Title Page

Protocol Title:

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

Study Code: VAT00001

Protocol Version Number: 5.0

Amendment Number: Amendment 1

Compound:

SARS-CoV2 prefusion Spike delta TM (CoV2 preS dTM): antigen Formulation 1 (low-dose [5 µg] or Formulation 2 (high-dose [15 µg])

AF03: CoV2 preS dTM-AF03, Squalene-based adjuvant 2.5%

AS03: CoV2 preS dTM-AS03, Squalene-based adjuvant 2.1%

Study Phase: Phase I/II

Short Title:

Study of Recombinant Protein Vaccine Formulations against COVID-19 in Healthy Adults 18 Years of Age and Older

Sponsor Name and Legal Registered Address:

Sanofi Pasteur Inc.
Discovery Drive, Swiftwater, PA 18370-0187, USA

Manufacturer:

CoV2 preS dTM and AF03 adjuvant: Same as Sponsor

AS03 adjuvant: GlaxoSmithKline (Vaccines)

Regulatory Agency Identifier Numbers:

BB-IND: 23143

WHO UTN: U1111-1250-4757

Approval Date: 05 February 2021

Medical Monitor Name and Contact Information are provided in the Operating Guidelines.

The study centers, the Investigators at each center, and the Coordinating Investigator(s) are listed in a separate document.

Document History and Protocol Amendment Rationale

Previous Version	Date	Comments
1.0	11 May 2020	Submitted to CBER for pre-IND submission only.
2.0	24 July 2020	Submitted to CBER for IND submission and to IRB only before study start.
3.0	26 August 2020	Submitted to IRB
4.0	28 August 2020	Version approved by IRB and first version used in the study

Overall Rationale for Amendment 1:

The protocol was amended from v4.0 dated 28 August 2020 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. In addition, the 4-month interim analysis will not be conducted as efficacy analysis is moved to the 6-month interim analysis.

Major revisions between Version 4.0 and Version 5.0	
Revision	**Rationale**
Table 1.1 and Table 1.2: Collection of concomitant medications Revised to include participants can receive an approved/authorized COVID-19 vaccine	Since the protocol was first approved, 2 COVID-19 vaccines have received emergency use authorization by the FDA
Section 7.1.2: language added to contraindications paragraph regarding subjects who receive an approved/authorized COVID-19 vaccine	Since the protocol was first approved, 2 COVID-19 vaccines have received emergency use authorization by the FDA
Section 9.5: removed the sentence, “Another interim analysis will be performed on efficacy data obtained up to 4-month follow up for assessment of early efficacy (Visit 5 for participants in each cohort)”	Efficacy analysis moved to the 6-month interim analysis; 4-month analysis not needed

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1 Protocol Summary

1.1 Synopsis

Protocol Title:

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

Short Title:

Study of Recombinant Protein Vaccine Formulations against COVID-19 in Healthy Adults 18 Years of Age and Older

Rationale:

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 25 August 2020, the virus has been detected in 188 countries/regions and infected over 23.7 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, or formulations, and an injection schedule to proceed to efficacy evaluation as rapidly as possible.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
Immunogenicity To describe the neutralizing antibody profile at Day (D)01, D22, and D36 of each study intervention group.	***Immunogenicity*** Neutralizing antibody titers will be measured with the neutralization assay. • Antibody titer at D01, D22, and D36 • Fold-rise (fold-rise in serum antibody neutralization titer post-vaccination relative to D01) at D22, and D36 • 2-fold and 4-fold rise in serum neutralization titer (post/pre) relative to D01 at D22, and D36) • Occurrence of neutralizing antibody seroconversion, defined as baseline values below lower limit of quantification (LLOQ) with detectable neutralization titer above assay LLOQ at D22 and D36
Safety To describe the safety profile of all participants in each age group and each study intervention group up to 12 months post-last injection.	***Safety*** • Presence of unsolicited systemic adverse events (AEs) reported in the 30 minutes after each injection • Presence of solicited (pre-listed in the participant's diary card and Case Report Form [CRF]) injection site reactions and systemic reactions occurring up to 7 days after each injection • Presence of unsolicited AEs reported up to 21 days after each injection. • Presence of medically attended adverse event (MAAEs) throughout the study • Presence of serious adverse events (SAEs) and adverse events of special interest (AESIs) throughout the study • Presence of out-of-range biological test results up to 7 days post-last injection (ie, up to D09 for Cohort 1 and up to D30 for Cohort 2)

Secondary	
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 D366 (Cohort 1) and D387 (Cohort 2) of each study intervention group.	***Immunogenicity*** Binding antibody titers to full-length SARS-CoV-2 S protein will be measured for each study intervention group with the enzyme-linked immunosorbent assay (ELISA) method. • Individual anti-S antibody concentration at D01, D22, D36, D181 (Cohort 1) or D202 (Cohort 2), and D366 (Cohort 1) or D387 (Cohort 2) • Individual anti-S antibody concentration ratio (fold-rise in serum ELISA concentration post-vaccination relative to D01) at D22, D36, D181 (Cohort 1) or D202 (Cohort 2), and D366 (Cohort 1) or D387 (Cohort 2) • Fold-rise in anti-S antibody concentration (post/pre) ≥ 2 and ≥ 4 at D22, D36, D181 (Cohort 1) or D202 (Cohort 2), and D366 (Cohort 1) or D387 (Cohort 2) Neutralizing antibody titers will be measured with the neutralization assay. • Antibody titer at D181 (Cohort 1) or D202 (Cohort 2) and D366 (Cohort 1) or D387 (Cohort 2) • Fold-rise (fold-rise in serum neutralization titer post-vaccination relative to D01) at D181 (Cohort 1) or D202 (Cohort 2) and D366 (Cohort 1) or D387 (Cohort 2) • 2-fold and 4-fold rise in serum neutralization titer (post/pre) relative to D01 at D181 (Cohort 1) or D202 (Cohort 2) and D366 (Cohort 1) or D387 (Cohort 2) • Occurrence of neutralizing antibody seroconversion, defined as values below LLOQ at baseline with detectable neutralization titer above assay LLOQ at D181 (Cohort 1) or D202 (Cohort 2) and D366 (Cohort 1) or D387 (Cohort 2)

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.	***Efficacy*** • Virologically-confirmed COVID-19-like illness as defined by specified clinical symptoms and signs and confirmed by nucleic acid viral detection assay • Serologically-confirmed SARS-CoV-2 infection is defined by SARS-CoV-2-specific antibody detection in a non-S ELISA • Correlates of risk / protection based on antibody responses to SARS-CoV-2 as evaluated using virus neutralization or ELISA, considering virologically-confirmed COVID-19-like illness and/or serologically-confirmed SARS-CoV-2 infection as defined above

Overall Design

Type of design	Parallel group, first-in-human, dose-ranging, multi-center study with a Sentinel Safety Cohort and Early Safety Data Review (ESDR)
Phase	I/II
Control method	Placebo-controlled
Study population	Healthy, seronegative adults 18 years of age and older
Countries	United States
Level and method of blinding	• Blinding for vaccine group assignment (formulation and adjuvant): participants, outcome assessors, Investigators, laboratory personnel, Sponsor study staff (except those involved in ESDR, and for concerned participants only) • No blinding for injection schedule • No blinding for vaccine group assignment: those preparing/administering the study interventions
Study intervention assignment method	Randomization for study intervention and assigned stratification by age

Disclosure Statement:

This is a parallel group prevention study, stratified into 2 age groups based on age at enrollment: the younger adult age group (18-49 years) will be randomly assigned to one of 11 arms; the older adult age group (≥ 50 years) will be randomly assigned to one of 10 arms. Participants, outcome assessors, Investigators, laboratory personnel, and the majority of sponsor study staff (except those involved in the ESDR and for concerned participants only) will be blinded to vaccine assignment group (formulation and adjuvant); injection schedule will be unblinded; and those preparing/administering the study interventions will be unblinded to vaccine group assignment.

Number of Participants:

Approximately 440 participants 18 years of age and older (300 adults 18 through 49 years of age and 140 adults 50 years of age and older) are planned to be randomized.

As a precautionary step, a Sentinel Safety Cohort of 6 participants (younger adults only) within each dosing group from Cohort 1 will be enrolled. An ESDR will be performed, including evaluation of safety data and laboratory measures to D09 in Cohort 1 among younger adults 18-49 years of age. Upon acceptable safety demonstrated from unblinded data review by limited members of the Sponsor Study Team (Responsible Medical Officer [RMO], Study 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.

Intervention Groups and Duration:

A total of 440 participants are planned to be enrolled as shown below:

Participants 18-49 years of age					
Cohort	**Group**	**Dose Level***	**Adjuvant**	**N**	
				Sentinel Safety† (N=30)	**Total (N=300)**
Cohort 1: 1 injection	**1**	5 µg	AF03	6	20
	2	5 µg	AS03	6	20
	3	15 µg	AF03	6	20
	4	15 µg	AS03	6	20
	5	Placebo	None	6	20
Cohort 2: 2 injections	**6**	5 µg	AF03	N/A	20
	7	5 µg	AS03	N/A	60
	8	15 µg	AF03	N/A	20
	9	15 µg	AS03	N/A	60
	10	15 µg	None	N/A	20
	11	Placebo	None	N/A	20

Participants 50 years of age and older				
Cohort	**Group**	**Dose Level***	**Adjuvant**	**N (N=140)**
Cohort 1: 1 injection	**1**	5 µg	AF03	10
	2	5 µg	AS03	10
	3	15 µg	AF03	10
	4	15 µg	AS03	10
	5	Placebo	None	10
Cohort 2: 2 injections	**6**	5 µg	AF03	10
	7	5 µg	AS03	30
	8	15 µg	AF03	10
	9	15 µg	AS03	30
	10	15 µg	None	N/A‡
	11	Placebo	None	10

*Antigen Formulation naming for each dose level: CoV2 preS dTM antigen: Formulation 1 (low-dose [5 µg]); Formulation 2 (high-dose [15 µg])

† Sentinel Safety Cohort: 6 participants within each dosing group from Cohort 1 (18-49 years of age only) will be included in the Sentinel Safety Cohort.

‡ As part of risk mitigation for enhanced COVID-19, the older age stratification (≥ 50 years) will not be allocated to this study arm.

Note: 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 D01 (Vaccination [VAC] 1). Participants in Cohort 2 will receive a second injection of study vaccine formulation or placebo at D22 (VAC2).

If a COVID-19 vaccine becomes available from a company other than Sanofi Pasteur, then participants are free to receive that vaccine. Participants who receive a COVID-19 vaccine will still be followed for safety until the end of the study but will be discontinued from study intervention administration thereafter.

Enrolled participants who seek vaccination of an authorized/approved vaccine outside of the study will be encouraged to discuss this intention proactively with the study investigator and will be permitted to receive the authorized vaccine at any time. As efficacy has not been demonstrated for any of the investigational formulations under evaluation in the current study, it is not required to unblind participants to the VAT00001 study assignment prior to administration of an authorized COVID-19 vaccine.

If the participant receives the authorized/approved 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. Participants will be invited to a visit prior to receiving the vaccine and invited to provide a blood sample for immunological assessment.

The duration of each participant's participation in the study will be approximately 365 days post-last injection:

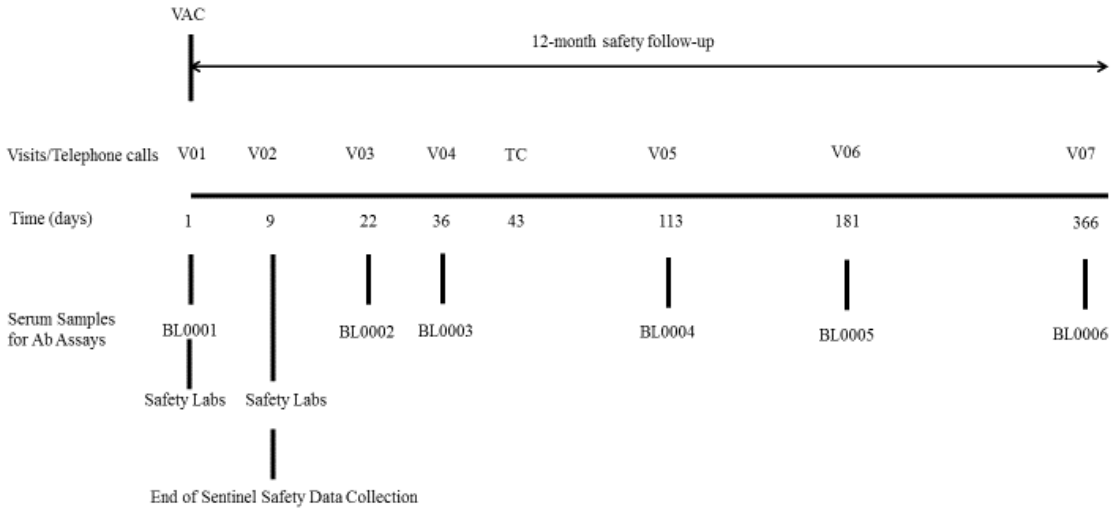
- Cohort 1: approximately 365 days duration total
- Cohort 2: approximately 386 days duration total

Data Monitoring Committee: No

1.2 Schema

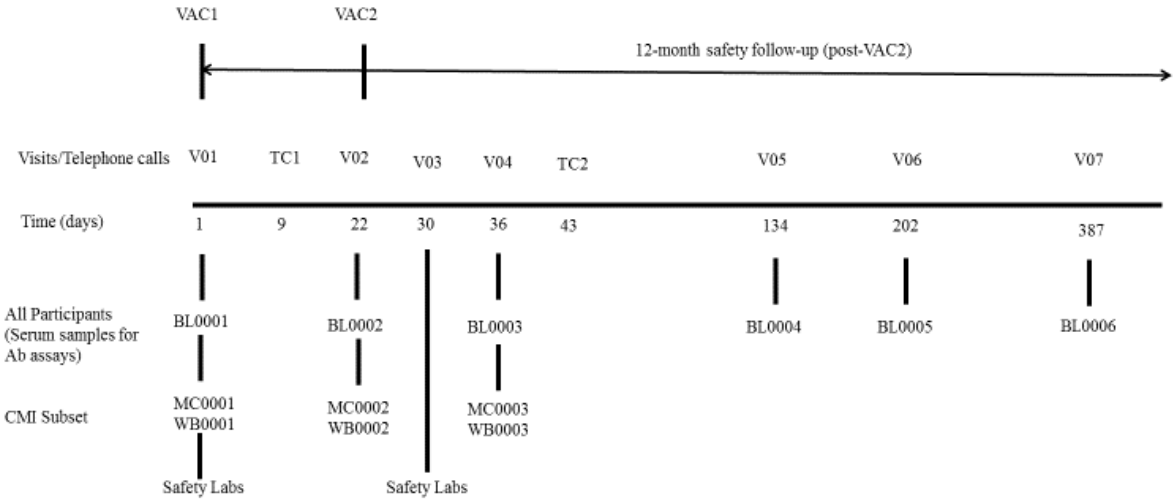
The graphical design of VAT00001 study is as presented in Figure 1.1 (Cohort 1) and Figure 1.2 (Cohort 2).

Figure 1.1: Graphical study design (Cohort 1)



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

Figure 1.2: 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

1.3 Schedule of Activities (SoA)

Visits and procedures are detailed in the Operating Guidelines.

Table 1.1: 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 1.3 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 1.2: 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 1.3 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 1.3: 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.

2 Introduction

Sanofi Pasteur's Recombinant severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) protein vaccine is being developed in the setting of a pandemic for the active immunization for the prevention of SARS-CoV-2 infection and/or COVID-19 disease. The initial intended use of the vaccine is for adults, 18 years of age and older. It is planned that studies to support use of the vaccine in children 6 months to 17 years of age will be conducted after the initial data from studies in adults are available.

The candidate antigen is a stabilized prefusion trimer of the SARS-CoV-2 S protein. The coronavirus Spike (S) protein is the major viral envelope glycoprotein and mediates attachment and entry into host cells. The S protein precursor is cleaved to form non-covalently associated subunits, S1 and S2 (5). The S protein appears on the surface of the virus as a mushroom-like structure, containing a cap of three S1 subunits and a stem of three S2 subunits. The S1 subunit contains the receptor binding domain (RBD), which attaches to the host cellular receptor. In the case of SARS-CoV-2, the receptor is Angiotensin Converting Enzyme-Related Peptidase 2, a membrane-bound carboxypeptidase localized to vascular endothelial as well as epithelial surfaces (6). The RBD is a major antigenic target for immune responses. The S2 domain contains the fusion peptide and transmembrane regions. Upon binding to the cellular receptor, S1 is cleaved from the virus and the S2 subunit undergoes a conformational change to mediate viral membrane fusion with the host cell membrane.

Prior research with Middle East Respiratory Syndrome (MERS)-CoV identified that the introduction of double proline substitutions (2P) at the beginning of the central helix of the S2 subunit could stabilize the structure and prevent conformational changes in the S trimer (7). When used to immunize mice, the MERS-CoV 2P construct was associated with improved breadth and potency of neutralizing responses compared to monomeric MERS-CoV S1 or wild-type S. This strategy was identified as being of general relevance to betacoronaviruses, which include HCoV-NL63, MERS-CoV, and SARS-CoV-1, and by extrapolation to SARS-CoV-2 (4). The pre-fusion stabilized SARS-CoV-2 Spike construct to be evaluated in the current study is based on this research.

The antigen will be manufactured using the same technology as is used to manufacture Flublok vaccine, which is a recombinant hemagglutinin (HA) vaccine licensed for the prevention of influenza in adults 18 years of age and older (8). In this system, the gene of interest is cloned into a baculovirus transfer vector, which is used to form recombinant baculoviruses. The viral stock is used to infect an insect cell line (*Expres*SF+). The recombinant protein is expressed in the infected insect cells. After incubation, the recombinant protein is purified. This process is adaptable to a variety of antigens. Millions of doses of Flublok vaccine have been administered since its approval for human use corresponding to HAs of different influenza strains (H1, H3, and B) covering multiple influenza seasons. Additionally, the process has previously been applied to the development of candidate SARS-CoV-1 vaccines. Following the SARS outbreak, Protein Sciences developed candidate S protein vaccines, including a full-length S protein and a transmembrane-deleted ectodomain antigen. These were tested in a variety of preclinical models and found to induce neutralizing antibody responses and to be partially protective in a ferret challenge model.

It is anticipated that, owing to the need to mobilize naïve B and T cell responses, the magnitude and quality of the immune response to the candidate antigen will be enhanced through delivery with an adjuvant. This may allow for titration of the amount of antigen used; and, thus, be antigen-sparing and potentially increase the available supply of antigen. In addition, the adjuvant may influence the quality of the immune response. Prior mouse experiments with candidate SARS-CoV-1 vaccines had identified that recombinant S protein candidates were immunogenic and that adjuvantation with alum could improve the titer of neutralizing antibodies (9). However, in these experiments it was observed that mice receiving the alum-adjuvanted, recombinant S protein vaccine displayed immunopathology in the lungs that was suggestive of a T-helper (Th)2-type response. Therefore, in this program to develop a SARS-CoV-2 vaccine with recombinant protein (SARS CoV2 prefusion Spike delta TM [SARS CoV2 preS dTM]), the adjuvants AS03 and AF03, that may promote a more balanced Th1/Th2 response (10) (11), are being investigated.

AS03 and AF03 are both oil-in-water emulsions containing squalene. Both have been evaluated in the context of pandemic or pre-pandemic influenza vaccines. Safety of AS03-adjuvanted products has been extensively evaluated and found to be generally well tolerated with an acceptable safety profile (12). AS03 was evaluated with pandemic H7 HA manufactured by Protein Sciences in humans, demonstrating robust neutralizing antibody responses and hemagglutination inhibition, together with an acceptable safety profile. As has been the case for several pandemic agents, unadjuvanted H7 HA-containing influenza vaccines were poorly immunogenic (13) (14).

AF03 has been administered to over 1,500 humans in the setting of clinical trials and was approved for use in Europe as a component of Humenza®, an H1N1 pandemic influenza vaccine (15). In a more recent study, AF03 was demonstrated to have strong effects on the magnitude and breadth of neutralizing responses to influenza in mice (16). A preclinical study in macaques demonstrated a higher level of protection following AF03-adjuvanted vaccination from pneumonia and decrease severity of lung disease on challenge with the homologous H5N1 influenza strain than alum-adjuvanted or unadjuvanted comparators. The protection was correlated with the level of neutralizing antibodies (17). Recent human clinical experience has included use of AF03 in combination with quadrivalent inactivated influenza antigens (n=40, 15 µg of HA per strain, total of 60 µg of protein) and quadrivalent baculovirus recombinant influenza antigens (n=40, 45 µg of HA per strain, total of 180 µg of protein manufactured by Protein Sciences) in a Phase I trial (NCT03945825); the formulations were found to be generally well tolerated, and review by the study Data and Safety Monitoring Board revealed no safety concerns.

A potential safety issue with coronavirus vaccines is the ability to potentiate immunopathology in vaccinees upon exposure to wild-type virus (18). The molecular mechanism for this phenomenon, sometimes termed Antibody Dependent Enhancement, Vaccine-Associated Enhanced Respiratory Disease, or Immune Enhancement of viral infection, is also not fully understood. In the context of coronavirus infections, various factors have been suggested as potentially contributing to the phenomenon. These include the epitope targeted, the method of delivery of the antigen, the magnitude of the immune responses, the balance between binding and functional antibodies, the elicitation of antibodies with functional characteristics such as binding to particular Fc receptors, and the nature of the Th cell response (9) (19) (20). It is anticipated that the design of the candidate SARS-CoV-2 antigen selected for this study will promote generation of robust neutralizing antibodies over binding antibodies, based on data generated with other coronavirus vaccine antigens (4) (7). The inclusion of adjuvanted formulations is anticipated to further

enhance the magnitude of neutralizing antibody responses and induce a balanced Th1/Th-2 cell responses (10) (11). Taken together, these strategies mitigate by design theoretical risks of immune enhancement of viral infection.

2.1 Study Rationale

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

2.2 Background

SARS-CoV-2 is a novel coronavirus that emerged in the human population and has led to a pandemic of acute respiratory disease named COVID-19. Coronaviruses are a family of large, enveloped, positive-sense, single-stranded ribonucleic acid (RNA) viruses that infect a wide variety of mammalian and avian species. The viral genome is packed into a capsid comprised of the viral nucleocapsid protein, which is in turn surrounded by an envelope. Viral proteins associated with the envelope include the S protein, which mediates viral attachment and entry into cells.

The burden of SARS-CoV-2 morbidity and mortality has been catastrophic with greater than 815,000 deaths recorded since first emerging in December 2019 among over 23.7 million confirmed cases (as of 25 August 2020) (2). In many locations, the rapid emergence of COVID-19 has overwhelmed the capacity of health systems to provide care for COVID-19-affected patients, let alone unaffected patients. Interventions to reduce transmission through reduction of population contact has had economic consequences. A safe and effective vaccine would be a vital tool to address the significant medical and societal burden caused by the pandemic.

The CoV2 preS dTM recombinant protein vaccine belongs to the pharmacotherapeutic group of “Other viral vaccines”. The vaccine contains recombinant S protein, stabilized to maintain native prefusion trimer configuration as present on the viral envelope.

Further details of the chemistry, pharmacology, and safety of the CoV2 preS dTM recombinant protein vaccine are provided in the Investigator’s Brochure (IB).

2.3 Benefit/Risk Assessment

The novel coronavirus outbreak started in December 2019 in Wuhan City, Hubei Province, China. Since the end of 2019, more than 80,000 COVID-19 cases have been reported in China, mostly in Hubei and surrounding provinces. Following the lock down in China, the incidence had decreased at the beginning of March but had already rapidly spread globally. As of 25 August 2020, the virus has been detected in 188 countries/regions, infected over 23.7 million individuals, and over 815,000 persons have died from COVID-19 (2).

The investigational recombinant protein vaccine consists of a stabilized prefusion trimer of the SARS-CoV-2 S protein. The coronavirus S protein precursor is cleaved to form non-covalently associated subunits, S1 and S2 (5). The S1 subunit contains the RBD, which attaches to the viral receptor; the RBD is the major antigenic target for immune responses. The S2 domain contains

the fusion peptide and transmembrane regions, which undergoes a conformational change to mediate viral fusion with the host cell. The S1 and S2 subunits combine as a trimer of each subunit.

It is anticipated that owing to the need to mobilize naïve B and T cell responses, the magnitude of the immune response to the candidate antigen will be enhanced through delivery with an adjuvant. This may allow for titration of the amount of antigen used; and, thus, be antigen-sparing and potentially increase the available supply of antigen. In addition, the adjuvant may influence the character of the immune response. Prior mouse experiments with candidate SARS-CoV-1 vaccines had identified that recombinant S protein candidates were immunogenic and that adjuvantation with alum could improve the titer of neutralizing antibodies (9). However, in these experiments it was observed that mice receiving the alum-adjuvanted, recombinant S protein vaccine displayed immunopathology in the lungs that was suggestive of a Th2-type response. Therefore, the adjuvants AS03 and AF03, that may promote a more balanced Th1/Th2 response (10) (11), will be investigated.

A potential safety issue with coronavirus vaccines is the ability to potentiate immunopathology in vaccinees upon exposure to wild-type virus (18). The potential for a coronavirus vaccine to exacerbate disease is a theoretical concern that has not been documented to date, but that will be explained as a theoretical risk in the Informed Consent document.

AF03 is a squalene emulsion-based adjuvant similar to MF59 and AS03 adjuvants but utilizes an alternative manufacturing process that involves phase inversion temperature emulsification and incorporates 2 non-ionic surfactants (15). During the 2009 H1N1 pandemic, Sanofi Pasteur developed an AF03 adjuvanted A/H1N1 pandemic influenza vaccine (Humenza) and performed clinical studies to support the licensure of the vaccine. Clinical trials using AF03 with A/H5N1 and A/H1N1 pandemic influenza antigen have been performed in adults (21); elderly; and children, including infants (22). Taken together, the data from these studies showed that AF03 enhanced the magnitude of antibody response, proportion of participants with seroprotective titers and durability of antibody responses. With regards to safety, the addition of AF03 was associated with a higher frequency of solicited injection site reactions as expected with any adjuvanted vaccine, while solicited systemic reactions and unsolicited adverse events (AEs) varied in each age group. Overall, AF03 appears to be safe and well tolerated when administered as half- or full-dose (6.2 mg or 12.5 mg of squalene per vaccine dose) and in any age group. No safety signals were detected with AF03 adjuvanted pandemic influenza vaccines in any of the populations included in the clinical studies.

Like AF03 adjuvant, AS03 is an oil-in-water emulsion containing squalene. To support the licensing of A/H1N1 pandemic influenza vaccines in elderly people, Pandemrix® and Arepanrix®, 2 large clinical studies were carried out in participants aged 61 years and above (23). Additional clinical studies were conducted in adults ≥ 18 years of age, children from 6 months to 18 years, and older adults ≥ 65 years of age as well as post-licensure safety studies (12). All these studies but 2 were conducted with vaccine antigen of H1N1 strain. The 2 other clinical studies assessed the vaccines antigens H7N1 and H9N2 (24). Q-Pan®, an Influenza A (H5N1) Virus Monovalent Vaccine adjuvanted with AS03 is licensed by the US FDA. AS03 was also assessed in the development of an adjuvanted trivalent influenza vaccine (TIV). A Phase III efficacy trial evaluated efficacy of AS03-adjuvanted TIV compared to unadjuvanted TIV among 43,695

volunteers 65 years of age or older. Taken together, these studies and post-licensure data showed that AS03 enhanced antibody and T cell responses with an acceptable safety profile.

Of note, based on the theoretical concern that vaccination with an adjuvanted vaccine containing potent immunostimulants may interfere with immunological self-tolerance, pIMDs (potential Immune-Mediated Diseases) are adverse events of special interest (AESIs) undergoing special safety monitoring for vaccines containing Adjuvant Systems. pIMDs are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurological disorders of interest which may or may not have an autoimmune etiology (see Table 10.5 for a full list).

The efficacy of the candidate vaccine formulations has not been established. CoV2 preS dTM Recombinant Protein Candidate Vaccine Benefit/Risk Profile is expected to be positive based on available evidence. Study participation and study conduct is considered fundamental from the societal perspective towards the goal of finding a vaccine to help control the pandemic and decrease individual and public health burden of COVID-19 illness and SARS-CoV-2 infection.

The CoV2 preS dTM vaccine is expected to confer protection against SARS-CoV-2 infection and/or COVID-19 disease and its complications with a clinical benefit of reduction of the associated burden of disease in population over 18 years of age.

More detailed information about the known and expected benefits and risks, reasonably expected AEs, the potential risks, and uncertainties of CoV2 preS dTM vaccine may be found in the CoV2 preS dTM vaccine IB.

In addition, information related to the AF03 adjuvant may be found in the AF03 IB.

Also, more detailed information related to the AS03 adjuvant will be made available by GlaxoSmithKline (GSK).

2.3.1 Risks from Study Participation

The potential risks of clinical significance and risk management are summarized in Table 2.1.

Table 2.1: Potential risks of clinical significance and risk management

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
Investigated Vaccine: CoV2 preS dTM (AF03 or AS03)		
Anaphylactic reactions	Class-effect for all vaccines (even not adjuvanted)	Observation period after vaccination for early detection and treatment Risk management will also be based on Exclusion criterion E08 (see Section 5.2).
Enhanced COVID-19	A potential safety issue with coronavirus vaccines is the ability to potentiate immunopathology in vaccinees upon exposure to wild-type virus (18). The molecular mechanism for this phenomenon, sometimes termed Antibody Dependent Enhancement, Vaccine-Associated Enhanced Respiratory Disease, or Immune Enhancement of viral infection, is also not fully understood. In the context of coronavirus infections, various factors have been suggested as potentially contributing to the phenomenon. These include the epitope targeted, the method of delivery of the antigen, the magnitude of the immune responses, the balance between binding and functional antibodies, the elicitation of antibodies with functional characteristics such as binding to particular Fc receptors, and the nature of the T-helper cell response (9) (19) (20) (25)	COVID-19-like illness will be part of the efficacy objective with active and passive surveillance. It is anticipated that the design of the candidate SARS-CoV-2 antigen selected for this study will promote generation of robust neutralizing antibodies over binding antibodies, based on data generated with other coronavirus vaccine antigens (4) (7). The inclusion of adjuvanted formulations is anticipated to further enhance the magnitude of neutralizing antibody responses and induce a balanced Th1/Th-2 cell responses (10) (11). Taken together, these strategies mitigate by design theoretical risks of immune enhancement of viral infection. Individuals with chronic comorbid conditions considered to be associated with an increased risk of severe COVID-19 will be excluded (26). Number of study participants of older age group will be minimized to balance the theoretical risks and the ability to determine the consistency of the immune responses compared to younger adults. In addition, no older age group study participants are included in the antigen-only group (without adjuvant).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
Potential Immune-Mediated Diseases	Based on the theoretical concern that vaccination with an adjuvanted vaccine containing potent immunostimulants may interfere with immunological self-tolerance, pIMDs are AESIs undergoing special safety monitoring for vaccines containing Adjuvant Systems. pIMDs are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurological disorders of interest which may or may not have an autoimmune etiology.	During the informed consent process, the participants enrolling in the study will be informed of this potential risk and the need to attend the clinic if they are unwell. pIMD is an AESI and will be collected until study end. The occurrence of pIMD cases will be described.
Refer to IBs' Section 5 and Section 6 for more information regarding potential risks.	Refer to the IB Section 5 and Section 6 for more information regarding the data from previous experience with the adjuvants in the investigated vaccine.	
Study Procedures		
Vasovagal reactions (near-syncope or syncope), or psychogenic reactions to needle (vaccine injection or blood sampling)	Anxiety-related reactions can occur following, or even before, any vaccination as a psychogenic response to the needle injection or blood draw, and may be accompanied by several neurological signs such as transient visual disturbance, paresthesia or seizure-like activity	Observation period after vaccination for early detection and treatment
Theoretical risk that participant can be exposed to other SARS-CoV-2 infected individuals	SARS-CoV-2 infection is highly contagious. SARS-CoV-2 spreads through respiratory secretion or droplets. Transmission may also be possible via contaminated surfaces. Exposure can theoretically occur as a result of study procedures, including visits to the investigational sites and physical interactions with study staff.	Participant contact with other individuals when visiting study site (study site to set up system) should be minimized Protective material (eg, masks for participants, clothing, goggles) to be used in sites. Home visit option for completion of study procedures in the setting of containment measures to minimize exposure.

2.3.2 Benefits from Study Participation

While the benefit and risks of the candidate vaccine formulations at the individual level are largely unknown, study participation and study conduct is considered fundamental from the societal perspective towards the goal of finding a vaccine to help control the pandemic and decrease individual and public health burden of COVID-19 illness and SARS-CoV-2 infection.

2.3.3 Overall Benefit-Risk Conclusion

Considering the significant medical need, scale of the pandemic, urgent requirement for measures to address the pandemic, together with actions taken to minimize risk to participants enrolled in the study, there is no unreasonable and significant risk of illness or injury for the participants.

3 Objectives and Endpoints

The study objectives and the corresponding endpoints are described in Table 3.1.

Table 3.1: Objectives and endpoints

Objectives	Endpoints
Primary	
Immunogenicity To describe the neutralizing antibody profile at D01, D22, and D36 of each study intervention group.	***Immunogenicity*** Neutralizing antibody titers will be measured with the neutralization assay. • Antibody titer at D01, D22, and D36 • Fold-rise (fold-rise in serum antibody neutralization titer post-vaccination relative to D01) at D22, and D36 • 2-fold and 4-fold rise in serum neutralization titer (post/pre) relative to D01 at D22, and D36 • Occurrence of neutralizing antibody seroconversion, defined as baseline values below lower limit of quantification (LLOQ) with detectable neutralization titer above assay LLOQ at D22 and D36
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.	***Safety*** • Presence of unsolicited systemic AEs reported in the 30 minutes after each injection • Presence of solicited (pre-listed in the participant's diary card and Case Report Form [CRF]) injection site reactions and systemic reactions occurring up to 7 days after each injection • Presence of unsolicited AEs reported up to 21 days after each injection • Presence of medically attended adverse events (MAAEs) throughout the study • Presence of serious adverse events (SAEs) and adverse events of special interest (AESIs) throughout the study • 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)

Secondary	
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 D366 (Cohort 1) or D387 (Cohort 2) of each study intervention group.	***Immunogenicity*** Binding antibody titers to full-length SARS-CoV-2 Spike protein will be measured for each study intervention group with the enzyme-linked immunosorbent assay (ELISA) method. • Individual anti-S antibody concentration at D01, D22, D36, D181 (Cohort 1) or D202 (Cohort 2), and D366 (Cohort 1) or D387 (Cohort 2) • Individual anti-S antibody concentration ratio (fold-rise in serum ELISA concentration post-vaccination relative to D01) at D22, D36, D181 (Cohort 1) or D202 (Cohort 2), and D366 (Cohort 1) or D387 (Cohort 2) • Fold-rise in anti-S antibody concentration (post/pre) ≥ 2 and ≥ 4 at D22, D36, D181 (Cohort 1) or D202 (Cohort 2), and D366 (Cohort 1) or D387 (Cohort 2) Neutralizing antibody titers will be measured with the neutralization assay. • Antibody titer at D181 (Cohort 1) or D202 (Cohort 2) and D366 (Cohort 1) or D387 (Cohort 2) • Fold-rise (fold-rise in serum neutralization titer post-vaccination relative to D01) at D181 (Cohort 1) or D202 (Cohort 2) and D366 (Cohort 1) or D387 (Cohort 2) • 2-fold and 4-fold rise in serum neutralization titer [post/pre] relative to D01 at D181 (Cohort 1) or D202 (Cohort 2) and D366 (Cohort 1) or D387 (Cohort 2) • Occurrence of neutralizing antibody seroconversion, defined as values below LLOQ at baseline with detectable neutralization titer above assay LLOQ at D181 (Cohort 1) or D202 (Cohort 2) and D366 (Cohort 1) or D387 (Cohort 2)
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.	***Efficacy*** • Virologically-confirmed COVID-19-like illness as defined by specified clinical symptoms and signs and confirmed by nucleic acid viral detection assay • Serologically-confirmed SARS-CoV-2 infection as defined by SARS-CoV-2-specific antibody detection in a non-S ELISA • Correlates of risk / protection based on antibody responses to SARS-CoV-2 as evaluated using virus neutralization or ELISA, considering virologically-confirmed COVID-19-like illness and/or serologically-confirmed SARS-CoV-2 infection as defined above

Exploratory	
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.	***Immunogenicity*** • T-helper cell (Th)1 and Th2 cytokines will be measured in whole blood following stimulation with full-length S protein and/or pools of S-antigen peptides • Ratio between binding antibody (ELISA) concentration and neutralizing antibody titer
Other To evaluate other emerging biomarkers as effect modifiers or as correlates of risk / protection.	Biomarker measurement at baseline and/or post-vaccination visits (D22, D36, D113 [Cohort 1] or D134 [Cohort 2], D181 [Cohort1] or D202 [Cohort 2]), and D366 [Cohort 1] or D387 [Cohort 2])

4 Study Design

4.1 Overall Design

The design of the study is summarized in Table 4.1.

Table 4.1: Overall design

Type of design	Parallel group, first-in-human, placebo-controlled, dose-ranging, multi-center study with a Sentinel Safety Cohort and Early Safety Data Review (ESDR)
Phase	I/II
Control method	Placebo-controlled
Study population	Healthy, seronegative adults 18 years of age and older
Level and method of blinding	• Blinding for vaccine group assignment (formulation and adjuvant): participants, outcome assessors, Investigators, laboratory personnel, Sponsor study staff (except those involved in ESDR, and for concerned participants only) • No blinding for injection schedule • No blinding for vaccine group assignment: those preparing/administering the study interventions
Study intervention assignment method	Enrollment will be stratified by age: 300 participants 18-49 years of age and 140 participant ≥ 50 years of age. All 440 participants will be randomized to receive either 1 injection (Cohort 1) or 2 injections (Cohort 2) of the study intervention to which they are randomized.

Number of participants	Approximately 440 participants 18 years of age and older (300 adults 18 through 49 years of age and 140 adults ≥ 50 years of age) are planned to be randomized

Intervention groups	Within each cohort:
	• 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
	See also Table 4.2 below.

Total duration of study participation	Approximately 365 days post-last dose: • Cohort 1: approximately 365 days duration total • Cohort 2: approximately 386 days duration total
Countries	United States
Use of an Independent Data Monitoring Committee, Dose Escalation Committee, or similar review group	NO

A total of 440 participants are planned to be enrolled. At the time of inclusion, participants will be screened for SARS-CoV-2 seropositivity status and stratified according to age. Those who are seronegative will be randomized as shown in Table 4.2.

As a precautionary step, a Sentinel Safety Cohort of 6 participants (younger adults only) within each dosing group from Cohort 1 will be enrolled. An Early Safety Data Review (ESDR) will be performed, including evaluation of safety data and laboratory measures to D09 in Cohort 1 among younger adults 18-49 years of age. Upon acceptable safety demonstrated from unblinded data review by limited members of the Sponsor Study Team (RMO, 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. Further details are provided in Section 8.4.

Table 4.2: Planned sample size

Participants 18-49 years of age					
Cohort	**Group**	**Dose Level***	**Adjuvant**	**N**	
				Sentinel Safety† (N=30)	**Total (N=300)**
Cohort 1: 1 injection	**1**	5 µg	AF03	6	20
	2	5 µg	AS03	6	20
	3	15 µg	AF03	6	20
	4	15 µg	AS03	6	20
	5	Placebo	None	6	20
Cohort 2: 2 injections	**6**	5 µg	AF03	N/A	20
	7	5 µg	AS03	N/A	60
	8	15 µg	AF03	N/A	20
	9	15 µg	AS03	N/A	60
	10	15 µg	None	N/A	20
	11	Placebo	None	N/A	20
Participants 50 years of age and older					
Cohort	**Group**	**Dose Level***	**Adjuvant**	**N (N=140)**	
Cohort 1: 1 injection	**1**	5 µg	AF03	10	
	2	5 µg	AS03	10	
	3	15 µg	AF03	10	
	4	15 µg	AS03	10	
	5	Placebo	None	10	
Cohort 2: 2 injections	**6**	5 µg	AF03	10	
	7	5 µg	AS03	30	
	8	15 µg	AF03	10	
	9	15 µg	AS03	30	
	10	15 µg	None	N/A‡	
	11	Placebo	None	10	

*Antigen Formulation naming for each dose level: CoV2 preS dTM antigen: Formulation 1 (low-dose [5 µg]); Formulation 2 (high-dose [15 µg])

† Sentinel Safety Cohort: 6 participants within each dosing group from Cohort 1 (18-49 years of age only) will be included in the Sentinel Safety Cohort.

‡ As part of risk mitigation for enhanced COVID-19, the older age stratification (≥ 50 years) will not be allocated to this study arm.

Note: 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 the same intervention as received at D01) of study vaccine formulation or placebo at D22 (VAC2).

If a COVID-19 vaccine becomes available from a company other than Sanofi Pasteur, then participants are free to receive that vaccine. Participants who receive a COVID-19 vaccine will still be followed for safety until the end of the study but will be discontinued from study intervention administration thereafter.

4.2 Scientific Rationale for Study Design

Rationale for Development Approach

The development approach for the CoV2 preS dTM vaccine candidate is undergirded by the fact that it is taking place in the setting of a pandemic. As such, the emphasis of the development plan is rapidly generating the data required to support approval and vaccine deployment to the field.

Acceleration of the evaluation in this first-in-human trial is justified by the extensive characterization available for both the manufacturing system used to produce the recombinant antigen and the adjuvants to be administered in the trial.

The manufacturing platform is the same as is used to produce Flublok vaccine, a licensed recombinant HA influenza vaccine. In the context of influenza vaccine development, thousands of younger and older adults have received proteins manufactured utilizing the same technology and process employed for this CoV2 preS dTM vaccine candidate. Furthermore, millions of younger and older adults have received recombinant protein vaccines using this manufacturing system post-marketing, at total protein doses several times higher than the highest dose targeted in the present study (quadrivalent Flublok vaccine contains a total of 180 µg of HA protein; the highest dose of this CoV2 preS dTM vaccine is 15 µg in the study). While clinical and post-marketing experience with proteins manufactured with the baculovirus manufacturing system is specific for influenza proteins, it is relevant to point out that these include different proteins (H1, H3, B Yamagata, B Victoria HAs), with each one changed over time to support the recommended compositions of seasonal influenza vaccines. This provides reassurance about the safety of the protein manufacturing platform, at protein doses higher than planned in this study, and for a variety of different protein constructs.

AF03 was administered to more than 1500 individuals as part of the clinical development of adjuvanted influenza vaccines. This included exposure of children and adults, including elderly adults; more than 200 older adults received inactivated influenza vaccine in combination with AF03. No safety concerns were identified in these studies, and AF03 adjuvanted vaccines were safe and well tolerated. The clinical development of AF03-adjuvanted H1N1 influenza vaccine led to regulatory approval of the Humenza vaccine by the European Medicines Agency (EMA).

AS03 has been administered to thousands of individuals (adults and elderly) as part of clinical trials of influenza vaccines as well as other vaccines (27). Notably, more than 20,000 older adults

received AS03-adjuvanted influenza vaccine in a large, multi-country efficacy trial (24). Furthermore, hundreds of millions of doses of AS03-adjuvanted H1N1 vaccines were administered post-licensure in the context of H1N1 pandemic control. The vaccines were found to be well tolerated. Of note, an increased risk of narcolepsy was observed in some individuals after the vaccination campaign with Pandemrix in 2009-2010. A similar risk of narcolepsy was not identified with other non-adjuvanted influenza vaccines or other AS03-adjuvanted vaccines, like Arepanrix (28) (29). Current data suggest that cases of narcolepsy seen immediately following the 2009/2010 pandemic were the result of an immune cascade, triggered by CD4 T cell cross-reactivity to HA proteins from the H1N1 virus itself and hypocretin. This conclusion is consistent with the position reached by the EMA in 2016 when it concluded that: "*Based on the evidence generated so far, a hypothesis that takes into account the potential role of antigen is more likely to explain the increased risk of narcolepsy observed with Pandemrix than hypotheses that are based on a direct role for the AS03 adjuvant*" (30).

Recombinant proteins produced in the baculovirus manufacturing platform by Protein Sciences have been administered with both AF03 and AS03. AF03 was administered to 40 adults 18 through 45 years of age in a Phase I trial (NCT03945825) as the adjuvant of a quadrivalent recombinant influenza vaccine (total of 180 µg of HA protein, 4 different HA proteins at 45 µg each). The study is ongoing, and more than 8 months of follow-up have been completed; and Independent Data and Monitoring Committee (IDMC) has evaluated the safety data and has not raised any safety concerns. AS03 was administered to 184 adults 18 through 49 years of age with an H7 recombinant influenza vaccine in study BP-I-17-002 (NCT03283319) sponsored by the Biomedical Advanced Research and Development Authority (BARDA). The AS03 adjuvanted H7 recombinant protein vaccine was found to be safe and well tolerated and led to robust immune responses.

As a precautionary step, a Sentinel Safety Cohort of 6 participants (younger adults only) within each dosing group from Cohort 1 will be enrolled. An ESDR will be performed, including evaluation of safety data and laboratory measures to D09 in Cohort 1 among younger adults 18-49 years of age. Upon acceptable safety demonstrated from unblinded review by limited members of the Sponsor Study Team (RMO, 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. A non-clinical toxicology study in New Zealand White Rabbits is planned and will provide rabbit first-dose safety data prior to initiation of human clinical testing. Additional non-clinical safety evaluations will proceed in parallel to this human clinical trial.

Data up to D43, in addition to preclinical data, will support the selection of a formulation or formulations and dosing schedule to proceed to further testing in Phase III.

Rationale for Injection Schedule

In the setting of a pandemic, a single injection would be ideal to be able to protect vaccinees as early as possible and better manage vaccine supply. However, given the lack of pre-existing immune responses to SARS-CoV-2, it is most likely that 2 injections may be necessary.

A separation of 21 days for the 2-injection schedule is proposed for this program, mirroring the schedule that was evaluated and approved for pandemic influenza vaccines to address the 2009 H1N1 influenza pandemic (AS03 adjuvanted vaccines Pandemrix™, Arepanrix™; and AF03 adjuvanted Humenza vaccine). This schedule results in a second injection of the vaccine being administered earlier than with other common vaccines with longer separations between injections (ie, 28 days), thus aiming at earlier generation of potentially protective immune responses. This may be of particular interest in an ongoing pandemic setting.

In addition to antibody response 21 days after the first injection, durability after a single injection also needs to be taken into account for schedule selection decisions, as peak immune responses after 1 injection may be adequate but could (at least theoretically) wane rapidly, potentially leaving vaccinees at risk in the event of ongoing circulation of the novel coronavirus. A further consideration is allowing sufficient time for contraction of innate immune responses and expansion of the adaptive immune response after dosing, which would be underestimated if evaluated too soon after the dose. In this regard, at least fourteen days after a second dose is deemed sufficient, based on experience with other vaccines (27) (31) (32).Therefore, antibody titers at D22 (21 days after the first injection) and D36 (14 days after a second injection) after a single injection or after 2 injections are considered relevant for informing schedule selection.

Rationale for Primary Immunogenicity Endpoint

Human experimental coronavirus infection studies have identified that the presence of pre-challenge neutralizing antibodies were predictive of protection from infection or symptoms following challenge (33) (34). For this reason, neutralizing responses are expected to provide the most relevant functional evaluation of immune responses for this vaccine candidate.

Rationale for Study Population

The study will enroll participants with no history of COVID-19 or serologic evidence of SARS-CoV-2 infection by rapid diagnostic test at the baseline visit. Inclusion of individuals with prior exposure to SARS-CoV-2 would be expected to influence immunogenicity measures. This trial is geared to identifying the dose-level of CoV2 preS dTM vaccine formulation that best supports an immune response in the naïve population, considered the population most at need for a preventive solution against SARS-CoV-2. Therefore, the immunogenicity and safety data in this study are targeted to be generated in individuals without evidence of prior exposure to SARS-CoV-2 infection.

The study will be conducted in adults 18 years of age and older. Clinical and epidemiological data from the COVID-19 pandemic have consistently indicated a higher risk of severe complications and death in older adults (35) (36). Therefore, it is considered of great relevance to generate data in the older adult population to inform schedule and formulation selection that will serve the general adult population, including those at particular risk of poor outcomes. A Sentinel Safety Cohort among younger adults is included to provide preliminary short-term safety data prior to enrollment of older adult participants. The study incorporates several measures to mitigate the theoretical risk of vaccine-associated ERD. These include a higher representation of the younger adult strata for the same reason, given that adults over 50 years of age have also been overrepresented in studies describing critical illness and death, although to a lesser degree than those older than 75 years (35). Therefore, the proposed design aims at generating data that will allow selection of the relevant formulations and injection schedule accounting for potential age

effects. Data for each formulation will be generated in both younger adults and older adults, allowing the evaluation of the consistency in the patterns of immune response for each formulation between the 2 age strata; additionally, aggregated "main" effects by age will be evaluable by comparing pooled older adult data (n=120 across vaccine formulations) and pooled younger adult data (n=240 across vaccine formulations with corresponding data in the older strata).

Evidence to date indicates that individuals with chronic medical conditions are at increased risk of severe outcomes associated with COVID-19 (37). The exclusion of individuals with chronic underlying conditions is considered an additional risk mitigation measure to address the theoretical phenomenon of immune enhancement. Clinical and epidemiological data indicates that the overrepresentation of older adults among those with critical or fatal COVID-19 illness is meaningfully ameliorated when stratified/controlled for the presence of chronic medical conditions (26). Exclusion of individuals with chronic medical conditions from this trial mitigates the potential (theoretical) risk of exacerbating the occurrence of critical or fatal outcomes as a result of study participation.

Rationale for Active Arms

The study aims at selecting schedule and formulation to progress to further clinical development. The importance of the schedule evaluation has been stated above, and it is the justification for inclusion of Cohort 1 and Cohort 2 in each age strata in the study. Within each cohort, the study design allows the evaluation of the candidate vaccine protein dose level (2 different dose levels) adjuvanted with AS03 or AF03. A range of dose level evaluation is of particular interest in the setting of a pandemic: if adequate responses are observed with lower doses of antigen, higher number of doses of vaccine could be supplied to address the anticipated large demand that will be needed to end the pandemic.

Within Cohort 2, the study includes an arm with the higher dose level of protein antigen alone (unadjuvanted). This arm allows the evaluation and demonstration of the expected adjuvant effects (magnitude and quality of the immune response and dose-sparing effect). While it is anticipated that an adjuvanted formulation will be optimal, this study design will allow the generation of empirical data supporting such assumption. The unadjuvanted arm is restricted to the younger adult stratum, as a risk mitigation measure: previous studies with SARS-CoV-1 inactivated and protein-based vaccines suggested the possibility of vaccine-induced immunopathology upon viral infection when used alone or with a Th2-based adjuvant (alum) (9). AS03 and AF03 adjuvants have been generally associated with a balanced Th1/Th2 immune response (10) (11). Exclusion of unadjuvanted arms from the older adult stratum mitigates the potential (theoretical) risk of vaccine-induced immunopathology occurring in those who are already at higher risk of more severe COVID-19 illness.

Rationale for Higher Sample Size for AS03 Cohort 2 Arms, and Rationale for Including AF03

Given the large clinical and post-marketing experience with AS03, in addition to its readiness for large-scale supply and the extensive and multi-national regulatory experience, higher priority will be given to AS03 adjuvanted formulations for advancement into Phase III development. Nevertheless, generating meaningful Phase I/II clinical data with AF03 adjuvanted formulations is still of interest for several reasons: 1) AF03 can serve as an alternative adjuvant system, should any issues arise during development with AS03; 2) the AF03 adjuvant may still allow to increase

future supply, in the event supply beyond AS03 capacity is possible with the recombinant protein and needed to address the pandemic; 3) the AF03 adjuvant may be of interest in the future if COVID-19 becomes seasonal, in which case a co-formulated vaccine would be attractive; in such circumstances, co-formulation with AF03 will be more feasible than with AS03 as both protein and adjuvant are proprietary to Sanofi Pasteur. The higher priority given to AS03 adjuvanted formulations and the higher likelihood of robust immune responses with a 2-injection schedule provides rationale to generate more precise data for AS03 formulations in Cohort 2 of this Phase I/II study; this is the justification for a sample size of 90 across age groups for the AS03 adjuvanted arms in Cohort 2. All other arms in the study will have a size of 30 total, except for the un-adjuvanted arm which would only comprise 20 younger adults.

Rationale for Blinding

This is an observer-blind study for formulation and adjuvant. Owing to the need for mixing of study formulations from separately supplied antigen, adjuvants, and / or diluent, the person preparing and administering the vaccine will be unblinded to vaccine group assignment. Blinding of all "observers" will minimize the risk of bias arising from the possibility of consciously or unconsciously influencing the reporting of study outcome measures due and knowledge of the formulation administered.

Rationale for Placebo

Placebo, rather than a benefit licensed vaccine, will be used for comparison to vaccine to allow safety comparisons between vaccine and placebo as there are no other licensed COVID-19 vaccines on the market. The inclusion of placebo groups will also maintain the blind, allowing the unbiased evaluation of clinical outcomes related to COVID-19-like illness and SARS-CoV-2 infection by treatment group (secondary efficacy objective).

4.3 Justification for Protein Dose Levels

Dose levels are based on data from previous studies with AF03 for Sanofi Pasteur's Influenza vaccine products, a study done with Sanofi Pasteur-manufactured monovalent H7N9 influenza vaccine adjuvanted with AS03 or MF59 (38), and on studies done with Panblok H7 adjuvanted with AS03 and MF59. Additionally, formulations of SARS candidates and recently reported data from candidate SARS-CoV-2 vaccines that were developed and tested preclinically informed the range of antigen dosing that was considered.

- For Sanofi Pasteur's pandemic influenza vaccine projects, the main doses evaluated with H1 and H5 antigens adjuvanted with AF03 were 3.8 µg, 7.5 µg, and 15 µg.
- For monovalent H7N9 influenza vaccine, 2 doses of 3.75 µg, 7.5 µg or 15 µg of H7 antigen adjuvanted with AS03 were compared to a variety of other formulations and vaccine combinations, including 2 doses of 45 µg of H7 antigen alone.
- For Panblok H7, the doses evaluated in Study BP-I-17-002 with MF59 and AS03 were: 3.75 µg, 7.5 µg, and 15 µg.
- For Protein Sciences' SARS-CoV dTM S protein vaccine, the doses evaluated with or without Alhydrogel® were 5 µg, 15 µg, and 45 µg.

- A recombinant prefusion stabilized SARS-CoV-2 S protein vaccine manufactured in baculovirus expression system was tested in non-human primates at doses of 1 µg, 5 µg, and 25 µg, delivered with a proprietary adjuvant (39).
- An inactivate whole virus SARS-CoV-2 candidate vaccine adjuvant with Alum was tested in non-human primates at doses of 2 µg and 8 µg per dose (40).

It is unknown how immunogenic the CoV2 preS dTM vaccine will be compared to recombinant influenza antigens. Assuming conservatively that it will be weakly immunogenic, the responses following administration of H7 Panblok with MF59 and AS03 are informative. H7 (in common with H5) is weakly immunogenic (13) (14) and could frame dosing expectations under this conservative assumption.

The homologous and heterologous seroprotection (hemagglutination inhibition [HAI] titer ≥ 1:40) rate responses at D50 to H7 with MF59 were generally lower than H7 with AS03. With AS03, homologous and heterologous HAI seroprotection rates above 95% were seen with the 7.5 µg and the 15 µg dose groups, and homologous seroprotection responses of 94.6% were seen with the 3.75 µg dose. With MF59, the homologous HAI seroprotection responses seen with the highest dose (15 µg) were lower than the heterologous HAI seroprotection observed with the lowest dose of AS03 (3.75 µg). These findings highlight that even for immunogens considered poorly immunogenic, robust immune responses can be generated with lower antigen doses when delivered in a 2-dose series with a suitable adjuvant.

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed the last contact planned in the SoA.

The end of the study is defined as the date of the last contact of the last participant in the study.

However, for periodic safety reports, the study is considered completed when the Clinical Study Report is finalized.

5 Study Population

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

5.1 Inclusion Criteria

Participants are eligible for the study only if all of the following criteria are met:

I01: Aged 18 years of age or older on the day of inclusion
I02: Informed consent form has been signed and dated
I03: Able to attend all scheduled visits and to comply with all study procedures

5.2 Exclusion Criteria

Participants are not eligible for the study if any of the following criteria are met:

E01: Participant is pregnant, or lactating, or of childbearing potential and not using an effective method of contraception or abstinence from at least 4 weeks prior to the first vaccination until at least 12 weeks after the last vaccination. To be considered of non-childbearing potential, a female must be post-menopausal for at least 1 year or surgically sterile.

E02: Participation at the time of study enrollment (or in the 30 days preceding the first study vaccination) or planned participation during the present study period in another clinical trial investigating a vaccine, drug, medical device, or medical procedure

E03: Receipt of any vaccine in the 30 days preceding the first study vaccination or planned receipt of any vaccine in the 30 days following the last study vaccination except for influenza vaccination, which may be received at least 2 weeks before and a minimum of 2 weeks after study vaccines.[a]

E04: Prior administration of a coronavirus vaccine (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2], SARS-CoV, Middle East Respiratory Syndrome [MERS-CoV])

E05: Receipt of immune globulins, blood or blood-derived products in the past 3 months

E06: Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months)

E07: History of SARS-CoV-2 infection, confirmed either clinically, serologically[b], or microbiologically

E08: Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to a vaccine containing any of the same substances[c]

E09: Self-reported thrombocytopenia, contraindicating intramuscular (IM) vaccination based on Investigator's judgment

E10: Bleeding disorder, or receipt of anticoagulants in the 3 weeks preceding inclusion, contraindicating IM vaccination based on Investigator's judgment

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[a] While receipt of any vaccine as listed in this criterion is exclusionary for this study, enrolled participants are free to receive an authorized/approved COVID-19 vaccine during the follow-up period. As efficacy has not been demonstrated for any of the investigational formulations under evaluation in the current study, it is not required to unblind participants to the VAT00001 study assignment prior to administration of an authorized COVID-19 vaccine. If the participant receives the authorized/approved 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 trial as per scheduled visits and procedures. (see Section 7.1.2: Definitive Contraindications).

[b] Potential study participants will need to have a negative SARS-CoV-2 antibody test at time of enrollment.

[c] The components of SARS-CoV-2 Recombinant Protein vaccine are listed in Section 6.1 and in the SARS-CoV-2 Recombinant Protein Investigator's Brochure. In addition, information for the AF03 adjuvant are listed in the AF03 Investigator's Brochure.

E11: Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily

E12: Current alcohol abuse or drug addiction

E13: Chronic illness or condition considered to potentially increase the risk for severe COVID illness[a] (26) or that, in the opinion of the Investigator, is at a stage where it might interfere with study conduct or completion[b]

E14: Moderate or severe acute illness/infection (according to Investigator judgment) on the day of vaccination or febrile illness (temperature ≥ 38.0°C [≥ 100.4°F]). A prospective participant should not be included in the study until the condition has resolved or the febrile event has subsided

E15: Receipt of any therapy known to have in-vitro antiviral activity against SARS-CoV-2[c] within 72 hours prior to the first blood draw

E16: Identified as an Investigator or employee of the Investigator or study center with direct involvement in the proposed study, or identified as an immediate family member (ie, parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study

E17: Residence in a nursing home or long-term care facility

E18: Health care workers providing direct patient care for COVID-19 patients

E19: Participants with active or prior documented autoimmune disorder (such as potential immune-mediated diseases [pIMDs])

If the participant has a primary physician who is not the Investigator, the site should contact this physician with the participant's consent to inform him / her of the participant's participation in the study. In addition, the site should ask this primary physician to verify exclusion criteria relating to previous therapies, such as receipt of blood products or previous vaccines.

5.3 Lifestyle Considerations

No other restrictions than the ones listed in the exclusion criteria or in the contraindications for subsequent vaccinations are required.

[a] Factors that may increase the risk of severe COVID illness include: autoimmune disease (see also Appendix 10.5 for a list of potential immune-mediated medical conditions); cerebrovascular disease; chronic pulmonary disease (including asthma, chronic obstructive pulmonary disease, emphysema, cystic fibrosis, pulmonary fibrosis); current smoking or former smoking; current vaping; diabetes mellitus; cardiovascular disease (including hypertension); chronic renal disease; chronic liver disease; immunocompromised condition; neurologic disorder (including dementia); obesity (body mass index ≥ 30); sickle cell disease; thalassemia.

[b] Chronic illness may include, but is not limited to, psychiatric disorders.

[c] Therapy/treatment including, but not limited to, favipiravir, lopinavir/ritonavir, remdesivir, arbidol, chloroquine, hydroxychloroquine.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. Screening information is recorded in the source documents.

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.

6.1 Study Interventions Administered

Study interventions are described in Table 6.1.

Table 6.1: Identity of study interventions

CoV2 preS dTM-AF03		
Intervention Name	**CoV2 preS dTM-AF03 (low-dose)**	**CoV2 preS dTM-AF03 (high-dose)**
Study Groups	1 and 6	3 and 8
Use	Experimental	
Type	Vaccine	
Dose Formulation	Liquid, mix at bedside pre-injection according to dose preparation protocol	
Unit Dose Strengths	Each 0.5 mL dose of Study Intervention will contain the following:	
	• preS-deltaTM monovalent: prefusion S delta TM COVID19 antigen, low-dose (5 µg)	• preS-deltaTM monovalent: prefusion S delta TM COVID19 antigen, high-dose (15 µg)
Excipients/Diluent	Each mono-dose vial of squalene-based AF03 adjuvant 2.5% contains: • Diluent: Phosphate-buffered saline (PBS) • Sorbitan monooleate (Dehymuls SMO™) (1.85 mg) • POE (12) Cetostearyl ether (Kolliphor CS12™) (2.38 mg) • Mannitol (2.31 mg)	
Dosage Level	0.5 mL per dose	
Number of Doses / Dosing Interval	Cohort 1 : 1 injection / Cohort 2 : 2 injections, 21 days apart	
Route of Administration	IM injection	
Site of Administration	Deltoid muscle in the upper arm	
Sourcing	Provided by the Sponsor	
Packaging and Labeling	Each study intervention will be provided in an individual box (antigen and adjuvant will be kitted together in a 2-vial box). Each study intervention (vial) will bear one fixed label and each box will bear detachable label(s) and one fixed label containing the dose number. All will be labeled as required per US requirement.	
Batch Number	TBD	

CoV2 preS dTM-AS03		
Intervention Name	**CoV2 preS dTM-AS03 (low-dose)**	**CoV2 preS dTM-AS03 (high-dose)**
Study Groups	2 and 7	4 and 9
Use	Experimental	
Type	Vaccine	
Dose Formulation	Liquid, mix at bedside pre-injection according to dose preparation protocol	
Unit Dose Strengths	Each 0.5 mL dose of Study Intervention will contain the following:	
	• preS-deltaTM monovalent: prefusion S delta TM COVID19 antigen, low-dose (5 µg)	• preS-deltaTM monovalent: prefusion S delta TM COVID19 antigen, high-dose (15 µg)
Excipients/Diluent	Each multi-dose vial of squalene-based AS03 adjuvant 2.1% contains: • Diluent: PBS • Tocopherol (antioxidant) (11.86 mg) • Polysorbate 80 (Tween®80) (4.86 mg)	
Dosage Level	0.5 mL per dose	
Number of Doses / Dosing Interval	Cohort 1 : 1 injection / Cohort 2 : 2 injections, 21 days apart	
Route of Administration	IM injection	
Site of Administration	Deltoid muscle in the upper arm	
Sourcing	CoV preS dTM : Provided by the Sponsor AS03: Provided by GSK	
Packaging and Labeling	Each study intervention will be provided in an individual box (antigen and adjuvant will be kitted together in a 2-vial box). Each study intervention (vial) will bear one fixed label and each box will bear detachable label(s) and one fixed label containing the dose number. All will be labeled as required per US requirement.	
Batch Number	TBD	

CoV2 preS dTM	
Intervention Name	**CoV2 preS dTM** (high-dose)
Study Groups	10 (18-49 years of age in Cohort 2 only)
Use	Experimental
Type	Vaccine
Dose Formulation	Liquid, mix at bedside pre-injection according to dose preparation protocol
Unit Dose Strengths	Each 0.5 mL dose of CoV2 preS dTM antigen (high-dose) will contain the following: • preS-deltaTM monovalent: prefusion S delta TM COVID19 antigen, high-dose (15 µg)
Excipients/Diluents	Diluent : PBS
Dosage Level	0.5 mL per dose
Number of Doses / Dosing Interval	Cohort 1 : 1 injection / Cohort 2 : 2 injections, 21 days apart

Route of Administration	IM injection
Site of Administration	Deltoid muscle in the upper arm
Sourcing	Provided by the Sponsor
Packaging and Labeling	Each study intervention will be provided in an individual box (antigen and diluent will be kitted together in a 2-vial box). Each study intervention (vial) will bear one fixed label and each box will bear detachable label(s) and one fixed label containing the dose number. All will be labeled as required per US requirement.
Batch Number	TBD
Placebo	
Intervention Name	**Placebo**
Study Groups	5 and 11
Use	Placebo - comparator
Type	Vaccine
Dose Formulation	Liquid, in a single-vial presentation
Unit Dose Strengths	0.9% normal saline
Dosage Level	0.5 mL per dose
Number of Doses / Dosing Interval	Cohort 1 : 1 injection / Cohort 2 : 2 injections, 21 days apart
Route of Administration	IM injection
Site of Administration	Deltoid muscle in the upper arm
Sourcing	Provided by the Sponsor
Packaging and Labeling	Each study intervention will be provided in an individual box similar to the kits used for other study interventions. Each study intervention (vial) will bear one fixed label and each box will bear detachable label(s) and one fixed label containing the dose number. All will be labeled as required per US requirement.
Batch Number	TBD

6.2 Preparation/Handling/Storage/Accountability

Detailed guidance and information are provided in the Operating Guidelines.

1) 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.
2) Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention 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.

3) The CoV2 preS dTM antigen will be mixed with the mono-dose vial of AF03 adjuvant, multi-dose vial of AS03 adjuvant, or PBS at the site prior to administration. Vaccine formulations will be prepared in the CoV2 preS dTM antigen vials by adding an equal volume of adjuvant (AF03 or AS03) or PBS.
4) 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).
5) Further guidance and information for the final disposition of unused study interventions are provided in the Operating Guidelines.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization and Allocation Procedures

On the day of enrollment, participants who meet the eligibility criteria and sign the Informed Consent Form (ICF) will be stratified by 2 age groups (18-49 years and ≥ 50 years) and then be randomly assigned to receive 1 injection (Cohort 1) or 2 injections (Cohort 2) of CoV2 preS DTM investigational study vaccine or placebo. As shown in Table 4.2, within each cohort:

- 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

The study will initially enroll 30 participants (6 within each dosing group from Cohort 1) 18-49 years of age, who will comprise the Sentinel Safety Cohort. Participants in this cohort will receive 1 injection of study intervention to which they were randomized, and safety and laboratory parameters up to D09 will be evaluated. Upon demonstration of acceptable safety, the remaining participants in Cohort 1 and all participants in Cohort 2 will be enrolled and randomized.

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.

Site staff will connect to the Interactive Response Technology (IRT), enter the identification, security information, and confirm a minimal amount of data in response to IRT prompts. The IRT will then provide the group assignment and have the site staff confirm it. The full detailed

procedures for group allocation are described in the Operating Guidelines. If the participant is not eligible to participate in the study, then the information will only be recorded on the participant recruitment log.
Participant numbers that are assigned by the IRT will consist of a 12-digit string (a 3-digit country identifier, a 4-digit study center identifier, and a 5-digit participant identifier). For example, Participant 840000100005 is the fifth participant enrolled in Center Number 1 in the US (840 being the US country code).

Participant numbers should not be reassigned for any reason. The randomization codes will be kept securely in the IRT system.

6.3.2 Blinding and Code-breaking Procedures

The study will be performed in a modified double-blind (observer-blind) fashion:

- Investigators and study staff who conduct the safety assessment and the participant will not know which vaccine is administered in order to decrease the risk of potential bias
- Only the study site staff who prepare and administer the vaccine and are not involved with the safety and efficacy evaluation will know which vaccine is administered
- Testing laboratories will be blinded

The code may be broken in the event of an AE only when the identification of the vaccine received could influence the treatment of the participant. Code-breaking should be limited to the participant(s) experiencing the AE.

The blind of individual participants can be broken by the Investigator or a delegate through the IRT system, as explained in the code-breaking procedures described in the Operating Guidelines. Once the emergency has been addressed by the site, the Investigator or a delegate must notify the Sanofi Pasteur RMO if a participant's code was broken. All contact attempts with the Sponsor prior to unblinding are to be documented in the source documents, and the code-breaking CRF is to be completed.

The Institutional Review Board/Independent Ethics Committee (IRB / IEC) must be notified of the code-breaking, in accordance with local regulations. All documentation pertaining to the event must be retained in the site's study records and in Sanofi Pasteur's files. Any intentional or unintentional code-breaking must be reported, documented, and explained, and the name of the person who requested it must be provided to the Sponsor.

A request for the code to be broken may also be made by the Global Pharmacovigilance (GPV) Department through an internal system for reporting to Health Authorities in the case of an SAE, as described in International Council for Harmonisation (ICH) E2A[a]. In this case, the code will be broken only for the participant(s) in question. The information resulting from code-breaking (ie, the participant's vaccine or group assignment) will not be communicated to either the Investigator or the immediate team working on the study, except for the GPV representative.
The code-breaking procedures are described in the Operating Guidelines.

[a] All unexpected and related SAEs submitted to European Union competent authorities must be unblinded.

The blind will be broken by the Sponsor at the time of the ESDR (with access to study intervention assignments [for the Sentinel Safety Cohort participants only] to a limited number of Sponsor Study Staff members comprising the Core Safety Management Team) and at the time of the first interim analysis after the first database lock. However, participant-level data will be maintained blinded on site until the end of the study/until the interim Clinical Study Report approval.

6.4 Study Intervention Compliance

The following measures will ensure that the study interventions are administered as planned and that any noncompliance is documented so that it can be accounted for in the data analyses:

- All vaccinations will be administered by qualified and trained study personnel
- The person in charge of study intervention management at the site will maintain accountability records of study intervention delivery to the study site, study intervention inventory at the site, dose(s) given to each participant, and unused or wasted doses

6.5 Concomitant Therapy

At the time of enrollment, ongoing medications and other therapies (eg, blood products) should be recorded in the source document as well as new medications prescribed for new medical conditions / AEs during study participation.

Documentation in the CRF of ongoing concomitant medication(s) will be limited to specific categories of medication(s) of interest beginning on the day of first vaccination. This may include medications of interest that were started prior to the day of vaccination or stopped prior to enrollment.

Reportable medications will be collected in the CRF from the day of each vaccination to the end of the solicited and unsolicited follow-up period after each vaccination, with the exception of influenza vaccination which will be collected throughout the study.

Reportable medications include medications that impact or may impact the consistency of the safety information collected after any vaccination and/or the immune response to vaccination. Three standard categories of reportable medications are defined:

- Category 1: medications impacting or that may have an impact on the evaluation of the safety (eg, antipyretics, analgesics, and non-steroidal anti-inflammatory drugs [NSAIDs], systemic steroids/corticosteroids)
- Category 2: medications impacting or that may have an impact on the immune response (eg, hydroxychloroquine, other vaccines, blood products, antibiotic classes that may interfere with bioassays used by the Global Clinical Immunology [GCI] department or other testing laboratories, systemic steroids/corticosteroids, immune-suppressors, immune-modulators with immunosuppressive properties, anti-proliferative drugs such as DNA synthesis inhibitors)
- Category 3: medications impacting or that may have an impact on both the safety and the immune response (eg, systemic steroids/corticosteroids)

Dosage and administration route, homeopathic medication, topical and inhaled steroids, as well as topical treatments, ophthalmic and ear treatments will not be recorded. Topical analgesics should not be applied at the site of vaccination; however, if they are applied inadvertently to the vaccination site, they should be recorded as a Category 1 medication in this specific instance.

Medications given in response to an AE will be captured in the "Action Taken" section of the AE CRF only. No details will be recorded in the concomitant medication CRF unless the medication(s) received belongs to one of the pre-listed categories. Medications will not be coded.

6.5.1 Rescue Medicine

Appropriate medical equipment and emergency medications, including epinephrine (1:1000), must be available on site in the event of an anaphylactic, vasovagal, or other immediate allergic reaction.

6.6 Dose Modification

Not applicable.

6.7 Intervention After the End of the Study

In the event that one of the vaccines formulations evaluated in this study is demonstrated safe and efficacious and is authorized/approved by the FDA, such vaccine formulation(s) may be offered as soon as possible to participants in this study who received placebo or different formulations, if permitted by local regulations.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

Section 7.1.1 and Section 7.1.2 are applicable to Cohort 2 only.

These sections are not applicable to Cohort 1 as they are planned to receive only 1 vaccination in the study.

7.1.1 Temporary Contraindications

Should a participant experience one of the conditions listed below, the Investigator will postpone further vaccination until the condition is resolved. Postponement must still be within the timeframe for vaccination indicated in the SoA.

TCI01: Febrile illness (temperature ≥ 38.0°C [≥ 100.4°F]) or moderate or severe acute illness / infection on the day of vaccination, according to Investigator judgment

TCI02: Receipt of any vaccine (other than the study vaccine[s]) in the 21 days preceding the second study vaccination or planned receipt of any vaccine in the 30 days following the second study vaccination except for influenza vaccination, which may be received at least 2 weeks before and a minimum of 2 weeks after study vaccines. This exception includes monovalent pandemic influenza vaccines and multivalent influenza vaccines.

7.1.2 Definitive Contraindications

Participants will permanently discontinue (definitive discontinuation) study intervention for the reasons listed below. These participants must not receive any additional dose of study intervention but should continue to be followed for safety. Additional unscheduled visits may be performed for safety reasons and information will be reported in the source documents.

Should a participant experience 1 of the conditions listed below, the Investigator will discontinue vaccination:

DCI01: Pregnancy, as indicated by a positive urine test

DCI02: An anaphylactic or other significant allergic reaction to the previous dose of vaccine

DCI03: SAE assessed as related to the study vaccine following the previous dose of vaccine, based on Investigator's judgment

DCI04: Grade 3 AE, assessed as related to the study vaccine that, in the opinion of the investigator, may place the participant at unreasonable or significant risk of injury or illness following repeat exposure to study vaccine

In the event of a local or national immunization program with a SARS-CoV-2 or a COVID-19 pandemic vaccine, participants who receive SARS-CoV-2 or a COVID-19 pandemic vaccine at any time during the study will not be withdrawn from the study. As efficacy has not been demonstrated for any of the investigational formulations under evaluation in the current study, it is not required to unblind participants to the VAT00001 study assignment prior to administration of an authorized COVID-19 vaccine.

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.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- The reason for withdrawal should be clearly documented in the source documents and in the CRF: AE, Lost to Follow-up, Protocol Deviation, or Withdrawal by Participant.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws consent, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.
- Withdrawn participants will not be replaced.

Follow-up of Discontinuations

For participants who have prematurely terminated the study, the site should attempt to contact them and complete all scheduled safety follow-ups, except if they specified that they do not want to be contacted again and it is documented in the source document.

For participants where the reason for early termination is lost to follow-up, the site will not attempt to obtain further safety information. See Section 7.3 for definition of "lost to follow-up".

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the site for a required study visit or cannot be contacted as planned in the SoA:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods), or at least to determine his/her health status while fully respecting his/her rights. These contact attempts should be documented in the participant's source documents.
- Should the participant continue to be unreachable, he/she will be considered discontinued from the study with lost to follow-up as reason for discontinuation.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 10.1.

8 Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- 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.

Urine, blood, respiratory samples will be collected as described in the SoA tables (Section 1.3).

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, is not planned to exceed 340 mL (cumulative total) (see Table 8.1). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Table 8.1: Blood sampling per visit

N=440	D1	D09	D22	D30	D36	D113/D134	D181/D202	D366/D387
Vaccination	X		X*					
Safety Labs	Cohorts 1 and 2	Cohort 1 only		Cohort 2 only				
Sera (N=440)	BL0001		BL0002		BL0003	BL0004	BL0005	BL0006
SARS CoV2 Microneut	X		X		X		X	X
Anti-S IgG ELISA	X		X		X		X	X
Anti-N IgG ELISA	X		X		X	X	X	X
Anti-PanCoV IgG ELISA	X							
PBMC/CMI (N=87)	MC0001*		MC0002*		MC0003*			
Whole Blood (N=87)	WB0001*		WB0002*		WB0003*			
COVID PCR on respiratory sample †	Illness visit							
POC Rapid Test ‡	X							

* Cohort 2 only

† 1 swab per illness visit; until day 366/387

‡ Test at site

Guidance and information for the sample collection, preparation, storage, and shipment are provided in the Operating Guidelines.

8.1 Baseline Screening for SARS-CoV-2 antibodies

A blood sample will be obtained before study enrollment to exclude from participation individuals with evidence of SARS-CoV-2 antibodies by a lateral flow immunoassay.

8.2 Efficacy and Immunogenicity Assessments

8.2.1 Immunogenicity Assessments

8.2.1.1 SARS-CoV-2 Neutralizing Antibody Assessment

SARS-CoV-2 neutralizing antibodies will be measured using a neutralization assay.

Serum samples are mixed with constant concentration of the SARS-CoV2 virus. A reduction in virus infectivity (viral antigen production) due to neutralization by antibody present in serum samples can be detected by ELISA. After washing and fixation, SARS-CoV-2 antigen production in cells can be detected by successive incubations with an anti-SARS-CoV-2-specific antibody, horseradish peroxide (HRP) Immunoglobulin G (IgG) conjugate, and a chromogenic substrate. The resulting optical density (OD) is measured using a microplate reader. The reduction in SARS-CoV-2 infectivity as compared to that in the virus control wells constitutes a positive neutralization reaction indicating the presence of neutralizing antibodies in the serum sample.

8.2.1.2 SARS-CoV-2 Spike Protein Antibody Serum IgG ELISA

SARS-CoV-2 anti-S protein IgG antibodies will be measured using an ELISA. Microtiter plates will be coated with SARS-CoV-2 Spike protein antigen diluted in coating buffer to the optimal concentration.

Plates may be blocked by the addition of a blocking buffer to all wells and incubation for a defined period. Following incubation, plates will be washed. All controls, reference, and samples will be pre-diluted with dilution buffer. The pre-diluted controls, reference and samples will then be further serially diluted in the wells of the coated test plate.

The plates will be incubated for a defined period. Following incubation, plates will be washed, an optimized dilution of goat anti-human IgG enzyme conjugate will be added to all wells, and plates will be further incubated. Following this incubation, the plates will be washed, and enzyme substrate solution will be added to all wells. Plates will be incubated for a defined period to allow the substrate to develop. Substrate development will be stopped by the addition of a stop solution to each well. An ELISA microtiter plate reader will be used to read the test plates using assay specific SoftMax Pro templates.

The average OD value for the plate blank will be subtracted from all the ODs within each plate. The sample titers will be derived using the measured values of the blanks, controls, and the reference standard curve, which will be included on each assay plate within the run.

8.2.1.3 Cellular-Mediated Immunity (using whole blood)

Cytokines will be measured in whole blood following stimulation with full-length S protein and/or pools of S-antigen peptides.

8.2.2 Efficacy Assessments

8.2.2.1 Definitions

COVID-19-like illness

Symptoms of COVID-19-like illness are as listed below, along with an accompanying tabulation of terms used in the CRFs versus diary cards / memory aids (Table 8.2).

Any ONE of the following (that persist for a period of at least 12 hours or reoccur within a 12-hour period):

- Cough (dry or productive)
- Fever
- Anosmia
- Ageusia
- Chillblains (COVID-toes)
- Difficulty breathing or shortness of breath
- Clinical or radiographic evidence of pneumonia
- Any hospitalization with the following clinical diagnosis:
  - Stroke, myocarditis, myocardial infarction
  - Thromboembolic event (blood clots [eg, pulmonary embolism, deep vein thrombosis, stroke])
  - Purpura fulminans

OR

Any TWO of the following (that persist for a period of at least 12 hours or reoccur within a 12-hour period):

- Pharyngitis
- Chills
- Myalgia
- Headache
- Rhinorrhea
- Abdominal pain
- At least one of nausea, diarrhea, vomiting

Table 8.2: COVID-19-like illness symptoms: CRF and Diary Card / Memory Aid terms

CRF term	Diary Card / Memory Aid term
Cough	Cough
Fever	Temperature measured as 100.4ºF or higher
Anosmia	Loss of smell
Ageusia	Loss of taste
Chillblains	Pain, redness, sores in your fingers and toes exposed to cold
Difficulty breathing	Difficulty breathing
Shortness of breath	Feeling short winded
Pneumonia	Infection of the lungs
Stroke	Stroke
Myocarditis	Heart inflammation
Myocardial infarction	Heart attack
Thromboembolic event	Blood clots
Purpura fulminans	A type of purplish skin rash
Pharyngitis	Sore Throat
Chills	Chills
Myalgia	Muscle aches and pains
Headache	Headache
Rhinorrhea	Runny nose
Abdominal Pain	Belly pain
Nausea	Feeling queasy
Diarrhea	Loose stools
Vomiting	Throwing up

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.

Serologically-confirmed SARS-CoV-2 infection

Serologically-confirmed 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.

8.2.2.2 COVID-19-like Illness Surveillance

Passive Surveillance

Following randomization and vaccination all 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

Following randomization and vaccination, active surveillance will be used to identify potential COVID-19 clinical illness cases.

All participants will be contacted by study site or delegated call center D57 (2 weeks after D43 contact) after vaccination and continuing until D181 (Cohort 1) or D202 (Cohort 2). The frequency of contacts will be once every 2 weeks. Prior to these specified time-points, active surveillance will still occur during the established contacts (phone calls and visits) as described in the SoA. After active surveillance has ended at D181 (Cohort 1) or D202 (Cohort 2), passive surveillance will continue through the end of the study as previously stated above.

Collection of respiratory samples

For the duration of the study, the site will arrange for a respiratory sample to be taken if the participant experiences symptoms of COVID-19-like illness (see Section 8.2.2.1). The respiratory sample will be obtained as soon as possible from the onset of clinical manifestations of COVID-19-like illness.

Reporting of events temporally associated with a COVID-19-like illness

In addition to obtaining a respiratory sample, the site will collect detailed information about the symptoms, severity and duration of illness, as well as information on healthcare utilization events (hospitalizations, emergency room visits, and non-routine office visits [including urgent care visits]) and medication use (eg, antibiotics, antivirals).

In the event of hospitalization during the course of illness, detailed information on the course of the illness including duration of symptoms, oxygen requirements, laboratory tests, imaging investigations (including computerized tomography), use of mechanical ventilation and other respiratory support medications used, and outcome will be collected.

In the event that a respiratory sample swab cannot be collected, the research site will still obtain the above information. All participants reporting a COVID-19-like illness will have a 30-day follow-up telephone call.

8.2.2.3 SARS-CoV-2 Nucleoprotein Antibody Serum IgG ELISA

SARS-CoV-2 anti-nucleoprotein antibodies will be measured using an ELISA. Microtiter plates will be coated with SARS-CoV-2 nucleoprotein antigen diluted in coating buffer to the optimal concentration.

Plates may be blocked by the addition of a blocking buffer to all wells and incubation for a defined period. Following incubation, plates will be washed. All controls, reference, and samples will be pre-diluted with dilution buffer. The pre-diluted controls, reference and samples will then be further serially diluted in the wells of the coated test plate.

The plates will be incubated for a defined period. Following incubation, plates will be washed, an optimized dilution of goat anti-human IgG enzyme conjugate will be added to all wells, and plates will be further incubated. Following this incubation, the plates will be washed, and enzyme substrate solution will be added to all wells. Plates will be incubated for a defined period to allow the substrate to develop. Substrate development will be stopped by the addition of a stop solution to each well. An ELISA microtiter plate reader will be used to read the test plates using assay specific SoftMax Pro templates.

The average OD value for the plate blank will be subtracted from all the ODs within each plate. The sample titers will be derived using the measured values of the blanks, controls, and the reference standard curve, which will be included on each assay plate within the run.

8.2.2.4 Nucleic Acid Amplification Test (NAAT) for COVID-19 Case Detection

In the assay, respiratory samples will be collected, and the RNA is extracted. The purified template is then evaluated by an NAAT using SARS-CoV-2 specific primers to specifically amplify SARS-CoV-2 targets.

8.3 Safety Assessments

This section presents safety assessments other than AEs which are presented in Section 8.4.

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.3.1 Medical History

Prior to enrollment, participants will be assessed for pre-existing conditions and illnesses, both past and ongoing. Any such conditions will be documented in the source document. Significant (clinically relevant) medical history (reported as diagnosis) including conditions/illnesses for which the participant is or has been followed by a physician or conditions/illnesses that could resume during the course of the study or lead to an SAE or to a repetitive outpatient care will be collected in the CRF.

8.3.2 Physical Examinations

At designated visits, the Investigator or a delegate will perform a targeted physical examination based on the participant's medical history and the examiner's medical judgment. Information will be recorded in the source document.

8.3.3 Vital Signs

Oral pre-vaccination temperature and other vital signs will be systematically collected by the Investigator on the source document. Tympanic, skin, and temporal artery thermometers must not be used.

8.3.4 Clinical Safety Laboratory Assessments

Urine pregnancy testing will be performed in women of childbearing potential before each vaccination.

- See Appendix 10.2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The Investigator 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 laboratory tests with values considered clinically significantly abnormal during participation in the study or after the last injection of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or medical monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
    - All protocol-required laboratory assessments, as defined in Appendix 10.2, must be conducted in accordance with the laboratory manual/operating guidelines and the SoA.
    - If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory of choice require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE), then the results must be recorded in the CRF.

8.4 Adverse Events and Serious Adverse Events

Safety will be described in all study participants.

The definitions of an AE, SAE, and the different categories of AEs can be found in Appendix 10.3.

AEs will be reported by the participants to the investigator, then by the Investigator to the Sponsor.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (see Section 7).

An ESDR will be performed for Sentinel Safety Cohort participants. The goal of ESDR is to allow the preliminary safety assessment for a cautious, step-wise approach to vaccine administration, starting with participants aged 18-49 years, as there is no previous human data for the CoV2 preS dTM candidate vaccine.

Sentinel Safety Cohort

The participants' enrollment will include the following sequential steps:

- Step 1:
  - Thirty participants aged 18-49 years from Cohort 1 will be enrolled in the Sentinel Safety Cohort, whereafter enrollment will be paused.
  - Six participants will be randomly assigned to each of the 5 dosing groups defined in Cohort 1: 5 µg and 15 µg AF03-adjuvanted groups, 5 µg and 15 µg AS03-adjuvanted groups, and placebo.
  - Early safety data collection is planned 8 days after the completion of the vaccination (D09, including safety laboratory data); and ESDR is to be planned as soon as possible. Limited members of the Sponsor Study Team (RMO, Biostatistician and Programmer, Pharmacovigilance Science Expert, and Global Safety Officer) will review unblinded safety data and will provide their recommendation to continue the recruitment.
- Step 2: If there is no safety signal after the ESDR after the completion of the vaccination in Sentinel Safety Cohort, recruitment will reopen to all dosing groups and both age strata.

ESDR

The safety data collected for ESDR for Sentinel Safety Cohort will be reviewed by the Investigator. The intensity of non-serious AEs/adverse reactions (ARs) will be assessed using the Sanofi Pasteur scale.

The following safety parameters will be assessed as part of the early safety data review for the Sentinel Safety Cohort participants after the first injection of CoV2 preS dTM candidate vaccine:

- Immediate reactions
- Solicited injection site and systemic reactions
- Laboratory abnormalities (including hematology, chemistry, coagulation time, and urinalysis)
- Unsolicited AEs reported as vaccine related by the Investigator
- SAEs and AESIs

If any of the below criteria are met, the data on the particular alert threshold event will be reviewed by the SMT and a decision will be made as to whether subsequent vaccinations in the study will be allowed to resume. Enrollment will be paused during the ESDR, and the following safety parameters will be examined:

- ≥ 2 participants per dosing group (n=6) experiencing Grade 3 systemic reaction (without concurrent infectious disease)
- ≥ 2 participants per dosing group (n=6) experiencing Grade 3 solicited injection site pain
- ≥ 2 participants per dosing group (n=6) experiencing Grade 3 unsolicited non serious reactions (reactions not explained by any other possible etiology)
- ≥ 2 participants with Grade 3 laboratory AE (Grade 3 abnormality if Grade 1 or 2 at baseline) of the same type (reactions not explained by any other possible etiology)

- ≥ 2 participants with Grade 2 laboratory AE (Grade 2 abnormality if normal at baseline) of the same type (reactions not explained by any other possible etiology) and judged by the Investigator to be clinically meaningful
- Any related SAEs

Following the ESDR and resumption of enrollment and dosing, occurrence of any one of these criteria will result in a pause in enrollment and vaccination pending Sponsor decision. The study status and final Sponsor decision will be submitted for notification to the IRB/IEC.

Halting Rules throughout the Study

Blinded safety data will be reviewed by limited members of the Sponsor Study Team (RMO, Biostatistician and Programmer, Pharmacovigilance Science Expert, and Global Safety Officer) at regular intervals to identify any new safety signals or safety concerns during the conduct of the study. A pause might be recommended in both recruitment and/or further vaccination while it investigates any potential signal or concern.

Enrollment will be paused during the review and the data will be examined if:

- Any of the following events, assessed as related to the vaccine by the Investigator and the Sponsor, are reported in the study:
  - SAE
  - New Onset of Potential immune-mediated diseases (pIMDs)
  - Ulceration, abscess or necrosis at the injection site
  - Four or more participants across treatment groups experience the same Grade 3 AE of the same type in the absence of any other etiology
  - Two or more participants across treatment groups experience the same Grade 3 laboratory abnormality assessed by the investigator as clinically significant
- Any of the following events, suggestive of vaccine associated enhanced disease, are detected in the study including:
  - Any death due to SARS-CoV-2 infection
  - > 10% of the study population is hospitalized due to SARS-CoV-2 infection
  - ≥ 4 ICU admissions among participants ≥ 50 years due to SARS-CoV-2 infection
  - ≥ 8 ICU admissions among participants 18-49 years due to SARS-CoV-2 infection

Case unblinding may be performed if necessary.

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

Immediate Post-vaccination Observation Period

Participants will be kept under observation for 30 minutes after each vaccination to ensure their safety. The post-vaccination observation should be documented in the source document.

Reactogenicity

Solicited injection site reactions will be collected from D01 to D08 after each vaccination.

Solicited systemic reactions will be collected from D01 to D08 after each vaccination.

The solicited injection site reactions and systemic reactions that are pre-listed in the diary cards and CRF, together with the intensity scales, are presented in Appendix 10.3.5.1.1.

Unsolicited Adverse Events

Unsolicited AEs include unsolicited non-serious AEs and SAEs. The intensity grading scale for unsolicited non-serious AEs is presented in Appendix 10.3.5.1.2.

Unsolicited non-serious AEs will be collected from D01 to D22 after each vaccination.

SAEs will be collected and assessed throughout the study, from inclusion until 12 months after the last vaccination (up to D366 for Cohort 1 and up to D387 for Cohort 2). However, before the first study intervention administration, only SAEs related to study procedures are to be collected (eg, SAEs related to blood sampling).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will not be recorded on the AE section of the CRF.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 10.3. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. 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.

Medically Attended Adverse Events (MAAEs)

MAAEs will be collected at any time during the study.

Adverse Events of Special Interest (AESIs)

AESIs will be collected at any time during the study.

See Section 8.4.6 for the list of AESIs.

8.4.2 Method of Detecting AEs and SAEs

Individual diary cards, specifically designed for this study by the Sponsor and provided to the study sites, will be given to study participants for the recording of daily safety information. These diary cards will include pre-listed terms and intensity scales as well as areas for free text to capture additional safety information or other relevant details. Participants will also be provided with rulers for measuring the size of injection site reactions, and with standard digital thermometers for measuring daily temperatures. To ensure consistency of reporting, the study sites will instruct participants on how to correctly use these tools.

At specified intervals, the Investigator or an authorized designee will interview the participants to collect the information recorded in the diary card and will attempt to clarify anything that is incomplete or unclear. All clinical study information gathered by the study site will be reported electronically by the Investigator or authorized designee using a web-based CRF. Any information that was not documented in the diary card will first be captured in the source document and then reported electronically.

The 12-month (post-last injection) follow-up will be done by interviewing participants either during a visit or over the telephone using a questionnaire to capture SAEs and AESIs, if applicable.

The method of recording, evaluating, and assessing causal relationship of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3 Follow-up of AEs and SAEs

Unless a participant refuses further contact, each participant who experiences an AE (whether serious or non-serious) during the study must be followed until the condition resolves, becomes stable, or becomes chronic (even after the end of the participant's participation in the study) if *either* of the following is true:

- The AE is considered by the Investigator to be related to the study intervention administered
- The AE caused the discontinuation of the participant from the study or from vaccination

The Investigator will inform the Sponsor of the date of final disappearance of the event or the date of "chronicity" establishment.

8.4.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a 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 relating to safety reporting to the regulatory authority, IRB / IEC, and investigators.
- For all studies except those investigating medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy

Pregnancy is an exclusion criterion for enrollment in this study, but a participant could potentially become pregnant during her participation.

- Details of all pregnancies in female participants will be collected after the start of study intervention and until delivery by the Investigator and recorded in the Pregnancy CRF. Any data collected after CRF lock will be transmitted to the pharmacovigilance department on the paper form.

- The collection period of pregnancy information will correspond at least to the period during which the participant is requested to be under contraception. (according to protocol: effective method of contraception or abstinence from at least 4 weeks prior to the first vaccination until at least 12 weeks after the last vaccination). If there are any pregnancies during this period, follow-up should be conducted up to delivery: this will be covered by the 12-month surveillance of the study.
- If a pregnancy is reported, the Investigator should inform the Sponsor within 1 month of learning of the pregnancy and should follow the procedures outlined in Appendix 10.4.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4.6 Adverse Events of Special Interest

AESIs will include:

- Anaphylactic reactions, Generalized convulsion, Thrombocytopenia, Lacrimal and salivary disorders (tearing, dry mouth, dry eyes).
- New-onset chronic medical conditions (NOCMCs) and pIMDs (see Appendix 10.5).

8.4.7 Medically Attended Adverse Events

MAAEs will be collected using the same process as other AEs. See Appendix 10.3.1 for definition of MAAEs.

8.5 Treatment of Overdose

Since the study intervention is administered by a health care professional, it is unlikely that overdose by injection occurs.

However, in the event of an overdose, the Investigator should:

1) Contact the RMO immediately.
2) Closely monitor the participant for any AE/SAE.
3) Document the quantity of the excess of the overdose in the source documents.

8.6 Pharmacokinetics

Pharmacokinetics parameters are not evaluated in this study.

8.7 Pharmacodynamics

As with most vaccines for active immunization, the mechanism of action consists of the induction of immune responses against the antigens contained in the vaccine. Therefore, the pharmacodynamic profile of the investigational study intervention is defined by its immunogenicity profile.

8.8 Genetics

Genetics are not evaluated in this study.

8.9 Biomarkers

Besides the biomarkers described in the immunogenicity and efficacy assessments sections (Section 8.2.1 and Section 8.2.2, respectively), other emerging biomarkers may be evaluated in this study which may be relevant for evaluating scientific aspects of COVID-19 illness, or SARS-CoV-2 infection, or for the evaluation of effect modification, correlates of risk/protection, or participants' baseline characteristics.

8.10 Immunogenicity Assessments

See Section 8.2.1.

8.11 Medical Resource Utilization and Health Economics

Medical Resource Utilization will be collected as part of COVID-illness in this study (see Section 8.1), as well as for SAE narrative and categorization.

9 Statistical Considerations

9.1 Statistical Hypotheses

All analyses will be descriptive; no hypotheses are planned to be tested.

9.2 Sample Size Determination

This is a first-in-human study to assess the safety profile and immune responses to different formulations of the study vaccine when compared to placebo. A total of 440 participants will be enrolled. No formal power calculation has been performed. The sample size was determined based on logistical considerations and common practices for first-in-human trials.

Vaccine arms will be aggregated to perform complementary assessments on the following main effects: age [(18-49 years [N=240], ≥ 50 years [N=120]), dose (low [N=180], high [N=180]), injection schedule (1-injection [N=120], 2-injection [N=240]), adjuvant type (AS03 [N=240], AF03 [N=120]), overall adjuvant (high-dose with adjuvants [N=180], high-dose without adjuvants [N=20]), and dose-sparing adjuvant (low-dose with adjuvants [N=180], high-dose without adjuvants [N=20]).

9.3 Populations for Analyses

The following populations are defined:

Population	Description
Randomized	All participants with a randomized group that has been allocated by IRT
Safety Analysis Set (SafAS)	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. Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately).
Full analysis set (FAS)	Subset of randomized participants who received at least 1 injection of the study intervention. Participants will be analyzed according to the study intervention group to which they were randomized.
Per-protocol analysis set (PPAS)	Subset of the FAS. Participants presenting with at least one of the following relevant 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 • Participant received a Category 2 or Category 3 therapy / medication / as stated in Section 6.5 • Participant with positive test results in the ELISA and/or neutralization test at baseline • Additional conditions for exclusion may be identified during the review of protocol deviations; such conditions will be documented in the Statistical Analysis Plan (SAP)
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.
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.

9.4 Statistical Analyses

The SAP will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the critical endpoints including but not limited to primary and secondary endpoints.

All statistical analyses will be performed under the responsibility of the Sponsor's Biostatistics Platform using the SAS® software, Version 9.4 or above (SAS Institute, Cary, North Carolina, USA).

9.4.1 General Considerations

All analyses will be descriptive. Summaries will be provided for main effects (see Section 9.2) as well as individual study arms. Details will be provided in the SAP.

9.4.2 Primary Endpoints

9.4.2.1 Immunogenicity

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 that will be performed for the following primary endpoints are as presented in Table 3.1.

Pre-vaccination titers at < LLOQ will be converted to half LLOQ.

The 95% CIs for the GMTs/GMCs and GMT ratios will be calculated using normal approximation of log-transformed titers. The 95% CIs for the proportions will be based on the Clopper-Pearson method. The ratios of GMTs will be obtained between groups with the 95% CIs calculated using normal approximation of log-transformed titers. The differences in the seroconversion rates between groups will be computed along with the 2 sided 95% CIs by the Wilson-Score method without continuity correction. Additional parameters may be displayed as appropriate.

Additionally, to evaluate independent determinants of primary immunogenicity endpoints, regression models may be constructed for GMT titers and occurrence of neutralizing antibody seroconversion. 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 or high), and adjuvant (none, AS03, AF03). Models evaluating antibody titers or rates at D36 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 can be removed from the models.

Immunogenicity analyses will be performed on PPAS-IAS, unless otherwise specified.

9.4.2.2 Safety

The primary endpoints for the evaluation of safety are as presented in Table 3.1.

Primary safety endpoints will be summarized by vaccine group, as well as aggregate groups specified in the SAP. The 95% CIs will be calculated using the Clopper-Pearson method.

The SafAS will be used for the safety analyses.

9.4.3 Secondary Endpoints

9.4.3.1 Immunogenicity

The secondary endpoints for the evaluation of immunogenicity are as presented in Table 3.1.

The 95% CIs for the anti-S antibody concentration and anti-S antibody concentration ratio will be calculated using normal approximation of log-transformed titers. The 95% CIs for the proportions will be based on the Clopper-Pearson method. The ratios of anti-S antibody concentration will be obtained between groups with the 95% CIs calculated using normal approximation of log-transformed titers. The differences in the seroconversion rates between groups will be computed along with the 2-sided 95% CIs by the Wilson-Score method without continuity correction. Additional parameters may be displayed as appropriate.

Regression models may be utilized for further assessment of secondary immunogenicity endpoints, as described in Section 9.4.2.1.

Immunogenicity analyses will be performed on PPAS-IAS, unless otherwise specified.

9.4.3.2 Efficacy

Virologically-confirmed COVID-19 illness is defined by the occurrence of a COVID-19 illness as described in Section 8.2.2.1 associated with a positive NAAT for SARS-CoV-2 in a respiratory sample.

Serologically-confirmed SARS-CoV-2 infection is defined as a change from negative to positive (see Section 8.2.2.1) in the non-S ELISA assay from any post-baseline sampling time point compared to the baseline value, as measured in a SARS-CoV-2 non-S ELISA.

Correlates of risk / protection analysis will be performed based on antibody responses to SARS-CoV-2 as evaluated using virus neutralization and binding antibody (ELISA), considering cases of virologically-confirmed COVID-19 and/or serologically-confirmed SARS-CoV-2 infection as defined above. Detailed statistical methods will be described in an SAP.

Efficacy analyses will be performed on FAS and PPAS-IAS, unless otherwise specified.

9.4.4 Exploratory Endpoint

9.4.4.1 Immunogenicity

Th1 and Th2 cytokines will be measured and summarized for individual and aggregate study arms.

Detailed CMI analyses will be defined in the SAP. The CMI analysis will be based on PPAS-CMI set.

The ratio between binding antibody (ELISA) concentration and neutralizing antibody titer will be summarized for individual and aggregate study arms. The ratio (neutralizing antibody / binding

antibody) will be calculated as difference in log_{10} scale and with the 95% CIs calculated using normal approximation will be provided. The analyses will be performed on PPAS-IAS, unless otherwise specified.

9.5 Interim Analyses

An interim analysis will be performed on data collected for primary immunogenicity and exploratory CMI objectives obtained up to D36 and primary safety data collected up to D43, upon the data availability and when a partial database lock has been conducted. Statistical analysis of data described above will be conducted to support formulation selection for further investigation. The analyses results will also be generated to communicate with regulatory agencies. The study blind will be broken at the group level to the Sponsor at that time.

After the 6-month data have been collected, a further interim analysis will be performed on 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 Amendment 1, 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.

The SAP will describe the planned interim analyses in greater detail.

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 for halting rules).

9.6 Data Monitoring Committee (DMC)

Not applicable.

10 Supporting Documentation and Operational Considerations

10.1 Appendix: Regulatory, Ethical, and Study Oversight Considerations

Note: The term "participant" is used throughout this protocol. However, the term "subject" will be used in the CRF in order to comply with the Clinical Data Interchange Standards Consortium (CDISC) requirements.

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure (IB), and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator or the Sponsor (according to local regulations) and reviewed and approved by the IRB/IEC before the study is initiated
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants
- The Investigator or the Sponsor (according to local regulations) will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- The Investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2 Financial Disclosure

Information related to financial disclosure is described in the Investigator's contract.

10.1.3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- The actual ICF used at each center may differ, depending on local regulations and IEC / IRB requirements. However, all versions must contain the standard information found in the sample ICF provided by the Sponsor. Any change to the content of the ICF must be approved by the Sponsor and the IEC / IRB prior to the form being used.
- If new information becomes available that may be relevant to the participant's willingness to continue participation in the study, this will be communicated to him / her in a timely manner. Such information will be provided via a revised ICF or an addendum to the original ICF.
- Participants must be re-consented to the most current version of the ICF during their participation in the study.
- A copy of the ICF must be provided to the participant.
- The ICF will contain a specific section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

Recruitment Procedures

Before the start of the study, the Investigator or sub-investigator will contact an appropriate pool of potential participants and invite them to participate in the study. The site will ensure that any advertisements used to recruit participants (eg, letters, pamphlets, posters) are submitted to Sanofi Pasteur prior to submission to the IEC / IRB for approval.

10.1.4 Data Protection and Future Use of Stored Samples

- All personal data collected related to participants, Investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in compliance with all applicable laws and regulations including the Global Data Protection Regulation (GDPR). Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

- Participants race and ethnicity will be collected in this study because these data are required by regulatory agencies (41).
- 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 which would make the participant identifiable will not be transferred to the Sponsor.
- 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 as described in the informed consent.
- 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.
- When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- Participant data will be used for this study and in support of the whole drug development program for the Investigational Product, including negotiations with payers and publication of results.
- Any unused part of the serum, respiratory, or PBMC samples will be securely stored at the Sanofi Pasteur laboratory (GCI) or Contract Research Organization for up to 25 years after the end of the study. Unused samples may also be sent to another long-term repository, as necessary. These samples are being retained in long-term storage to support answers to regulatory questions related to the product's licensure and the potential revalidation of the study results.

  The other biological samples collected to qualify the participant for inclusion in the study or to monitor his/her health are dedicated for immediate use. In case they are not completely used up, they will be destroyed at the latest at the end of the study or after the time requested by local law.

  In addition, participants will be asked to indicate in the ICF whether they will permit the future use of any unused stored serum samples for tests not related to the study objectives. If they refuse permission, the samples will not be used for any testing other than that directly related to this study. If they agree to this use, they will not be paid for giving permission. Anonymity of samples will be ensured. The aim of any possible future research is unknown today and may not be related to this particular study. It may be to improve the knowledge of vaccines or infectious diseases, or to improve existing tests or develop new tests to assess vaccines. Human genetic tests will never be performed on these samples without specific individual informed consent.

10.1.5 Committees Structure

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.

10.1.6 Dissemination of Clinical Study Data

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinicaltrialregister (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical trials in patients are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance, and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: clinicalstudydatarequest.com.

10.1.7 Data Quality Assurance

- All participant data relating to the study will be recorded on electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- 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.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).

- Study monitors will perform ongoing source data 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 signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report 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.

10.1.8 Source Documents

"Source data" are the data contained in source documents. Source documents are original documents or certified copies, and include, but are not limited to, diary cards, medical and hospital records, screening logs, informed consent / assent forms, telephone contact logs, and worksheets.

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Detailed guidance and information are provided in the Operating Guidelines.

10.1.9 Study and Site Start and Closure

Details on which clinical supplies are provided by the Sponsor or the site are described in the Operating Guidelines.

The study start date is considered the date of the first visit planned in the SoA of the first participant.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been either destroyed or returned to the Sponsor, all samples are shipped to the appropriate laboratories, the center study-site has all the documents necessary for archiving and a study-site closure visit has been performed along with a Site Close Out Form submitted to the IRB, as required.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10 Publication Policy

Information related to publication policy is described in the Investigator's contract.

10.2 Appendix: Clinical Laboratory Tests

A urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential) will be performed before each vaccination.

- The tests detailed in Table 10.1 will be performed by the site-selected local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 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.
- Pregnancy Testing

Table 10.1: Protocol-required safety laboratory assessments

Laboratory Assessments	Time period for assessment	Parameters			
Hematology	Cohort 1: D01 and V02 (D09) Cohort 2: D01 and V03 (D30)	Platelet Count	White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils		
		Hemoglobin			
		Hematocrit			
Clinical Chemistry	Cohort 1: D01 and V02 (D09) Cohort 2: D01 and V03 (D30)	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			
Routine Urinalysis	Cohort 1: D01 and V02 (D09) Cohort 2: D01 and V03 (D30)	• Glucose, protein, blood, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	Cohort 1: pre-injection 1 at D01 Cohort 2: pre-injections 1 and 2 at D01 and V02 (D22), respectively	Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential*)			
	D01	Rapid diagnostic testing for SARS-CoV2 antibody screening			

* To be considered of non-childbearing potential, a female must be post-menopausal for at least 1 year or surgically sterile.

Investigators must document their review of each laboratory safety report.

Participants, outcome assessors, Investigators, laboratory personnel, and the majority of sponsor study staff (except those involved in the ESDR and for concerned participants only) will be blinded to vaccine assignment group (formulation and adjuvant); injection schedule will be unblinded; and those preparing/administering the study interventions will be unblinded to vaccine group assignment.

Laboratory 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: 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 patient or 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 study intervention.

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 (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after 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. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- 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.

Other Definitions

Adverse Reaction:

All noxious and unintended responses to a study intervention related to any dose should be considered adverse reactions (AR).

(The phrase "responses to a study intervention" means that a causal relationship between a study intervention and an AE is at least a reasonable possibility)

Immediate Event/Reaction:

Immediate events are recorded to capture medically relevant unsolicited systemic AEs (including those related to the study intervention administered) that occur within the first 30 minutes after vaccination.

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.

Injection Site Reaction/Administration Site Reactions:

An injection/administration site reaction is an AR at and around the injection/administration site. Injection/administration site reactions are commonly inflammatory reactions. They are considered to be related to the study intervention administered.

Systemic AE/AR:

Systemic AEs are all AEs that are not injection or administration site reactions. They should therefore include systemic manifestations such as headache, fever, as well as localized or topical manifestations that are not associated with the vaccination or administration site (eg, erythema that is localized but that is not occurring at the injection site).

Systemic AEs assessed as related to study intervention are referred as systemic ARs. Solicited systemic reactions occurring during the specified collection period are always considered related to the study vaccine even if there is evidence or alternative etiology.

Adverse Event of Special Interest (AESI):

An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's study intervention or program, for which ongoing monitoring

and rapid communication by the Investigator to the Sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the study Sponsor to other parties (eg, regulators) might also be warranted.

New-Onset Chronic Medical Conditions (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.

Potential Immune-Mediated Disease (pIMDs): pIMDs constitute a group of AEs that includes diseases which are clearly autoimmune in etiology and other inflammatory and/or neurologic disorders which may or may not have autoimmune etiologies. pIMDs currently in effect are presented in Appendix 10.5:Adverse Events of Special Interest.

Reactogenicity / Solicited Reactions

A solicited reaction is an "expected" adverse reaction (sign or symptom) observed and reported under the conditions (nature and onset) pre-listed in the protocol and CRF (eg, injection site pain or headache occurring between the day of vaccination and the next 7 days).

By definition, solicited reactions are considered as being related to the study intervention administered.

For injectable vaccines, solicited reactions can either be solicited injection/administration site reactions or solicited systemic reactions.

Unsolicited AE/AR

An unsolicited AE is an observed AE that does not fulfill the conditions of solicited reactions, ie, pre-listed in the CRF in terms of diagnosis and/or onset window post-vaccination. For example, varicella or a solicited term such as headache starting after the solicited observation period (headache starting on Day 10 post-vaccination in the case where headache occurring between the day of vaccination and the next 7 days is pre-listed in the protocol and CRF as a solicited reaction).

An unsolicited AR is an unsolicited AE that is considered related to study intervention. Unsolicited AEs includes both serious (SAEs) and non-serious unsolicited AEs.

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 (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A 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

- In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other important medical event

- Medical or scientific judgment should be exercised in deciding whether expedited 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 health of the participant or may require intervention to prevent one of the other outcomes listed in the above definition. These important medical events should also usually be considered serious.
- Examples of such events are 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, new-onset diabetes or autoimmune disease.

Note: *Serious* and *severe* are not synonymous. The term *severe* is often used to describe the intensity of a specific event as corresponding to Grade 3. This is not the same as *serious,* which is based on participant / event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning.

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- 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 CRF pages.
- 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 redacted 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. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Causal Relationship

By convention, all AEs reported at the injection site (whether solicited or unsolicited) and all solicited systemic AEs are considered to be related to the study intervention and therefore are referred to as reactions and do not require the Investigator's opinion on relatedness.

- Causal relationship of unsolicited systemic AEs and SAEs will be recorded as follows:
  - For non-serious unsolicited systemic AEs (except for non-serious AESIs), relationship to study intervention will usually be assessed by the Investigator only.
  - For SAEs and non-serious AESIs, relationship to study intervention will be assessed by both the Investigator and the Sponsor. Sponsor assessment is entered in the GPV database only.
  - For SAEs only, the causal relationship to study procedures (related/not related to study procedures) will be assessed by both the Investigator and the Sponsor. Sponsor assessment is entered in the GPV database only.
- The Investigator will assess the causal relationship between each unsolicited systemic AE and the study intervention administered[a] as either not related or related, based on the following definitions:

[a] Study intervention administered can correspond to either the investigational product or other products when no investigational product is administered at the visit

- Not related – The AE is clearly / most probably caused by other etiologies such as an underlying condition, therapeutic intervention, or concomitant therapy; or the delay between vaccination and the onset of the AE is incompatible with a causal relationship; or the AE started before the first vaccination (screening phase, if applicable)
- Related – There is a "reasonable possibility" that the AE was caused by the study intervention administered, meaning that there is evidence or arguments to suggest a causal relationship

- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causal relationship.
- 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 causal relationship for every event before the initial transmission of the SAE data to the Sponsor.
- The Investigator may change his/her opinion of causal relationship in light of follow-up information and send a SAE follow-up report with the updated causal relationship assessment.
- The causal relationship assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causal relationship of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, when available the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.

- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.
- Adverse events likely to be related to the study intervention, whether serious or not, that persist at the end of the study will be followed up by the Investigator until their complete disappearance or the stabilization of the participant's condition. The Investigator will inform the Sponsor of the date of final disappearance of the event or the date of "chronicity" establishment.

10.3.4 Reporting of SAEs

SAE Reporting to the Sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the Sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. 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 electronic data collection 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 electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section).
- Details regarding SAE reporting can be found in the Operating Guidelines.

SAE Reporting to the Sponsor via Paper CRF

- The SAE paper CRF can be sent to the Sponsor by one of the following means:
  - By fax, to the following number: 570-957-2782
  - In PDF format to the following e-mail address, using a method of transmission that includes password protection: PV.outsourcing@sanofi.com
  - By express mail, to the following address:

    Global Pharmacovigilance, Sanofi Pasteur
    Discovery Drive
    Swiftwater, PA 18370

Safety Emergency Call
If, as per the Investigator's judgment, a participant experiences a medical emergency, the Investigator may contact the Sponsor's RMO for advice on how to address any study-related medical question or problem. If the RMO is not available, then the Investigator may contact the Call Center—available 24 hours a day, 7 days a week—that will forward all safety emergency calls to the appropriate primary or back-up Sanofi Pasteur contact, as needed. The toll-free contact information for the Call Center is provided in the Operating Guidelines. This process does not replace the need to report an SAE. The Investigator is still required to follow the protocol-defined process for reporting SAEs to the GPV Department. In case of emergency code-breaking, the Investigator is required to follow the code-breaking procedures described in Section 6.3.2.

10.3.5 Assessment of Intensity

The Investigator will make an assessment of intensity for each AE reported during the study. An intensity grade will be assigned to each AE. The intensity 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".

10.3.5.1 Tables for Clinical Abnormalities

10.3.5.1.1 Solicited AR Intensity Grading Scale

Table 10.2: Solicited injection site reactions: terminology, definitions, and intensity scales

CRF term (MedDRA lowest level term [LLT])	Injection site pain	Injection site erythema	Injection site swelling
Diary card term	Pain	Redness	Swelling
Definition	Pain either present spontaneously or when the injection site is touched or injected limb is mobilized	Presence of a redness including the approximate point of needle entry	Swelling at or near the injection site Swelling or edema is caused by a fluid infiltration in tissue or cavity and, depending on the space available for the fluid to disperse, swelling may be either soft (typically) or firm (less typical) to touch and thus can be best described by looking at the size of the swelling

Intensity scale*	**CRF:** Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living. Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant. Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. **Diary card:** Grade 1: No interference with usual activities Grade 2: Some interference with usual activities Grade 3: Significant; prevents usual activities	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm

MedDRA: Medical Dictionary for Regulatory Activities
* For the subjective reaction of pain, participants will record the intensity level (Grade 1, 2, or 3) in the diary card. For the measurable reactions of redness and swelling, they will record just the size of the reaction, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis

Table 10.3: Solicited systemic reactions: terminology, definitions, and intensity scales

CRF term (MedDRA lowest level term [LLT])	Fever	Headache	Malaise	Myalgia
Diary card term	Temperature	Headache	Feeling unwell	Muscle aches and pains
Definition	Elevation of temperature to ≥°38.0°C (≥ 100.4°F)	Pain or discomfort in the head or scalp. Does not include migraine.	General ill feeling. Malaise is a generalized feeling of discomfort, illness, or lack of well-being that can be associated with a disease state. It can be accompanied by a sensation of exhaustion or inadequate energy to accomplish usual activities.	Muscle aches and pains are common and can involve more than one muscle at the same time. Muscle pain can also involve the soft tissues that surround muscles. These structures, which are often referred to as connective tissues, include ligaments, tendons, and fascia (thick bands of tendons). Does not apply to muscle pain at the injection site which should be reported as injection site pain.
Intensity scale*	Grade 1: ≥ 38.0°C to ≤ 38.4°C, **or** ≥ 100.4°F to ≤ 101.1°F	**CRF:** Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.	**CRF:** Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.	**CRF:** Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

	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	Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant. Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. **Diary card:** Grade 1: No interference with usual activities Grade 2: Some interference with usual activities Grade 3: Significant; prevents usual activities	Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant. Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. **Diary card:** Grade 1: No interference with usual activities Grade 2: Some interference with usual activities Grade 3: Significant; prevents usual activities	Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant. Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. **Diary card:** Grade 1: No interference with usual activities Grade 2: Some interference with usual activities Grade 3: Significant; prevents usual activities

MedDRA: Medical Dictionary for Regulatory Activities

* For all reactions but fever, participants will record the intensity level (Grade 1, 2, or 3) in the diary card. For fever, they will record the body temperature, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis based on the unit used to measure the temperature and the intensity scale.

Important notes for the accurate assessment of temperature:

Participants are to measure body temperature once per day, preferably always at the same time. The optimal time for measurement is the evening, when body temperature is the highest. Temperature is also to be measured at the time of any apparent fever. The observed daily temperature and the route of measurement are to be recorded in the diary card, and the highest temperature will be recorded by the site in the CRF. The preferred route for this study is oral.

10.3.5.1.2 Unsolicited AE Intensity Grading Scale

For measurable unsolicited AEs that are part of the list of solicited reactions, the corresponding scale for solicited reactions will be used (see Section 10.3.5.1.1).

All other unsolicited AEs will be classified according to the following intensity scale:

- Grade 1
  - CRF: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
  - Diary card: No interference with usual activities.
- Grade 2
  - CRF: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
  - Diary card: Some interference with usual activities.
- Grade 3
  - CRF: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
  - Diary card: Significant; prevents usual activities.

10.3.5.2 Tables for Laboratory Abnormalities

The pre-defined intensity thresholds for laboratories abnormalities are shown in Table 10.4.

Table 10.4: Intensity thresholds for laboratories abnormalities

Endpoint	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Hemoglobin (Female) – gm/dL	11.0 – 12.0	9.5 – 10.9	≤ 9.4
Hemoglobin (Female) (Change from baseline value) – gm/dL	Any decrease – 1.5	1.6 – 2.0	≥ 2.1
Hemoglobin (Male) – gm/dL	12.5 – 13.5	10.5 – 12.4	≤ 10.5
Hemoglobin (Male) (Change from baseline value) – gm/dL	Any decrease – 1.5	1.6 – 2.0	≥ 2.1
Above normal WBC – cell/mm^3	10,800 – 15,000	15,001 – 20,000	≥ 20,001
Below normal WBC – cell/mm^3	2,500 – 3,500	1,500 – 2,499	≤ 1,499
Absolute Lymphocytes Decreased – cell/mm^3	750 – 1,000	500 – 749	< 499
Absolute Neutrophils Decreased – cell/mm^3	1,500 – 2,000	1,000 – 1,499	< 999
Absolute Eosinophils – cell/mm^3	650 – 1500	1501 - 5000	> 5000
Platelets Decreased – cell/mm^3	125,000 – 140,000	100,000 – 124,000	≤ 99,000
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	≥ 2.1 or requires dialysis
Blood Urea Nitrogen (BUN) – mg/dL	23 – 26	27 – 31	> 31 or require dialysis
Sodium – Hyponatremia – mEq/L	132 – 134	130 – 131	< 130
Sodium – Hypernatremia – mEq/L	144 – 145	146 – 147	> 148
Potassium – Hyperkalemia – mEq/L	5.1 – 5.2	5.3 – 5.4	> 5.4
Potassium – Hypokalemia – mEq/L	3.5 – 3.6	3.3 – 3.4	< 3.3
Glucose – Hyperglycemia (fasting) – mg/dL	100 - 110	111 - 125	> 125
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 ULN
LFT (ALT, AST) (Increase by factor)	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	≥ 5.1 ULN
Bilirubin – with any increase in LFT (Increase by factor)	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	≥ 1.51 ULN

Endpoint	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Bilirubin – with normal LFT (Increase by factor)	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	≥ 2.1 ULN
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	≥ 2.1 ULN
Urine - protein	Trace	1+	2+
Urine - glucose	Trace	1+	2+
Urine – blood (microscopic) - RBCs per high power field (rbc/hpf)	1 - 10	11 - 50	> 50 and/or gross blood

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; CRP, C-reactive protein; dL, deciliter; gm, gram; LFT, liver function test; mg, milligram; mm^3, cubic millimeter; RBC, red blood cell; ULN, upper limit of normal; WBC, white blood cell

10.4 Appendix: Collection of Pregnancy Information

DEFINITIONS:

Woman 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

1) Premenarchal
2) 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.
3) Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal 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.

COLLECTION OF PREGNANCY INFORMATION

The collection period of pregnancy information will correspond at least to the period during which the participant is requested to be under contraception. (according to protocol: effective method of contraception or abstinence from at least 4 weeks prior to the first vaccination until at least 12 weeks after the last vaccination). If there are any pregnancy during this period, follow-up should be conducted up to delivery: this will be covered by the 12-month surveillance of the study.

Female Participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information together with the contraceptive method if any will be recorded on the appropriate form and submitted to the Sponsor within 1 month of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date, but will be in accordance with local regulations. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- In case of pregnancy during the primary series and if at least 1 dose of the study vaccine(s) has been administered, the participant will not be discontinued from the study, but no further vaccination will be administered until after delivery (if applicable and still within the study vaccination window). However, the participant will be followed for safety assessment (and may be followed for immunogenicity assessment, if applicable).
- If primary series have been completed and the delivery occurs between the primary series and the booster, the booster dose can be administered. However, if vaccination is a contraindication for lactation (ie, live-attenuated vaccine), the participant may not be vaccinated with a booster dose.

10.5 Appendix: AESIs

Events potentially associated with coronavirus vaccine

Anaphylactic reactions

Generalized convulsion

Thrombocytopenia

Events potentially associated with AFO3 adjuvant use

Dry eyes

Tearing

Dry mouth

Events potentially associated with the adjuvants use (AF03 or AS03) and/or coronavirus vaccine

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.

However, the Investigator will exercise their medical and scientific judgment in deciding whether other diseases have an autoimmune origin (that is pathophysiology involving systemic or organ-specific pathogenic autoantibodies) and should also be recorded as a pIMD.

When there is enough evidence to make any of the diagnoses mentioned in Table 10.5, the AE must be reported as a pIMD. Symptoms, signs or conditions which might (or might not) represent the above diagnoses, should be recorded and reported as AEs but not as pIMDs until the final or definitive diagnosis has been determined, and alternative diagnoses have been eliminated or shown to be less likely.

In order to facilitate the documentation of pIMDs in the eCRF, a pIMD standard questionnaire and a list of preferred terms (PTs) and PT codes corresponding to the above diagnoses will be available to investigators at study start.

Once a pIMD is diagnosed (serious or non-serious) in a study subject, the Investigator (or designate) must complete, date and sign an electronic Expedited Adverse Events Report.

Table 10.5: List of potential immune-mediated diseases

Neuroinflammatory disorders	Musculoskeletal disorders	Skin disorders
• Cranial nerve neuropathy, including paralysis and paresis (eg, Bell's palsy). • Optic neuritis. • Multiple sclerosis. • Transverse myelitis. • Guillain-Barré syndrome*, including Miller Fisher syndrome and other variants. • Acute disseminated encephalomyelitis*, including site specific variants, eg, noninfectious encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis. • Myasthenia gravis, including Lambert-Eaton myasthenic syndrome. • Demyelinating peripheral neuropathies including: - Chronic inflammatory demyelinating polyneuropathy. - Multifocal motor neuropathy. - Polyneuropathies associated with monoclonal gammopathy. • Narcolepsy*.	• Systemic lupus erythematosus and associated conditions. • Systemic scleroderma (systemic sclerosis), including: • Diffuse scleroderma. • CREST syndrome. • Idiopathic inflammatory myopathies, including: • Dermatomyositis. • Polymyositis. • Anti-synthetase syndrome. • Rheumatoid arthritis and associated conditions including: • Juvenile idiopathic arthritis. • Still's disease. • Polymyalgia rheumatica. • Spondyloarthropathies, including: - Ankylosing spondylitis. - Reactive arthritis (Reiter's syndrome). - Undifferentiated spondyloarthritis. - Psoriatic arthritis. - Enteropathic arthritis. • Relapsing polychondritis. • Mixed connective tissue disorder. • Gout.	• Psoriasis. • Vitiligo. • Erythema nodosum. • Autoimmune bullous skin diseases (including pemphigus, pemphigoid, and dermatitis herpetiformis). • Lichen planus. • Sweet's syndrome. • Localized scleroderma (morphea).
Vasculitis	**Blood disorders**	**Others**
• Large vessels vasculitis* including: - Giant cell arteritis (temporal arteritis). - Takayasu's arteritis. • Medium sized and/or small vessels vasculitis* including:	• Autoimmune hemolytic anemia. • Autoimmune thrombocytopenia. • Antiphospholipid syndrome. • Pernicious anemia. • Autoimmune aplastic anemia.	• Autoimmune glomerulonephritis including: - IgA nephropathy. - Glomerulonephritis rapidly progressive. - Membranous glomerulonephritis.

- Polyarteritis nodosa. - Kawasaki's disease. - Microscopic polyangiitis. - Wegener's granulomatosis (granulomatosis with polyangiitis). - Churg–Strauss syndrome (allergic granulomatous angiitis or eosinophilic granulomatosis with polyangiitis). - Buerger's disease (thromboangiitis obliterans). - Necrotizing vasculitis (cutaneous or systemic). - Antineutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified). - Henoch-Schonlein purpura (IgA vasculitis). - Behcet's syndrome. - Leukocytoclastic vasculitis.	• Autoimmune neutropenia. • Autoimmune pancytopenia.	- Membranoproliferative glomerulonephritis. - Mesangioproliferative glomerulonephritis. - Tubulointerstitial nephritis and uveitis syndrome. • Ocular autoimmune diseases including: • Autoimmune uveitis. • Autoimmune retinitis. • Autoimmune myocarditis. • Sarcoidosis. • Stevens-Johnson syndrome. • Sjögren's syndrome. • Alopecia areata. • Idiopathic pulmonary fibrosis. • Goodpasture syndrome. • Raynaud's phenomenon.
Liver disorders	**Gastrointestinal disorders**	**Endocrine disorders**
• Autoimmune hepatitis. • Primary biliary cirrhosis. • Primary sclerosing cholangitis. • Autoimmune cholangitis.	• Inflammatory bowel disease, including: - Crohn's disease. - Ulcerative colitis. - Microscopic colitis. - Ulcerative proctitis. • Celiac disease. • Autoimmune pancreatitis.	• Autoimmune thyroiditis (Hashimoto thyroiditis). • Grave's or Basedow's disease. • Diabetes mellitus type 1. • Addison's disease. • Polyglandular autoimmune syndrome. • Autoimmune hypophysitis.

***** Events potentially associated with coronavirus vaccine

10.6 Appendix: Risk-based Approach

ICH E6-R2 guideline for GCP is introducing the « risk-based approach » concept which permits to focus efforts on what is critical for a study and most specifically on Critical Data and Critical Processes. Critical data and processes are defined for the study with associated risks in the Study Risk Management Plan.

10.7 Appendix: Abbreviations

AE	Adverse Events
AESI	Adverse events of special interest
AR	Adverse reactions
BARDA	Biomedical Advanced Research and Development Authority
CI	Confidence interval
CMI	Cellular-mediated Immunity
CoV2 preS dTM:	SARS-CoV2 prefusion Spike delta TM
CPE	Cytopathic effect
CRF	Case report form
D	Day
DMC	Data Monitoring Committee
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
FAS	Full analysis set
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
GMC	Geometric mean concentration
GMT	Geometric mean titer
GPV	Global Pharmacovigilance
GSK	GlaxoSmithKline
HA	hemagglutinin
HAI	hemagglutination inhibition
IDMC	Independent Data and Monitoring Committee
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
IgG	Immunoglobulin G
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committees
IMP	Investigational Medicinal Product
IRB	Institutional Review Boards

IRT	Interactive Response Technology
LLOQ	lower limit of quantification
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
NAAT	nucleic acid amplification test
NIMP	Non- Investigational Medicinal Product
NOCMC	new-onset chronic medical conditions
OD	Optical density
pIMD	potential immune-mediated disease
PPAS	Per-protocol analysis set
PPAS-CMI	Per-protocol analysis set for CMI
PPAS-IAS	Per-protocol analysis set for immunogenicity
PT	preferred term
RBD	receptor binding domain
RMO	Responsible Medical Officer
S	Spike
SAE	Serious adverse events
SafAS	Safety Analysis Set
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SoA	Schedule of Activities
TBD	to be determined
TIV	trivalent influenza vaccine
VAC	Vaccination (as in Vaccination #)
WOCBP	Woman of Childbearing Potential

10.8 Appendix: Protocol Amendment/Update History

Revisions and rationale for revisions for protocol Version 2.0, Version 3.0, and Version 4.0 are as follows.

Protocol Version 2.0, dated 24 July 2020 (was an update only before study start))

The protocol was updated from the Version 1.0 mainly due to CBER feedback from the pre-IND submission, along with other feedback from GlaxoSmithKline.

Revision	Rationale
Population: No upper limit on age	It is considered of great relevance to generate data in the older adult population to inform schedule and formulation selection that will serve the general adult population, including those at particular risk of poor outcomes. CBER concurred and agreed to no upper age limit.
Sentinel Safety Cohort and Early Safety Data Review added (with halting rules)	As Phase I/II VAT00001 is a relatively large first-in-human study of novel antigen and adjuvant combinations, to improve the safety of the protocol, CBER requested a small sentinel cohort made up of participants 18-49 years of age in Cohort 1 (single dose). If safety data and laboratory measures to D09 in Cohort 1 are considered as acceptable based on unblinded data review by limited members of the Sponsor Study Team (Responsible Medical Officer, Study Biostatistician and Programmer, Pharmacovigilance Science Expert, and Global Safety Officer) and do not meet any halting rules, concurrent enrollment and vaccinations at all dose levels in both age groups may proceed as planned.
Removed 45 µg formulation	Recently reported and historical data suggest that antigen doses lower than 45 µg can result in robust immune responses. The choice of antigen dose is also driven by the industrial capacity needed to support the number of doses required for a pandemic response.
Sample Sizes revised throughout	Due to addition of Sentinel Safety Cohort, removal of 45 µg formulation, and increased focus on the AS03 adjuvant.
Blood Sample 3 (BL0003) (Cohort 1 and Cohort 2) and PBMC Sample 3 (MC0003) (Cohort 2) changed from Day (D)43 to D36; D43 Visit replaced by telephone call	Post-vaccination 2 samples (BL0003 and MC0003) for Cohort 2 were shifted from D43 to D36 as a means of acceleration of serological data for early information on vaccine performance. The D43 blood sample for Cohort 1 was also shifted to D36 for consistency. D43 contact then became a telephone call for safety only.
Blood Draw added at Month 12 resulting in a Visit 7 for both Cohorts instead of 12-month safety follow-up call	Per CBER feedback: To further evaluate safety (risk of vaccine-enhanced disease), monitoring for the occurrence and severity of NAAT- and serologically-confirmed COVID-like illness extended to 12 months after the last vaccination.
Additions and revisions for text on narcolepsy / pIMD	Since narcolepsy is part of the list of Potential Immune-Mediated Diseases, it will be included in the risk 'Potential Immune-Mediated Diseases'.
Additions of terms in list of Adverse Events of Special Interest (AESIs)	Following Safety Platform for Emergency Vaccines (SPEAC) and Priority List of AESI: COVID-19 dated 25 May 2020 (Version 2.0), "Generalized convulsion" and "Thrombocytopenia" have been added as AESIs.

Exclusion Criteria: Added footnote to criterion #3: "While receipt of any vaccine as listed in this criterion is exclusionary for this study, if a COVID-19 vaccine becomes available from a company other than Sanofi Pasteur, then participants are free to receive that vaccine. Participants who receive a COVID-19 vaccine will still be followed for safety until the end of the study but will be discontinued from study intervention administration thereafter (see Section 7.1.2: Definitive Contraindications)." Added to Criterion #12 footnote: "current vaping" Added new previous vaccination criterion: - Prior administration of a coronavirus vaccine (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2], SARS-CoV, Middle East Respiratory Syndrome [MERS-CoV]) Added 3 new criteria for risk-management: - Residence in a nursing home or long-term care facility - Health care workers providing direct patient care for COVID-19 patients - Participants with active or prior documented autoimmune disorder (such as potential immune-mediated diseases [pIMDs])	Revisions made due to CBER/GSK feedback: - Per FDA guidance, it needs to be clear that participants may choose to receive an approved COVID-19 vaccine if available from another company. - Previous plan was to exclude former and current smokers. For completeness, criterion is extended to exclude persons who currently vape. - Although there are currently no licensed/marketed COVID vaccines at the moment, participants may have participated in another COVID study. - Added 3 exclusion criteria for persons at higher risk for severe COVID-19 disease or at increased risk for exposure to SARS-CoV-2.

Protocol Version 3.0 (dated 26 August 2020) and Version 4.0 (dated 27 August 2020)

The protocol was updated from Version 2.0 (dated 24 July 2020) to Version 3.0 (dated 26 August 2020) due to CBER feedback from its review of the IND submission. One day after approval of Version 3.0 on 26 August 2020, additional revisions were requested by CBER on 27 August 2020, resulting in Version 4.0.

Version 3.0 was submitted to the IRB; however, since the protocol was pulled less than 1 day later, the below revisions section includes changes between Version 2.0 through Version 4.0, inclusive.

Major revisions between Version 2.0 and Version 3.0	
Revision	**Rationale**
Section 8.4: Halting Rules subheading Revised pause bullets #4 and #5	Revised per CBER feedback: Halting Rules throughout the Study, ≥10% of participants equates to at least n=44 across treatment groups who could have a Grade 3 AE of the same type before the study is halted and ≥5% of participants equates to at least n=22 across treatment groups who could have Grade 3 laboratory abnormalities of the same type before the study is halted. These numbers exceed the thresholds that we recommended in our pre-IND comments and could result in an unreasonable risk of injury or harm.
Section 8.4: ESDR subheading If any of the below criteria are met, the data on the particular alert threshold event will be reviewed by the SMT and a decision will be made as to whether subsequent vaccinations in the study will be allowed to resume. Enrollment will be paused during the ESDR, and the following safety parameters will be examined: • ≥ 2 participants per dosing group (n=6) experiencing Grade 3 systemic reaction (without concurrent infectious disease) • ≥ 2 participants per dosing group (n=6) experiencing Grade 3 solicited injection site pain • ≥ 2 participants per dosing group (n=6) experiencing Grade 3 unsolicited non serious reactions (reactions not explained by any other possible etiology) • ≥ ~~2~~ participants with Grade 3 laboratory AE (Grade 3 abnormality if Grade 1 or 2 at baseline) of the same type (reactions not explained by any other possible etiology) • ≥ 2 participants with Grade 2 laboratory AE (Grade 2 abnormality if normal at baseline) of the same type (reactions not explained by any other possible etiology) and judged by the Investigator to be clinically meaningful	Changed bullet #4 to from “3” to “2” to make it consistent with the overall halting rules (3 would be less strict than the overall halting rules).
Major revision between Version 3.0 and Version 4.0	
Revision	**Rationale**
For Section 4.2: "Scientific Rationale for Study Design", sentence below was removed: The adjuvants that will be utilized in this study also have a well-established safety profile”.	Given ongoing concerns for potential immune-mediated adverse events and the relatively small clinical trial safety database for AF03, this sentence was requested to be deleted by CBER on 27 AUG 2020.

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12 Sponsor Signature Page

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