's proprietary AF03 adjuvant will be utilized for this vaccine development, it is anticipated that the demand for a protective vaccine will likely exceed the supply capacity for any single adjuvant; thus, a second adjuvant supplied by GlaxoSmithKline, AS03, will also be evaluated.

The current first-in-human study will evaluate the immunogenicity and safety of the candidate vaccine with the goal of selecting a formulation, and an injection schedule to proceed to efficacy evaluation as rapidly as possible.

2 Trial Objectives

2.1 Primary Objectives

Immunogenicity

To describe the neutralizing antibody profile at D01, D22, and D36 of each study intervention group.

Safety

To describe the safety profile of all participants in each age group and each study intervention group up to 12 months post-last dose.

2.2 Secondary Objectives

Immunogenicity

1. To describe binding antibody profile at D01, D22, D36, D181 (Cohort 1) or D202 (Cohort 2), and D366 (Cohort 1) or D387 (Cohort 2) of each study intervention group
2. To describe the neutralizing antibody profile at D181 (Cohort 1) or D202 (Cohort 2) and at D366 (Cohort 1) or D387 (Cohort 2) of each study intervention group.

Efficacy

1. To describe the occurrence of virologically-confirmed COVID-19-like illness and serologically confirmed SARS-CoV-2 infection.
2. To evaluate the correlation / association between antibody responses to SARS-CoV-2 Recombinant Protein and the risk of virologically-confirmed COVID-19-like illness and/or serologically confirmed SARS-CoV-2 infection.

2.3 Exploratory Objectives

Immunogenicity

1. To describe cellular immune response profile at D01, D22, and D36 for each study intervention group in a subset of Cohort 2.
2. To describe the ratio between neutralizing antibodies and binding antibodies.

2.4 Other Objective

To evaluate other emerging biomarkers as effect modifiers or as correlates of risk / protection.

3 Description of the Overall Trial Design and Plan

3.1 Trial Design

This is a Phase I/II, randomized, modified double -blind (observer-blind), first-in-human, parallel group, placebo-controlled, dose ranging, multi-center study with a Sentinel Safety Cohort and Early Safety Data Review (ESDR) to evaluate the safety and immunogenicity profile of a COVID-19 vaccine in the population of healthy seronegative adults 18 years or older in the US. Enrollment will be stratified by age: 300 participants18-49 years of age and 140 participant aged 50 years or older. All 440 participants will be randomized to receive either 1 injection (Cohort 1) or 2 injections (Cohort 2) of the study intervention.

As a precautionary step, a Sentinel Safety Cohort of 6 participants (younger adults only) within each dosing group from Cohort 1 will be enrolled. Upon demonstration of acceptable safety demonstrated from unblinded data review by limited members of the Sponsor Study Team (Responsible Medical Officer, Biostatistician and Programmer, Pharmacovigilance Science

Expert, and Global Safety Officer), the remaining participants in Cohort 1 and all participants in Cohort 2 will be enrolled.

Participants aged 18-49 years:

will be randomized to 6 groups to receive Antigen Formulation 1 (low-dose [5 µg]) with either AF03 or AS03 adjuvant; Formulation 2 (high-dose [15 µg]) with either AF03, AS03, or no adjuvant; or placebo (Note: unadjuvanted arm included in Cohort 2 only)

N = 20 participants in each group, except for AS03-adjuvanted groups in Cohort 2 with 60 participants in each group

Participants aged ≥ 50 years:

will be randomized to 5 groups to receive Antigen Formulation 1 (low-dose [5 µg]) or Formulation 2 (high-dose [15 µg]) each with either AF03 or AS03; or placebo

N = 10 participants in each group, except for AS03-adjuvanted groups in Cohort 2 with 30 participants in each group

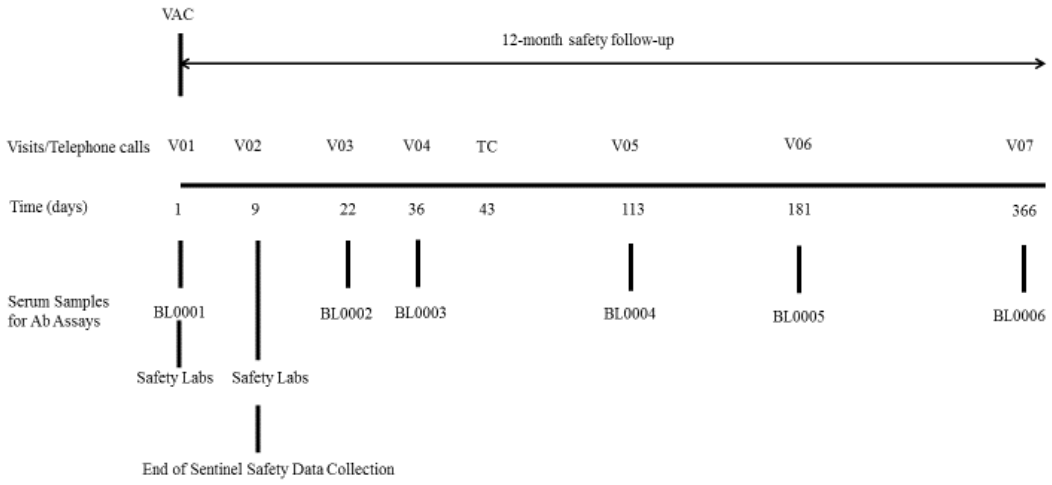
A subset of 87 participants in Cohort 2 (60 participants 18-49 years of age [18 per group in AS03-adjuvanted vaccines; 6 per group in all other study groups]) and 27 participants ≥ 50 years of age [9 per group in AS03-adjuvanted groups; 3 per group in all other study groups, with the exception of the unadjuvanted group for which there will be no older adults]), will be randomly assigned to a cellular-mediated immune (CMI) subset

All participants will receive 1 injection of either one of the investigational study vaccine formulations or the placebo control at Day (D)01 (Vaccination [VAC] 1). Participants in Cohort 2 will receive a second injection of study vaccine formulation or placebo at D22 (VAC2). Participants are planned to be followed approximately 365 days post-last dose

3.2 Trial Plan

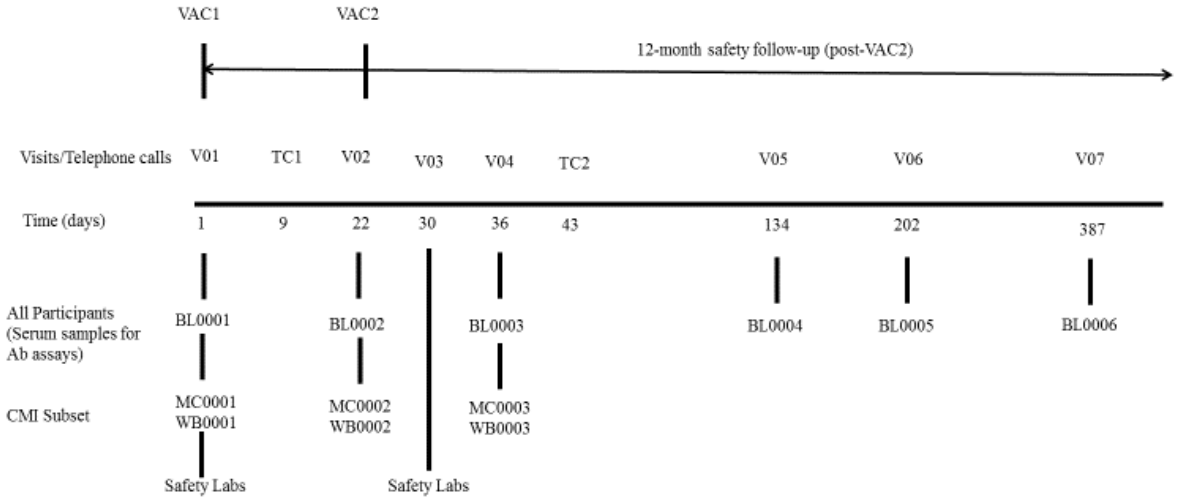
The graphical design of VAT00001 study is as presented in Figure 3.1 (Cohort 1) and Figure 3.2 (Cohort 2).

Figure 3.1: Graphical study design (Cohort 1)



Ab, antibody; BL, blood sample; TC, telephone call; V, visit; VAC, vaccination

Figure 3.2: Graphical study design (Cohort 2)



Ab, antibody; BL, blood sample; CMI, cellular-mediated immunity; MC, mononuclear cell; TC, telephone call; V, visit; VAC, vaccination; WB, whole blood

Study vaccines will be administered on the following schedules as presented in Table 3.1 to Table 3.3:

Table 3.1: Schedule of activities 1 (Cohort 1)

Phase I/II Study, 7 Visits, 1 Telephone Call, 1 Injection, 6 Blood Sample Time-points, Approximately 12 Months' Duration Per Participant

Visit (V) / Contact	*Collection of information in the CRF*	**V01**	**V02**	**V03**	**V04**	**Telephone Call**	**V05**	**V06**	**V07 or Safety Follow-up Call§§§§**
Study timelines (Day [D])		D01	D09	D22	D36	D43	D113	D181	D366
Time Interval (days)			V01 + 8 days	V01 + 21 days	V01 + 35 days	V01 + 42 days	V01 +112 days	V01 + 180 days	V01 + 365 days
Time windows (days)		N/A	[+2 days]	[+7 days]	[+7 days]	[+2 days]	[+7 days]	[+14 days]	[+14 days]
Visit procedures:									
Informed consent	X	X							
Point-of-care SARS-CoV-2 antibody test		X							
Inclusion/exclusion criteria	X	X							
Collection of demographic data	X	X							
Collection of medical history	X Significant Medical History	X							
Physical examination*		X							
Pre-vaccination temperature		X							
Urine pregnancy test (if applicable) †		X							
Contact IRT system for randomization, participant number, and unique dose number allocation.	X	X							
Respiratory sample collection		Can occur at any time during the study as unscheduled visit(s)							

Visit (V) / Contact	*Collection of information in the CRF*	**V01**	**V02**	**V03**	**V04**	**Telephone Call**	**V05**	**V06**	**V07 or Safety Follow-up Call§§§§**
Study timelines (Day [D])		D01	D09	D22	D36	D43	D113	D181	D366
Time Interval (days)			V01 + 8 days	V01 + 21 days	V01 + 35 days	V01 + 42 days	V01 +112 days	V01 + 180 days	V01 + 365 days
Time windows (days)		N/A	[+2 days]	[+7 days]	[+7 days]	[+2 days]	[+7 days]	[+14 days]	[+14 days]
Visit procedures:									
Clinical safety laboratory assessments ‡ (10 mL) *(All participants)*	X	X§	X						
Serum samples for Ab assays (30 mL) *(All participants)*	X	BL0001§		BL0002	BL0003		BL0004	BL0005	BL0006
Vaccination (VAC)	X	X							
Immediate surveillance (30 minutes)	X	X							
Diary Card provided		DC1**		DC2§§	DC3***		DC4†††	DC5‡‡‡	
Diary Card reviewed			DC1††			DC3††			
Diary Card collected				DC1‡‡	DC2‡‡		DC3‡‡	DC4‡‡	DC5‡‡
Collection of solicited injection site & systemic reactions	X	D01-D08							
Collection of unsolicited AEs	X	D01-D22							
Collection of concomitant medications	X Reportable concomitant medication	All reportable concomitant medications (including influenza vaccination)			Influenza and COVID-19 vaccinations only				
Telephone call	X					X‡‡‡‡			X§§§§
Passive surveillance	X		Participants will be instructed to contact the site if they experience symptoms of a COVID-19-like illness at any time during the study.						

Visit (V) / Contact	*Collection of information in the CRF*	**V01**	**V02**	**V03**	**V04**	**Telephone Call**	**V05**	**V06**	**V07 or Safety Follow-up Call§§§§**
Study timelines (Day [D])		D01	D09	D22	D36	D43	D113	D181	D366
Time Interval (days)			V01 + 8 days	V01 + 21 days	V01 + 35 days	V01 + 42 days	V01 +112 days	V01 + 180 days	V01 + 365 days
Time windows (days)		N/A	[+2 days]	[+7 days]	[+7 days]	[+2 days]	[+7 days]	[+14 days]	[+14 days]
Visit procedures:									
Active surveillance calls	X					TC to occur every 2 weeks after the D43 contact until D181§§§ (See also Schedule of Activities Table 3.3 for follow-up)			
Collection of SAEs, AESIs ****, and MAAEs	X	To be reported at any time during the study							
Collection of pregnancies	X								
End of phase participation record††††	X					X	X	X	
End of active phase participation record	X								X
12 Month Follow-up participation record (only for those discontinued early) §§§§	X								X

Abbreviations: Ab, Antibody; AE, adverse event; AESI, adverse event of special interest; BL, blood sample (#); CRF, Case Report Form; DC, Diary Card; IRT, interactive response technology; MAAE, medically attended adverse event; S, Spike; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; V, visit; VAC, vaccination

*Targeted physical examination based on the participant's medical history and the examiner's medical judgment will be performed at V01.

† Urine pregnancy test is applicable to childbearing potential female participant (to be considered of non-childbearing potential, a female must be post-menopausal for at least 1 year or surgically sterile). Urine pregnancy test is to be performed before vaccination.

‡ Safety laboratory assessments will include: Serum Chemistries (liver enzymes / Chem 7, lipase, and amylase); hematology (complete blood count with differential); Urinalysis; Microscopy. In cases of abnormal safety laboratory results, unscheduled visits may occur, based on Investigator's judgment.

§ BL0001 and the first safety laboratory assessment sample will be collected at pre-vaccination (baseline).

Visit (V) / Contact	*Collection of information in the CRF*	**V01**	**V02**	**V03**	**V04**	**Telephone Call**	**V05**	**V06**	**V07 or Safety Follow-up Call§§§§**
Study timelines (Day [D])		D01	D09	D22	D36	D43	D113	D181	D366
Time Interval (days)			V01 + 8 days	V01 + 21 days	V01 + 35 days	V01 + 42 days	V01 +112 days	V01 + 180 days	V01 + 365 days
Time windows (days)		N/A	[+2 days]	[+7 days]	[+7 days]	[+2 days]	[+7 days]	[+14 days]	[+14 days]
Visit procedures:									

** Participants will use this DC1 to record information about solicited reactions, unsolicited AEs, SAEs, and AESIs from D01 to D08 after vaccination and will continue to record information about unsolicited AEs, SAEs, and AESIs from D09 to V03.

†† The Investigator or an authorized designee will remind the participants to bring back the DC at the next visit and will answer any questions.

‡‡ The Investigator or an authorized designee will interview the participants to collect the information recorded in the DC and will attempt to clarify anything that is incomplete or unclear.

§§ Participants will use this DC2 for SAEs, AESIs, and COVID-19-like illness follow-up from V03 to V04.

*** Participants will use this DC3 for SAEs, AESIs, and COVID-19-like illness follow-up from V04 to V05.

††† Participants will use this DC4 for SAEs, AESIs, and COVID-19-like illness follow-up from V05 to V06.

‡‡‡ Participants will use this DC5 for SAEs, AESIs, and COVID-19-like illness follow-up from V06 to V07.

§§§ Prior to these specified time-points, active surveillance will still occur during the established contacts (phone calls and visits).

**** AESIs (serious and non-serious) will be collected throughout the study as SAEs to ensure that events are communicated to the Sponsor in an expedited manner and followed-up until the end of the follow-up period or resolution, as per the assigned causal relationship. These include: Anaphylactic reactions, Generalized convulsion, Thrombocytopenia, Lacrimal and salivary disorders (tearing, dry mouth, dry eyes), any new-onset chronic medical conditions, and potential immune-mediated diseases.

†††† In case of participant discontinuation at a visit, the entire visit will be completed

‡‡‡‡ During the D43 telephone call, staff will review the DC3 pertaining to SAE, AESI, and COVID-19-like illness between V04 and the call and will remind the participant to bring back the DC3 for V05. This telephone call will NOT be collected in the CRF.

§§§§ All participants will be scheduled to attend V07 for blood sampling and 12-Month Safety Follow-up. However, if any participants discontinue the study early, they are still to be followed for safety and are to be contacted with a 12-Month Safety Follow-up call to identify the occurrence of any SAEs and AESIs that had not yet been reported. If discontinuation occurs at a scheduled visit, the participant will be provided a Memory Aid instead of a DC for SAE follow-up (including AESIs) until the 12-Month

Visit (V) / Contact	*Collection of information in the CRF*	**V01**	**V02**	**V03**	**V04**	**Telephone Call**	**V05**	**V06**	**V07 or Safety Follow-up Call§§§§**
Study timelines (Day [D])		D01	D09	D22	D36	D43	D113	D181	D366
Time Interval (days)			V01 + 8 days	V01 + 21 days	V01 + 35 days	V01 + 42 days	V01 +112 days	V01 + 180 days	V01 + 365 days
Time windows (days)		N/A	[+2 days]	[+7 days]	[+7 days]	[+2 days]	[+7 days]	[+14 days]	[+14 days]
Visit procedures:									

Safety Follow-up call. If a participant discontinues between visits (with no Memory Aid provided yet), the participant will use the last DC received to collect information for the 12-Month Safety Follow-up call.

Table 3.2: Schedule of activities 2 (Cohort 2)

Phase I/II Study, 7 Visits, 2 Telephone Calls, 2 Injections, 6 Blood Sample Time-points, Approximately 13 Months' Duration Per Participant

Visit (V) / Contact	*Collection of information in the CRF*	**V01**	**Telephone Call 1**	**V02**	**V03**	**V04**	**Telephone Call 2**	**V05**	**V06**	**V07 or Safety Follow-up Call*****
Study timelines (Day [D])		D01	D09	D22	D30	D36	D43	D134	D202	D387
Time Interval (days)			V01 + 8 days	V01 + 21 days	V02 + 8 days	V02 + 14 days	V02 + 21 days	V02 + 112 days	V02 + 180 days	V02 + 365 days
Time windows (days)		N/A	[+2 days]	[+7 days]	[+2 days]	[+7 days]	[+2 days]	[+7 days]	[+14 days]	[+14 days]
Visit procedures:										
Informed consent	X	X								
Point-of-care SARS-CoV-2 antibody test		X								
Inclusion/exclusion criteria	X	X								
Collection of demographic data	X	X								
Collection of medical history	X Significant Medical History	X								
Physical examination*		X								
Pre-vaccination temperature		X		X						
Urine pregnancy test (if applicable) †		X		X						
Contact IRT system for randomization, participant number, and unique dose number allocation.	X	X								
Contact IRT system for unique dose number allocation.	X			X						

Visit (V) / Contact	*Collection of information in the CRF*	**V01**	**Telephone Call 1**	**V02**	**V03**	**V04**	**Telephone Call 2**	**V05**	**V06**	**V07 or Safety Follow-up Call*****
Study timelines (Day [D])		D01	D09	D22	D30	D36	D43	D134	D202	D387
Time Interval (days)			V01 + 8 days	V01 + 21 days	V02 + 8 days	V02 + 14 days	V02 + 21 days	V02 + 112 days	V02 + 180 days	V02 + 365 days
Time windows (days)		N/A	[+2 days]	[+7 days]	[+2 days]	[+7 days]	[+2 days]	[+7 days]	[+14 days]	[+14 days]
Visit procedures:										
Temporary and definitive contraindications	X			X						
Respiratory sample collection		Can occur at any time during the study as unscheduled visit(s)								
Clinical safety laboratory assessments ‡ (10 mL) *(All participants)*	X	X§			X					
Serum samples for Ab assays (30 mL) *(All participants)*	X	BL0001§		BL0002§		BL0003		BL0004	BL0005	BL0006
Cellular-mediated Immunity (40 mL) *(Subset of 87 participants in Cohort 2)*	X	MC0001§		MC0002§		MC0003				
TruCulture (4 mL) *(Subset of 87 participants in Cohort 2)*	X	WB0001§		WB0002§		WB0003				
Vaccination (VAC)	X	X		X						
Immediate surveillance (30 minutes)	X	X		X						
Diary Card provided		DC1**		DC2§§		DC3***		DC4†††	DC5‡‡‡	
Diary Card reviewed			DC1††		DC2††		DC3††			
Diary Card collected				DC1‡‡		DC2‡‡		DC3‡‡	DC4‡‡	DC5‡‡

Visit (V) / Contact	*Collection of information in the CRF*	**V01**	**Telephone Call 1**	**V02**	**V03**	**V04**	**Telephone Call 2**	**V05**	**V06**	**V07 or Safety Follow-up Call*****
Study timelines (Day [D])		D01	D09	D22	D30	D36	D43	D134	D202	D387
Time Interval (days)			V01 + 8 days	V01 + 21 days	V02 + 8 days	V02 + 14 days	V02 + 21 days	V02 + 112 days	V02 + 180 days	V02 + 365 days
Time windows (days)		N/A	[+2 days]	[+7 days]	[+2 days]	[+7 days]	[+2 days]	[+7 days]	[+14 days]	[+14 days]
Visit procedures:										
Collection of solicited injection site & systemic reactions	X	D01-D08 *(up to 7 days post-VAC1)*		D01-D08 *(up to 7 days post-VAC2)*						
Collection of unsolicited AEs	X	D01-D22 *(up to 21 days post-VAC1)*								
				D01-D22 *(up to 21 days post-VAC2)*						
Collection of concomitant medications	X Reportable concomitant medication	All reportable concomitant medications (including influenza vaccination)						Influenza and COVID-19 vaccinations only		
Telephone call	X		X§§§				X§§§§			X*****
Passive surveillance	X	Participants will be instructed to contact the site if they experience symptoms of a COVID-19-like illness at any time during the study.								
Active surveillance calls	X						TC to occur every 2 weeks after the D43 contact until D202**** (See also Schedule of Activities Table 3.3 for follow-up)			
Collection of SAEs, AESIs††††, and MAAEs	X	To be reported at any time during the study								

Visit (V) / Contact	*Collection of information in the CRF*	**V01**	**Telephone Call 1**	**V02**	**V03**	**V04**	**Telephone Call 2**	**V05**	**V06**	**V07 or Safety Follow-up Call*****
Study timelines (Day [D])		D01	D09	D22	D30	D36	D43	D134	D202	D387
Time Interval (days)			V01 + 8 days	V01 + 21 days	V02 + 8 days	V02 + 14 days	V02 + 21 days	V02 + 112 days	V02 + 180 days	V02 + 365 days
Time windows (days)		N/A	[+2 days]	[+7 days]	[+2 days]	[+7 days]	[+2 days]	[+7 days]	[+14 days]	[+14 days]
Visit procedures:										
Collection of pregnancies	X									
End of phase participation record‡‡‡‡	X						X	X	X	
End of active phase participation record	X									X
12 Month Post-VAC2 Follow-up participation record (only for those discontinued early) *****	X									X

Abbreviations: Ab, Antibody; AE, adverse event; AESI, adverse event of special interest; BL, blood sample (#); CRF, Case Report Form; DC, Diary Card; IRT, interactive response technology; MAAE, medically attended adverse event; MC, mononuclear cell; S, Spike; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; V, visit; VAC, Vaccination; WB, whole blood

*Targeted physical examination based on the participant's medical history and the examiner's medical judgment will be performed at V01.

† Urine pregnancy test is applicable to childbearing potential female participant (to be considered of non-childbearing potential, a female must be post-menopausal for at least 1 year or surgically sterile). Urine pregnancy test is to be performed before vaccination.

‡ Safety laboratory assessments will include: Serum Chemistries (liver enzymes / Chem 7, lipase, and amylase); hematology (complete blood count with differential); Urinalysis; Microscopy. In cases of abnormal safety laboratory results, unscheduled visits may occur, based on Investigator's judgment.

§ BL0001, MC0001, WB0001 and the first safety laboratory assessment sample will be collected at pre-VAC1 (baseline); and BL0002, MC0002, and WB0002 samples will be collected at pre-VAC2.

** Participants will use this DC1 to record information about solicited reactions, unsolicited AEs, SAEs, and AESIs from D01 to D08 after vaccination and will continue to record information about unsolicited AEs, SAEs, and AESIs from D09 to V02.

†† The Investigator or an authorized designee will remind the participants to bring back the DC at the next visit and will answer any questions.

‡‡ The Investigator or an authorized designee will interview the participants to collect the information recorded in the DC and will attempt to clarify anything that is incomplete or unclear.

§§ Participants will use this DC2 to record solicited reactions, unsolicited AEs, SAEs, and AESIs (from V02 to V03) and will continue to collect unsolicited AEs, SAEs, and AESIs (from V03 to V04).

*** Participants will use this DC3 for unsolicited AEs follow-up until D43 and SAEs, AESIs, and COVID-19-like illness follow-up from V04 to V05.

††† Participants will use this DC4 for SAEs, AESIs, and COVID-19-like illness follow-up from V05 to V06.

‡‡‡ Participants will use this DC5 for SAEs, AESIs, and COVID-19-like illness follow-up from V06 to V07.

§§§ During the D09 telephone call, staff will review the DC1 for solicited reactions from D01 to D08 after vaccination, inquire whether the participant experiences any SAE or AESI not yet reported, and remind the participant to bring back DC1 for V02. This telephone call will NOT be documented in the CRF.

**** Prior to these specified time-points, active surveillance will still occur during the established contacts (phone calls and visits).

†††† AESIs (serious and non-serious) will be collected throughout the study as SAEs to ensure that events are communicated to the Sponsor in an expedited manner and followed-up until the end of the follow-up period or resolution, as per the assigned causal relationship. These include: Anaphylactic reactions, Generalized convulsion, Thrombocytopenia, Lacrimal and salivary disorders (tearing, dry mouth, dry eyes), any new-onset chronic medical conditions, and potential immune-mediated diseases.

‡‡‡‡ In case of participant discontinuation at a visit, the entire visit will be completed.

§§§§ During the D43 telephone call, staff will review the DC3 pertaining to unsolicited AEs, SAE, AESI, and COVID-19-like illness between V04 and the call and will remind the participant to bring back the DC3 for V05. This telephone call will NOT be documented in the CRF.

***** All participants will be scheduled to attend V07 for blood sampling and 12-Month (post-VAC2) Safety Follow-up. However, if any participants discontinue the study early, they are still to be followed for safety and are to be contacted with a Safety Follow-up call to identify the occurrence of any SAEs and AESIs that had not yet been reported. If discontinuation occurs at a scheduled visit, the participant will be provided a Memory Aid instead of a DC for SAE follow-up (including AESIs) until the Safety Follow-up call. If a participant discontinues between visits (with no Memory Aid provided yet), the participant will use the last DC received to collect information for the Safety Follow-up call.

Table 3.3: Schedule of activities 3: Follow-up of COVID-19-like illness

Contact Type	Initial Telephone Call*	Visit	Follow-up Telephone Call†
Verify information on COVID-19-like illnesses and schedule appointment for collection of respiratory sample as soon as possible after illness start date‡	X		
Remind participant to complete Memory Aid or Diary Card	X		
Collection of respiratory sample		NPXXXX§	
Collection of disease burden and health care information	X	X	X
Collection of treatments received during COVID-19-like illness	X	X	X
Collection of information on respiratory illness symptoms	X	X	X

* Initial illness identification phone call

† Follow-up telephone call approximately 30 days after illness

‡ Start of first clinical manifestation of COVID-19-like illness

§ "X" indicates that the nasopharyngeal swab number will be unique to each site. Further details are provided in the Operating Guidelines.

4 Endpoints and Assessment Methods

4.1 Primary Endpoints and Assessment Methods

See Table 3.1 of the protocol for endpoints. For Assessments methods, see protocol Section 8.2.1.1 for primary immunogenicity; and see protocol Section 8.4 for primary safety.

4.2 Secondary Endpoints and Assessment Methods

See Table 3.1 of the protocol for endpoints. For Assessments methods, see protocol Section 8.2.1.1 and Section 8.2.1.2 for secondary immunogenicity; And see protocol Section 8.2.2 for secondary efficacy;

4.3 Exploratory Endpoints and Assessment Methods

See Table 3.1 of the protocol for endpoints. For Assessments methods, see protocol Section 8.2.1.2 for exploratory immunogenicity and 8.2.1.3 for cellular-mediated immunity.

4.4 Derived Endpoints: Calculation Methods

4.4.1 Safety

The safety analysis will include all events or reactions with time of onset before the date of receiving a non-study authorized/approved COVID-19 vaccine and will include only the corresponding safety data collected before the date of receiving a non-study authorized/approved COVID-19 vaccine. The endpoints derivations for safety analysis are detailed in the following sections. Events or reactions with time of onset on or after the date of receiving a non-study authorized/approved COVID-19 vaccine will be listed separately.

4.4.1.1 Solicited Reactions

4.4.1.1.1 Daily Intensity

All daily records for solicited reactions will be derived into daily intensity according to the following classification: None, Grade 1, Grade 2, Grade 3, or Missing.

For measurable injection site reactions:

- None: > 0 to < 25 mm
- Grade 1: ≥ 25 to ≤ 50 mm
- Grade 2: ≥ 51 to ≤ 100 mm
- Grade 3: > 100 mm

For Fever:

- None: < 38.0°C or <100.4°F
- Grade 1: ≥ 38.0°C to ≤ 38.4°C or ≥100.4°F to ≤ 101.1°F
- Grade 2: ≥ 38.5°C to ≤ 38.9°C or ≥ 101.2°F to ≤ 102.0°F
- Grade 3: ≥ 39.0°C or ≥ 102.1°F

For the derivation of daily intensities, the following sequential steps will be applied:

1) Solicited reactions (except fever/pyrexia) with an Investigator presence recorded as “No” and with all daily records missing then all daily intensities will be derived as None.
2) For non-measurable solicited reactions, daily intensities will correspond to daily records reported in the clinical database. For measurable solicited reactions the daily measurements reported in the clinical database will be converted based upon the intensity scales defined in the protocol; this assumes a reaction that is too large to measure (non-measurable, “NM”) is Grade 3. Note the intensity could be considered “None” (not a reaction) in the analysis despite being considered a reaction by the investigator (e.g., swelling measurement > 0 mm but < 25 mm in adults).

Note: The maximum intensity on the ongoing period is derived from the record of the maximum intensity/measurement after the end of the solicited period following the rule described above.

4.4.1.1.2 Maximum Intensity

Maximum intensity is derived from the daily intensities computed as described in Section 4.4.1.1.1 and is calculated as the maximum of the daily intensities over the period considered.

Note: The maximum intensity could be considered "None" (not a reaction) in the analysis despite being considered a reaction by the investigator (e.g., swelling measurement > 0 mm but < 25 mm in adults).

For those participants receiving a non-study authorized/approved COVID-19 vaccine (e.g., on Day X) within the solicited collection period, the maximum intensity of solicited reactions in safety analysis is derived on daily intensities from D01 to Day X-1.

4.4.1.1.3 Presence

Presence is derived from the maximum overall intensity on the period considered:

- None: No presence
- Grade 1, Grade 2, or Grade 3: Presence
- Missing: Missing presence

Subjects with at least one non-missing presence for a specific endpoint will be included in the analysis. Conversely, those without a non-missing presence will not be included in the analysis of the endpoint.

4.4.1.1.4 Time of Onset

Time of onset is derived from the daily intensities computed as described in Section 4.4.1.1.1. It corresponds to the first day with intensity of Grade 1, Grade 2, or Grade 3.

Note: If a reaction is not continuous (i.e., reaction occurs over two separate periods of time intervened by at least one daily intensity Missing or None) then the time of onset is the first day of the first occurrence.

Table 4.1: Categories for time of onset

Injection Site and Systemic Reactions (D01-D08)
D01-D04
D05-D08

4.4.1.1.5 Number of Days of Occurrence

Number of days of occurrence over the period considered is derived from the daily intensities computed as described in Section 4.4.1.1.1. It corresponds to the number of days with daily

intensities of Grade 1, Grade 2, or Grade 3. But if a reaction is ongoing at the time of receiving an authorized/approved COVID-19 vaccine, the daily intensities on or after that day will not be considered. Number of days of occurrence on the solicited period with a specified intensity may also be derived.

The number of days of occurrence for safety analysis will treat the date of receiving non-study authorized/approved COVID-19 vaccine as the censored date and only daily intensities that occurred before the vaccination date will be analyzed.

Table 4.2: Categories for number of days of occurrence during the solicited period

Injection Site Reactions (D01-D08)	Systemic Reactions (D01-D08)
1-3 days	1-3 days
4-7 days	4-7 days
8 days	8 days

4.4.1.1.6 Overall Number of Days of Occurrence

If a reaction is ongoing at the end of the solicited period, then the overall number of days of occurrence is derived from the daily intensities and the stop date of the reaction after the end of the solicited period. The overall number of days of occurrence is:

- (stop date – last vaccination date) + (number of days of occurrence within the solicited period) – length of the solicited period + 1

If the stop date is missing or incomplete (contains missing data [MD]), the overall number of days of occurrence will be considered as Missing. If a participant received a non-study authorized/approved COVID-19 vaccine within the solicited period and the solicited reaction is ongoing at the time of the receipt of the authorized/approved COVID-19 vaccine, the overall number of days of occurrence will be analyzed as Missing for main safety analysis.

Table 4.3: Categories for overall number of days of occurrence

Injection Site Reactions (D01-D08)	Systemic Reactions (D01-D08)
1-3 days	1-3 days
4-7 days	4-7 days
8 days or more	8 days or more
Missing	Missing

4.4.1.1.7 Ongoing

Ongoing is derived from the last daily intensity of the solicited period computed as described in Section 4.4.1.1.1 and the maximum intensity in the ongoing period. The Investigator's ongoing flag is not used because the measurement would determine the ongoing status of the reaction.

- Ongoing: if the last daily intensity of the solicited period is at least Grade 1 and the maximum intensity on the ongoing period is at least Grade 1
- Not ongoing: if the last daily intensity of the solicited period is None or the maximum intensity on the ongoing period is None.
- Missing: all other conditions (in this case, it is not included in the denominator of the ongoing analysis in the safety tables).

If a participant received a non-study authorized/approved COVID-19 vaccine within the solicited period, the ongoing status will be derived as "Missing".

4.4.1.2 Unsolicited AEs

Unsolicited AEs include non-serious unsolicited AEs and SAEs.

4.4.1.2.1 Occurrence

An observation was considered an event if it had at least a verbatim term and was not a Grade 0 intensity event.

Grade 0 events should be included in a separate listing "Unsolicited AEs not included in the safety analysis".

4.4.1.2.2 Intensity

Intensity for unsolicited AE will be derived according to the following classification: None, Grade 1, Grade 2, Grade 3, or Missing.

If the unsolicited AE is measurable and its preferred term is part of the list of solicited reactions, then the measurement is derived based upon and following the same rule of the intensity scales defined in the protocol for that measurable injection site or systemic reaction.

Note the intensity could be considered "None" (not a reaction) in the analysis despite being considered a reaction by the investigator (e.g., swelling measurement > 0 mm but < 25 mm in adults).

Intensity for the other unsolicited AEs will correspond to the value reported in the eCRF.

The maximum intensity corresponds to the highest intensity for a unique term.

For those participants receiving a non-study authorized/approved COVID-19 vaccine (e.g., on Day X), the maximum intensity of an unsolicited AE is analyzed as following:

- If an unsolicited AE with both time of onset and stop date before Day X, then the maximum

intensity for that AE will be analyzed as collected in CRF.

- If an unsolicited AE with time of onset before Day X and the corresponding stop date is on or after Day X, then the maximum intensity for that AE will be analyzed as Missing.

4.4.1.2.3 Last Vaccination

The last vaccination before an unsolicited AE is derived from the start date of the unsolicited AE provided in the clinical database and is calculated as follows:

- If an unsolicited AE has a complete start date and different to any of the vaccination dates, the start date is used to determine the last vaccination before the unsolicited AE.
- If the start date is missing or partially missing, or equal to any vaccination date, then the visit number in the "Appeared after Visit" or similar field, is used to determine the last vaccination before the unsolicited AE.

4.4.1.2.4 Time of Onset

Time of onset is derived from the start date of the unsolicited AE provided in the clinical database and the date of last vaccination as described in Section 4.4.1.2.2:

Time of Onset = start date of the unsolicited AE – date of last vaccination before the unsolicited AE + 1

The time of onset should be considered as missing only if one or both of the dates are missing or partially missing.

The unsolicited AEs will be analyzed "Within 21 days", which corresponds to AEs with a time of onset between 1 and 22 days or missing.

An AE with missing time of onset will be considered to have occurred just after the vaccination indicated by the visit number in "Appeared after visit" or similar filed, so will be included in these tables.

Time of onset will be displayed as follows:

- D01-D04
- D05-D08
- D09-D15
- D16 or later
- Missing

Note: To further clarify the analysis:

- Any unsolicited AEs reported up to the entire study period (SAEs, MAAEs, AESIs) with time of onset > 22 days after each injection will not be presented in tables of unsolicited AEs within 21 days but only in tables of SAEs, MAAEs, AESIs and NOCMCs.

- Any unsolicited AEs reported up to 21 days with time of onset between 1 and 22 days or missing after each injection will be presented in the tables of unsolicited AEs within 21 days.
- Any unsolicited AEs reported up to 21 days with time of onset > 22 days after each injection will not be presented in any tables but listed separately.
- Any unsolicited AEs with null (0) or negative time of onset will be excluded from the above tables and listed separately

Safety analysis will include only those unsolicited AEs with time of onset before a participant received a non-study authorized/approved COVID-19 vaccine if applicable. Events with time of onset on or after the date of receiving a non-study authorized/approved COVID-19 vaccine will be listed separately.

4.4.1.2.5 Duration

Duration is derived from the start and end dates of the unsolicited AE:

Duration = stop date of unsolicited AE - start date of unsolicited AE + 1.

The duration should be considered as missing only if one or both of the start and end dates of the unsolicited AE is missing or partially missing.

For those participants receiving a non-study authorized/approved COVID-19 vaccine (e.g., on Day X), the duration is categorized as following:

- If an unsolicited AE with both time of onset and stop date before Day X, then the duration for that AE will be derived same as above.
- If an unsolicited AE with time of onset before Day X and the corresponding stop date is on or after Day X, then the duration will be derived as Missing.

Duration will be displayed by period as following:

- 1-3 days
- 4-7 days
- 8 days or more
- Missing

4.4.1.2.6 Serious Adverse Event (SAE)

SAEs will be analyzed throughout the study using the following periods:

- During post-Dose 1 period (i.e., between injection 1 and injection 2), and during 21 days after the last injection
- During the 6-month follow-up period
- During the 12-month follow-up period

- During the study (i.e., all SAEs occurred during the study)

Additionally, a table will present all SAEs during the study in order to count all SAE collected.

Note: SAE that occurred before vaccination (negative time of onset) will not be included in analysis, but will be listed separately.

Safety analysis will include only those SAEs with time of onset before a participant received a non-study authorized/approved COVID-19 vaccine, if applicable. SAEs with time of onset on or after the date of receiving a non-study authorized/approved COVID-19 vaccine will be listed separately.

4.4.1.3 Laboratory test Results

Biological safety tests (biochemistry and hematology) will be performed at local laboratory. Biological endpoints will be assessed on samples taken at screening, V01, V02 (Cohort 1), V03 (Cohort 2), and unscheduled visits based on investigator's judgment, in cases of abnormal safety laboratory results.

The parameters to be evaluated will include serum chemistries (blood urea nitrogen (BUN), potassium, Aspartate Aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT), total and direct bilirubin, creatinine, sodium, alanine aminotransferase (ALT)/ serum glutamic-pyruvic transaminase (SGPT), total protein, glucose (nonfasting), alkaline phosphatase, lipase, amylase; hematology (platelet count, hemoglobin, hematocrit, white blood cell (WBC) count with differential, neutrophils, lymphocytes, monocytes, eosinophils, basophils); and Urinalysis (Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick, microscopic examination). The microscopic examination will be done if blood or protein is abnormal.

Endpoints will be defined as either within or outside normal range. Normal ranges for each endpoint will be provided by the study center. The biological safety information will be entered by the site staff in the appropriate CRF forms along with units and normal ranges. In case of out-of-range values, specific endpoints may be rechecked and additional biological parameters may be evaluated, based on the Investigator's judgement. This complementary safety information will also be entered by the site staff in the appropriate CRF forms along with units and normal ranges.

Any change in the testing equipment using different ranges should be reported on an ongoing basis to the Sponsor so that any value can be interpreted at a given time against the appropriate range of values.

Biological safety endpoints will be assessed on whether or not they reach the pre-defined intensity levels (Grade 1, 2, or 3) for analytes with applicable toxicity grading, as specified in the protocol. Table 10.4 of the protocol contains the pre-defined intensity scales according to which the biological safety parameters will be assessed. If at least one of these intensity levels is reached, the Investigator will evaluate the clinical significance of the results and report clinically significant abnormal values as AEs in the CRF.

4.4.1.4 Other Safety Endpoints

4.4.1.4.1 Pregnancy

This information will be listed as collected. No derivation or imputation will be done.

4.4.1.4.2 Action Taken

Solicited injection site/systemic reactions after any vaccine injection(s) will be summarized, by action taken.

4.4.1.4.3 Seriousness

This information will be summarized as collected. No derivation or imputation will be done.

4.4.1.4.4 Outcome

This information will be summarized as collected. No derivation or imputation will be done.

4.4.1.4.5 Causality

This information will be summarized as collected. Missing causality (relationship) will be handled as described in Section 5.3.1.2.

4.4.1.4.6 AEs Leading to Study Discontinuation

A flag will be available in the clinical database for all AEs in order to identify AEs leading to discontinuation.

In general, the items that are counted are:

- For subject disposition: if subject did not complete the study due to AE as recorded in Completion at End of Study form
- For safety overview: if subject did not complete the study due to AE as recorded in Completion at End of Study form or had any solicited or unsolicited AEs causing study discontinuation / termination as recorded in solicited reaction or unsolicited AE forms within the time period indicated
- For summary of unsolicited AEs by system organ class (SOC) / PT: A solicited AE that has “Caused Study Termination” checked that is at least Grade 1 or an unsolicited AE hat has “Caused Study Termination” checked that is at least Grade 1 or missing and is within the time period indicated

4.4.1.4.7 AESI

AESIs (serious and non-serious) will be collected throughout the study to ensure that events are communicated to the Sponsor in an expedited manner and followed-up until the end of the follow-up period or resolution, as per the assigned causality.

Anaphylactic reactions, generalized convulsions, thrombocytopenia, dry eyes, tearing, dry mouth, NOCMCs and pIMDs.

NOCMCs

NOCMCs are defined as any new ICD-10 diagnosis (10th revision of the International Statistical Classification of Diseases and Related Health Problems) that is applied to the participant during the course of the study, after receipt of the study agent, that is expected to continue for at least 3 months and requires continued health care intervention.

pIMDs

Potential immune-mediated diseases (pIMDs) are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune etiology. AEs that need to be recorded and reported as pIMDs include those listed in Table 10.5 of the protocol.

AESIs will be analyzed throughout the study using the following periods:

- During post-Dose 1 period (i.e., between injection 1 and injection 2), and during 21 days after the last injection
- During the 6-month follow-up period
- During the 12-month follow-up period
- During the study (i.e., all AESIs occurred during the study)

Safety analysis will include only those AESIs with time of onset before a participant received a non-study authorized/approved COVID-19 vaccine, if applicable. AESIs with time of onset on or after the date of receiving a non-study authorized/approved COVID-19 vaccine will be listed separately.

4.4.1.4.8 Medically Attended AE (MAAE)

An MAAE is a new onset or a worsening of a condition that prompts the participant to seek unplanned medical advice at a physician's office or Emergency Department. Physician contact made over the phone or by e-mail will be considered a physician office visit for the purpose of MAAE collection. This includes medical advice seeking during the study visit or routine medical care. This definition excludes pediatric check-ups, follow-up visits of chronic conditions with an onset prior to entry in the study, and solicited reactions.

MAAE will be analyzed during the following time periods:

- During post-Dose 1 period (i.e., between injection 1 and injection 2), and during 21 days after the last injection
- During the 6-month follow-up period
- During the 12-month follow-up period
- During the study (i.e., all MAAEs occurred during the study)

Safety analysis will include only those MAAEs with time of onset before a participant received a non-study authorized/approved COVID-19 vaccine, if applicable. MAAEs with time of onset on

or after the date of receiving a non-study authorized/approved COVID-19 vaccine will be listed separately.

4.4.2 Immunogenicity

4.4.2.1 Computed Values for Analysis

In order to appropriately manage extreme values (< lower limit of quantification (LLOQ)) for analysis purposes, the following computational rule is applied to the values provided in the clinical database for each blood sample (BL) drawn:

- If a value is < LLOQ, then use the computed value LLOQ/2.
- If a value is ≥ LLOQ, then use the value.

4.4.2.2 Fold-rise

The derived endpoint fold-rise is driven by both baseline and post-vaccination computed values as described in Section 4.4.2.1 and is computed as individual titer ratio:

- Post-vaccination value divided by baseline value.

Note: If baseline or post-baseline is missing, then fold-rise is missing.

4.4.2.3 Seroconversion

The seroconversion endpoint is driven by both baseline and post-baseline computed values (assuming replicate values have been reduced to one value as described in Section 4.4.2.1) and a subject will have seroconverted if baseline values below LLOQ with detectable neutralization titer above assay LLOQ at D22, D36, D181 (Cohort 1) or D202 (Cohort 2), and at D366 (Cohort 1) or D387 (Cohort 2).

Note: If baseline or post-baseline is missing, then seroconversion is missing.

4.4.3 Cell-Mediated Immunity

4.4.3.1 Cell-Mediated Immunity Assessment Methods

Helper T cell type 1 (TH1) and Helper T cell type 2 (TH2) Cytokines will be collected for CMI analyses. TH1 cytokines include IFN-gamma (IFNg), Interleukin (IL)-2, IL-6, Tumor Necrosis Factor alpha (TNFα). TH2 cytokines include IL-4, IL-5, IL-10, IL-13. Additionally, Helper T cell type 17 (TH17) cytokine IL-17 and Granulocyte-macrophage-colony-stimulating Factor (GM-CSF)-producing T Helper (THGM) will also be collected and measured.

The list of cytokines is subject to be updated based on more information and knowledge on SARS-CoV-2 before the enrollment of participants of Cohort 2.

All cytokines above will be measured in whole blood following stimulation with pools of S-antigen peptides or full length S protein at D0, D22, and D36 for randomly selected participants from each study intervention group in Cohort 2.

Computed values for analysis

For each participant and each cytokine listed above, 3 measurements will be available for analysis. The 3 measurements are positive control, negative control, and spike stimulant. Each measurement has its own LLOQ and upper limit of quantification (ULOQ). Similar as described in Section 4.4.2.1, the computational rule below is applied to the CMI measurements.

- If a value is < LLOQ, then use the computed value LLOQ/2
- If a value is between ≥ LLOQ and < ULOQ, then use the value
- If a value is ≥ ULOQ, then use the computed value ULOQ

Two subtractions will be calculated as below for each cytokine with computed values described above:

- Subtraction 1: (spike stimulant – negative control)
- Subtraction 2: (positive control - negative control)

Fold-rise

To derive the fold-rise of cytokines, the ratio of post-vaccination and baseline values of the corresponding subtractions above are used. Therefore, there are 2-fold rise ratios for each cytokine per participant per visit with CMI samples:

- Value of a post-baseline visit (spike stimulant – negative control) / baseline value of (spike stimulant – negative control)
- Value of a post-baseline visit (positive control – negative control) / baseline value of (positive control – negative control)

Note: If baseline or post-baseline computed value is missing, then fold-rise is missing.

4.4.4 Efficacy

The efficacy endpoints are the virologically-confirmed COVID-19 illness and serologic SARS-CoV-2 infection.

Virologically-confirmed COVID-19 illness

Virologically-confirmed COVID-19 illness is defined as a positive result for SARS-CoV-2 by Nucleic Acid Amplification Test (NAAT) on a respiratory sample in association with a COVID-19-like illness, which is defined in the protocol section 8.2.2.1.

Serologic SARS-CoV-2 infection

Serologic SARS-CoV-2 infection is defined as a positive result in serum for presence of antibodies specific to non-Spike protein of SARS-CoV-2 detected by ELISA assay.

4.4.5 Other Derived Variables

4.4.5.1 Age for Demographics

The quantitative descriptive statistics (e.g., Mean, SD, Max, Min, Median, Q1 and Q3) of age in demographics summary table(s) is based on the age in year collected in eCRF.

Age group

The age in year collected in eCRF will be used for demographics summary and age sub-groups definition. The age groups of a participant used in the study are as follows:

"18 to 49 years", "Over 50 years" and "Over 60 years"

4.4.5.2 Duration of the Study

The duration of the study is computed in days as follows:

- Maximum (latest date of Visit, latest date of termination) – minimum (date of V01) +1

4.4.5.3 Subject Duration

The duration of a subject participation in the study is computed as follows:

Maximum (Visit dates, Termination date) – V01 date + 1.

5 Statistical Methods and Determination of Sample Size

The statistical analyses will be performed under the responsibility of the Sponsor's Biostatistics platform using SAS® Version 9.4 or later.

The results of the statistical analysis will be available in the final clinical study report (CSR).

For descriptive purposes, the following statistics will be presented:

Table 5.1: Descriptive statistics produced

Baseline characteristics and follow-up description	**Categorical data**	Number of subjects. Percentage of subjects.
	Continuous data	Mean, standard deviation, quartiles, minimum, and maximum.
Clinical safety results	**Categorical data**	Solicited: Number and percentage (95% CIs) of subjects. Unsolicited: Number and percentage (95% CIs) of subjects, and number of events.
	Continuous data	Mean, standard deviation, quartiles, minimum, and maximum.
Immunogenicity results	**Categorical data (seroconversion, 2 fold-rise, 4 fold-rise)**	Number and percentage (95% CIs) of subjects.
	Continuous data (titer / data†)	Log10: Mean and standard deviation. Anti-Log10 (work on Log10 distribution, and anti-Log10 applied): Geometric mean, 95% CI of the geometric mean, quartiles, minimum, and maximum. Graphical representation by Reverse Cumulative Distribution Curve (RCDC).
Efficacy results	**Categorical data**	Number and percentage (95% CIs) of subjects.

The CI for the single proportion will be calculated using the exact binomial method (Clopper-Pearson method, quoted by Newcombe (5), i.e., using the inverse of the beta integral with SAS®.

For immunogenicity results, assuming that Log10 transformation of the titers / data follows a normal distribution, at first, the mean and the 95% CI will be calculated on Log10 (titers / data) using the usual calculation for normal distribution (using Student's t distribution with n-1 degree of freedom), then antilog transformations will be applied to the results of calculations, in order to provide geometric means (GMs) and their 95% CI.

5.1 Statistical Methods

Safety, immunogenicity, and efficacy analyses will be undertaken including those data collected before the date of receiving an authorized/approved COVID-19 vaccine. Those data collected on or after receiving an authorized/approved COVID-19 vaccine will be listed separately.

5.1.1 Hypotheses and Statistical Methods for Primary Objectives

5.1.1.1 Primary Safety Hypotheses

No hypotheses will be tested.

5.1.1.2 Statistical Methods for Primary Safety Objective

Safety results will be described for each age and vaccine group. The homogeneity of pooled groups will be assessed on the main parameters. The main parameters will be described with 95% CI.

Safety analyses will be performed based on safety analysis set including safety data collected before the date of receiving an authorized/approved COVID-19 vaccine. Safety data collected on or after the day of receiving an authorized/approved COVID-19 vaccine will be listed separately.

Solicited Reactions

Number and percentage of subjects with:

- Presence of solicited injection site reactions and systemic reactions occurring up to 7 days after injection
- Each solicited reaction according to time of onset, maximum intensity, and number of days of occurrence over the solicited period

Unsolicited Events and Reactions

Number and percentage of subjects with:

- Any unsolicited immediate systemic event in the 30 minutes after injection
- Any unsolicited event and reaction (using the current MedDRA version) 21 days after injection
- Any unsolicited event/reaction according to time of onset, maximum intensity, and duration

SAEs

Number and percentage of subjects with:

- any SAE within 21 days after injection and during the 6 months and 12 months follow-up periods according to SOC and PT, seriousness and outcome

AEs of special interest

- Number and percentage of subjects with any/each AESI within 21 days after injection and during the 6 month and 12 months follow-up periods will be presented according to SOC and PT, seriousness and outcome.

MAAE

- Presence of medically attended adverse events (MAAEs) throughout the study

Laboratory tests

- Presence of out-of-range biological test results up to 7 days post-last dose (ie, up to D09 for Cohort 1 and up to D30 for Cohort 2)

The following analyses will be performed for laboratory tests in addition to the summary of out of range tests above:

- Biological test results and toxicity grade by visit,

- Summary of toxicity grade shift from baseline,

For descriptive purposes, the statistics presented on Table 5.1 will be produced.

In addition to analyses by each intervention group, aggregated groups will be used to perform complementary assessments for above parameters, including:

1. aggregated vaccine group, ie, all vaccine arms pooled
2. aggregated placebo group, ie, two placebo arms pooled
3. aggregated dose-level group, ie, low-dose arms pooled, or high-dose arms pooled
4. aggregated adjuvant type group, ie, AF03 arms pooled or AS03 arms pooled

The analyses by aggregated groups will also be conducted in overall population and by age group.

5.1.1.3 Primary Immunogenicity Hypotheses

No hypotheses will be tested.

5.1.1.4 Statistical Methods for Primary Immunogenicity Objective

The primary endpoints for the evaluation of immunogenicity are based on neutralizing antibody titers, which will be measured with the neutralization assay. The statistical analyses will be performed for the following primary endpoints below on overall population and by age group:

1. Antibody titer on D01, D22, and D36
2. Fold-rise (fold-rise in serum antibody neutralization titer post-vaccination relative to D01) at D22, and D36
3. 2-fold and 4-fold rise in serum neutralization titer relative to D01 at D22, and D36
4. Occurrence of neutralizing antibody seroconversion, defined as baseline values below LLOQ with detectable neutralization titer above assay LLOQ at D22 and D36.

Vaccine arms will be aggregated to perform complementary assessments on the following main effects. The primary endpoints above will also be summarized for the main effects.

1. age [(18-49 years, ≥ 50 years), where the category of 18-49 years (N=240) includes all vaccine arms except high dose no adjuvant arm aged 18-49 years old; the category of ≥ 50 years (N=120) includes all vaccine arms aged 18-49 years old.
2. dose (low, high), where the category of low (N=180) includes vaccine arms of low dose with either AF03 or AS03 adjuvant; the category of high (N=180) includes vaccine arms of high dose with either AF03 or AS03 adjuvant.
3. injection schedule (1-injection, 2-injection), where the category of 1-injection (N=120) includes vaccine arms in cohort 1; the category of 2-injection (N=240) includes vaccine arms in cohort 2 except the high-dose with no adjuvant arm.

4. adjuvant type (AS03, AF03), where the category of AS03 (N=240) includes vaccine arms with adjuvant AS03; the category of AF03 (N=120) includes vaccine arms with adjuvant AF03.
5. overall adjuvant (high-dose with adjuvants, high-dose without adjuvants), where the category of high-dose with adjuvants (N=180) includes vaccine arms of high-dose with either AS03 or AF03; the category of high-dose without adjuvants (N=20) includes the vaccine arm with high-dose and no adjuvant.
6. dose-sparing adjuvant (low-dose with adjuvants, high-dose without adjuvants); where the category of low-dose with adjuvants (N=180) includes vaccine arms of low-dose with either AS03 or AF03; the category of high-dose without adjuvants (N=20) includes the vaccine arm with high-dose and no adjuvant.

Additionally, to evaluate independent determinants of primary immunogenicity endpoints, regression models may be constructed for GMT titers and occurrence of 4-fold rise in serum neutralization titer relative to D01 at D22 for cohort 1 and D36 for cohort 2. When the outcome/dependent variable is a continuous numerical variable, linear models may be utilized; when the outcome/dependent variable is a categorical variable, logistic regression models may be utilized. Explanatory/independent variables inserted in these models would include age group (18-49 years, ≥50 years), antigen dose level (low-dose, high-dose), and adjuvant (none, AS03, AF03). Models evaluating antibody titers or rates at D22 for cohort 1 and D36 for cohort 2 as the outcome variable would include also an explanatory variable corresponding to the injection schedule (1-injection, 2-injections). Multiplicative interaction terms will be included in expanded models to assess for evidence of effect modification. Non-significant interaction terms with critical value < 0.05 can be removed from the models.

For descriptive purposes, the statistics presented on Table 5.1 will be produced.

5.1.2 Hypotheses and Statistical Methods for Secondary Objectives

5.1.2.1 Secondary Immunogenicity Hypotheses

No hypotheses were tested.

5.1.2.2 Statistical Methods for Secondary Immunogenicity Objectives

For descriptive purposes, the statistics presented on Table 5.1 will be produced.

Immunogenicity analyses will be performed in those BL collected before receiving an authorized/approved COVID-19 vaccine. Immunogenicity data after receiving an authorized/approved COVID-19 vaccine will be listed separately.

5.1.2.3 Secondary Efficacy Hypotheses

No hypotheses were tested.

5.1.2.4 Statistical Methods for Secondary Efficacy Objectives

The efficacy profile of the study vaccine candidate will be investigated with collected COVID-19 cases of efficacy endpoints including virologically-confirmed COVID-19-like illness and serologically-confirmed SARS-CoV-2 infection. Efficacy analyses will be performed on COVID-19 cases collected before receiving an authorized/approved COVID-19 vaccine. COVID-19 cases before, on and after receiving an authorized/approved COVID-19 vaccine will be listed. As the vaccine formulation used in VAT00001 is no longer investigated further and the number of COVID-19 cases collected before receiving an authorized/approved COVID-19 vaccine would be limited, planned efficacy analyses might not be performed for the final analysis.

Correlates of risk

To evaluate the correlate of risk of the collected COVID-19 cases including virologically-confirmed COVID-19-like illness and serologically-confirmed SARS-CoV-2 infection, logistic regression models will be conducted to investigate the relationship of COVID-19 cases defined above and immunogenicity responses measured by neutralization assay and ELISA. In addition, Other explanatory/independent variables under consideration are intervention groups ([vaccine, placebo]; [low-dose, high-dose, placebo]). Separate models will be performed for different consideration of intervention groups. The log10 value of neutralizing antibody titers at D36 for cohort 2 and D21 for cohort 1 are the main immunogenicity responses for this analysis. In case the majority of participants have below LLOQ neutralizing antibody titers in the placebo group, the value of below LLOQ will be treated as ½ LLOQ. Alternatively, the antibody titers of immunogenicity responses will be categorized as a discrete variable by quantile. Dose-response curve will be modeled based on the analyses in a Bayesian manner.

Vaccine efficacy

Vaccine efficacy (VE) will be assessed with the collected COVID-19 cases. The VE will be estimated as follows:

$$VE = 1 - \frac{C_V / N_V}{C_P / N_P}$$

where

- C_V and C_P are the numbers of COVID-19 cases meeting the considered secondary endpoint definition in the vaccine and placebo groups, respectively;
- N_V and N_P are the numbers of subjects in the vaccine and placebo groups, respectively.

The aggregated vaccine groups will be used for VE assessment include 1) pooled all vaccine arms; 2) pooled low-dose and high-dose with adjuvants arms; 3) pooled high dose with adjuvants arms; 4) pooled cohort 1 vaccine arms and cohort 2 vaccine arms.

The statistical methodology will be based on the use of the two-sided CI of VE. The CIs for VEs will be calculated by an exact method assuming a binomial distribution of the number of cases in vaccine group conditional on the total number of cases:

Let $q = \frac{C_V}{C_V + C_P}$, the proportion of cases belonging to vaccine group among the total number of cases. Given the total number of cases, C_V has a binomial distribution (q,C_V+C_P). Thus, a CI for q may be constructed using the exact Clopper-Pearson method for binomial proportions.

As $\frac{q}{1-q} = \frac{C_V}{C_P}$, the VE estimate given above may be restated as follows:

$$VE = 1 - \frac{C_V/N_V}{C_P/N_P} = 1 - \frac{N_P}{N_V} \times \frac{q}{1-q}$$, which is a strictly decreasing function of q.

Finally, CI of the VE will be constructed based on the CI of q.

Bayesian inference will be performed on VE to assessed the conditional probability Prob(VE > VE_0)>95%| observed number of COVID-19 cases), where VE_0 is a threshold from 0% and 30%, through the posterior distribution of q. Non-informative uniform beta(1, 1) prior will be used.

Analyses can be performed for pooled vaccine groups as specified above.

For descriptive purposes, the statistics presented on Table 5.1 will be produced.

5.1.3 Statistical Methods for Exploratory Objective(s)

No hypotheses will be tested.

Ratio between binding antibody (ELISA) concentration and neutralizing antibody titer will be calculated and provided with 95% CI by intervention arm and main effects group. Analyses will be conducted on overall population and by age group.

Immunogenicity parameters for antibody persistence will be described with 95% CI for each age and vaccine group. The Reverse Cumulative Distribution Curves and distribution tables will also be produced in each age and vaccine group.

Last available neutralizing antibody titer and binding antibody (ELISA) concentration before infection will be described with 95% CI in aggregated vaccine group and aggregated placebo group.

Cell-Mediated Immunity

All cytokines collected will be summarized by visit.

TH1/TH2 ratios below will be summarized by treatment group on overall population and by age group for data collected at D22 and D36:

1. IFNg/ IL-4
2. IFNg/IL-5
3. IFNg /IL-13
4. IL-2 /IL-4
5. IL-2 /IL-5

6. IL-2/IL-13
7. TNFa/IL-4
8. TNFa/IL-5
9. TNFa/IL-13

The ratios above are based on fold-rise as defined in Section 4.4.3.1. That is for each cytokine, there are two Th1/TH2 ratios, one for each subtraction described in Section 4.4.3.1. The ratio based on subtraction of spike stimulate – negative control will be used as main supportive information for Th1/Th2 results. Among all ratios listed, IFNg/IL-4 is the main TH1/TH2 ratio for charactering Helper T cell polarization.

Post-vaccination antibody titers for the different study arms may be compared with human convalescent sera antibody titers, conditional to convalescent sample availability.

For descriptive purposes, the statistics presented on Table 5.1 will be produced.

A principle component analysis (PCA) will be performed on collected CMI data to identify linear combinations, i.e., principle components, of the biological variables. PCA analyses will be conducted for the two subtractions described in Section 4.4.3, separately. All cytokines will be involved in the PCA analysis. The variables were $\log_{10}$-transformed and centered to 0 mean and scaled to the standard deviation; the covariance matrix will be used and for each analysis two principal components (PC1 and PC2) will be extracted accounting for a given proportion of data variability. Each component will be characterized by its loadings, i.e., weights quantifying how much each original variable contributes to the component. PCA will be applied to PPAS-CMI analysis set.

5.2 Analysis Sets

Five main analysis sets will be used: The Per-Protocol Analysis Set (PPAS), the Per-Protocol Analysis Set for immunogenicity (PPAS-IAS), the Per-Protocol Analysis Set for CMI (PPAS-CMI), the Full Analysis Set (FAS), and the Safety Analysis Set (SafAS).

5.2.1 Full Analysis Set

Subset of randomized participants who received at least 1 injection of the study intervention. Subjects will be analysed according to the vaccine group to which they were randomized.

5.2.2 Safety Analysis Set

Subset of randomized participants who have received at least one injection of study intervention. Participants will have their safety analyzed according to the study intervention they actually received. All subjects will be analyzed after each dose according to the vaccine they actually received, and after any dose according to the vaccine received at the 1st dose.

Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately).

5.2.3 Per-Protocol Analysis Set

Subset of the FAS. Participants presenting with at least one of the following conditions will be excluded from the PPAS:

- Participant did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Participant did not complete the protocol-defined vaccination schedule
- Participant received a study intervention other than the one that he / she was randomized to receive
- Preparation and / or administration of study intervention was not done as per-protocol
- Participant did not receive study intervention in the proper time window as defined in the protocol visits.
- Participant received a Category 2 or Category 3 therapy /medication / as stated in Section 6.5 of the Protocol
- Participant with positive test results in the neutralization test at baseline.

The above conditions leading to exclusion from the PPAS may be detailed and completed if necessary following the data review. In any case, if PPAS definition is modified, the PPAS definition will be finalized before the database lock and documented in an SAP update.

5.2.3.1 Per-Protocol Analysis Set for immunogenicity (PPAS-IAS)

Subset of PPAS excluding participants who provided all post-dose serology samples outside the proper time window or no post-dose serology sample was drawn

For participants with just part of expected post-dose serology samples outside the proper time window or without a valid test result, participants will be kept in PPAS-IAS and only samples within the time window and with a valid result will be included in immunogenicity analyses.

5.2.3.2 Per-Protocol Analysis Set for CMI (PPAS-CMI)

Subset of PPAS excluding participants who provided all post-dose CMI samples outside the proper time window or no post-dose CMI sample was drawn.

5.2.4 Other Analysis Sets

Randomized subjects

A randomized subject is a subject for whom a randomized group has been allocated by IRT.

Subjects with data in CRF

Subjects with data in CRF are subjects for whom data were recorded at a visit (except screening).

5.2.5 Populations Used in Analyses

The primary immunogenicity analyses, the secondary immunogenicity analyses, and the exploratory immunogenicity analyses (excluding CMI analyses) will be performed on the PPAS-IAS, and will be confirmed on the FAS.

The primary safety analysis will be performed on the SafAS.

The secondary efficacy analyses will be performed on FAS and PPAS-IAS.

The CMI analyses in the exploratory objective will be performed on PPAS-CMI, and will be confirmed on the FAS.

5.3 Handling of Missing Data and Outliers

5.3.1 Safety

Generally, no replacement will be done. However, imputations may be done for a limited number of scenarios, some of which are described in this section.

5.3.1.1 Immediate

Unsolicited systemic AEs with a missing response to the “Immediate” field will be assumed to have occurred within the 30-minute surveillance period.

5.3.1.2 Causality

By convention, all events reported at the injection site (either solicited or unsolicited) will be considered as related to the administered product and then referred to as reactions. In a same way, all solicited systemic events pre-listed in the CRF are also considered as related to vaccination and will be considered as reactions. Missing causality for unsolicited non-serious AEs and SAEs will be considered at the time of analysis as related to vaccination.

5.3.1.3 Measurements

Partially missing temperatures will be handled as described in Section 4.4.1.1.1.

5.3.1.4 Intensity

For solicited reactions, missing intensities will be handled as described in Section 4.4.1.1.1. For unsolicited non-serious AEs, missing intensities will remain missing and will not be imputed.

5.3.1.5 Start Date and Stop Date

Missing or partially missing start dates for unsolicited AEs will remain missing and not be imputed. If either the start or stop date is missing or partially missing, the time of onset will be considered to be missing. Nevertheless, unsolicited AEs with missing time of onset will be included in analyses according to the visit collected.

Missing or partially missing stop dates for AEs (solicited reactions and unsolicited AEs) will remain missing and not be imputed.

5.3.2 Immunogenicity

No test or search for outliers will be performed.

5.3.3 Laboratory safety

No imputation of missing values and no search for outliers will be performed.
For the computation of descriptive statistics, a value reported as:

- "< X" will be converted to a value of 0.5 *X,
- ">X" will be replaced by the X

If a subject has a missing baseline then the data for this subject will be included in the category "missing at baseline" in the table taking into account the baseline status.

5.3.4 Cell-Mediated Immunity

The values will be reported as recorded.

5.3.5 Efficacy

Missing data will not be imputed. No test or search for outliers will be performed.

5.4 Interim / Preliminary Analysis

An interim analysis will be performed on data collected for primary immunogenicity and exploratory CMI objectives obtained up to D36 and primary safety objectives obtained up to D43, upon the data availability and when a partial database lock has been conducted. Statistical analysis of data described in Section 5.1.1 and Section 5.1.3 (CMI analyses except the PCA analysis) will be conducted to support formulation selection for further investigation. The analyses results will also be generated to communicate with regulatory agencies. If sufficient efficacy data are available at this interim analysis, the assessment of early efficacy will be performed as described in Section 5.1.2.4.

At the first interim analysis, an independent statistical group includes an independent statistician and an independent programmer will be unblinded at subject level to generate interim outputs including tables, listings, and figures. The treatment code will be masked from the interim outputs to ensure that subject-level unblinding is not available outside the independent statistical group. A group of study members will review the interim outputs unblinded at group level, to perform decision-making on dose-selection and generate the abbreviated clinical study report (CSR) and interim CSR. This group will include study statisticians and study programmers, clinical study leads, pharmacovigilance, Global Clinical Immunology project representatives, and medical writer. Study statisticians and programmers will validate and perform quality control of group-unblinded statistical outputs. Additionally, certain members of the project team and certain Sanofi Pasteur management will be consulted in the course of the formulation selection, and thus be aware of the group-level data. Regulatory personnel will communicate to CBER with interim

outputs and abbreviated CSR. In addition, any subject experiencing a SUSAR (Suspected Unexpected Serious Adverse Reaction) will be unblinded to pharmacovigilance or in case any condition is met as described in the protocol. Parties remaining blinded includes participants, lab analysts, site investigators, and study team other than specified above. Furthermore, the study team will remain blinded on data collected after date cut of the interim analysis.

In the interests of transparency, it is the intention of Sanofi Pasteur to submit the results of the interim analysis to a peer-reviewed journal and/or pre-print server once the approval to begin the Phase III trial is received and ideally prior to the first enrollment of the Phase III trial. It is planned that all study investigators will be co-authors of this manuscript. Work on this manuscript will begin after the brief study report is submitted to CBER. As such, once these interim results are published, it will be widely known, including possibly to study participants and site staff.

For interim analyses specified below, the above unblinding process for functions in the Sponsor Study team will be the same. Dose-selection will apply only at the first interim.

After the 6-month data have been collected, a further interim analysis will be performed on all immunogenicity, safety, and efficacy endpoints. The study blind will be broken at the group level to the Sponsor at that time. At the time of protocol version 4.0, a partial database lock has been conducted.

A final analysis for all data collected will be conducted once the 12-month safety data have been collected and the final database lock has occurred.

Participant safety will be continuously monitored by the Sponsor's internal safety review committee which includes safety signal detection at any time during the study (see also Section 8.4 of the protocol for halting rules).

5.5 Determination of Sample Size and Power Calculation

No sample size calculations were performed. Approximately 440 participants are planned to be enrolled in this study, with 300 participants aged 18-49 years old and 140 participants aged 50 years or older randomized to intervention groups as described in Section 3. 87 subjects (60 participants aged 18-49 years old and 27 participants aged 50 years or older) will be randomly selected from cohort 2 for CMI analyses.

5.6 Data Review for Statistical Purposes

A data review process will be led by data management before database lock. This review of the data includes statistical review.

5.7 Changes in the Conduct of the Trial or Planned Analyses

The protocol was amended for a study design change that allows participants, if they are eligible, to receive one of the COVID-19 vaccines currently available via emergency use authorization. If the participant receives an authorized/approved COVID-19 vaccine, this information would be collected and the participant's data up to the point of receipt of authorized/approved vaccine will be included in the primary analysis for immunogenicity and safety. Participants will continue to

be followed for the duration of the study as per scheduled visits and procedures. In addition, the 4-month interim analysis will be removed.

As the vaccine formulation used in VAT00001 is no longer investigated further and the number of COVID-19 cases collected before receiving an authorized/approved COVID-19 vaccine would be limited, planned efficacy analyses might not be performed for the final analysis.

6 References List

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