Title Page

Protocol Title:
A parallel-group, Phase III, multi-stage, modified double-blind, multi-armed study to assess the efficacy, safety, and immunogenicity of two SARS-CoV-2 Adjuvanted Recombinant Protein Vaccines (monovalent and bivalent) for prevention against COVID-19 in adults 18 years of age and older as a primary series and open-label extension to assess immunogenicity, safety, efficacy of a monovalent booster dose of SARS-CoV2 Adjuvanted Recombinant Protein Vaccine

Study Code: VAT00008

Amendment Number: Amendment 4

Compounds:
SARS-CoV2 prefusion Spike delta TM with AS03 adjuvant, monovalent D614 (CoV2 preS dTM-AS03 [D614]): monovalent vaccine with the Spike (S) protein sequence from the D614 variant

SARS-CoV2 prefusion Spike delta TM with AS03 adjuvant, bivalent D614/B.1.351 (CoV2 preS dTM-AS03 [D614 + B.1.351]): bivalent vaccine with the S protein sequence from the D614 variant and the B.1.351 variant

SARS-CoV2 prefusion Spike delta TM with AS03 adjuvant, monovalent B.1.351 (CoV2 preS dTM-AS03 [B.1.351]): monovalent vaccine with the S protein sequence from the B.1.351 variant

Brief Title:
Study of Monovalent and Bivalent Recombinant Protein Vaccines against COVID-19 in Adults 18 Years of Age and Older

Study Phase: Phase III

Sponsor Name and Legal Registered Address:
Sanofi Pasteur Inc.
Discovery Drive, Swiftwater, PA 18370-0187, USA

Manufacturer:
CoV2 preS dTM: Same as Sponsor

AS03 adjuvant: GlaxoSmithKline (Vaccines)

Regulatory Agency Identifier Numbers:
BB-IND: 23143

WHO UTN: U1111-1264-3238

Protocol Version Number: 8.0

Approval Date: 08 September 2022

Responsible Medical Officer (RMO) and pharmacovigilance (PV) representative names 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	30 March 2021	Internal version not submitted
2.0	16 April 2021	Submitted to Independent Ethics Committees / Institutional Review Boards and Health Authorities, but not used in the study.
3.0	18 May 2021	Original version used in the study
4.0	11 August 2021	Submitted to Independent Ethics Committees / Institutional Review Boards and Health Authorities, but not used in the study in most countries. However, enrollment needed to start in India and version 4.0 was used while waiting for Ethics Committee review of version 5.0.
5.0	08 September 2021	Amendment #1, version used in the study
6.0	11 April 2022	Amendment #2: Substantial amendment submitted and used in some countries but not others
7.0	02 August 2022	Amendment #3: Clinical protocol amendment submitted to United States Food and Drug Administration (FDA); not submitted to other countries/sites.

** Versions in bold font have been approved by the IEC(s) / IRB(s) and used in the study.*

Amendment 4 (08 September 2022)

This amendment is considered to be **non-substantial** based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union **because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study**.

Overall Rationale for the Protocol Amendment:

The main reason for updating the protocol is based on a recent US FDA request. The request required the inclusion of information in the protocol on the risk of myocarditis and/or pericarditis associated with COVID-19 vaccines, and measures to mitigate this risk since these conditions have been reported in individuals vaccinated with some COVID-19 vaccines containing the SARS-CoV-2 S antigen. History of myocarditis and/or pericarditis prior to each vaccination was included as a definitive contraindication to enrollment in the crossover/booster stage of the study. Additionally, participants experiencing myocarditis and/or pericarditis will be referred to a cardiologist for evaluation and management and discontinued from further vaccination. Reference

to the Centers for Disease Control and Prevention (CDC) case definitions for myocarditis and pericarditis was also included.

Further details are described in the table below:

Revision	Rationale
Throughout: Replaced "Sanofi Pasteur" with "Sanofi"	Company name updated to reflect change made within the organization.
Document History and Protocol Amendment Rationale; Appendix 10.10: - Revised document history table - Added overall rationale for major changes from version 7.0 to version 8.0 - Moved changes from previous version to Appendix 10.10	Updates due to change in version, per Common Protocol Template instructions.
Synopsis: Procedures: Follow-up of participants who report symptoms of myocarditis and/or pericarditis within 6 weeks of vaccination is now described.	Text added to address how risk of myocarditis and/or pericarditis will be mitigated by the Sponsor with regards to signal detection, case evaluation and management, and discontinuation from further vaccination.
Synopsis: Data Monitoring/Other Committee: Statement added: "In the event that a participant develops symptoms that are suspected to be caused by myocarditis and/or pericarditis, the case will be referred to an external cardiac adjudication committee for assessment and confirmation."	External cardiac adjudication committee will be utilized for facilitate signal management of suspected cases of myocarditis and/or pericarditis.
Table 1.5 and Table 1.6: Table note added to "Safety follow-up (MAAEs, SAEs, and AESIs)" row: AESIs (serious and non-serious) will be collected throughout the study and will be communicated to the Sponsor in an expedited manner similar to the reporting of SAEs and followed-up until the end of the follow-up period or resolution, as per the assigned causality. These include: Anaphylactic reactions, Generalized convulsion, Thrombocytopenia, Thrombosis with Thrombocytopenia Syndrome, Myocarditis, Pericarditis, and potential immune-mediated diseases (pIMDs).	Added for clarity and consistency with Table 1.3.
Section 2.3 and Table 2.2: Text added to clarify that, although no safety concern has been identified for the CoV2 preS dTM vaccine to date, myocarditis and pericarditis have	Text added to communicate risk of myocarditis and/or pericarditis due to vaccination with a COVID-19 vaccine.

been reported following vaccination with other COVID-19 vaccines manufactured using both the mRNA and protein/adjuvant platforms. Available data on the epidemiology and clinical course of myocarditis and pericarditis were included.	
Section 4.1 Overall Design: Procedures: Follow-up of participants who report symptoms of myocarditis and/or pericarditis within 6 weeks of vaccination is now described.	Text added to address how risk of myocarditis and/or pericarditis will be mitigated by the Sponsor with regards to signal detection, case evaluation and management, and discontinuation from further vaccination.
Section 7.1.4 (Definitive Contraindication #9 for Crossover/Booster Design): Included history of myocarditis and/or pericarditis prior to vaccination as definitive contraindication to further vaccination in the crossover/booster stage of the study.	Added as a definitive contraindication to ensure that participants with a history of myocarditis and/or pericarditis are excluded from further vaccination in the crossover/booster stage of the study. History of myocarditis and/or pericarditis were not added to exclusion criteria since the study has finished recruitment.
Section 8.4.6: - Replaced previous references for myocarditis and pericarditis with reference to the Centers for Disease Control and Prevention (CDC) case definitions. - Relocated all case definition references to footnotes for readability.	The CDC case definitions for myocarditis and pericarditis were included as they are more specific than the Brighton Collaboration case definitions.
Section 10.1.5: Added new subsection 10.1.5.2 Cardiac Adjudication Committee.	Subsection added to reflect implementation of an external cardiac adjudication committee for assessment/confirmation of suspected cases of myocarditis and/or pericarditis to mitigate risk due to these events.
Section 10.5: Included definitions for probable and confirmed cases of myocarditis, as well as acute pericarditis.	Text added to guide the investigator in the reporting of suspected cases of myocarditis and/or pericarditis.

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1 Protocol Summary

1.1 Synopsis

Protocol Title:

A parallel-group, Phase III, multi-stage, modified double-blind, multi-armed study to assess the efficacy, safety, and immunogenicity of two SARS-CoV-2 Adjuvanted Recombinant Protein Vaccines (monovalent and bivalent) for prevention against COVID-19 in adults 18 years of age and older as a primary series and open-label extension to assess immunogenicity, safety, efficacy of a monovalent booster dose of SARS-CoV2 Adjuvanted Recombinant Protein Vaccine

Brief Title:

Study of Monovalent and Bivalent Recombinant Protein Vaccines against COVID-19 in 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 (1) on 20 January 2020 of a Public Health Emergency of International Concern, followed by the declaration on 11 March 2020 of a pandemic (2). The virus has been detected in 192 countries/regions and led to significant morbidity, mortality, and economic impact (3). Despite unprecedented measures of isolation, quarantine, social distancing, and community containment, to curb the spread of the virus, and the rapid development and global deployment of multiple locally approved/authorized SARS-CoV-2 vaccines, the global burden of SARS-CoV-2 infections and associated disease remains substantial, highlighting the need for more safe and effective vaccines.

New, highly transmissible SARS-CoV-2 variants of concern (VOCs) have emerged and are spreading globally. The Alpha (B.1.1.7) variant first identified in the United Kingdom (UK) has been shown to be more transmissible and has since been detected in many other countries around the world (4). Other VOCs have emerged which were first identified in South Africa (Beta [B.1.351] variant), Brazil (Gamma [P.1] variant), India (Delta [B.1.617.2] variant) and a new variant of concern (Omicron [B.1.1.529]) and have now been detected in other countries. A key question is whether currently authorized and available COVID-19 vaccines will be able to protect against infection or disease from these variants. Recent preliminary data using an adjuvanted protein sub-unit vaccine (Novavax) and the ChAdOx1 nCoV-19 vaccine (AZD1222 [Oxford University/AstraZeneca]) showed lower efficacy against mild to moderate COVID-19 in South Africa where the Beta (B.1.351) variant predominated, compared to the efficacy observed for these vaccines in studies conducted in the UK where Alpha (B.1.1.7) variant predominated (5) (6) (7). However, data from the Ad26CoV2.S vaccine (Janssen) showed efficacy against symptomatic disease in South Africa suggestive of some evidence for the prototype vaccines to confer protection against the Beta (B.1.351) variant. Sera from individuals immunized with prototype COVID-19 vaccines show an ability to neutralize the variants but to a lesser extent than the

prototype strain. This decrease in neutralization is higher against the South African Beta (B.1.351) variant which has a characteristic E484K mutation in the receptor-binding domain along with other mutations in the N-terminal domain of the Spike (S) protein and highest against Omicron (B.1.1.529). These findings have led to the development of variant strain vaccines and regulatory guidance for the development of vaccines against the variant strains for products that have already demonstrated efficacy with the prototype vaccines (8). There has been particular emphasis on developing variant strain vaccines to protect against the Beta (B.1.351) variant. The Delta (B.1.617.2) variant first identified in India includes the characteristic E484Q and L452R mutations in the receptor-binding domain of the S protein and the P681R mutation in the polybasic cleavage site region and is currently the most prevalent circulating variant in many countries and regions of the world. This variant has been shown to have higher infectivity in cell lines, increased pathogenicity in hamsters, was resistant against an authorized monoclonal antibody treatment for COVID-19 and was less efficiently neutralized by post-infection and post-vaccination sera (9) (10) (11). Real-world data from the UK has shown a modest decrease in vaccine effectiveness against symptomatic COVID-19 caused by the delta variant compared to the alpha variant in participants receiving two doses of the ChaAdOx-1 and BNT162b2 nCoV-19 vaccines which encode the parental D614 variant S protein sequence (12). Preliminary data from Israel show a high level of vaccine effectiveness against hospitalization and severe disease at a time when the Delta (B.1.617.2) variant is prevalent in individuals who received 2 doses of the BNT-162b2 vaccine. These data suggest that parental D614 vaccines provide significant, albeit lower magnitude of protection against the Delta (B.1.617.2) variant. Ongoing evolution of SARS-CoV-2 variants, especially in light of the growing prevalence of vaccination and the selection pressure that this may exert, raises the strong public health requirement for SARS-CoV-2 vaccines, including those protective against emergent VOCs.

To address the medical need caused by this pandemic, Sanofi initiated development of a recombinant protein vaccine consisting of a stabilized prefusion trimer of the SARS-CoV-2 S protein based on the work by Wrapp and colleagues (13). The recombinant protein vaccine is used in combination with an adjuvant system, named AS03, to optimize the immune response. A monovalent vaccine with the S protein sequence from the original variant (first identified in Wuhan) with D614 in the receptor-binding domain of the S protein was developed.

Following the global spread of the D614 strain first identified in Wuhan, China, new, highly transmissible SARS-CoV-2 VOCs have emerged and are spreading globally. There has been particular emphasis on developing variant strain vaccines to protect against new variants emerge as current COVID-19 vaccines based on Spike protein from the D614 strains show modest levels of protection against new variants. To combat the emergence of variant strains, Sanofi is also developing a bivalent vaccine formulation with 2 recombinant prefusion delta TM proteins encoding the S protein sequence from the D614 strain and the Beta (B.1.351) variant (CoV2 preS dTM-AS03 [D614 + B.1.351]). This bivalent vaccine adjuvanted with AS03 is being tested in the Phase III efficacy study VAT00008 and Phase III Supplemental cohorts of study VAT00002. In this later study (VAT00002 - Supplemental Phase III Cohorts), Sanofi is developing a universal booster of the CoV2 preS dTM-AS03 vaccine as both monovalent vaccines containing either D614 strain or Beta (B.1.351) strain.

A Phase I/II study in healthy adults 18 years of age and older to evaluate the safety and immunogenicity of the recombinant CoV2 prefusion Spike delta TM (CoV2 preS dTM)

monovalent D614 vaccine adjuvanted with the AS03 or AF03 adjuvants was initiated in September 2020 and is currently ongoing. Interim results from this Phase I/II study showed lower than expected immunogenicity in combination with higher-than-expected reactogenicity (14). The effective antigen dose levels administered in a 0.5 mL vaccine dose in this study were 1.3 µg (Low Dose) and 2.6 µg (High Dose) of functional SARS-CoV-2 preS protein with differences between the targeted and the effective antigen dose levels corresponding to an excess of Host Cell Protein (HCP) content in the clinical materials (recalculated HCP content, 3.7 µg and 12.4 µg). These data indicated that assessment of optimized antigen formulations (with higher antigen dose and lower HCP content) is necessary to select an antigen dose to progress to Phase III evaluation. Following VAT00001 study, the manufacturing process had been further developed increasing the purity of the vaccine candidate to > 90% for the Phase II and Phase III clinical materials.

A Phase II study (VAT00002 [NCT04762680]) designed as a dose-finding, safety and immunogenicity study (hereafter referred to as the Original Cohort of VAT00002) is ongoing to evaluate 5 µg, 10 µg, and 15 µg of the pre-S antigen dose in combination with AS03 adjuvant to select an antigen dose to progress to Phase III. As part of an amendment to the original VAT00002 study, Supplemental Phase III Cohorts will be tested to address various prime-boost options and variant vaccines for primary immunization. These will allow the evaluation of the potential use of CoV2 preS dTM-AS03 to boost responses in individuals previously vaccinated with other platforms; for this purpose the study will assess the safety and immunogenicity of different formulations of the CoV2 preS dTM-AS03 vaccine, including monovalent and bivalent formulations, for use as a universal booster. The study will also further evaluate the safety and immunogenicity of Beta (B.1.351) variant-containing vaccines (monovalent [B.1.351] and bivalent [D614 + B.1.351]) in the context of primary immunization of naïve, previously unvaccinated individuals.

Interim results from the Original Cohort of VAT00002, evaluating 5 µg, 10 µg, and 15 µg of the pre-S antigen dose in combination with AS03, included safety and reactogenicity data collected up to day 43 (21 days post-injection 2) and neutralizing and binding antibodies to D614G variant measured at baseline, prior to second injection and 14 days after the second injection. The data showed a similar safety profile across all antigen dose groups. At D36, the proportion of SARS-CoV-2 naïve participants with a 2-fold and 4-fold or greater rise in neutralizing antibody titers against D614G after 2 injections was > 90% in both younger and older naïve adults and similar proportions were observed across the different antigen dose groups. Neutralizing antibody titers against D614G were generally consistent, comparable to a panel of human convalescent sera and without clear evidence of a dose effect across treatment groups in the overall naive study population (18 years and older). There was indication of higher neutralizing antibody responses in younger adults with higher antigen doses; this pattern was not observed in the older adults. These observations were also observed with binding antibodies to the S-antigen (15). The pattern of neutralizing antibody responses suggests that while expected protection may not differ largely between antigen dose levels for homologous strains or variants with limited impact on neutralizing activity, higher antigen doses may provide some risk mitigation for protection against variants associated with decrease in neutralizing activity.

The bivalent, D614 + B.1.351, vaccine adjuvanted with AS03 will be tested in this Phase III efficacy study without a safety lead-in based on the clinical data on safety, reactogenicity, and immunogenicity generated with the monovalent D614 vaccine; similarity in manufacturing

process for two CoV2 preS dTM components of the bivalent product compared to the monovalent product; similarity in construct design supporting a similar safety profile of the bivalent product to the monovalent vaccine; and the total antigen content of the pre-S antigen in the bivalent vaccine (10 µg) is the same as the monovalent vaccine used in the Phase III study. The bivalent vaccine was tested in an immunogenicity study in naive non-human primates (NHPs) assessing the bivalent formulation at doses of 2.5 µg, 5 µg, and 10 µg per component adjuvanted with AS03 alongside the monovalent D614 and monovalent B.1.351 vaccines. Three weeks after the second vaccination, neutralizing and binding antibodies were observed in all macaques with all 3 antigen doses of the bivalent vaccine. The neutralizing antibody titers against the D614G strains induced by the bivalent vaccine were slightly lower to those induced by the monovalent D614 vaccine (2- to 3-fold lower and mainly in the low-dose group). Comparing the bivalent at 5 µg + 5 µg with monovalent D614 vaccine at 10 µg, the actual planned doses for VAT00008, the differences on D614 neutralizing antibody titers where not statistically significant suggesting limited immune interference at higher antigen doses and when comparing the same total antigen dose between the monovalent and bivalent vaccine. Neutralizing antibody titers against known VOCs (B.1.351, B.1.1.7, B.1.1.28, B.1.617.2, and B.1.1.529) were assessed in the study. Compared to the monovalent D614 vaccine, the bivalent vaccine induced much higher titers against the B.1.351 and B.1.1.28 variants, and comparable neutralization of the currently 2 most widely circulating B.1.1.7 and B.1.617.2 variants. Compared to the monovalent B.1.351 vaccine, the bivalent vaccine induced much higher neutralizing antibody titers against the parental D614 and D614G strains, as well as against B.1.1.7 and B.1.617.2 variants (16). These data generated in naïve NHPs showing balanced neutralization of all known VOCs to date with the bivalent vaccine (D614+B.1.351), limited interference against the D614G variant compared to the monovalent D614 vaccine support the evaluation of the bivalent vaccine in VAT00008 Stage 2.

In the VAT00008 efficacy study, the antigen dose for both the monovalent and bivalent vaccines was determined based on safety and immunogenicity data observed in the Original Cohort of the VAT00002 Phase II study, results of nonclinical studies, and information on manufacturing capacity. The interim data from the VAT00002 study were used to select the 10 µg dose for the monovalent D614 vaccine to be tested in Stage 1 of the Phase III study; and for Stage 2 of the Phase III study with the bivalent D614 + B.1.351 vaccine, a 5 µg (D614 component) + 5 µg (B.1.351 component) antigen dose. As stated above, the data from the VAT00002 study suggest that protection with antigen dose of 5 µg may be sufficient against homologous strains or variants with limited impact on neutralizing activity and that a higher antigen dose may provide some risk mitigation against a decrease in neutralizing antibody titers against circulating variants. As observed in the NHP studies with the bivalent candidate vaccine, the inclusion of a variant component in the formulation mitigates by design the potential impact of circulating variants associated with decreased neutralization by inducing a balanced neutralizing antibody response across a panel of known VOCs. The bivalent vaccine will be used along with a fixed amount of AS03 as used in the Phase II study with the monovalent vaccine.

VAT00008 is a Phase III, randomized, modified double-blind, placebo-controlled, multi-stage, multi-center, multi-country study to assess the efficacy, safety, and immunogenicity of two CoV2 preS dTM-AS03 vaccines (monovalent and bivalent) in adults 18 years of age and older with 2 stages. In Stage 1, the AS03 adjuvanted monovalent vaccine with the prefusion S protein from the prototype (D614) variant will be evaluated against a placebo control. In Stage 2, the AS03 adjuvanted bivalent vaccine with prefusion S protein from the prototype and South African Beta

variant (D614 + B.1.351) will be assessed against a placebo control. Both stages are considered independent to enable generation of data to support licensure of each candidate vaccine (ie, the monovalent and bivalent vaccine).

The study is designed to demonstrate clinical efficacy of each of the two SARS-CoV-2 recombinant protein vaccines (monovalent and bivalent) with AS03 adjuvant in preventing the occurrence of symptomatic COVID-19 with onset at least 14 days after the second injection of the vaccine in SARS-CoV-2 naïve individuals for Stage 1 and in all individuals regardless of their prior SARS-CoV-2 infection status for Stage 2. Symptomatic COVID-19 is defined as having virologically-confirmed SARS-CoV-2 infection with symptoms of a protocol-defined COVID-19-like illness.

Participants will be categorized based on prior SARS-CoV-2 infection as naïve (not previously infected) and non-naïve (evidence of previous infection) determined serologically (Roche Anti-N-Immunoassay and Roche Anti-S-Immunoassay) or virologically (Nucleic Acid Amplification Test [NAAT]). A naïve individual (no evidence of prior SARS-CoV-2 infection) is defined as being negative by the Anti-N-immunoassay and the Anti-S immunoassay in serum sample(s) and a negative NAAT in a respiratory specimen at the time of enrollment, while a non-naïve individual (evidence of prior SARS-CoV-2 infection) is defined as being positive by the Anti-N-immunoassay OR the Anti-S-immunoassay in serum sample(s) OR a positive NAAT in a respiratory specimen at the time of enrollment.

The goal of this study is to generate data required for approval of each of the vaccines for the prevention of COVID-19 disease caused by SARS-CoV-2 in adults. The data collected during this study are planned to support future development in other populations (eg, pediatrics, pregnant women).

Based on decisions of the Study Oversight Group (OG) after assessment of interim results, an unblinded Crossover / Booster study design will be implemented among participants initially enrolled in the double-blind primary series design.

Objectives and Endpoints: Initial double-blind primary series design: (These apply to Stage 1 and Stage 2 of the initial, double-blind primary series study design, unless otherwise specified)

Objectives	Endpoints
Primary Efficacy (Stage 1 only)	
To assess, in participants who are SARS-CoV-2 naïve, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for the prevention of symptomatic COVID-19 occurring ≥ 14 days after the second injection.	• Occurrences of symptomatic COVID-19
Primary Efficacy (Stage 2 only)	
To assess, in all participants regardless of prior SARS-CoV-2 infection, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for prevention of symptomatic COVID-19 ≥ 14 days after the second injection.	• Occurrences of symptomatic COVID-19
Primary Safety	
To assess the safety of the CoV2 preS dTM-AS03 vaccines compared to placebo throughout the study.	For participants in the Reactogenicity Subset: • Presence of solicited (pre-listed in the participant's diary card / electronic diary card [DC/eDC] and [electronic] Case Report Form [CRF]) injection site reactions and systemic reactions occurring up to 7 days after each vaccination • Presence of non-serious unsolicited adverse events (AEs) reported up to 21 days after the last vaccination For all participants in the study: • Presence of unsolicited injection site and systemic AEs reported in the 30 minutes after each vaccination • Presence of medically-attended adverse events (MAAEs) throughout the study • Presence of serious adverse events (SAEs) throughout the study • Presence of adverse events of special interest (AESIs) throughout the study • Presence of virologically-confirmed SARS-CoV-2 infections and/or symptomatic COVID-19
Key Secondary Efficacy Objective (Stage 1)	
1) To assess, in participants who are SARS-CoV-2 naïve, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for prevention of the following occurring ≥ 14 days after the second injection: • Prevention of SARS-CoV-2 infection • Prevention of severe COVID-19	Endpoints for secondary efficacy objective #1: • Occurrences of SARS-CoV-2 infection • Occurrence of severe COVID-19
Key Secondary Efficacy Objective (Stage 2)	
2) To assess: • Prevention of SARS-CoV-2 infection in participants who are SARS-CoV-2 naïve, occurring ≥ 14 days after the second injection	Endpoints for secondary efficacy objective #2: • Occurrences of SARS-CoV-2 infection • Occurrence of severe COVID-19

Objectives	Endpoints
• Prevention of severe COVID-19 in participants regardless of prior SARS-CoV-2 infection occurring ≥ 14 days after the second injection	
Other Secondary Efficacy Objectives	
3) To assess, in participants who are SARS-CoV-2 naïve, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for the prevention of symptomatic COVID-19 occurring ≥ 14 days after the first injection.	Endpoint for secondary efficacy objective #3: • Occurrences of symptomatic COVID-19
4) Stage 1 only: To assess, in all participants regardless of prior SARS-CoV-2 infection, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for: • Prevention of symptomatic COVID-19 • Prevention of severe COVID-19	Stage 1 only: Endpoints for secondary efficacy objective #4: • Occurrences of symptomatic COVID-19 • Occurrence of severe COVID-19
5) To assess, in participants who are SARS-CoV-2 non-naïve, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for: • Prevention of symptomatic COVID-19 • Prevention of severe COVID-19	Endpoints for secondary efficacy objective #5: • Occurrences of symptomatic COVID-19 • Occurrence of severe COVID-19
6) To assess, in participants who are SARS-CoV-2 naïve, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for the prevention of asymptomatic SARS-CoV-2 infection.	Endpoint for secondary efficacy objective #6: • Occurrences of asymptomatic SARS-CoV-2 infection
7) To assess the impact of the CoV2 preS dTM-AS03 vaccines in the reduction of viral burden and shedding among participants with symptomatic COVID-19.	Endpoints for secondary efficacy objective #7: • Viral copies/mL in respiratory samples collected at each follow-up timepoint • Number of days with positive NAAT • Occurrences of positive NAAT in respiratory samples at each follow-up timepoint during symptomatic COVID-19
8) To assess, in all participants regardless of prior SARS-CoV-2 infection and in participants who are SARS-CoV-2 non-naïve and naïve, clinical efficacy of the CoV2 preS dTM-AS03 vaccines for: • Prevention of CDC-defined COVID-19 • Prevention of hospitalized COVID-19 • Prevention of symptomatic COVID-19 with severity of moderate COVID-19 or worse (composite endpoint of moderate or severe COVID-19)	Endpoints for secondary efficacy objective #8: • Occurrences of CDC-defined COVID-19 • Occurrences of hospitalized COVID-19 • Occurrences of symptomatic COVID-19 with severity of moderate COVID-19 or worse (composite endpoint of at least one of moderate or severe COVID-19)
9) To assess the durability of clinical efficacy of the CoV2 preS dTM-AS03 vaccines over time in SARS-CoV-2 naïve participants against: • SARS-CoV-2 infection • Asymptomatic SARS-CoV-2 infection	Endpoints for secondary efficacy objective #9: • Occurrences of SARS-CoV-2 infection • Occurrences of asymptomatic SARS-CoV-2 infection
10) To assess the durability of clinical efficacy of the CoV2 preS dTM-AS03 vaccines over time in all participants and by prior SARS-CoV-2 infection (naïve and non-naïve) for:	Endpoints for secondary efficacy objective #10: • Occurrences of symptomatic COVID-19 • Occurrences of severe COVID-19 • Occurrences of CDC-defined COVID-19

Objectives	Endpoints
• Prevention of symptomatic COVID-19 • Prevention of severe COVID-19 • Prevention of CDC-defined COVID-19 • Prevention of hospitalized COVID-19	• Occurrences of hospitalized COVID-19
11) To assess, in participants who are SARS-CoV-2 naïve, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for the prevention of symptomatic COVID-19 occurring ≥ 7 days after the second injection.	Endpoint for secondary efficacy objective #11: • Occurrences of symptomatic COVID-19
12) Stage 2 only: To assess, in participants who are SARS-CoV-2 naïve, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for: • Prevention of symptomatic COVID-19 • Prevention of severe COVID-19	Stage 2 only: Endpoints for secondary efficacy objective #12: • Occurrences of symptomatic COVID-19 • Occurrence of severe COVID-19
Secondary Immunogenicity	
1) To compare the neutralizing antibody response 21 days after last vaccination (D43) to the D614G variant between the monovalent and bivalent vaccines in SARS-CoV-2 naïve and non-naïve participants in the Random Immunogenicity Subcohort. 2) To compare the neutralizing antibody response 21 days after last vaccination (D43) to the Beta (B.1.351) variant between the monovalent and bivalent vaccines in SARS-CoV-2 naïve and non-naïve participants in the Random Immunogenicity Subcohort. 3) To compare the neutralizing antibody response 21 days after last vaccination (D43) to the Beta (B.1.351) variant in the bivalent vaccine group and the neutralizing antibody response to the D614G variant in the monovalent vaccine group in SARS-CoV-2 naïve and non-naïve participants in the Random Immunogenicity Subcohort.	Endpoints for secondary immunogenicity objectives #1 - 3: • Individual serum neutralizing titer at D01 and D43 • Responders, defined as participants who had baseline values below lower limit of quantification (LLOQ) with quantifiable neutralization titer above assay LLOQ at each pre-defined post-vaccination time point and participants with baseline values above LLOQ with a 4-fold increase in neutralizing antibody titers at each pre-defined post-vaccination time point • Seroresponse, defined as a 4-fold or greater rise in serum neutralization titer [pre/post] at D43 relative to D01
The following objectives will be assessed in participants regardless of prior SARS-CoV-2 infection and in SARS-CoV-2 non-naïve and naïve participants. 4) To describe the neutralizing antibody profile at D01, D22, D43, D78, D134, D202, D292, and D387 in each study group for participants in the Random Immunogenicity Subcohort. 5) To describe the neutralizing antibody profile at D01, D22, D43, D78, D134, D202, D292, and D387 in each study group for participants aged 18-25 years in the Random Immunogenicity Subcohort. 6) To describe the association of neutralizing antibody responses and the risk of symptomatic COVID-19. 7) To describe the association of neutralizing antibody responses and the risk of SARS-CoV-2 infection.	Endpoints for secondary immunogenicity objectives #4 - 9: Neutralizing antibody titers will be measured in participants for each study group against the D614G and B.1.351 variants. • Individual serum neutralizing titer at each pre-defined time point • Individual serum neutralization titer fold-rise post-vaccination relative to D01 at each pre-defined time point • 2-fold rise and 4-fold-rise in serum neutralization titer [post/pre] (fold rise ≥ 2 and ≥ 4) at each pre-defined post-vaccination timepoint • Responders, defined as participants who had baseline values below LLOQ with quantifiable neutralization titer above assay LLOQ at each pre-defined post-vaccination time point and

Objectives	Endpoints
8) To describe the association of neutralizing antibody responses and the risk of other COVID-19 disease endpoints. 9) To evaluate the immunological correlates of risk and correlates of protection against symptomatic COVID-19, SARS-CoV-2 infection, and other COVID-19 disease endpoints.	participants with baseline values above LLOQ with a 4-fold increase in neutralizing antibody titers at each pre-defined post-vaccination timepoint
Secondary Safety	
1) To describe the frequency and spectrum of disease in episodes of symptomatic COVID-19 in SARS-CoV-2 non-naïve adults in each study group.	Endpoints for secondary safety objective #1: For SARS-CoV-2 non-naïve participants in the study: • Severity of symptoms associated with symptomatic COVID-19 episode • Occurrences of hospitalized COVID-19 • Occurrence of severe COVID-19 • Occurrences of COVID-19 in each severity rating on the 7-point ordinal scale • Death associated with COVID-19
2) To assess the safety of the CoV2 preS dTM-AS03 vaccines compared to placebo in participants aged 18-25 years throughout the study.	Endpoints for secondary safety objective #2: For participants in the Reactogenicity Subset: • Presence of solicited (pre-listed in the participant's diary card / electronic diary card [DC/eDC] and [electronic] Case Report Form [CRF]) injection site reactions and systemic reactions occurring up to 7 days after each vaccination • Presence of non-serious unsolicited adverse events (AEs) reported up to 21 days after the last vaccination For all participants in the study: • Presence of unsolicited injection site and systemic AEs reported in the 30 minutes after each vaccination • Presence of medically-attended adverse events (MAAEs) throughout the study • Presence of serious adverse events (SAEs) throughout the study • Presence of adverse events of special interest (AESIs) throughout the study • Presence of virologically-confirmed SARS-CoV-2 infections and/or symptomatic COVID-19

Objectives and Endpoints: Crossover / Booster Study Design

Objectives	Endpoints
Secondary Immunogenicity	
To describe the neutralizing antibody profile at D01 and at 21 days and 6 months after last crossover injection in the placebo group and booster injection in each study group for participants in the Random Immunogenicity Subcohort.	Endpoints for secondary immunogenicity objective: Neutralizing antibody titers will be measured in participants for each study group against the D614G and B.1.351 variants. • Individual serum neutralizing titer at each pre-defined time point • Individual serum neutralization titer fold-rise post-vaccination relative to D01 at each pre-defined time point • 2-fold rise and 4-fold-rise in serum neutralization titer [post/pre] (fold rise ≥ 2 and ≥ 4) at each pre-defined post-vaccination timepoint • Responders, defined as participants who had baseline values below LLOQ with quantifiable neutralization titer above assay LLOQ at each pre-defined post-vaccination time point and participants with baseline values above LLOQ with a 4-fold increase in neutralizing antibody
Secondary Safety	
1) To describe the frequency and spectrum of disease in episodes of symptomatic COVID-19 in SARS-CoV-2 non-naïve adults after the crossover or booster vaccinations with the CoV2 preSdTM-AS03 vaccines.	Endpoints for secondary safety objective #1: For SARS-CoV-2 non-naïve participants in the study: • Severity of symptoms associated with symptomatic COVID-19 episode • Occurrences of hospitalized COVID-19 • Occurrence of severe COVID-19 • Occurrences of COVID-19 in each severity rating on the 7-point ordinal scale • Death associated with COVID-19
2) To assess the safety of the CoV2 preS dTM-AS03 vaccines after the crossover or booster vaccinations	Endpoints for secondary safety objective #2: For all participants in the study: • Presence of unsolicited injection site and systemic AEs reported in the 30 minutes after each vaccination • Presence of non-serious unsolicited AEs reported up to 21 days after the booster vaccination • Presence of MAAEs throughout the study • Presence of SAEs throughout the study • Presence of AESIs throughout the study

Overall Design

Type of design	Parallel, multi-center, multi-country, multi-stage
Phase	III
Control method	Placebo-controlled
Study population	Adults 18 years of age and older
Countries	Stage 1: United States, Honduras, Japan, Colombia, Kenya, India, Ghana, Nepal Stage 2: Colombia, Kenya, Uganda, India, Ghana, Nepal, Ukraine and Mexico
Level and method of blinding	Modified double-blind (observer-blind) for initial, double-blind, primary series design of study. Crossover / Booster study design details are as stated below in Crossover / Booster section: • Blinding for vaccine group assignment: participants, outcome assessors, Investigators, laboratory personnel, Sponsor study staff, those administering the study intervention if not involved in preparing study intervention • No blinding for those preparing the study interventions
Study intervention assignment method	Participants will be screened for eligibility criteria at the time of inclusion and then randomized to either the investigational vaccine or placebo in a 1:1 ratio in each stage as shown below: • Stage 1: eligible participants will be randomized to receive either CoV2 preS dTM-AS03 (D614) vaccine or Placebo 1 (participants who receive the placebo as part of Stage 1) • Stage 2: eligible participants will be randomized to receive either CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine or Placebo 2 (participants who receive placebo as part of Stage 2) Randomization will be stratified by age groups (18-59 years of age and 60 years of age and older), baseline SARS-CoV-2 rapid serodiagnostic test positivity, and site. In the time period where the enrollment in Stage 1 overlaps with enrollment in Stage 2, participants will continue to be randomly allocated to one of the

	investigational vaccine groups and their matched placebo group in a 1:1 ratio. There will be no sharing of the placebo participants between the 2 stages.
Unblinded Crossover / Booster	All participants in Stage 1 and Stage 2 will be unblinded and informed of the results of the study. Study Investigators will discuss the possibility of receiving the (authorized/approved) vaccines available to them outside of the study. Based on decisions of the Study Oversight Group (OG), participants will be invited upon consent to continue participation as part of an unblinded crossover / booster study design. The participant unblinding and consent will trigger the end of the initial double-blind primary series design and the start of the Crossover / Booster design, which includes a primary series vaccination for initial placebo recipients (ie, crossover vaccination) and a booster for both initial placebo and vaccine recipients (ie, booster vaccination). Non-naïve participants who initially received placebo and are 18-59 years of age will be offered the opportunity to receive the investigational CoV2 preS dTM-AS03 monovalent (D614) vaccine if authorized/approved vaccines are not available or if they choose not to receive an authorized/approved vaccine series. Naïve participants 18-59 years of age and all participants ≥ 60 years of age who initially received placebo will be recommended to receive an authorized/approved vaccination series. If initial placebo recipients of any age received the complete primary series of an authorized/approved vaccine outside of the study or the investigational study vaccine as a primary series, they will also be offered the opportunity to receive Sanofi's investigational Cov2 preS dTM-AS03 monovalent (B.1.351) booster vaccine ≥ 4 months post-last dose of the primary series or encouraged to receive an authorized/approved vaccine according to local guidance.

	Participants who initially received the complete primary series of the CoV2 preS dTM-AS03 monovalent (D614) vaccine (Stage 1) or CoV2 preS dTM-AS03 bivalent (D614+B.1.351) vaccine (Stage 2) will be offered the opportunity to receive Sanofi's investigational CoV2 preS dTM-AS03 monovalent (B.1.351) booster vaccine ≥ 4 months post-last dose of the primary series or encouraged to receive an authorized/approved vaccine according to local guidance. If participants do not consent to continue with the unblinded Crossover / Booster, all study procedures will be stopped, and participants will be discontinued from the study and recommended to receive the authorized/approved vaccination series per local guidance.

Brief Summary:

The purpose of this Phase III study is to assess the efficacy, safety, and immunogenicity of two CoV2 preS dTM-AS03 vaccines (monovalent and bivalent) as part of primary series vaccinations in a multi-stage approach, as well as a booster injection of a CoV2 preS dTM-AS03 vaccine, in adults 18 years of age and older.

Study Duration: Initial, double-blind, primary series study design planned for 365 days post-last Initial injection (ie, approximately 386 days total) for each participant. Based on decisions of the Study OG, Stage 1 and Stage 2 participants will be invited to participate in an unblinded Crossover / Booster study design with duration as follows:

- For participants who initially received vaccine: 12 months post-booster (ie, approximately 18 to 24 months)
- For participants who initially received placebo: ≥ 4 months post-last dose of the primary series + 12 months post-booster (ie, approximately 28 to 34 months)
- For participants who do not consent to continue in the unblinded Crossover / Booster part of the study, all study procedures will be stopped and participants will be discontinued from the study.

Treatment Duration:

Initial Injections: 2 injections of either CoV2 preS dTM-AS03 monovalent (D614) vaccine (Stage 1), CoV2 preS dTM-AS03 bivalent (D614 + B.1.351) vaccine (Stage 2), or placebo will be administered 21 days apart.

Crossover Injection(s) (Stage 1 and Stage 2): If initial injection was placebo, primary injection(s) of an authorized/approved vaccine outside of the study (interval of doses dependent on available vaccine and following local standard of care) or 2 primary series injections administered 21 days apart of CoV2 preS dTM-AS03 monovalent (D614) vaccine.

Booster Injection (Stage 1 and Stage 2): A single injection of Sanofi's investigational CoV2 preS dTM-AS03 monovalent (B.1.351) 5 µg antigen dose of booster vaccine ≥ 4 months post-last dose of the primary series.

Planned Visit Frequency: The planned initial visits include 8 visits at D01, D22, D43, D78, D134, D202, D292, and D387. However, if participants do not agree to participate in the Crossover / Booster, all study procedures will be stopped, and participants will be discontinued from the study.

For participants who agree to participate in the Crossover / Booster design, it will include:

- For those who initially received an investigational CoV2 preS dTM-AS03 vaccine:
  - 3 blood sample visits: day of booster vaccination (pre-booster) and then 21 days and 6 months post-booster
  - Efficacy follow-up: 12 months post-booster
  - Safety follow-up phone call: 12 months post-booster
- For those who initially received placebo and then receive an authorized vaccine (outside of the study) or Sanofi's CoV2 preS dTM-AS03 monovalent (D614) vaccine (Stage 1) or CoV2 preS dTM-AS03 bivalent (D614+B.1.351) vaccines as primary series:
  - 5 blood sample visits: day of first primary series vaccination (pre-vaccination 1)*, 21 days post-last dose of primary series*, day of the booster dose at ≥ 4 months post-last dose of primary series, 21 days post-booster, and 6 months post-booster
  - Efficacy follow-up: visit ≥ 4 months post-last dose of the primary series and phone call 12 months post-booster
  - Safety follow-up: visit ≥ 4 months post-last dose of the primary series and phone call 12 months post-booster

  * Note for those who receive authorized vaccine (outside of the study) as primary series (Crossover vaccination), no protocol deviation will be considered if the corresponding blood sample is missed.

Condition/Disease: COVID-19 disease prevention

Study Hypotheses:

CoV2 preS dTM-AS03 monovalent (D614) vaccine (Stage 1) will be safe and provide protection against COVID-19 in naïve adults 18 years of age and older.

CoV2 preS dTM-AS03 bivalent (D614 + B.1.351) vaccine (Stage 2) will be safe and provide protection against COVID-19 in naïve adults 18 years of age and older.

Health Measurement/Observation (Initial, double-blind, primary series design):

For the original phase of the study, some participants were assigned to a Reactogenicity Subset and the following information will be collected for the initial, double-blind, primary series design:

- Presence of solicited injection site reactions and systemic reactions occurring up to 7 days after each injection

- Presence of non-serious unsolicited adverse events (AEs) reported up to 21 days after the last injection

All participants will be followed for up to one year after the last Initial injection to collect information on the following:

- Presence of unsolicited injection site and systemic AEs reported in the 30 minutes after each injection
- Presence of serious adverse events (SAEs), adverse events of special interest (AESIs), and medically-attended adverse events (MAAEs) throughout the study
- Presence of virologically-confirmed SARS-CoV-2 infections and/or symptomatic COVID-19

For efficacy, COVID-19-like illness will be monitored through active and passive surveillance. Participants will be contacted once a week over the entire duration of the study to inquire about the development of symptoms of COVID-19-like-illness and to remind participants to contact study staff if they experience symptoms of COVID-19-like illness. Active surveillance can be completed directly by study staff or through the use of the electronic Diary Card (eDC). In addition to this active surveillance, 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 or if they have a positive COVID-19 test from any other source. To surveil for COVID-19, symptoms for COVID-19-like-illness will be elicited weekly from the participants and presence of COVID-19-like-illness would result in the site arranging a COVID-19-like-illness visit to collect respiratory specimens as soon as possible. All participants will be required to record their symptoms and severity of symptoms on a daily basis at least until the result of all their protocol-defined NAAT or local clinical test (if taken) is available. In participants testing positive for SARS-CoV-2, daily recording of symptoms, severity of symptoms, medication taken, health care visit, and outcome of illness will be collected. In participants who are hospitalized, medical records will be requested to collect information on the course of their illness during hospitalization.

Investigators will be encouraged to collect an additional respiratory specimen for local clinical laboratory testing to enable medical management and early diagnosis of participants with COVID-19 if deemed necessary. All participants with symptoms will be informed by Investigators of the local guidance and advice for suspected COVID-19 and be advised to follow local health guidelines regarding COVID-19 prevention (eg, quarantine, avoidance of use of public transportation) until the availability of the results of the local or protocol-defined NAAT test. All participants seen for suspected COVID-19 will be notified of their swab results within 24 hours of the result becoming available to the Investigator. This will include results of any local testing as well as protocol-defined NAAT results.

The ascertainment of serological SARS-CoV-2 infection will test serum samples collected at all time points for antibodies against the Nucleocapsid protein of SARS-CoV-2 virus that would enable differentiation of antibodies induced by infection and vaccination (because vaccination is only expected to generate antibody responses to the S protein, while infection is expected to generate antibodies against non-S proteins as well). For immunogenicity, neutralizing antibody titers to the variants in the vaccines (D614 and B.1.351 variants) and binding antibody titers to full length SARS-CoV-2 S protein from D614 will be measured with the pseudovirus neutralization

assay and anti-S immunoglobulin G (IgG) enzyme-linked immunosorbent assay (ELISA), respectively, in naïve and non-naïve participants in the Random Immunogenicity Subset.

Number of Participants:

A total of approximately 21 046 participants are planned to be enrolled (5080 per study intervention group in Stage 1 and 5443 per study intervention group in Stage 2). If the crossover is not implemented, recruitment will continue until the minimally required number of naïve participants to assess efficacy is enrolled (even if the overall enrollment target is reached).

Participants who are SARS-CoV-2 non-naïve at baseline will be capped to approximately 30% of the total study population in Stage 1 (up to ~1524 participants/arm). The target for SARS-CoV-2 non-naïves is ~1633 participants/arm in Stage 2. The objective is to ensure a sufficient number of participants/arm who are SARS-CoV-2 naïve at baseline are enrolled to achieve the power of the study.

The study will target enrollment of older adults (≥ 60 years of age) with a recruitment target of approximately 40% of the study population in each stage.

Within the age group of 18-59 years, the study will target inclusion of approximately 35% of participants with high-risk medical conditions for COVID-19. The study will target recruitment of racial and ethnic diversity that will be representative of the countries in which the study will be conducted.

Pre-Crossover / - Booster Intervention Groups and Duration:

Stage 1:
Participants in Stage 1 will be randomized in a 1:1 ratio to receive 2 injections 21 days apart of either CoV2 preS dTM-AS03 (D614) or Placebo 1.

Stage 2:
Participants in Stage 2 will be randomized in a 1:1 ratio to receive 2 injections 21 days apart of either CoV2 preS dTM-AS03 (D614 + B.1.351) or Placebo 2.

Table 1.1: Planned sample size and approximate size of subsets in Stage 1

		Study Intervention Groups (Stage 1)	
		Vaccine 1	Placebo 1
		CoV2 preS dTM-AS03 (D614)	Placebo
Total Overall		5080	5080
Prior exposure to SARS-CoV-2	**SARS-CoV-2 naïves**	3556	3556
	SARS-CoV-2 non-naïves	Up to 1524	Up to 1524
Reactogenicity Subset		2000	2000
Random Immunogenicity Subset*		1415	559

Non-naive: Capped at approximately 30% of study population in this stage.
* Details of the random subset and subcohort are described below and in Appendix 10.6.

Table 1.2: Planned sample size and approximate size of subsets in Stage 2

		Study Intervention Groups (Stage 2)	
		Vaccine 2	Placebo 2
		CoV2 preS dTM-AS03 (D614 + B.1.351)	Placebo
Total Overall		5443	5443
Prior exposure to SARS-CoV-2	**SARS-CoV-2 naïves**	3810	3810
	SARS-CoV-2 non-naïves	1633	1633
Reactogenicity Subset		2000	2000
Random Immunogenicity Subset*		1415	559

If the crossover is not implemented, recruitment will continue until the minimally required number of naïve participants to assess efficacy is enrolled (even if the overall enrollment target is reached).
* Details of the random subset and subcohort are described below and in Appendix 10.6.

All participants will receive 2 injections given 3 weeks apart: the first injection will be at D01 (Vaccination [VAC] 1) and the second injection will be at D22 (VAC2).

Reactogenicity Subset: A subset of participants (approximately 2000 per study group in each stage) will be allocated to the reactogenicity subset to collect solicited AEs for 7 days after each vaccination and non-serious unsolicited AEs up to 21 days after the last vaccination. In Stage 1, 25% of the first 8000 participants will be randomly allocated to the reactogenicity subset after which a capping system will be used to ensure a targeted number of participants are assigned to the reactogenicity subset. In Stage 2, the first 4000 participants along with all participants above 60 years of age will be allocated to the reactogenicity subset.

Random Immunogenicity Subset: A random subset of study participants in each stage stratified by treatment group, SARS-CoV-2 positivity on the rapid serodiagnostic test at enrollment, and age-group will be randomly allocated at enrollment (Step 1) with pre-identified allocation ratio in each stratum to enable immunogenicity assessments and for case-cohort analysis. This immunogenicity subset will potentially be supplemented by a random selection in Step 2 to form the Random Immunogenicity Subcohort. This additional supplemental random selection will occur, if needed, after the availability of results to define SARS-CoV-2 D01 and D22 naïve/non-naïve status of all enrolled participants. Details are included in Appendix 10.6.

The Random Immunogenicity Subcohort will be utilized to build a case-cohort, where the case cohort is comprised of all participants belonging to the random subcohort plus those participants who develop any efficacy endpoint events during study follow-up and were not already included in the corresponding random subcohort (see Section 10.6.1 for details). This Random Immunogenicity Subcohort will be used for immunogenicity assessments, analysis of immunological correlates of risk, and correlates of protection.

Receipt of approved/authorized vaccines during the initial, double-blind, primary series study design

The statements below apply to study activities of participants during the initial, double-blind, primary series design.

If an approved/authorized vaccine is available in the country or region where the study is conducted and the participant is eligible for receiving vaccine (based on the country prioritization strategy for vaccine deployment) at the time of enrollment, Investigators will discuss this information with prospective study participants at the time of informed consent who will be encouraged to obtain the approved/authorized vaccine if applicable to them. Recruitment of eligible participants will proceed only if, despite encouragement, the candidate participant expresses no intention to seek an authorized or approved vaccine at the time of enrollment.

If the participant is enrolled and seeks vaccination of an authorized/approved vaccine outside of the study, he/she will be encouraged to discuss this intention proactively with the study investigator. The study investigators will inform and discuss with these study participants the possibility of being unblinded to the study intervention to enable the participant to make decisions on receiving the available (authorized or approved) vaccine. The Sponsor will maintain the study investigators updated on any new information related to the investigational products, so that such information can be provided to participants in discussions related to the potentially receiving the available authorized/approved vaccines. Participants should only request to be unblinded if they

decide to receive the approved/authorized vaccine. Participants who elect to be unblinded will have their code broken. Once unblinded, participants will be discontinued from study intervention administration.

If the participant is unblinded or receives the authorized/approved vaccine, this information would be collected. These study participants will be allowed to continue study participation if they choose to do so but will not be allowed to crossover; while continuation in the study will include all study procedures including safety follow-up, they will be censored from that point onward for efficacy and immunogenicity analysis for the primary vaccination/series.

Participants who decline the approved/authorized vaccine should remain blinded to treatment assignment for the entire duration of the study or until study discontinuation decisions are made with the appropriate regulatory agencies.

If at any time during study conduct it is determined that the vaccine candidates are not efficacious or that efficacy cannot be demonstrated, participants will be encouraged to seek vaccination of an authorized/approved vaccine if available to them.

Unblinded Crossover / Booster

All participants in Stage 1 and Stage 2 will be unblinded and informed of the results of the study. Study Investigators will discuss the possibility of receiving the (authorized/approved) vaccines available to them outside of the study.

Based on decisions of the Study OG, participants will be invited upon consent to continue participation as part of an unblinded crossover / booster study design. The participant unblinding and consent will trigger the end of the initial double-blind primary series design and the start of the Crossover / Booster design, which includes a primary series vaccination for initial placebo recipients (ie, crossover vaccination) and a booster for both initial placebo and vaccine recipients (ie, booster vaccination).

Non-naïve participants who initially received placebo and are 18-59 years of age will be offered the opportunity to receive the investigational CoV2 preS dTM-AS03 monovalent (D614) vaccine if authorized/approved vaccines are not available or if they choose not to receive an authorized/approved vaccine series.

Naïve participants 18-59 years of age and all participants ≥ 60 years of age who initially received placebo will be recommended to receive an authorized/approved vaccination series.

Placebo recipients	**18-59 years of age**	**≥ 60 years of age**
Non-naïves	CoV2 preS dTM-AS03 **MV(D614)** priming (if EUA vaccines not available or not preferred)	Priming with **EUA vaccines**
Naïves	Priming with **EUA vaccines**	Priming with **EUA vaccines**

Abbreviations: EUA: Emergency Use Authorization; MV monovalent

If initial placebo recipients of any age received the complete primary series of an authorized/approved vaccine outside of the study or the investigational study vaccine as a primary series, they will also be offered the opportunity to receive Sanofi's investigational CoV2 preS dTM-AS03 monovalent (B.1.351) booster vaccine ≥ 4 months post-last dose of the primary series or encouraged to receive an authorized/approved vaccine according to local guidance.

Participants who initially received the complete primary series of the CoV2 preS dTM-AS03 monovalent (D614) vaccine (Stage 1) or the CoV2 preS dTM-AS03 bivalent (D614+B.1.351) vaccine (Stage 2) will be offered the opportunity to receive Sanofi's investigational CoV2 preS dTM-AS03 monovalent (B.1.351) booster vaccine ≥ 4 months post-last dose of the primary series or encouraged to receive an authorized/approved vaccine according to local guidance.

Primed participants with complete primary series	
Placebo recipients who received **EUA vaccines or investigational study vaccine**	CoV2 preS dTM-AS03 **MV(Beta)** (≥ 4 months post-last dose of the primary series) or **EUA** booster vaccination
Participants who received CoV2 preS dTM-AS03 **MV(D614)** or **bivalent** vaccine	CoV2 preS dTM-AS03 **MV(Beta)** (≥ 4 months post-last dose of the primary series) or **EUA** booster vaccination

Abbreviations: EUA, Emergency Use Authorization; MV, monovalent

If participants do not consent to continue with the unblinded crossover/booster, all study procedures will be stopped, and participants will be discontinued from the study and recommended to receive the authorized/approved vaccination series per local guidance.

All participants in the Placebo group will be eligible for crossover vaccination, regardless of whether they have previously experienced SARS-CoV-2 infection or COVID-19.

Participants who are terminated or choose to withdraw from the study will not be eligible for unblinded crossover / booster.

Participants in the Vaccine group who completed the primary series of study vaccination and did not receive an authorized / approved vaccine will be eligible for a booster ≥ 4 months post-last dose of the primary CoV2 preS dTM-AS03 vaccine.

Participants in the Placebo group who received the complete primary series of either an authorized/approved vaccine before or as part of the Crossover/Booster design or CoV2 preS dTM-AS03 vaccine as part of the Crossover / Booster design will be eligible for a booster ≥ 4 months post-last dose of the primary series.

Treatment Duration: After obtaining consent for Crossover / Booster participation:

Crossover Injection(s) (Stage 1 and Stage 2): If initial injection was placebo, primary injection(s) of an authorized/approved vaccine outside of the study (interval of doses dependent on available vaccine and following local standard of care) or 2 primary series injections administered 21 days apart of CoV2 preS dTM-AS03 monovalent (D614) vaccine.

Booster Injection (Stage 1 and Stage 2): A single injection of Sanofi's investigational CoV2 preS dTM-AS03 monovalent (B.1.351) 5 µg antigen dose of booster vaccine ≥ 4 months post-last dose of the primary series.

Vaccine contraindications during the Crossover / Booster period are described in Section 7.1.3 and Section 7.1.4.

Procedures:

At the time of Crossover / Booster, participants will be unblinded and Investigators will inform participants of the available results of the investigational vaccine, provide information on the Crossover / Booster, and discuss the availability of a locally-authorized/approved vaccine (outside of the study) for them prior to obtaining consent for participation in the Crossover / Booster.

If participants do not consent to participation in the Crossover / Booster and a locally-authorized/approved vaccine is available outside of the study, they will be strongly encouraged to obtain the authorized/approved vaccine if available to them, clearly stating that obtaining an authorized/approved vaccines is expected to benefit them.

If participants do not consent to continue with the unblinded crossover/booster, all study procedures will be stopped, and participants will be discontinued from the study.

During participant contact at the time of the Crossover / Booster, the Investigator will provide the group assignment. After obtaining informed consent from participants to continue the study as part of the Crossover / Booster, participants will receive the primary series and booster injections, as described above.

- For those who initially received an investigational CoV2 preS dTM-AS03 vaccine (see also Table 1.5):
  - 3 blood sample visits: day of booster vaccination (pre-booster) and then 21 days and 6 months post-booster
  - Efficacy follow-up: 12 months post-booster
  - Safety follow-up phone call: 12 months post-booster
- For those who initially received placebo and then receive an authorized vaccine (outside of the study) or Sanofi's CoV2 preS dTM-AS03 monovalent (D614) vaccine as primary series (see also Table 1.6):
  - 5 blood sample visits: day of first primary series vaccination (pre-vaccination 1)*, 21 days post-last dose of primary series*, day of the booster dose at ≥ 4 months post-last dose of primary series, 21 days post-booster, and 6 months post-booster
  - Efficacy follow-up: visit ≥ 4 months post-last dose of the primary series and phone call 12 months post-booster
  - Safety follow-up: visit ≥ 4 months post-last dose of the primary series and phone call 12 months post-booster

*Note for those who receive authorized vaccine (outside of the study) as primary series (Crossover vaccination): No protocol deviation will be considered if the corresponding blood sample is missed.

The blood samples will be collected for immunogenicity assessments, correlates of risk analysis and for the determination of naive/non-naive status at the time of the Crossover needed for evaluating durability of vaccine efficacy post-crossover in naive/non-naive individuals.

Unsolicited AEs will be collected up to 21 days after the booster vaccination. MAAEs, SAEs, and AESIs will be collected over the duration of the study including the Crossover / Booster (up to 12 months post-booster). Immediate adverse reactions (ie, occurring in the 30 minutes after vaccination) will be collected after CoV2 preS dTM-AS03 (D614) crossover injections and after booster injection; but immediate adverse reactions will not be collected after receipt of authorized/approved vaccine outside of the study for those who initially received placebo.

In the event that a participant develops symptoms which, based on the investigator's judgement, are consistent with a case of suspected myocarditis and/or pericarditis (eg, acute chest pain, shortness of breath, palpitations, or other signs or symptoms of myocarditis and/or pericarditis) within 6 weeks after vaccination, the site will conduct an unscheduled visit. The site will coordinate an appropriate diagnostic workup to make a determination of probable or confirmed myocarditis and/or pericarditis which may include, but is not limited to, an electrocardiogram (ECG) and/or cardiac troponin testing (T or I). If the diagnostic workup shows abnormal results, the participant will be referred to a cardiologist for evaluation and management. The suspected myocarditis and/or pericarditis case should be reported immediately to the Sponsor within 24 hours as an AESI. Participants with events of myocarditis and/or pericarditis will be discontinued from further vaccination and followed for subsequent visits as per the protocol for safety, immunogenicity, and efficacy endpoints.

Following the Crossover and Booster injections, active and passive surveillance for COVID-19 symptoms will continue as described after the initial set of vaccinations.

Study interventions

Investigational medicinal product 1 (Stage 1 and Stage 2, Crossover): CoV2 preS dTM-AS03 (D614)

- Form: Solution and emulsion for injection
- Composition: prefusion S delta TM COVID-19 antigen D614 strain (*10 µg)* and AS03 adjuvant that is an oil-in-water emulsion containing squalene (10.69 milligrams), DL-α-tocopherol (11.86 milligrams) and polysorbate 80 (4.86 milligrams)
- Route of administration: Intramuscular (IM)

Investigational medicinal product 2 (Stage 2): CoV2 preS dTM-AS03 (D614 + B.1.351)

- Form: Solution and emulsion for injection
- Composition: prefusion S delta TM COVID-19 antigen D614 + B.1.351 (5 µg D614 antigen + 5 µg B.1.351 antigen) and AS03 adjuvant that is an oil-in-water emulsion containing squalene (10.69 milligrams), DL-α-tocopherol (11.86 milligrams) and polysorbate 80 (4.86 milligrams)
- Route of administration: IM

Investigational medicinal product 3 (Stage 1 and Stage 2): Placebo

- Form: Liquid
- Composition: 0.9% normal saline

- Route of administration: IM

Investigational medicinal product 4 (Booster): CoV2 preS dTM-AS03 (B.1.351), 5 µg antigen dose

- Form: Solution and emulsion for injection
- Composition: prefusion S delta TM COVID-19 antigen B.1.351 strain (*5 µg)* and AS03 adjuvant that is an oil-in-water emulsion containing squalene (10.69 milligrams), DL-α-tocopherol (11.86 milligrams) and polysorbate 80 (4.86 milligrams)
- Route of administration: IM

Statistical considerations (Stage 1 and Stage 2 [initial, double-blind, primary series study design]):

All statistical analysis described in this section will be applied for each stage based on the same methodology independently, unless otherwise specified. No formal multiplicity adjustment will be done in the statistical analysis of vaccine efficacy between the 2 stages. The analysis for each vaccine will be conducted against placebo controls enrolled contemporaneously.

Hypothesis testing:

Hypothesis testing will be conducted for the primary efficacy objectives and the 2 key secondary efficacy objectives. Analyses of the primary safety objectives, other secondary objectives and exploratory objectives will be descriptive.

Primary objective

The hypothesis testing of vaccine efficacy (VE) against the primary endpoint of symptomatic COVID-19 in each stage is as follows:

H0: VE ≤ 30%

HA: VE > 30%

The point estimate of VE is calculated by the incidence rate ratio (IRR):

$$\widehat{VE} = 1 - \frac{C_V/PY_V}{C_P/PY_P} \qquad \text{(Formula 1)}$$

where C_V and C_P represent the cases in vaccine group and placebo group respectively;

PY_V and PY_P represent total # of 1000 person-years in vaccine group and placebo group respectively;

The confidence interval (CI) for VE will be calculated by an exact method assuming a binomial distribution of the number of cases in vaccine group conditional on the total number of cases in the study:

Let $q = \frac{C_V}{C_V+C_P}$ represent the proportion of cases belonging to vaccine group among the total number of cases, and let $\theta = \frac{E(C_V)}{E(C_V)+E(C_P)} = \frac{1-VE}{1-VE+PY_P/PY_V}$. Given the total number of cases, C_V has a binomial distribution (C_V+C_P, θ). Thus, a CI for θ may be constructed using the exact Clopper-Pearson method for binomial proportions (exact method) (17).

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

$$\widehat{VE} = 1 - \frac{C_V/PY_V}{C_P/PY_P} = 1 - \frac{PY_P}{PY_V} \times \frac{q}{1-q},$$

which is a strictly decreasing function of q.

Finally, for the primary endpoint, a CI of the VE will be constructed based on the CI of θ.

Secondary objectives

Other hypothesis testing with a different lower bound (LB) will be applied to the key secondary objectives: SARS-CoV-2 infection and severe COVID-19:

H0: VE ≤ 0%

HA: VE > 0%

The point estimate of VE for severe COVID-19 is based on IRR (Formula 1) above with same methods to calculate the CI.

The point estimate of VE for SARS-CoV-2 infection is based on relative risk (RR) of COVID-19 case occurrence shown below:

$$\widehat{VE} = 1 - \frac{C_V/N_V}{C_P/N_P} \quad \text{(Formula 2)}$$

where C_V and C_P represent the cases in vaccine group and placebo group respectively;

N_V and N_P represent total # of participants in vaccine group and placebo group respectively;

The CI of VE by RR is calculated with the same method as described above for the CI of VE by IRR by replacing the 1000 person-years to number of participants in the denominators, respectively. It is proposed to use RR for evaluating SARS-CoV-2 infection as the ascertainment of serological infection using blood samples collected at serial intervals does not enable robust assessments of person-time at risk for each individual.

For participants experiencing multiple events of symptomatic COVID-19, SARS-CoV-2 infection, or severe COVID-19 during the duration of the study, the first event will be counted for the analyses of VE of the primary and key secondary efficacy objective.

Analysis sets:

The prior SARS-CoV-2 infection status of all randomized participants in the initial, double-blind, primary series design will be defined as follows:

Prior SARs-CoV-2 infection status	Description
SARS-CoV-2 Naïve at baseline (Naïve-D01)	• Negative by the anti-S immunoassay (Roche Elecsys) on D01 serum sample AND • Negative by the anti-N immunoassay on D01 serum sample AND • Negative NAAT for SARS-CoV-2 on respiratory sample collected on D01
SARS-CoV-2 Non-Naïve at baseline (Non-Naïve-D01)	• Positive by the anti-S immunoassay (Roche Elecsys) on D01 serum sample OR • Positive by the anti-N immunoassay on D01 serum sample OR • Positive NAAT for SARS-CoV-2 on respiratory sample collected on D01
SARS-CoV-2 Naïve at second injection (Naïve- D01+D22)	• Negative by the anti-S immunoassay (Roche Elecsys) on D01 serum sample AND • Negative by anti-N immunoassay on D01 and D22 serum samples AND • Negative NAAT for SARS-CoV-2 on respiratory samples collected on D01 and D22
SARS-CoV-2 Non-Naïve at second injection (Non-Naïve - D01/D22)	• Positive by the anti-S immunoassay (Roche Elecsys) on D01 serum sample OR • Positive by the anti-N immunoassay on D01 or D22 serum samples OR • Positive NAAT for SARS-CoV-2 on respiratory samples collected on D01 or D22

The following populations are defined and will be applied for each stage of the initial, double-blind, primary series design:

Population	Description
Screened	All participants screened for potential study enrollment will be included regardless of being enrolled or not being enrolled. The screening includes the SARS-CoV-2 rapid serodiagnosis test results, demographic information (age, ethnic/racial population, high-risk medical conditions), and inclusion/exclusion criteria. The participants reaching the enrollment cap identified in Interactive Response Technology (IRT) will be excluded from the study enrollment and will have no participant ID assigned.
Randomized	All participants with a randomized group that has been allocated by IRT
Safety Analysis Set (SafAS)	All randomized participants who have received at least one dose of the study vaccine or placebo. All participants will have their safety analyzed after each dose according to the intervention they actually received, and after any dose according to the intervention received at the first dose.

	Safety data recorded for participants not administered a study intervention will be excluded from the analysis (and listed separately).
Reactogenicity Safety Analysis Subset (RSafAS)	Subset of the SafAS and comprising all participants who receive at least one study injection and are randomized into the reactogenicity subset.
Full Analysis Set (FAS)	All randomized participants who receive at least one study injection. Participants will be analyzed according to the intervention to which they were randomized.
Modified Full Analysis Set post-dose 2 (mFAS-PD2)	Subset of the FAS excluding: • Participants who did not complete the vaccination schedule (2 injections) • Participants with onset of symptomatic COVID-19 episode between the date of the first injection and before 14 days after the second injection • Participant received the second injection despite meeting any of the definitive contraindication criteria • Participant discontinued from study before 14 days after the second injection
Per-Protocol Analysis Set (PPAS)	Subset of the mFAS-PD2. Participants presenting with at least one of the following relevant protocol deviations 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 received a vaccine / placebo other than the one that he / she was randomized to receive • Preparation and / or administration of vaccine was not done as per-protocol • Participant did not receive vaccine / placebo in the proper time window The definition may be complemented with additional criteria for exclusion after the blinded review of protocol deviations reported on site.

Primary efficacy endpoint:

For the primary objective in each stage, the point estimate of VE in the SARS-CoV-2 naïve in Stage 1 population and in all participants regardless of prior SARS-CoV-2 infection for Stage 2 is calculated based on the incidence rate per 1000 person-year (Formula 1) and the corresponding adjusted CIs for VE estimates based on adjusted alpha will be calculated by an exact method assuming a binomial distribution of the number of cases in vaccine group conditional on the total number of cases. For the presentation of the overall results of the study an unadjusted 95% CI for VE will also be calculated for each analysis.

The primary objective in each stage will be considered demonstrated if the point estimate of VE is > 50% and the LB of the adjusted CI is > 30% at the planned interim analysis or at the final analysis.

The analyses of the primary efficacy endpoint will be conducted in the Modified Full Analysis Set post-dose 2 (mFAS-PD2) Naïve-D01+D22 analysis set for Stage 1 and in the mFAS-PD2 analysis set for Stage 2 to conclude on demonstration of the primary objective.

Sensitivity Analysis 1:

Sensitivity analysis against symptomatic COVID-19 will be conducted with VE calculated by RR (Formula 2) in addition to person-year approach in the mFAS-PD2 Naïve-D01+D22 analysis set for Stage 1 and mFAS-PD2 analysis set for Stage 2.

Sensitivity Analysis 2:

Sensitivity analysis against symptomatic COVID-19 will be conducted in the Per-Protocol Analysis Set (PPAS) Naïve-D01+D22 analysis set for Stage 1 and PPAS analysis set for Stage 2.

Sensitivity Analysis 3 (Stage 1 only):

Sensitivity analysis against symptomatic COVID-19 will be conducted in the mFAS-PD2 in participants determined to be seronegative by the rapid diagnostic testing for SARS-CoV-2 at enrollment for Stage 1.

In addition, survival analyses of symptomatic COVID-19 endpoints will be conducted using a stratified Cox proportional hazard model with separate baseline strata of age group, sex, and high-risk medical condition groups for Stage 1; serostatus at D22 will also be included in the stratified Cox proportional hazard model for Stage 2. If informative censoring is observed in the study, a Cox model adjusting for this informative censoring may be conducted.

Survival analysis will be conducted in the mFAS-PD2 Naïve-D01+D22 and PPAS Naïve-D01+D22 analysis sets for Stage 1 (for both key secondary endpoints) and SARS-COV-2 infection endpoint for Stage 2. Survival analysis will be conducted in the mFAS-PD2 and PPAS analysis sets for severe COVID-19 endpoint for Stage 2.

Primary safety endpoints:

The main parameter will be described for all safety endpoints. The percentage of participants (denominator of number of participants) will be provided for all safety endpoints as the main analysis. In addition, incidence rate with denominator of 1000 person-years will be provided for analysis of SAEs, AESIs, MAAEs, and SARS-CoV-2 infection and/or symptomatic COVID-19 throughout the study. This analysis to calculate incidence rate of events using person-time as a denominator for the safety endpoints listed above will be complementary analysis to the primary safety analysis using cumulative frequency. This analysis is planned as participants in this study are given the option of unblinding to receive approved/authorized COVID-19 vaccines during the conduct of the study. In this situation, it is possible that the safety follow-up of the placebo group may be shorter than the one of the vaccine group. In this situation we believe that the duration of follow-up should be integrated in the presentation of the safety data, ie, using the person-time denominator to calculate the incidence rate of the events in addition to the cumulative frequency analysis (number of events with the number of participants as the denominator). This minimizes the likelihood of biased assessment given the potential for shorter duration of follow-up for the participants in the placebo group.

The corresponding 95% CIs for incidence rates will be calculated based on the Poisson method, and 95% CI for percentages and proportion will be calculated based on the Clopper-Pearson method. Subgroup analyses will be performed for at least age group and baseline SARS-CoV-2 serostatus (Naïve-D01 or Non-Naïve-D01) for main safety analyses.

The Reactogenicity Safety Analysis Subset (RSafAS) will be used for safety analyses for the following endpoints:

- Presence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (pre-listed in the participant's

diary card [DC]/eDC and case report form [CRF]) injection site reactions and systemic reactions occurring up to 7 days after each vaccination.

- Presence, nature (Medical Dictionary for Regulatory Activities [MedDRA] system organ class [SOC] and preferred term [PT]), time of onset, duration, intensity, relationship to vaccination and whether the event led to early termination from the study of non-serious unsolicited AEs reported up to 21 days after the last vaccination.

The Safety Analysis Set (SafAS) will be used for the safety analysis for the following endpoints:

- Presence, and relationship of unsolicited (immediate) injection site and systemic AEs reported in the 30 minutes after each vaccination.
- Presence, nature (MedDRA SOC and PT), time of onset, seriousness criteria, relationship to vaccination, outcome, and whether the event led to early termination from the study, of SAEs.
- Presence, nature (MedDRA SOC and PT), relationship to vaccination of all protocol-specified AESIs throughout the study.
- Presence of virologically-confirmed SARS-CoV-2 infections and/or symptomatic COVID-19.
- Presence, nature (MedDRA SOC and PT), relationship to vaccination of MAAEs throughout the study.

Key secondary endpoints:

Hypothesis testing for key secondary objectives in the SARS-CoV-2 naïve population will be performed for the SARS-CoV-2 infection endpoint and severe COVID-19 occurring ≥ 14 days after the second vaccination. This hypothesis testing of the 2 secondary endpoints is conditional to the success of the primary objective. The Holms procedure is applied to the 2 endpoints to control for the study wise error rate of 1-sided 0.025 (18).

The same statistical methods by IRR (Formula 1) will be applied for the endpoint of severe COVID-19. Statistical method by RR (Formula 2) for the SARS-CoV-2 infection endpoint will be applied due to the unknown time of infection onset. Survival analysis using Cox proportional hazard model will also be applied for severe COVID-19 endpoint only.

The conclusions of efficacy against each of the key secondary endpoints in Stage 1 will be based on mFAS-PD2 Naïve-D01+D22 analysis set by hypothesis testing. In Stage 2, the conclusions of efficacy against SARS-CoV-2 infection in Stage 2 will be based on mFAS-PD2 Naïve-D01+D22, and conclusion against severe COVID-19 endpoint will be based on mFAS-PD2 by hypothesis testing. Sensitivity analysis for key secondary efficacy endpoints will be conducted on PPAS Naive-D01+D22 analysis set for Stage 1. For Stage 2, same sensitivity analysis for severe COVID-19 endpoint will be conducted on PPAS analysis set and for SARS-CoV-2 infection will be based on PPAS Naïve-D01+D22. Survival analysis will be conducted in the mFAS-PD2 Naïve-D01+D22 analysis set for Stage 1. Same survival analysis will be conducted for severe COVID-19 endpoint in the mFAS-PD2 and for SARS-CoV-2 endpoint in the mFAS-PD2 Naïve D01+D22 in Stage 2.

Hypothesis testing for key secondary objectives will be conducted if both of the following conditions are met:

- The primary objective is demonstrated

- 22 severe cases and 162 infections are collected

If both of the criteria are met, the hypothesis testing of the key secondary endpoints will be done in the same timeframe as the efficacy analysis for the primary endpoint.

If either criteria are not met, hypothesis testing for the key secondary endpoints will be performed with final data available in comparison to a placebo control, (ie, at the time of the analysis with data prior to the cross-over) if at least a minimum of 11 severe events or 70 infections are collected.

Sample size determination:

A total of 10 160 participants in Stage 1 and 10 886 participants in Stage 2 are planned to be enrolled and randomized with allocation ratio (1:1) into vaccine group and placebo group. Among those, participants who are SARS-CoV-2 non-naïve at baseline will be capped to approximately 30% of the total population in Stage 1 (up to ~3048 participants [~1524/arm]). The target for SARS-CoV-2 non-naïves is ~3266 participants (~1633/arm) in Stage 2. If the crossover is not implemented, recruitment will continue until the minimally required number of naïve participants to assess efficacy is enrolled (even if the overall enrollment target is reached).To that end, the sample size of at least 7 112 SARS-CoV-2 naïve participants in Stage 1 and 7620 SARS-CoV-2 naïve participants in Stage 2 is powered independently to demonstrate the primary objective of VE against symptomatic COVID-19 in SARS-CoV-2 naïve adults in each stage. Of note, the primary endpoint for Stage 2, including both naïve and non-naïve participants, was changed after enrollment of Stage 2 was already completed; therefore, all sample size calculations were based on a primary endpoint that considered only naïve participants. The power of primary efficacy analysis is driven by the total number of symptomatic COVID-19 events.

Assumptions for sample size calculation are listed as follows [a]:

- The lower bound (LB) of adjusted CI for the VE estimate is > 30% for both stages
- The expected true VE for symptomatic COVID-19 is 70%
- The 1-sided type I error for each stage is 0.025 with sample size calculated based on adjusted alpha of 1-sided 0.02276 for final analysis including one interim at 70% data
- Power = 90% for each stage

Each stage is considered as independent of the other so that the type I error is controlled for each stage but not for the study. While the above assumptions remain the same for each stage of the study, the following assumptions are different for both stages because Stage 2 is expected to start after Stage 1.

- The incidence rate of symptomatic COVID-19 in Placebo is assumed as 2.25% illness rate in Stage 1 and 2.25% illness rate in Stage 2, per 2-months follow-up period
- Attrition rate = 25% in Stage 1 and 30% in Stage 2

The attrition rate is assumed to be higher for Stage 2 as larger parts of the population are eligible to receive vaccine.

[a] Assumptions were made before the primary objective change was made in the protocol. Enrollment was already completed before the change in the primary endpoint; however, the power calculations remain the same.

For each stage, the type I error of hypothesis testing is controlled as 1-sided 0.025, and O'Brien Fleming (OBF) spending function is applied to adjust for multiplicity of interim analysis for efficacy with one potential interim analysis when accrual of approximately 50%-70% of the total number of events is reached. The sample size calculated based on the adjusted final alpha of 0.02276 will ensure at least 90% power to conclude on primary objective when the interim analysis is conducted between 50% - 70% range of data. Adjusted alpha by OBF alpha spending function is applied and the corresponding adjusted CI will be used for hypothesis testing (by exact method) at each interim and at final analysis against symptomatic COVID-19 in each stage independently.

In each stage, with assumptions described above, a total of approximately 78 symptomatic COVID-19 events are required. The expected follow-up time to accrue the required number of events for 90% power is approximately 2 months post-second dose, given the incidence rate assumption in each stage respectively. However, the number of events may be reached earlier or later than the assumed 2-month period.

Because Omicron is the prevalent variant during case accrual for Stage 2 and the expected vaccine efficacy against Omicron is expected to be lower than the original assumption of 70%, the expected true VE for symptomatic COVID-19 for Stage 2 was estimated at 60%. Therefore, a total of approximately 125 symptomatic COVID-19 events will be required to achieve 80% power with 1-side type I error rate of 0.025, assuming no interim analysis. If any interim analysis is planned for Stage 2, type I error rate will be adjusted appropriately.

It is considered success for the key secondary endpoints if the LB of the CI for the corresponding VE is > 0% against either the SARS-CoV-2 infection endpoint, or severe COVID-19. The Holm's procedure (18) will be applied to control the overall 1-sided alpha 0.025 against key secondary objectives. Assuming the VE against SARS-CoV-2 infection endpoint is at least 40%, a total of 162 infections will provide at least 80% power to conclude at 0% LB. Assuming the VE against severe COVID is 80%, a total of 22 events will provide at least 80% power to conclude at 0% LB.

The study is planned to have 5080 participants in the vaccine group in Stage 1 which will provide at least 92.1% probability to detect an event with 0.05% rate. In Stage 2, 5443 participants in vaccine group will provide at least 93.4% probability to detect an event with 0.05% rate.

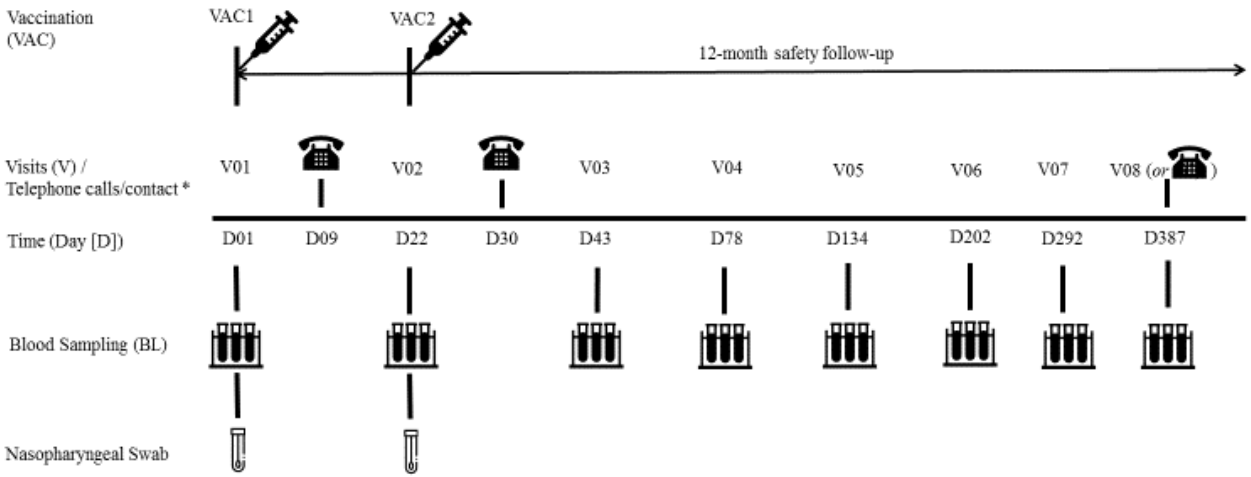
Data Monitoring/Other Committee:

Study oversight is provided by an independent Data Safety Monitoring Board (DSMB). The DSMB applies pre-defined, interim monitoring criteria, and reviews data unblinded on safety, efficacy, and study integrity. Recommendations for early vaccination termination, study termination, or design modifications are made to the Sponsor through the Study OG. The Sponsor/OG may determine adaptations in study design not predefined in the protocol, based on treatment-blinded data and DSMB recommendations. In the event that a participant develops symptoms that are suspected to be caused by myocarditis and/or pericarditis, the case will be referred to an external cardiac adjudication committee for assessment and confirmation.

1.2 Schema

The graphical design of the VAT00008 study is presented in Figure 1.1, and the graphical design for the COVID-19-like illness follow-up is presented in Figure 1.2. For the graphical design of the Crossover / Booster, see Figure 1.3 through Figure 1.5.

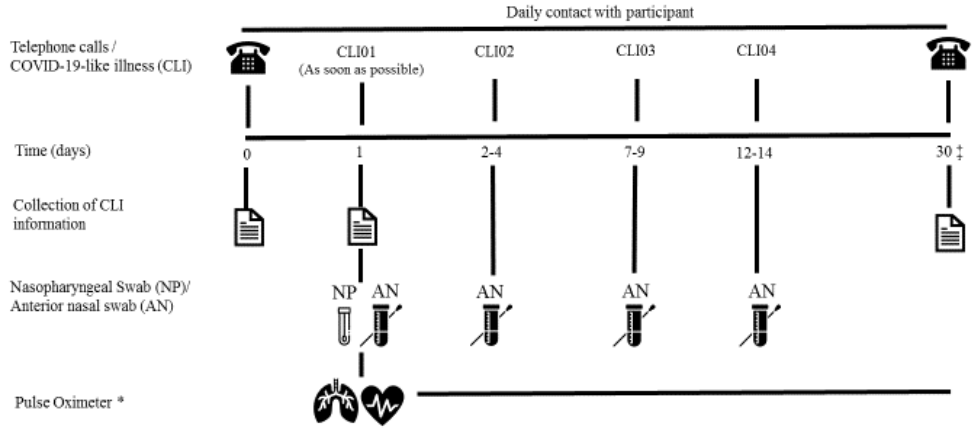
Figure 1.1: Graphical study design



* Telephone calls / contacts: D09 and D30 contacts are for those in the Reactogenicity subset only. During the D09 and D30 contacts, staff will review the DC pertaining to solicited AEs (D09 and D30 only), SAEs, AESIs, and COVID-19-like illness since the last visit and will remind participants to bring the DC for the next visit. These contacts could be made through a telephone call or alternative methods. In participants using a paper DC, a telephone call is preferred.

For the V08 contact, all participants will be scheduled to attend V08 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.

Figure 1.2: Follow-up of COVID-19-like illness

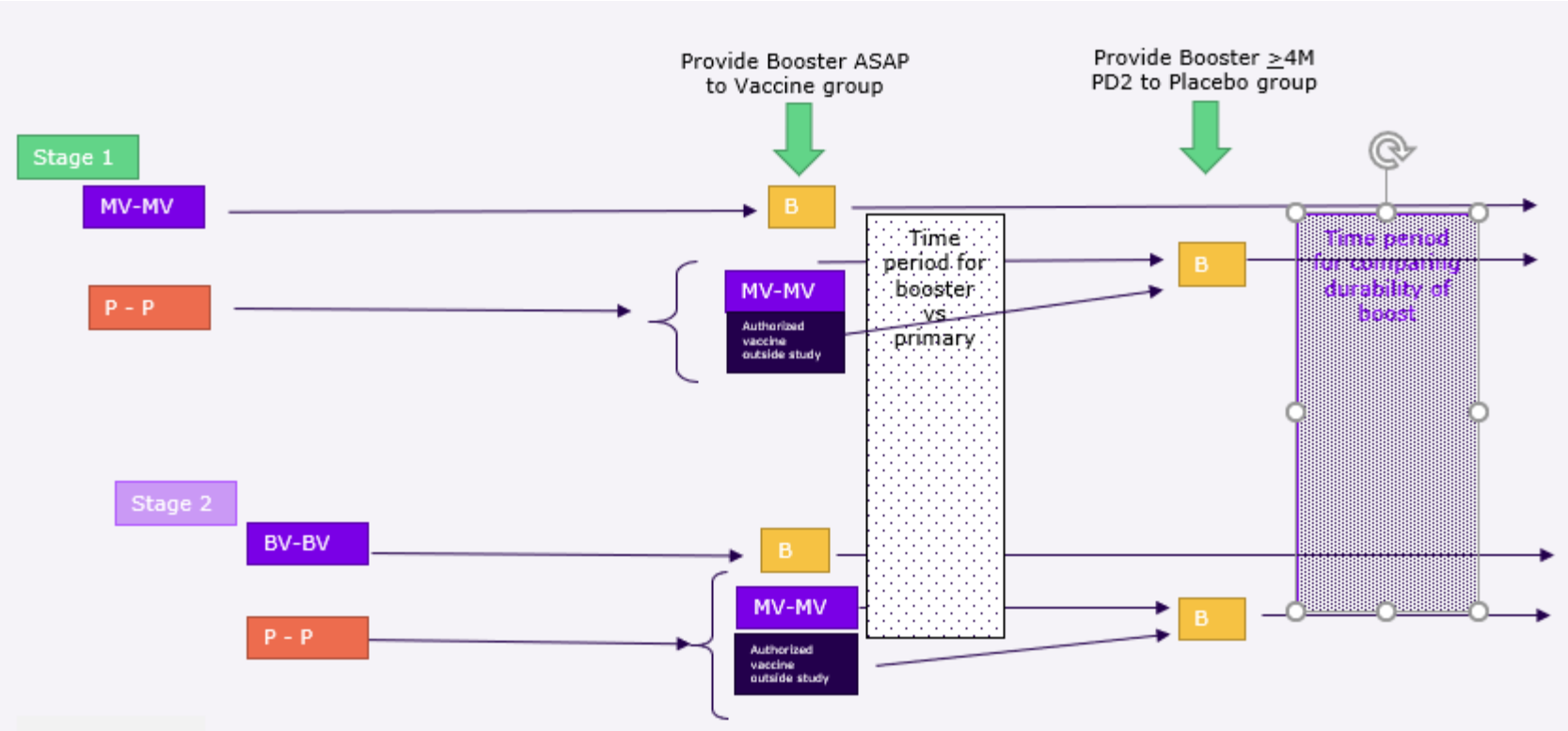


AN, anterior nasal; CLI, COVID-19-like illness, NP, nasopharyngeal

* Participants will be asked to record symptoms daily during their illness episode until the results of the NP swab at CLI01 and AN swab at CLI02 and any other swab collected for local NAAT testing at CLI01 are available. If negative in all specimens collected, the participants will be asked to stop recording daily. If positive in any of the specimens collected, the participant will be asked to continue recording symptoms daily until the end of their illness or up to 30 days from symptom onset. At the CLI01 visit, participants will be provided with a pulse oximeter and asked to record pulse oximetry readings every day from CLI01 until the results of the NP swab at CLI01 and AN swab at CLI02 and any other swab collected for local NAAT testing at CLI01 are available. If negative in all specimens collected, the participants will be asked to stop recording daily. If positive in any of the specimens collected, the participant will be asked to continue recording symptoms daily until the end of their illness or up to 30 days from symptom onset. If symptoms are not resolved 30 days after illness onset, participants will be asked to record the date when symptoms resolve.

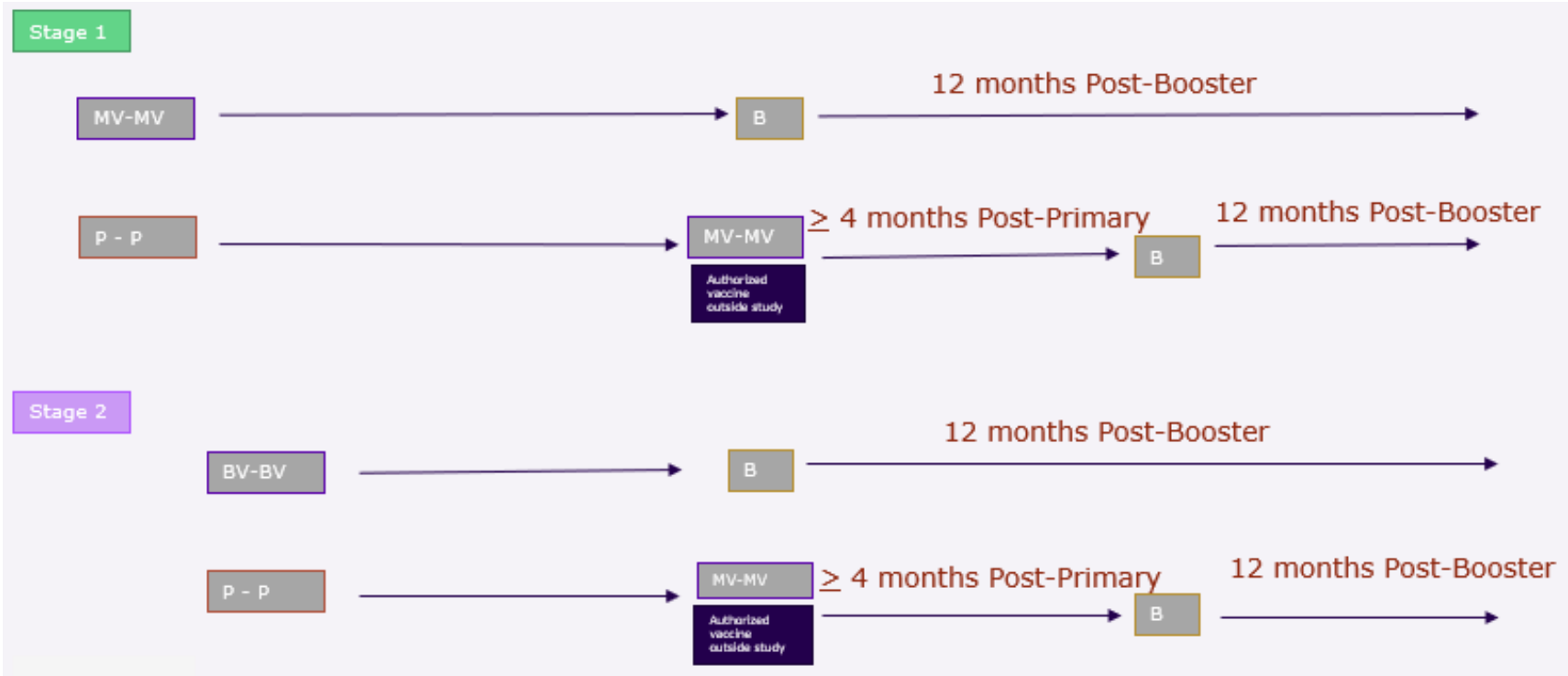
‡ Follow-up telephone call (TC) approximately 30 days after illness onset. If symptoms are not resolved at this follow-up TC, a second TC will be needed approximately 60 days after illness.

Figure 1.3: Graphical design of unblinded crossover / booster design



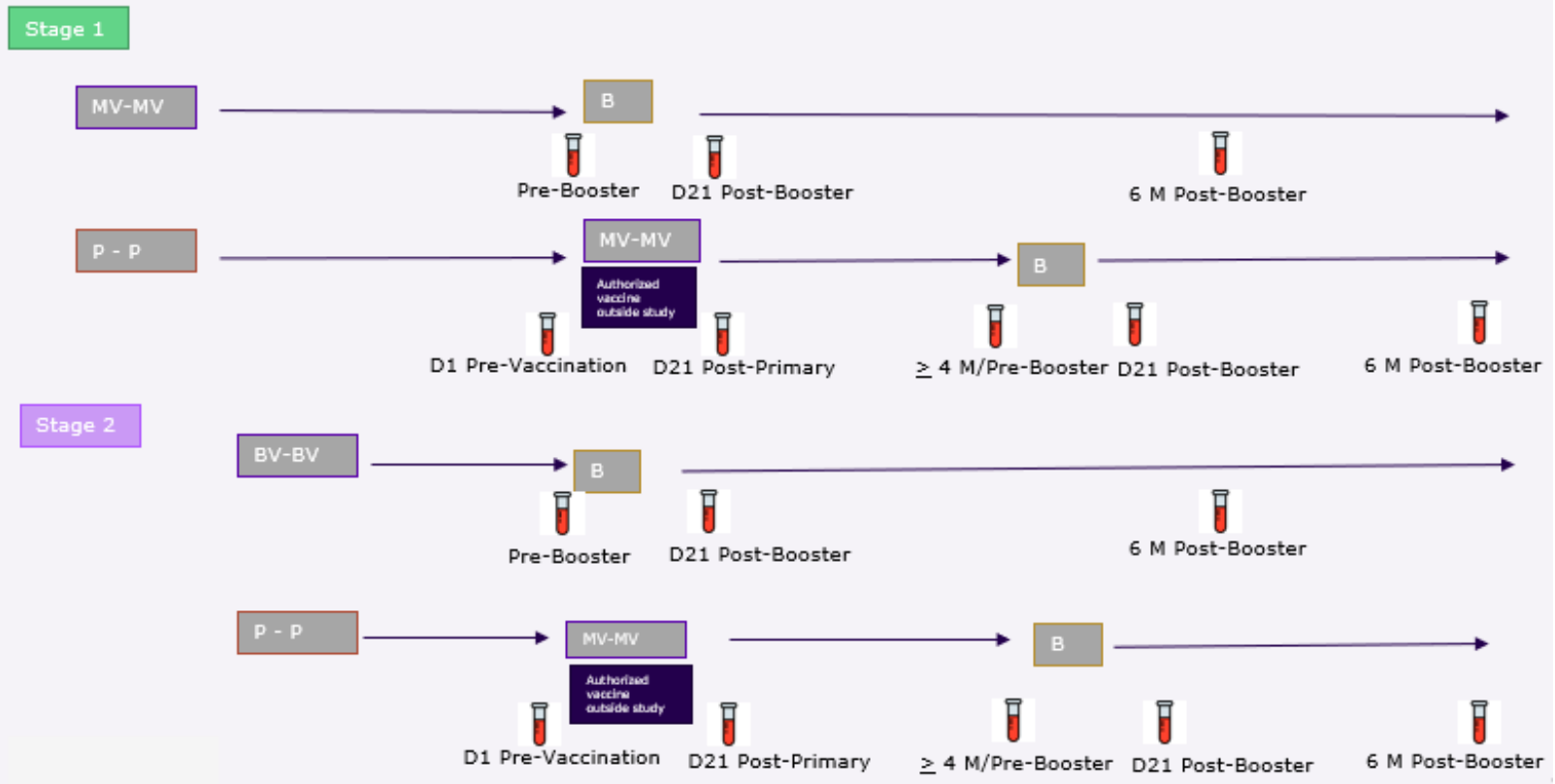
Abbreviations: B, Booster vaccination (CoV2 preS dTM-AS03 monovalent [B.1.351]); BV, bivalent vaccination (CoV2 preS dTM-AS03 [D614 + B.1.351]); MV, monovalent vaccination (CoV2 preS dTM-AS03 monovalent [D614]); P, Placebo

Figure 1.4: Crossover / booster efficacy and safety follow-up



Abbreviations: B, Booster vaccination (CoV2 preS dTM-AS03 monovalent [B.1.351]); BV, bivalent vaccination (CoV2 preS dTM-AS03 [D614 + B.1.351]); MV, monovalent vaccination (CoV2 preS dTM-AS03 monovalent [D614]); P, Placebo
Note: "≥ 4 months Post-Primary" means ≥ 4 months after the last dose of primary series

Figure 1.5: Crossover / booster immunogenicity follow-up



Abbreviations: B, Booster vaccination (CoV2 preS dTM-AS03 monovalent [B.1.351]); BV, bivalent vaccination (CoV2 preS dTM-AS03 [D614 + B.1.351]); MV, monovalent vaccination (CoV2 preS dTM-AS03 monovalent [D614]); P, Placebo

Notes:
"D21 Post-primary" means 21 days after the last dose of the primary series.
For those who receive authorized vaccine (outside of the study) as primary series (Crossover vaccination), no protocol deviation will be considered if the corresponding blood sample is missed.

1.3 Schedule of Activities (SoA)

Visit procedures are detailed in the Operating Guidelines.

Table 1.3 presents the overall study Schedule of Activities (SoA), Table 1.4 presents the SoA for the follow-up of COVID-19-like illness, Table 1.5 presents the Crossover / Booster SoA for those who initially received primary vaccine in the initial, double-blind, primary series design, and Table 1.6 presents the Crossover / Booster SoA for those who initially received placebo in the initial, double-blind, primary series design.

Table 1.3: Schedule of activities: Initial, double-blind, primary series design

Phase III Study, 8 Visits, 2 Telephone Calls (or Electronic Contacts), 2 Vaccinations, 8 Blood Sample Time Points, Approximately 13 Months' Duration Per Participant

Visit (V) / Contact ††††	***Collection of information in the CRF***	**V01**	**TC/Contact 1**	**V02**	**TC/Contact 2**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08 or Safety Follow-up Call******
Study timelines (Day [D])		D01	D09	D22	D30	D43	D78	D134	D202	D292	D387
Time interval (days)			V01 +8 days	V01 +21 days	V02 +8 days	V02 +21 days	V02 +56 days	V02 +112 days	V02 +180 days	V02 +270 days	V02 +365 days
Time windows (days)		N/A	[+4 days]	[+9 days]	[+4 days]	[+9 days]	[+/-14 days]	[+/-14 days]	[+/-14 days]	[+/-14 days]	[+/-14 days]
Visit procedures:											
Informed consent	X	X									
SARS-CoV-2 rapid serodiagnostic test	X	X									
Inclusion/exclusion criteria	X	X									
Collection of demographic data	X	X									
Collection of medical history	X	X									

Visit (V) / Contact ††††	***Collection of information in the CRF***	**V01**	**TC/Contact 1**	**V02**	**TC/Contact 2**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08 or Safety Follow-up Call******
Study timelines (Day [D])		D01	D09	D22	D30	D43	D78	D134	D202	D292	D387
Time interval (days)			V01 +8 days	V01 +21 days	V02 +8 days	V02 +21 days	V02 +56 days	V02 +112 days	V02 +180 days	V02 +270 days	V02 +365 days
Time windows (days)		N/A	[+4 days]	[+9 days]	[+4 days]	[+9 days]	[+/-14 days]	[+/-14 days]	[+/-14 days]	[+/-14 days]	[+/-14 days]
Visit procedures:											
including high-risk medical conditions	Significant Medical History										
Collection of risk factors for SARS-CoV-2 exposure and COVID-19	X	X		X		X	X	X	X	X	X
Physical examination*		X									
Pre-vaccination temperature		X		X							
Urine/serum pregnancy test (if applicable)†		X		X							

Visit (V) / Contact ††††	***Collection of information in the CRF***	**V01**	**TC/Contact 1**	**V02**	**TC/Contact 2**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08 or Safety Follow-up Call******
Study timelines (Day [D])		D01	D09	D22	D30	D43	D78	D134	D202	D292	D387
Time interval (days)			V01 +8 days	V01 +21 days	V02 +8 days	V02 +21 days	V02 +56 days	V02 +112 days	V02 +180 days	V02 +270 days	V02 +365 days
Time windows (days)		N/A	[+4 days]	[+9 days]	[+4 days]	[+9 days]	[+/-14 days]	[+/-14 days]	[+/-14 days]	[+/-14 days]	[+/-14 days]
Visit procedures:											
Contact IRT system for randomization, participant number, and unique dose number allocation	X	X									
Contact IRT system for unique dose number allocation	X			X							
Temporary and definitive contraindications	X			X							
Nasopharyngeal sample collection	X	X		X							

Visit (V) / Contact ††††	***Collection of information in the CRF***	**V01**	**TC/Contact 1**	**V02**	**TC/Contact 2**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08 or Safety Follow-up Call******
Study timelines (Day [D])		D01	D09	D22	D30	D43	D78	D134	D202	D292	D387
Time interval (days)			V01 +8 days	V01 +21 days	V02 +8 days	V02 +21 days	V02 +56 days	V02 +112 days	V02 +180 days	V02 +270 days	V02 +365 days
Time windows (days)		N/A	[+4 days]	[+9 days]	[+4 days]	[+9 days]	[+/-14 days]	[+/-14 days]	[+/-14 days]	[+/-14 days]	[+/-14 days]
Visit procedures:											
Blood sampling (BL): Serum samples for Ab assays (20 mL)	X	BL0001‡		BL0002‡		BL0003	BL0004	BL0005	BL0006	BL0007	BL0008
Vaccination (VAC)	X	X		X							
Telephone call / contact			X§		X**						X****
Immediate surveillance (30 minutes)	X	X		X							
DC/eDC provided		DC1/eDC ††		DC2/eDC ***		DC3/eDC †††					
DC/eDC reviewed			DC1/eDC ‡‡		DC2/eDC ‡‡		DC3/eDC ‡‡	DC3/eDC ‡‡	DC3/eDC ‡‡	DC3/eDC ‡‡	
DC/eDC collected				DC1/eDC §§		DC2/eDC §§					DC3/eDC §§

Visit (V) / Contact ††††	***Collection of information in the CRF***	**V01**	**TC/Contact 1**	**V02**	**TC/Contact 2**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08 or Safety Follow-up Call******
Study timelines (Day [D])		D01	D09	D22	D30	D43	D78	D134	D202	D292	D387
Time interval (days)			V01 +8 days	V01 +21 days	V02 +8 days	V02 +21 days	V02 +56 days	V02 +112 days	V02 +180 days	V02 +270 days	V02 +365 days
Time windows (days)		N/A	[+4 days]	[+9 days]	[+4 days]	[+9 days]	[+/-14 days]	[+/-14 days]	[+/-14 days]	[+/-14 days]	[+/-14 days]
Visit procedures:											
Collection of solicited injection site & systemic reactions (Reactogenicity Subset only)	X	D01-D08 *(up to 7 days post-VAC1)*		D01-D08 *(up to 7 days post-VAC2)*							
Collection of non-serious unsolicited AEs (Reactogenicity Subset only)	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 and COVID-19 vaccination)					Influenza and COVID-19 vaccination, COVID-19 prophylaxis (eg, SARS-CoV-2 antivirals, monoclonal antibodies, plasma) only				
Passive surveillance	X	Participants will be instructed to contact the site if they experience symptoms of a COVID-19-like illness or if they have a positive COVID-19 test from any other source at any time during the study.									

Visit (V) / Contact ††††	***Collection of information in the CRF***	**V01**	**TC/Contact 1**	**V02**	**TC/Contact 2**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08 or Safety Follow-up Call******
Study timelines (Day [D])		D01	D09	D22	D30	D43	D78	D134	D202	D292	D387
Time interval (days)			V01 +8 days	V01 +21 days	V02 +8 days	V02 +21 days	V02 +56 days	V02 +112 days	V02 +180 days	V02 +270 days	V02 +365 days
Time windows (days)		N/A	[+4 days]	[+9 days]	[+4 days]	[+9 days]	[+/-14 days]	[+/-14 days]	[+/-14 days]	[+/-14 days]	[+/-14 days]
Visit procedures:											
Active surveillance	X	Participants will be contacted once a week over the entire duration of the study to inquire about the development of symptoms of COVID-like illness and to remind participants to contact study staff if they experience symptoms of COVID-like illness (See also Schedule of Activities Table 1.4 for follow-up)									
Collection of SAEs (including those related to study procedures), MAAEs, and AESIs‡‡‡	X	To be reported at any time during the study									
Collection of pregnancies	X	To be reported at any time during the study									
End of active phase participation record§§§	X	End of active phase form to be completed for those who discontinue (either during the initial, double-blind, primary series design procedures or if participant does not consent to be part of Crossover / Booster)									

Visit (V) / Contact ††††	***Collection of information in the CRF***	**V01**	**TC/Contact 1**	**V02**	**TC/Contact 2**	**V03**	**V04**	**V05**	**V06**	**V07**	**V08 or Safety Follow-up Call******
Study timelines (Day [D])		D01	D09	D22	D30	D43	D78	D134	D202	D292	D387
Time interval (days)			V01 +8 days	V01 +21 days	V02 +8 days	V02 +21 days	V02 +56 days	V02 +112 days	V02 +180 days	V02 +270 days	V02 +365 days
Time windows (days)		N/A	[+4 days]	[+9 days]	[+4 days]	[+9 days]	[+/-14 days]	[+/-14 days]	[+/-14 days]	[+/-14 days]	[+/-14 days]
Visit procedures:											
End of primary phase participation record §§§	X	At the time that the participant is informed of the study information and invited to participate in the Crossover / Booster, all initial, double-blind, primary study design procedures outlined in this table will stop. If the participant agrees to be part of Crossover / Booster, the end of primary phase participation record will be completed.									
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, (electronic) Case Report Form; DC/eDC, Diary Card / electronic Diary Card; IRT, Interactive Response Technology; MAAE, medically-attended adverse event; SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TC, Telephone Call; V, visit; VAC, Vaccination

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

† Urine or serum pregnancy test is applicable to childbearing potential female participants (to be considered of non-childbearing potential, a female must be postmenopausal for

at least 1 year or surgically sterile). Urine or serum pregnancy test is to be performed before vaccination.

‡ BL0001 and BL0002 will be collected pre-vaccination.

§ This contact is for participants in the reactogenicity subset. During the D09 telephone call/contact, staff will review the DC1/eDC for solicited reactions from D01 to D08 after vaccination, inquire whether the participant experienced any SAE, MAAEs, or AESI not yet reported, and remind the participant to bring back DC1/eDC for V02. This contact could be made through a telephone call or alternative methods. In participants using a paper DC, a telephone call is preferred.

** This contact is for participants in the reactogenicity subset. During the D30 telephone call/contact, staff will review the DC2/eDC for solicited reactions from D01 to D08 post-VAC2, inquire whether the participant experienced any SAE, MAAEs, or AESI not yet reported, and remind the participant to bring back DC2/eDC for V03 for participants in the reactogenicity subset. This contact could be made through a telephone call or alternative methods. In participants using a paper DC, a telephone call is preferred

†† Participants will use this DC1/eDC to record information about solicited reactions, unsolicited AEs, SAEs, MAAEs, and AESIs from D01 to D08 after vaccination and will continue to record information about unsolicited AEs, MAAEs, SAEs, and AESIs from D09 to V02. In addition, the participant will use the DC/eDC to report the information related to COVID-19-like illness.

‡‡ The Investigator or an authorized designee will remind the participants to bring back the DC/eDC 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/eDC and will attempt to clarify anything that is incomplete or unclear.

*** Participants will use this DC2/eDC to record solicited reactions, unsolicited AEs, SAEs, MAAEs, and AESIs (from V02 to TC2) and will continue to collect unsolicited AEs, MAAE, SAEs, and AESIs (from TC2 to V03). In addition, the participant will use the DC/eDC to report the information related to COVID-19-like illness.

††† Participants will use this DC3/eDC for SAEs, MAAEs, AESIs, and information related to COVID-19-like-illness from V03 to V08.

‡‡‡ AESIs (serious and non-serious) will be collected throughout the study and will be communicated to the Sponsor in an expedited manner similar to the reporting of SAEs and followed-up until the end of the follow-up period or resolution, as per the assigned causality. These include: Anaphylactic reactions, Generalized convulsion, Thrombocytopenia, Thrombosis with Thrombocytopenia Syndrome, Myocarditis, Pericarditis, and potential immune-mediated diseases (pIMDs).

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

**** Participants who consent to continue with the unblinded crossover/booster design, will continue with the crossover/booster schedule of activities as described in Table 1.5 and Table 1.6. If participants do not consent to continue with the unblinded crossover/booster all study procedures will be stopped, and participants will be discontinued from the study. If discontinuation occurs at a scheduled visit, the participant will be provided a Memory Aid instead of a DC for SAEs, AESIs, and MAAEs follow-up 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.

†††† All procedures outlined in this table are part of initial, double-blind, primary series study design. At the time that the participant is informed of the study information and invited to participate in the Crossover / Booster, all initial study design procedures outlined in this table will stop (regardless of participant's decision for Crossover / Booster participation).

Table 1.4: Follow-up of COVID-19-like illness schedule of activities

Contact Type	Initial Telephone Call*	CLI01	CLI02 †	CLI03 †	CLI04 †	Follow-up Telephone Call‡‡
		As soon as possible after symptom onset	CLI01 +2-4 days	CLI01 +7-9 days	CLI01 +12-14 days	30 days after symptom onset
Verify information on COVID-19-like illness 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 / electronic Diary Card daily	X					
Collection of respiratory specimen		NPXXXX§				
Collection of anterior nasal swab		ANXXXX**	ANXXXX	ANXXXX††	ANXXXX††	
Remind participant to record pulse oximeter readings twice daily §§		X				
Collection of disease burden and health care information during COVID-19-like illness	X	X				X
Collection of treatments received during COVID-19-like illness	X	X				X
Collection of information on respiratory illness symptoms daily	Participants will be asked to record symptoms every day from the onset of symptoms until the results of the NP swab at CLI01 and AN swab at CLI02 and any other swab collected for local testing at CLI01. If negative in all specimens collected, the participant will be asked to stop recording symptoms daily and only report the end date for their symptoms. If positive in any of the specimens collected, the participant will be asked to continue recording symptoms daily until the end of their illness or up to 30 days. After 30 days, if symptoms continue, they will be required to report the end date for their symptoms.					
Daily contact with participant	Participants will be contacted daily to enquire/record symptoms. Daily contact will continue in individuals who have virologically-confirmed SARS-CoV-2 infection until the end of illness or up to 30 days after illness onset. In individuals who are SARS-CoV-2 negative, daily contact will not continue unless judged necessary by the Investigator for medical monitoring of the participant.					

* Initial illness identification phone call triggered by participant reporting of symptoms of COVID-19-like illness either through passive surveillance or active surveillance.
† Follow-up swabs after Visit 1 can either be collected from participants by investigators or through self-sampling by participants.
‡ 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.
** This anterior nasal swab will be used to test for other respiratory viruses other than SARS-CoV-2 and will be used to quantify viral burden in participants who have virologically-confirmed SARS-CoV-2.
†† This sample will only be collected in participants with a positive NAAT for SARS-CoV-2 on the first nasopharyngeal swab or second nasopharyngeal swab or local NAAT at CLI01.
‡‡ Follow-up telephone call approximately 30 days after illness. If symptoms are not resolved at this follow-up TC, a second TC will be needed approximately 60 days after illness.
§§ At the time of a CLI Visit, participants will be provided a pulse oximeter, explained about its use, and asked to record pulse oximetry readings every day from CLI01 until the results of the NP swab at CLI01 and AN swab at CLI02 and any other swab collected for local NAAT testing at CLI01. Participant-recorded pulse oximeter readings are for safety monitoring and will be collected in the DC/eDC. Continuation of pulse oximetry readings by the participant after availability of test results will be based on investigator judgment. Pulse oximeter readings collected by the site or a health care provider (eg, Emergency Room) will be collected in the CRF to determine severity of the COVID-19 episode.

Table 1.5: Crossover / Booster schedule of activities (for those who received primary series vaccine as initial injections during initial, double-blind, primary series design)

Visit (V) / Contact	***Collection of information in the CRF***	**Unblinding TC****	**BV01****	**BV02**	**BV03††**	**Efficacy Follow-up / Safety Follow-up Call††**
Study timelines (Day [D])			D01	D22	D202	D366
Time interval (days)			Last primary vaccination + ≥ 120 days	BV01 +21 days	BV01 +180 days	BV01 +365 days
Time windows (days)*			N/A	[+14 days]	[+28 days]	[+28 days]
Visit procedures:						
Unblinding	X	X				
Informed consent	X		X			
Pre-vaccination temperature			X			
Urine/serum pregnancy test (if applicable)†			X			
Contact IRT system for unique dose number allocation	X		X			
CR Temporary and definitive contraindications‡	X		X			
Blood sampling (BL): Serum samples for Ab assays (20 mL)	X		BL1003§	BL1004	BL1005	
Booster Vaccination (VAC)	X		Booster VAC			
Immediate surveillance (30 minutes)	X		X			
DC/eDC provided			DC4/eDC‡‡	DC5/eDC***		
DC/eDC collected				DC4/eDC§§	DC5/eDC§§	
Memory aid provided					X	
Collection of non-serious unsolicited AEs	X		D01-D22 *(up to 21 days post-Booster VAC)*			

Safety follow-up (MAAEs, SAEs, and AESIs†††)	X		To be reported at any time during the study			
Collection of concomitant medications	X		Influenza vaccination, COVID-19 prophylaxis (eg, SARS-CoV-2 antivirals, monoclonal antibodies, plasma) only			
Passive surveillance	X		Participants will be instructed to contact the site if they experience symptoms of a COVID-19-like illness or if they have a positive COVID-19 test from any other source at any time during the study.			
Active surveillance	X		Participants will be contacted once a week over the entire duration of the study to inquire about the development of symptoms of COVID-like illness and to remind participants to contact study staff if they experience symptoms of COVID-like illness. Study termination should be completed at the final efficacy follow up contact. (See also Schedule of Activities Table 1.4 for follow-up)			
End of active phase participation record	X				X	
12 Month Post-Booster Follow-up participation record ††	X					X††

Abbreviations: Ab, Antibody; BL, blood sample (#); BV, Booster Visit; CR, Crossover; CRF, (electronic) Case Report Form; DC/eDC, Diary Card / electronic Diary Card; IRT, Interactive Response Technology; VAC, Vaccination

* Following the crossover set of injections, active and passive surveillance for COVID-19 symptoms will continue as described after the initial, double-blind, primary series design set of vaccinations (see Table 1.4).

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

‡ Crossover temporary and definitive contraindications are separate list than Initial temporary and definitive contraindications.

§ BL1003 will be collected pre-booster.

** TC to occur upfront for unblinding, and this can be combined with BV01.

†† All participants will be scheduled to receive a 12-Month (post-Booster) Efficacy / Safety Follow-up call. 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, MAAEs 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 SAEs, AESIs, and MAAEs follow-up 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. For participants who have prematurely terminated the study, the site should attempt to contact them and complete this 12-month safety follow-up (and all other 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.

‡‡ Participants will use this DC4/eDC to record information about unsolicited AEs, MAAEs, SAEs, and AESIs from D01 to BV02. In addition, the participant will use the DC/eDC to report the information related to COVID-19-like illness.

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

*** Participants will use this DC5/eDC to record information about MAAEs, SAEs, and AESIs from BV02 to BV03. In addition, the participant will use the DC/eDC to report the information related to COVID-19-like illness.

††† AESIs (serious and non-serious) will be collected throughout the study and will be communicated to the Sponsor in an expedited manner similar to the reporting of SAEs and followed-up until the end of the follow-up period or resolution, as per the assigned causality. These include: Anaphylactic reactions, Generalized convulsion, Thrombocytopenia, Thrombosis with Thrombocytopenia Syndrome, Myocarditis, Pericarditis, and potential immune-mediated diseases (pIMDs).

Table 1.6: Crossover / Booster schedule of activities (for those who initially received placebo during initial, double-blind primary series design)

Visit (V) / Contact	***Collection of information in the CRF***	**Unblinding TC****	**CRV01****	**CRV02**	**CRV03**	**BV01**	**BV02**	**BV03**	**Efficacy Follow-up / Safety Follow-up Call §§**
Study timelines (Day [D])			D01	D22	D43	D142	D163	D322	D487
Time interval (days)				CRV01 +21 days	CRV02 +21 days	CRV02/last primary vaccination + ≥ 120 days	BV01+21 days	BV01 +180 days	BV01 +365 days
Time windows (days)*			N/A	[+9 days]	[+14 days]	N/A	[+14 days]	[+28 days]	[+28 days]
Visit procedures:									
Unblinding	X	X							
Informed consent	X		X						
Pre-vaccination temperature			X	X		X			
Urine/serum pregnancy test (if applicable)†			X	X		X			
Contact IRT system for unique dose number allocation or registering authorized/approved vaccine	X		X	X		X			
CR Temporary and definitive contraindications‡	X		X	X		X			
Collection of authorized / approved COVID-19 vaccine			X	X					

(outside of the study) as part of Crossover, if applicable									
Blood sampling (BL): Serum samples for Ab assays (20 mL) ††	X		BL1001§		BL1002§	BL1003	BL1004	BL1005	
Vaccination (VAC)	X		Primary VAC1	Primary VAC2		Booster VAC			
Immediate surveillance (30 minutes) ‡‡	X		X	X		X			
DC/eDC provided			DC4/eDC***			DC5/eDC§§§	DC6/eDC****		
DC/eDC reviewed				DC4/eDC†††	DC4/eDC†††				
DC/eDC collected						DC4/eDC‡‡‡	DC5/eDC‡‡‡	DC6/eDC‡‡‡	
Memory Aid provided								X	
Collection of non-serious unsolicited AEs	X					D01-D22 *(up to 21 days post-Booster VAC)*			
Safety follow-up (MAAEs, SAEs, and AESIs††††)	X		To be reported at any time during the study						
Collection of concomitant medications	X		Influenza vaccination, COVID-19 prophylaxis (eg, SARS-CoV-2 antivirals, monoclonal antibodies, plasma) only						
Passive surveillance	X		Participants will be instructed to contact the site if they experience symptoms of a COVID-19-like illness or if they have a positive COVID-19 test from any other source at any time during the study.						
Active surveillance	X		Participants will be contacted once a week over the entire duration of the study to inquire about the development of symptoms of COVID-like illness and to remind participants to contact study staff if they experience symptoms of COVID-like illness. Study termination should be completed at the final efficacy follow up contact. (See also Schedule of Activities Table 1.4 for follow-up).						
End of active phase participation record	X							X	
12 Month Post-Booster Follow-up participation record (only for those discontinued early) §§									X§§

Abbreviations: Ab, Antibody; BL, blood sample (#); BV, Booster Visit; CR, Crossover; CRF, (electronic) Case Report Form; CRV, Crossover Visit; DC/eDC, Diary Card / electronic Diary Card; IRT, Interactive Response Technology; m, month; VAC, Vaccination

* Following the crossover set of injections, active and passive surveillance for COVID-19 symptoms will continue as described after the initial, double-blind, primary series design set of vaccinations (see Table 1.4).

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

‡ Crossover temporary and definitive contraindications are separate list than Initial temporary and definitive contraindications.

§ BL1001 and BL1003 will be collected pre-vaccination.

** TC to occur upfront for unblinding. For the participants who initially received placebo, this can be combined CRV01. For participants receiving an authorized /approved vaccine, CRV01 must be completed to at a minimum to complete new consent.

†† Note for those who receive authorized vaccine (outside of the study) as primary series (Crossover vaccination), no protocol deviation will be considered if the corresponding blood sample is missed.

‡‡ Immediate adverse reactions (ie, 30 minutes after vaccination) will be collected after Crossover receipt of CoV2 preS dTM-AS03 (D614) as primary series for those who initially received placebo and after Booster receipt of CoV2 preS dTM-AS03 (B.1.351) for all participants; but immediate adverse reactions will not be collected after receipt of authorized/approved vaccine outside of the study for those who initially received placebo.

§§ All participants will be scheduled to receive a 12-Month (post-Booster) Efficacy / Safety Follow-up call. 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, MAAEs 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. For participants who have prematurely terminated the study, the site should attempt to contact them and complete this 12-month safety follow-up after the last dose received (and all other 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.

*** Participants will use this DC4/eDC to record information about MAAEs, SAEs, and AESIs from D01 to BV01. In addition, the participant will use the DC/eDC to report the information related to COVID-19-like illness.

††† The Investigator or an authorized designee will remind the participants to bring back the DC/eDC 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/eDC and will attempt to clarify anything that is incomplete or unclear.

§§§ Participants will use this DC5/eDC to record information about unsolicited AEs, MAAEs, SAEs, and AESIs from BV01 to BV02. In addition, the participant will use the DC/eDC to report the information related to COVID-19-like illness.

**** Participants will use this DC6/eDC to record information about MAAEs, SAEs, and AESIs from BV02 to BV03. In addition, the participant will use the DC/eDC to report the information related to COVID-19-like illness.

†††† AESIs (serious and non-serious) will be collected throughout the study and will be communicated to the Sponsor in an expedited manner similar to the reporting of SAEs and followed-up until the end of the follow-up period or resolution, as per the assigned causality. These include: Anaphylactic reactions, Generalized convulsion, Thrombocytopenia, Thrombosis with Thrombocytopenia Syndrome, Myocarditis, Pericarditis, and potential immune-mediated diseases (pIMDs).

2 Introduction

An outbreak of severe respiratory illnesses in Wuhan City, Hubei Province, China in December 2019 heralded the appearance of a novel coronavirus, SARS-CoV-2, in the human population. The rapid escalation of the outbreak led to a declaration by the World Health Organization (1) on 20 January 2020 of a Public Health Emergency of International Concern, followed by the declaration on 11 March 2020 of a pandemic (2). The virus has been detected in 192 countries/regions and led to significant morbidity, mortality, and economic impact (3). Despite unprecedented measures of isolation, quarantine, social distancing, and community containment, to curb the spread of the virus, and the rapid development and global deployment of multiple locally approved/authorized SARS-CoV-2 vaccines, the global burden of SARS-CoV-2 infections and associated disease remains substantial, highlighting the need for more safe and effective vaccines.

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. The clinical profile of COVID-19, the illness caused by SARS-CoV-2, is variable (19). In the majority of cases, the manifestations are mild, or individuals may be asymptomatic (20). 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. While mostly self-limited, symptoms such as fatigue and dyspnea appear to persist in many individuals for up to 2 months after illness onset despite viral clearance (21). Adults over 50 years of age and individuals with chronic medical conditions are at a higher risk of severe outcomes and death (22) (23).

A number of vaccine candidates are in clinical development including messenger RNA (mRNA), protein subunit, viral vector, and inactivated vaccines encoding the Spike protein of SARS-CoV-2 induce neutralizing antibodies. Two COVID-19 mRNA vaccine candidates, BNT162b2 from Pfizer and BioNTech and mRNA-1273 from Moderna; 2 viral vector vaccines, ChAdOx1 nCOV-19 (AZD1222) from Oxford University/AstraZeneca and Ad26CoV2.S from Janssen; and an adjuvanted protein sub-unit vaccine from Novavax have reported efficacy against COVID-19 illness and severe disease in their Phase III clinical studies (7) (24) (25) (26) (27). Emergency authorization or other forms of regulatory approval have been granted in multiple countries for vaccines against COVID-19.

Sanofi's CoV2 preS dTM-AS03 vaccine is being developed in the setting of a pandemic for the active immunization and prevention of SARS-CoV-2 infection and COVID-19 disease. The initial intended use of the vaccine is for adults, 18 years of age and older. Studies including pediatric populations will be completed later since this population is at lower risk to develop severe complications. A study to evaluate safety and immunogenicity in pregnant females will also be completed later, once results of nonclinical development and reproductive toxicity are available and initial results demonstrating safety and a positive benefit-risk in humans are available.

The candidate antigen is a stabilized prefusion trimer of the SARS-CoV-2 S protein. The coronavirus 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 (28). 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 (ACE2), a membrane-bound carboxypeptidase localized to vascular endothelial as well as epithelial surfaces (29). 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 (30). 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-OC43, MERS-CoV, and SARS-CoV-1, and by extrapolation to SARS-CoV-2 (13). The prefusion stabilized SARS-CoV-2 Spike construct to be evaluated in the current study is based on this research.

The S1 subunit and RBD of the prefusion SARS-CoV-2 Spike antigen used in this vaccine is similar in sequence to the Spike antigens encoded by the mRNA vaccine constructs that have been shown to induce neutralizing antibody responses and confer robust efficacy against COVID-19 (26) (24), suggesting that other vaccines capable of inducing similar levels of neutralizing antibodies may also provide protection.

The antigen of the CoV2 preS dTM vaccine is manufactured using the same expression system technology as is used to manufacture a recombinant quadrivalent influenza vaccine (rQIV), licensed in the United States (US) and European Union (EU) and commercialized as Flublok® and Supemtek®, respectively for the prevention of influenza in adults 18 years of age and older (26). In this manufacturing platform, 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 (expre*s*SF+). The recombinant protein is expressed in the infected insect cells. After incubation, the recombinant protein is purified by a series of filtration and chromatography steps. This process is adaptable to manufacture a variety of antigens. Millions of doses of recombinant influenza vaccine (trivalent and quadrivalent formulations) have been administered since its approval in the US for human use corresponding to hemagglutinins (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, candidate S protein vaccines were developed, 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 in mice and ferrets and to be partially protective in a ferret challenge model.

The magnitude and quality of the immune response to the candidate antigen will be enhanced through delivery with an adjuvant. In addition, the adjuvant may influence the quality of the immune response. Previous clinical trials with rH5 HA and rH7 HA pandemic antigens in naïve

individuals show that a 2-dose immunization regimen of antigen was poorly immunogenic in comparison to antigen delivered with an adjuvant (31). This may allow for titration of the amount of antigen used and, thus, be antigen-sparing and potentially increase the available supply of antigen doses.

AS03 is an oil-in-water emulsion containing α-tocopherol and squalene. Safety of AS03-adjuvanted products has been extensively evaluated and found to be generally well tolerated with an acceptable safety profile (32). AS03 has been approved as a component of Pandemrix and Arepanrix, two H1N1 pandemic influenza vaccines. AS03 was also evaluated with pandemic H7 rHA 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 (33) (34). In addition to a Phase I/II study using the Sanofi CoV2 preS dTM antigen with AS03-adjuvanted system (NCT04537208) (35), AS03 has also been used in combination with other AS03-adjuvanted recombinant S proteins (Medicago [NCT04450004] (36) and Clover Biopharmaceuticals [NCT04405908]).

A potential theoretical safety issue with coronavirus vaccines is the ability to potentiate immunopathology in vaccinees upon exposure to wild-type virus (37), called vaccine associated enhanced disease (VAED). The theoretical molecular mechanism for this phenomenon is 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 (T helper) cell response (38) (39) (40). It is anticipated that the design of the candidate CoV2 preS dTM antigen selected for this study will promote generation of robust neutralizing antibodies over binding but non-neutralizing antibodies, based on data generated with other coronavirus vaccine antigens (13) (30). The inclusion of adjuvanted formulation is anticipated to further enhance the magnitude of neutralizing antibody responses and induce balanced Th1/Th2 cell responses (41) (31). Taken together, these strategies mitigate by design the theoretical risks of immune enhancement of viral infection. Based on the primary analysis of VAT00008 Stage 1 and Stage 2, no evidence of VAED was found.

The clinical development plan gives priority to generating data in adults given the higher medical and public health need in this population compared to the pediatric population; pediatric studies are proposed to be de-linked from the critical path to first authorization/approval. Importantly, the Phase III study is designed to be pragmatic to maximize representation of a broader population by minimizing exclusionary eligibility criteria and allowing the participation of individuals with a range of medical conditions including controlled human immunodeficiency virus (HIV) infection, Hepatitis B, Hepatitis C, and conditions associated with an increased risk of severe COVID-19. It is also designed to be inclusive of other subpopulations affected by COVID-19, including older adults as well as ethnic and racial minorities.

The clinical development plan for CoV2 preS dTM-AS03 vaccine began with a Phase I/II study (VAT00001) in adults with the goal of identifying a formulation, antigen dose, and a dosing schedule for further development. In the VAT00001 study, the safety and immunogenicity of a low-dose and high-dose antigen formulation corresponding to effective antigen doses of 1.3 µg and 2.6 µg, respectively, of purified recombinant SARS-CoV-2 S-protein (from the prototype

D614 variant) with AF03 and AS03 adjuvant administered either as a single injection or 2 injections 21 days apart are being evaluated. Interim results of the VAT00001 study support the selection of the AS03 adjuvant system and a 2-injection schedule but also indicate that further optimization of the antigen formulation and dosage is needed. Data from the VAT00001 study informed the design of a Phase II study (VAT00002) aiming at selecting a suitable antigen dose adjuvanted with AS03 in a 2-injection schedule for further progression to this Phase III study.

In the Phase II (VAT00002 [NCT04762680]) dose-finding, safety and immunogenicity study, 5◦µg, 10◦µg, and 15◦µg of the pre-S antigen dose in combination with AS03 adjuvant was evaluated to select an antigen dose to progress to Phase◦III. Interim results on safety and immunogenicity from the study were used to select the 10 µg dose for the monovalent D614 vaccine to be tested in Stage 1 of the Phase III study; and for Stage 2 of the Phase III study with the bivalent D614 + B.1.351 vaccine, a 5 µg (D614 component) + 5 µg (B.1.351 component) antigen dose.

In addition, an investigator sponsored study, the Study VAT000013 - COVIBOOST, was conducted to compare an approved mRNA booster vaccine, CoV2 preS dTM AS03 (B.1.351), and CoV2 preS dTM AS03 (D614) booster vaccines (42). VAT00013 study is an ongoing randomized, single-blinded, multicenter, Phase III study sponsored by the Clinical Research and Innovation Department (DRCI) of Assistance Publique – Hôpitaux de Paris (APHP) and conducted in France. This study is assessing immunogenicity and reactogenicity of a booster dose of the 3 vaccines in adults aged 18 years or older who received a 2-dose primary series of Pfizer/BioNTech vaccine. This study provides evidence for the effectiveness of the Beta-containing vaccine by comparing the immunogenicity of a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine to the approved Pfizer/BioNTech booster vaccine, which is based on the D614 ancestral strain.

2.1 Study Rationale

New, highly transmissible SARS-CoV-2 VOCs have emerged and are spreading globally. The Alpha (B.1.1.7) variant first identified in the UK has been shown to be more transmissible and has since been detected in many other countries around the world (43). Other VOCs have emerged which were first identified in South Africa (Beta [B.1.351] variant), Brazil (Gamma [P.1] variant), and India (Delta [B.1.617.2] variant) and a VOC (Omicron [B.1.1.529]) and have now been detected in other countries. A key question is whether currently approved and available COVID-19 vaccines will be able to protect against infection or disease from these variants. Recent preliminary data using an adjuvanted protein sub-unit vaccine (Novavax) and the ChAdOx1 nCoV-19 vaccine (AZD1222 [Oxford University/AstraZeneca]) showed lower efficacy against mild to moderate COVID-19 in South Africa where the Beta (B.1.351) variant predominated compared to the efficacy observed for these vaccines in studies conducted in the UK (5) (6) (7). However, data from the Ad26CoV2.S vaccine (Janssen) showed efficacy against symptomatic disease in South Africa suggestive of some evidence for the prototype vaccines to confer protection against the Beta (B.1.351) variant. Sera from individuals immunized with prototype COVID-19 vaccines show an ability to neutralize the variants but to a lesser extent than the prototype strain (44) (45). This decrease in neutralization is higher against the South African Beta (B.1.351) variant which has a characteristic E484K mutation in the receptor-binding domain along

with other mutations in the N-terminal domain of the S protein and highest against Omicron (B.1.1.529). These findings have led to the development of variant strain vaccines and regulatory guidance for the development of vaccines against the variant strains for products that have already demonstrated efficacy with the prototype vaccines (46). There has been particular emphasis on developing variant strain vaccines to protect against the Beta (B.1.351) variant. Ongoing evolution of SARS-CoV-2 variants, especially in light of the growing prevalence of vaccination and the selection pressure that this may exert raises the strong public health requirement for SARS-CoV-2 vaccines, including those protective against emergent VOCs.

This Phase III study will assess efficacy, safety, and immunogenicity of two CoV2 preS dTM-AS03 vaccines (monovalent and bivalent) in adults 18 years of age and older with 2 stages. In Stage 1, the AS03 adjuvanted monovalent vaccine with the prefusion S protein from the prototype (D614) variant will be evaluated against a placebo control. In Stage 2, the AS03 adjuvanted bivalent vaccine with the prefusion S protein from the prototype and South African Beta variant (D614 + B.1.351) will be assessed against a placebo control. The goal of this study is to generate data required for approval of each of the vaccines for use in prevention against SARS-CoV-2 infection and disease in adults. The data collected during this study are planned to support future development in other populations (eg, pediatrics, pregnant women). Based on the interim results from this study, participants in the Placebo group will be offered to participate in an unblinded Crossover / Booster design. Both participants in the Placebo and Vaccine groups will also be offered to receive Sanofi's investigational CoV2 preS dTM-AS03 monovalent (B.1.351) vaccine to boost the immune response ≥ 4 months post-last dose of the primary vaccination series.

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. The virus has been detected in 192 countries/regions and led to significant morbidity, mortality, and economic impact (3). 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 (also called social distancing) has had profound economic consequences. Safe and effective vaccines with sufficient supply would be vital to address the significant medical and societal burden caused by the pandemic.

The CoV2 preS dTM-AS03 vaccines developed by Sanofi utilize a recombinant protein approach in combination with an oil-in-water adjuvant, AS03 provided by GlaxoSmithKline (GSK). The CoV2 preS dTM-AS03 vaccines belong to the pharmacotherapeutic group of "covid-19 vaccines".

The vaccines contain 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 monovalent and bivalent CoV2 preS dTM vaccines and the AS03 adjuvant are provided in the respective Investigator's Brochures (IBs).

Nonclinical Studies (monovalent vaccine with the prefusion S protein from the D614 prototype)

The nonclinical studies provided an assessment of vaccine immunogenicity in mice and in NHPs. The studies indicated that the CoV2 preS dTM vaccine formulated with either AF03 or AS03 induced high S-specific immunoglobulin G (IgG) and SARS-CoV-2 neutralizing responses in mice and NHPs, with evidence of a potent adjuvant-effect of AF03 and AS03 as well as a robust boost-effect after the second injection. Humoral responses were generally similar or higher than levels observed in human convalescent sera. Cell-mediated immune (CMI) responses suggested a mixed Th1/Th2 profile, with no evidence of Th17 responses. These studies supported the first-in-human Phase I/II study.

Nonclinical safety studies were performed in rabbits to support the first-in-human Phase I/II study. A single or repeated dose (3 doses) IM injection(s) of CoV2 preS dTM at an effective antigen dose level of 4.2 µg/dose alone or adjuvanted with AS03 or AF03 was well tolerated in rabbits. Administration of CoV2 preS dTM with AS03 adjuvant resulted in transient and non-adverse changes in hematology, coagulation and clinical chemistry parameters indicative of a transient acute phase response/inflammation. These changes correlated with non-adverse histopathology findings of increased severity of acute/subacute to subacute/chronic mixed cell inflammation at the injection site and in the overlying skin of animals administered CoV2 preS dTM with adjuvant. Animals injected on 3 occasions also showed increased lymphoid cellularity in the spleen (correlating with increased spleen weights) and lymph nodes. After the 2-week recovery period (single or repeated doses), the inflammation was still present at the injection site(s), but was more chronic in nature as expected with the healing process and was associated with vacuolated macrophages in animals administered CoV2 preS dTM with AS03; there was also increased lymphoid cellularity in the iliac and sacral lymph nodes in animals administered CoV2 preS dTM with either adjuvant. These changes were expected, being consistent with those usually observed following injection of an adjuvanted vaccine. Furthermore, a second repeated-dose toxicity study (Study No. 5003591) was conducted with 2 IM injections (ie, same number of injections to be administered to humans) 2 weeks apart in New Zealand White rabbits using a new product batch to support the bridging between formulations tested in the Phase I/II study and formulations more advanced in product development. The study design was similar to that of the initial toxicology study.

Vaccine efficacy studies were also performed in NHPs and hamsters. In one NHP study (CoV2-01_NHP), Rhesus macaques (6/study group) immunized twice on D0 and D21 either with 2 antigen-doses of CoV2 preS dTM formulated with AS03 or 1 dose of non-adjuvanted CoV2 preS dTM, and challenged 28 days post-dose 2 with 10^6 PFU of SARS-CoV-2 (D614) by both intranasal and intratracheal routes, animals administered both AS03-adjuvanted vaccine formulations were protected against viral replication in the lungs and lung pathology. In another NHP study (CoV2-04-NHP) with 24 Rhesus macaques (8/study group), using a formulation with an effective S antigen dose of 4 µg or 12 µg with AS03 adjuvant to assess immunogenicity and efficacy against SARS-CoV-2 viral challenge was performed. In addition, the ability of the vaccine to elicit cross-neutralization antibodies against Alpha (B.1.1.7), Beta (B.1.351), Gamma (B.1.1.28 or P.1), and Epsilon (B.1.429) SARS-CoV-2 virus variants was evaluated in NHP samples using the lentivirus-based pseudo-neutralization assay.

Both vaccine doses conferred robust protection against viral replication in the lower and upper airways after a challenge with a virulent viral stock (NR-53780 BEI stock). Strong reduction of

viral replication was demonstrated on D02 and D04, with a trend for a higher reduction in the high dose vaccine group. The pathology and inflammation in the lungs induced by infection 7 days post-challenge was clearly reduced in the immunized Rhesus macaques, and no increase in inflammatory cytokines or chemokines was observed. At both low and high doses, the AS03-adjuvanted vaccine elicited high humoral (binding, functional and neutralizing antibodies) and cellular (Th1/Th2 balanced S-specific cytokine responses and Tfh cells 2 weeks post-boost) responses. The high immunogenicity and efficacy demonstrated in Rhesus macaques using 4 and 12 µg effective doses (CoV2-04_NHP study) supported the VAT00002 Phase II dose-ranging clinical trial assessing 5 µg, 10 µg, and 15 µg of CoV2 preS dTM vaccine antigen adjuvanted with AS03, and supports the VAT00008 Phase III Stage 1 clinical trial with the selected human dose. With regards to the emerging virus variants Alpha (B.1.1.7) and Epsilon (B.1.429), no reduction in neutralization antibody titers were observed in the NHP studies with the AS03-adjuvanted CoV2 preS dTM vaccine. However, a significant decrease was observed in the antibody titers against the Gamma (B.1.1.28 or P.1) and Beta (B.1.351) variants, with a level of reduction consistent with that described for other vaccines (47). The data suggest that the parent D614 vaccine has the ability to induce antibodies that can neutralize most virus variants circulating in Europe and the US including Alpha (B.1.1.7) and Epsilon (B.1.429).

In addition, vaccine efficacy was evaluated in Golden Syrian hamsters (*Mesocricetus auratus*) showing AS03-adjuvanted vaccine was able to confer protection against viral replication in the lungs and upper respiratory tract.

Previous Experience in Humans (monovalent vaccine with the prefusion S protein from the D614 prototype)

The first-in-human study, VAT00001, is a randomized, parallel group, placebo-controlled, observer-blind, dose-ranging, multi-center study (35). The study objectives were to evaluate the safety and immunogenicity of the monovalent CoV2 preS dTM candidate vaccine (D614) administered alone or in combination of either AS03 or AF03 adjuvant by IM route in participants in the US with the goal of selecting a formulation, antigen dose, and an injection schedule. The targeted quantities of the CoV2 preS dTM antigen per vaccine dose were 5 µg for the low-dose formulation and 15 µg for the high-dose formulation. However, the effective dose levels administered in a 0.5 mL vaccine dose in this study were 1.3 µg (LD) and 2.6 µg (HD) of functional SARS-CoV-2 preS protein. The differences between the targeted and the effective dose levels correspond to an excess HCP content in the clinical materials (recalculated HCP content, 3.7 µg and 12.4 µg).

Two cohorts of participants were enrolled, ie, Cohort 1 receiving one injection at Day (D)01 and Cohort 2 receiving 2 injections, the first at D01 and the second at D22. Each cohort was separated into 2 age subgroups (18 through 49 years and 50 years of age and older). Four hundred thirty-nine participants 18 years of age and older (299 adults 18 through 49 years of age and 140 adults 50 years of age and older) received at least 1 dose of either a low-dose antigen formulation [effective dose of antigen 1.3 µg]) with either AF03 or AS03 adjuvant; or a high-dose S antigen formulation [effective dose of S antigen 2.6 µg]) with either AF03, AS03, or no adjuvant; or placebo.

Interim data showed that:

- A 2-injection schedule of the adjuvanted protein was necessary to induce neutralizing antibodies.
- The low-dose adjuvanted vaccine induced higher titers of neutralizing antibodies compared to high-dose unadjuvanted protein-alone vaccine demonstrating the benefit of the adjuvant.
- The CoV2 preS dTM antigen adjuvanted with AS03 induced higher titers of neutralizing antibodies compared to both the AF03 adjuvanted group and compared to the unadjuvanted groups with a 2-injection schedule.
- An antigen dose-response effect was observed with higher neutralizing antibody responses observed in the high-dose antigen groups compared to the low-dose antigen groups in the 2-injection schedule adjuvanted arms.

The high-dose group with AS03 administered in a 2-injection schedule induced the highest levels of neutralizing antibodies. However, even in the best performing vaccine group (2-injection schedule of high-dose + AS03), seroconversion rates were below 90% in all adults with lower rates in older adults (85% in 50 years and older, 62.5% in 60 years and older). The magnitude of neutralizing antibody responses was also lower in adults aged 50 years and older compared to the younger age group indicating the need for further optimization of the antigen formulation and dose, with doses higher than the effective high dose of 2.6 µg used in this study. In adjuvanted groups with the 2-injection schedule, there was no indication of a Th2-profile bias in the cell-mediated response with a consistent elicitation of Interferon-gamma responses.

There were no SAEs or AESIs considered related to the vaccine, no AEs leading to discontinuation nor immediate related reactions observed in the study at the time of the interim analysis. The frequency of solicited injection site and systemic reactions increased after the second dose, was higher in the adjuvanted groups compared to unadjuvanted groups and was higher in the younger age-group (18-49 years of age) compared to older adults. This reactogenicity was transient, self-limiting, non-serious and did not lead to study withdrawal of any participant. The frequency of Grade 3 systemic reactions was highest in the AS03-adjuvanted vaccine groups after the 2nd injection; 24% and 25% in the Low Dose and High Dose groups, respectively. The most frequent Grade 3 systemic reaction was malaise, reported in 17% of participants in each of the AS03-adjuvanted arms. Grade 3 fever was reported in 8.3% of participants in the high dose+AS03 arm and 3.8% in the low-dose +AS03 arm after the second injection. No Grade 3 systemic reactions were considered as serious and all resolved. This higher than expected reactogenicity is hypothesized to be due to higher than targeted content of HCP in the Phase I/II clinical material (14). The lower than expected immunogenicity in combination with the higher than expected reactogenicity observed in the Phase I/II study indicated that assessment of optimized antigen formulations (with higher antigen dose and lower HCP content) is necessary to select a formulation prior to progression to Phase III evaluation.

Therefore, a Phase II, randomized, modified double-blind, multi-center, dose-finding study (Original Cohort of VAT00002) conducted in the US and Honduras is ongoing in adults 18 years of age and older to evaluate the safety, reactogenicity, and immunogenicity of 3 different antigen

doses (effective doses of 5 µg, 10 µg, and 15 µg of CoV2 preS dTM antigen) with a fixed dose of AS03 adjuvant.

A 2-injection schedule with doses administered 21 days apart, as supported by data from the VAT00001 study, is being utilized in the VAT00002 study. Key interim safety, reactogenicity, and immunogenicity data from this Phase II study was used to decide on progression to Phase III and, for selecting an antigen dose formulation to progress to Phase III (VAT00008 and VAT00002 Supplemental Cohorts). The interim analysis occurred after availability of key data for reactogenicity up to 21 days post-injection 2 and neutralizing antibody responses against the homologous D614G variant 14 days post-injection 2.

A total of 722 participants were enrolled and randomized in Study VAT00002 with age stratification of 18 to 59 years (360 participants) and 60 years and older (362 participants).

Approximately 81% of the participants were from the US and 19% of participants were from Honduras. Approximately 22% of participants were from US minority racial groups (ie, Asian, Black or African American, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander) and 28% of participants were of Hispanic or Latino ethnicity, with similar proportions across study groups. Approximately 60% of participants presented with at least one high-risk medical condition with the proportion of participants with high-risk medical conditions similar across study groups.

Key interim data from the study showed that at D36 (14 days after the second injection), the proportion of SARS-CoV-2 naïve participants having 2-fold and 4-fold or higher rise in neutralizing antibodies against D614G was $\geq$ 95% in 18-59-year-old age-group and > 90% in 60 years and older age-group. No difference was observed across the study groups. GMT values of neutralizing antibodies against D614G were generally consistent, comparable to a panel of human convalescent sera and without clear evidence of a dose effect across treatment groups in the overall study population (18 years and older). No difference in GMTs were observed across treatment groups in 60 years and older age-group although an increase in GMTs were observed with higher antigen dose groups in 18-59-year-old age-group. The magnitude of neutralizing antibody responses was higher in 18-59-year-old age groups compared to the 60-year-old and older group (15).

Table 2.1: Pseudovirus neutralizing antibody titers to D614G variants at D36 in naïve adults

	Low Dose (5 µg)			Medium Dose (10 µg)			High Dose (15 µg)			Convalescent sera		
Age-group	**N**	**GMT**	**95%CI**	**N**	**GMT**	**95%CI**	**N**	**GMT**	**95%CI**	**N**	**GMT**	**95%CI**
All	119	2100	1616; 2729	129	2374	1832; 3076	124	2483	1920; 3210	79	2140	1543; 2967
18-59 years of age	53	2938	2155; 4007	58	3961	2795; 5612	54	4824	3637; 6399			
60 years and above	66	1604	1079; 2383	71	1563	1098; 2223	70	1487	1037; 2134			

Per-Protocol Analysis Set Naïve-D01+D22

In non-naïve adults, a single injection increased neutralizing antibody titers to levels above those observed after 2 injections in naïve adults in the overall study population.

For the interim analysis reporting period, there were no SAEs considered related to the vaccine, no AESIs, and no AEs leading to study discontinuation. Comparable frequency of MAAEs, unsolicited AEs and unsolicited adverse reactions was observed across treatment groups. Comparable frequency of solicited reactions including solicited injection site reactions and systemic reactions was observed across all treatment groups. In the overall study population (18 years of age and older), the frequency of Grade 3 injection site solicited reactions ranged from 7.1% to 9.7% and Grade 3 systemic solicited reactions ranged from 16.7% to 18.9% and was comparable across treatment groups. Higher frequency of solicited reactions of any grade and Grade 3 solicited reactions were observed in the 18-59 years of age group compared to ≥ 60 years of age group. There was an increased frequency and intensity of solicited reactions after the second injection compared to the first injection.

Injection site pain was the most frequently reported injection site reaction of any intensity and of Grade 3 intensity (ranged from 5.0% to 6.3%) in all treatment groups. The majority of injection site reactions occurred between D01 and D04 and resolved without intervention. The proportion of participants reporting solicited systemic reactions of any grade were highest for malaise (ranged from 58.0% to 60.6%), myalgia (ranged from 50.0% to 60.0%) and headache (56.1% to 57.1%) in all treatment groups. The majority of reactions occurred during the first 4 days from vaccination, lasted on average between 1-4 days, and resolved without intervention. The frequency of unsolicited AEs and unsolicited adverse reactions (ARs) was similar across treatment groups with a slight increase of Grade 3 unsolicited AEs in the 15 µg + AS03 group; most commonly reported unsolicited events were reactogenicity-like events (eg, fatigue, nausea, injection site pruritus [preferred terms]). Overall, a similar safety profile was observed across all

treatment groups with higher local and systemic solicited reactions observed after the second injection and in the younger age-group.

Supplemental Phase III Cohorts are being tested as part of VAT00002 study to allow the evaluation of the potential use of CoV2 preS dTM-AS03 to boost responses in individuals previously vaccinated with other platforms; for this purpose, the study is assessing the safety and immunogenicity of different formulations of the CoV2 preS dTM-AS03 vaccine, including monovalent (D614 and B1.351) and bivalent (D614 + B.1.351) formulations, for use as a universal booster. The study will also further evaluate the safety and immunogenicity of Beta (B.1.351) variant-containing vaccine formulation (CoV2 preS dTM-AS03 [B.1.351]) in the context of primary immunization of naïve, previously unvaccinated individuals. Interim analysis results from Supplemental Phase III Cohort 1, Cohort 2 (protein primed group), and comparator group of VAT00002 study showed that a single 5 µg dose of the CoV2 preS dTM-AS03 (D614) vaccine provided a robust boost to the neutralizing antibody (Ab) response among individuals primed with one of the four widely deployed priming vaccines (heterologous vaccine) or primed with homologous vaccine CoV2 preS dTM-AS03 (D614). Overall, no safety concerns were identified, nor any specific risk group identified for whom safety was of concern. Among participants receiving a 5 µg booster dose of the CoV2 preS dTM-AS03 (D614) vaccine, there was a favorable safety profile. The safety profile is consistent across all priming groups, except for an increase of reactogenicity with the homologous primed group. No safety issues were identified in subgroups (defined by age or the presence of a high-risk medical condition). These safety data are supportive of the use of CoV2 preS dTM (D614)-AS03 vaccine as a booster, regardless of priming vaccine.

The results of the primary analyses on efficacy in Stage 1 of the VAT00008 study showed that the efficacy against symptomatic COVID-19 in SARS-CoV-2 naïve adults, 14 days after the second injection was 57.9% [95.86% CI: 26.5; 76.7]. Although the vaccine efficacy point estimate was over 55%, the lower bound of the adjusted confidence interval was not above 30%; therefore, the primary endpoint of the study was not met.

The study was conducted in an epidemiological situation markedly distinct to the early stages of the pandemic. Most of the population (> 80%) was already infected at the time participants were recruited. This is reflected in the high rate of non-naïve participants identified in the study and limited the number of naive adults (primary efficacy population) recruited in the study. The fact that the study's naïve population was quite small resulted in a lower precision of estimate that ultimately contributed to missing the primary endpoint.

Interim analysis for a 2-dose primary series of 10 µg CoV2 preS dTM-AS03 (D614) vaccine given 21 days apart from Stage I of the VAT00008 study showed efficacy in preventing symptomatic COVID-19, severe COVID-19, hospitalized COVID-19, and death associated with symptomatic COVID-19 in 18 to 59 years of age. Data available for participants aged 60 years and older were limited and therefore insufficient to establish efficacy in this age group.

Vaccine efficacy against symptomatic COVID-19 with severity of moderate or worse 14 days after the second injection was 75.0%, with 3 cases in the vaccine group and 11 in the Placebo Group. Importantly, efficacy against severe COVID-19 was 100% with 4 cases in the Placebo Group and no cases in the Vaccine Group. VE against severe COVID-19 was also 100% after the

first injection in the naïve group including 10 cases in the Placebo Group and no cases in the Vaccine Group. Similar results were obtained for hospitalized COVID-19.

All 4 adjudicated severe COVID-19 cases after the second injection were in naïve participants, in the 18 to 64 years old group and with a high-risk medical condition (3 of them were obese).

In Stage 1 of VAT00008, no safety concern was identified neither in the overall population nor in subgroups (older adults, individuals with high-risk medical conditions, non-naive individuals). There was no safety concern with regards to anaphylaxis or VAED/vaccine-associated enhanced respiratory disease (VAERD).

Regarding reactogenicity, lower frequencies of solicited injection site and systemic reactions were observed after the second injection than after the first injection. Injection site pain was the most frequently reported injection site reaction in vaccine recipients, headache, myalgia and malaise were the most frequently reported solicited systemic reactions. Similar frequencies of solicited injection site reactions and solicited systemic reactions were observed in the 18 to 59 years age group and the 60 years and above age group.

No increase of frequency of SAEs or AESIs in the Vaccine group was observed compared to the Placebo Group. Frequency of MAAEs was similar in the Vaccine and Placebo Group. Also, when investigating the safety results from Stage 1 in subgroups (18 - 59 years versus ≥ 60 years age group, participants with high-risk medical condition versus participants without high-risk medical condition, participants SARS-CoV-2 naïve at baseline versus non-naïve participants at baseline), no safety concern was identified.

Nonclinical Studies (bivalent vaccine with the prefusion S protein D614 + B.1.351)

The bivalent vaccine was tested in an immunogenicity study in naive NHPs assessing the bivalent formulation at doses of 2.5 µg, 5 µg, and 10 µg per component adjuvanted with AS03 alongside the monovalent D614 and monovalent B.1.351 vaccines. Three weeks after the second vaccination, neutralizing and binding antibodies were observed in all macaques with all 3 antigen doses of the bivalent vaccine. The neutralizing antibody titers against the D614G strains induced by the bivalent vaccine were slightly lower to those induced by the monovalent D614 vaccine (2- to 3-fold lower and mainly in the low-dose group). Comparing the bivalent at 5 µg + 5 µg with monovalent D614 vaccine at 10 µg, the actual planned doses for VAT00008, the differences on D614 neutralizing antibody titers where not statistically significant suggesting limited immune interference at higher antigen doses and when comparing the same total antigen dose between the monovalent and bivalent vaccine. Neutralizing antibody titers against known VOCs (B.1.351, B.1.1.7, B.1.1.28, B.1.617.2, and B.1.1.529) were assessed in the study. Compared to the monovalent D614 vaccine, the bivalent vaccine induced much higher titers against the B.1.351 and B.1.1.28 variants, and comparable neutralization of the currently 2 most widely circulating B.1.1.7 and B.1.617.2 variants. Compared to the monovalent B.1.351 vaccine, the bivalent vaccine induced much higher neutralizing antibody titers against the parental D614 and D614G strains, as well as against B.1.1.7 and B.1.617.2 variants (16). These data generated in naïve NHPs showing balanced neutralization of all known VOCs to date with the bivalent vaccine (D614+B.1.351), limited interference against the D614G variant compared to the monovalent D614 vaccine support the evaluation of the bivalent vaccine in VAT00008 Stage 2.

The non-clinical studies showed that the bivalent CoV2 preS dTM-AS03 (D614+B.1.351)

induced strong neutralizing antibody responses against 4 known VOCs: Alpha (B.1.1.7), Beta (B.1.351), Gamma (B.1.1.28) and Delta (B.1.617.2) in naïve macaques (CoV2-06_NHP) with no evidence of significant interferences at doses of 5 µg and 10 µg for monovalent and bivalent vaccines. Evaluation of Omicron indicated a low but consistent neutralizing response against Omicron in macaques immunized with the bivalent vaccine as a primary series. Six months follow up of the Ab responses showed that, after an initial decline, the neutralizing antibody titers stabilized between 2 and 3 months after the prime. In a separate study in hamsters, the AS03-adjuvanted bivalent vaccine (D614+B.1.351), as well as the 2 monovalent vaccines (D614-AS03 and B.1.351-AS03) conferred protection against body weight loss, viral replication in lungs, and lung pathology induced by D614G, Alpha (B.1.1.7), and Beta (B.1.351) variants.

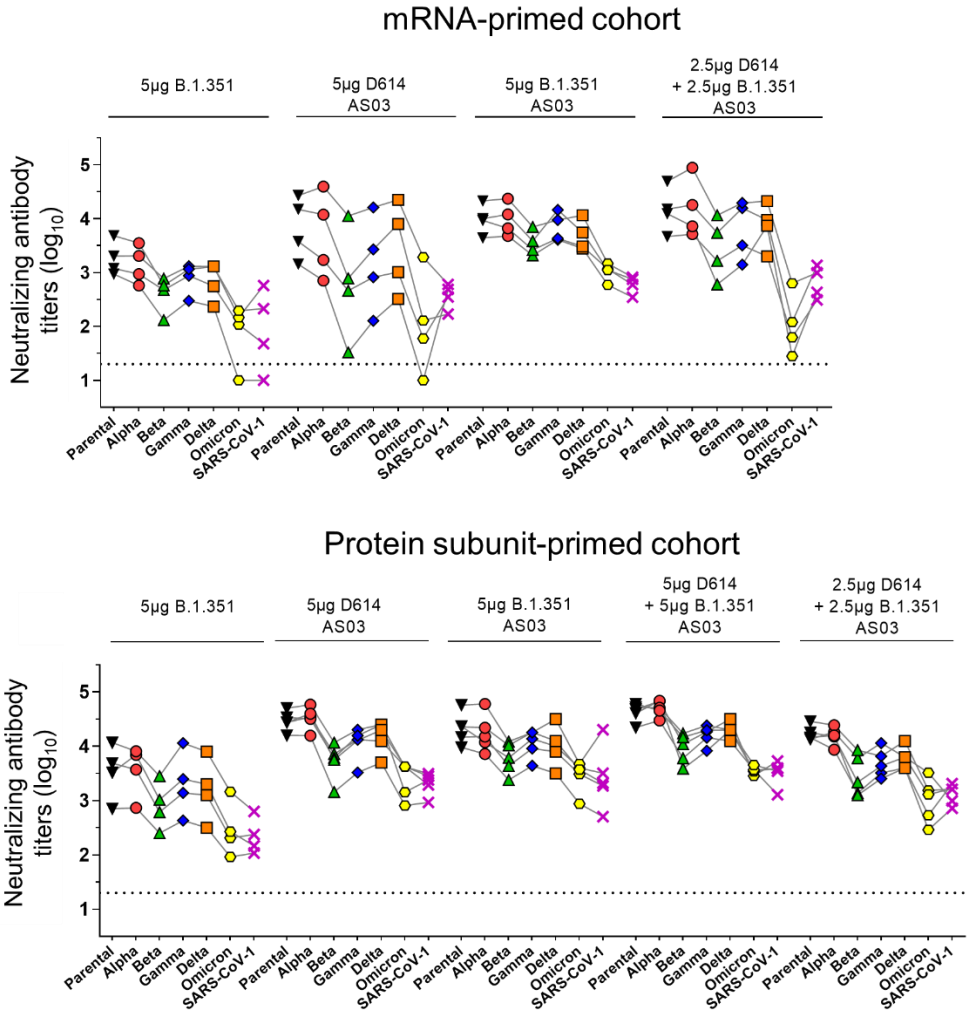
Based on available data, the results of the nonclinical studies demonstrated immunogenicity, efficacy and an adequate safety profile of the CoV2 preS dTM AF03- or AS03-adjuvanted formulations (D614 and B.1.351 monovalent, as well as D614+B/.1.351 bivalent) supporting their evaluation in clinical studies.

Non-human primate studies were conducted with the objective to document the immunogenicity of CoV2 preS dTM-AS03 (D614) and vaccine formulations containing the B.1.351 spike antigen (monovalent B.1.351 and bivalent D614 + B.1.351) when used as booster after a primary vaccination with different vaccine platforms.

Booster immunization was evaluated in cynomolgus macaques immunized with COVID-19 mRNA-lipid nanoparticle candidates developed by Sanofi (CoV2-07_NHP, mRNA-primed cohort) and in rhesus macaques immunized with CoV2 preS dTM-AS03 vaccine (CoV2-08_NHP, subunit-primed cohort). Both cohorts received the booster injection about 7 months after the primary vaccination.

In the mRNA-primed cohort (CoV2-07_NHP study), 16 Mauritian cynomolgus macaques (8 males and 8 females, 4 to 10 years of age), previously vaccinated with COVID-19 mRNA-lipid nanoparticle vaccine candidates (48) were randomized into 4 groups of 4 macaques. Only animals which developed a neutralizing Ab response against the D614 virus 2 weeks after the primary vaccination (D35) were selected for the study. In the subunit-primed cohort (CoV2-08_NHP study), 24 Indian rhesus macaques (males, at 2.7 to 4 years of age), previously immunized with CoV2 preS dTM-AS03 (Phase I/II or intermediate Phase III manufacturing process), were randomized into 5 groups of 4 to 5 macaques. All macaques developed D614 neutralizing antibody titers on D35 and were included in the booster study.

Figure 2.1: Individual PsV neutralizing antibody titers against VOC and SARS-CoV-1 after a late booster immunization in mRNA-primed (top) and subunit-primed (bottom) macaques



The data indicate that, in vaccine-primed macaques, a third injection with the various vaccine formulations (unadjuvanted monovalent B.1.351, AS03-adjuvanted monovalent D614 and B.1.351 or bivalent), induced a strong recall of the initial neutralizing Ab response against the D614 strain and extended the neutralization to the VOC. A trend for higher responses against Beta (B.1.351) and Gamma (B.1.1.28 or P1) variants was observed with vaccines containing the B.1.351 spike antigen (monovalent or bivalent), with mean neutralizing Ab against VOC greater than 3.5 log10 in both cohorts 2 weeks post-booster and mean neutralizing antibody titers against D614G greater than 4.0 log10.

Importantly, the antibody titers measured weekly post-booster (S-binding and neutralizing Ab against D614G and B.1.351) were stable from D07 to D28 and declined slightly in the following 5

months at a rate around 0.5 log10/100 days, irrespective of the vaccine formulations. At 6 months post-booster, Ab responses tended to stabilize.

Given the high neutralizing antibody titers against VOC, including Omicron (B.1.1.529), induced by the various booster vaccines, the slow Ab decay, and the direct correlation between circulating neutralizing Ab and vaccine efficacy (49) (50) (51),the data suggest that the monovalent Beta booster vaccine provide similar performance as the monovalent D614 booster vaccine.

Clinical Studies (bivalent vaccine with the prefusion S protein D614 + B.1.351)

The results of the primary analyses on efficacy in Stage 2 of the VAT00008 study for the bivalent CoV2 preS dTM-AS03 (D614+B.1.351) vaccine showed vaccine efficacy against symptomatic COVID-19 in all participants, regardless of prior SARS-CoV-2 infection, with a vaccine efficacy of 64.7% (95% CI: 46.6; 77.2) meeting the primary efficacy objective (ie, to obtain a point estimate of VE > 50%, as calculated by the incidence rate ratio [IRR], with the lower bound of the 95% CI > 30%).

The majority of cases were BA.1 and BA.2 Omicron subvariants. In all participants regardless of prior SARS-CoV-2 infection, the bivalent CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine showed an efficacy against symptomatic COVID-19 caused by Omicron variant of 72.5% (95% CI: 49.5; 86.0). Although sequencing results were available in approximately 44% of the cases in the mFAS-PD2 (ie, unknown variants and those that produced non-valid results), sensitivity analyses that considered them as caused by the Omicron variant showed that the VE was 63.1% (95% CI: 43.9; 76.2).

Most of the participants in VAT00008 had evidence of prior SARS-CoV-2 infection at the time of enrollment. This is reflected in the high rate of non-naïve participants identified in the study. The vaccine efficacy against symptomatic COVID-19 in these non-naïve participants was high and similar both after the first and second dose, 75.9% (95% CI: 63.9; 85.6) and 75.1% (95% CI: 56.3; 86.6), respectively. In Non-Naïve participants, the VE against symptomatic COVID-19 caused by Omicron after the second dose was 93.9% (95% CI: 75.9; 99.3). Following sensitivity analysis, the VE decreased, but was still high. Efficacy against symptomatic COVID-19 due to Omicron variant in non-naïve participants was 73.8% (95% CI: 53.9; 85.9). In naïve participants, the VE post-dose 1 against symptomatic COVID-19 was 38.2% (95% CI: 0.5; 62.2) and the VE post-dose 2 was 30.9% (95% CI: -39.3; 66.7).

Overall, there was no death associated with COVID-19; and in both the vaccine and placebo groups, there was a limited number of severe COVID-19 (3 cases and 2 cases, respectively) and hospitalized symptomatic COVID-19 (0 cases and 2 cases, respectively). Also, there were few cases of symptomatic COVID-19 with severity of moderate or worse.

As was the case for the > 60 years age group in Stage 1, the number of COVID-19 cases was limited as well in Stage 2 which precluded any valid conclusion on the efficacy of the vaccine in this age group. In Stage 2 of the study, out of the 13 506 enrolled and randomized, only 827 participants were enrolled and randomized to the ≥ 60 years age group. There were only 6 cases of symptomatic COVID-19 in the population used for VE analyses post-dose 2 among participants aged ≥ 60 years.

Primary series vaccination with 10 µg of bivalent CoV2 preS dTM-AS03 (D614 + B.1.351) was found to be well tolerated and with an acceptable safety profile in adults 18 years of age and older.

The frequency of solicited reactions was higher in vaccine recipients (57.8% of participants) than in placebo recipients (40.9% of participants) with injection site pain, headache, malaise, and myalgia being the most frequently reported solicited reactions. In the vaccine group, the proportion of participants reporting at least 1 solicited reaction was higher in the naïve than in the non-naïve participants with 64.0% compared to 55.3% of participants. In the placebo group, a similar trend was observed with 43.8% compared to 37.6% of participants reporting at least 1 solicited reaction in the naïve and non-naïve groups, respectively.

The rate of immediate AEs and ARs was similar between the vaccine and the placebo groups. The frequency of unsolicited AEs and unsolicited ARs was similar between the vaccine (AEs: 6.3%; ARs: 0.8%) and placebo (AEs: 8.1%; ARs: 0.7%) recipients, with comparable frequency between the first and second injection. There were no related SAEs, AESIs, or death. No SAEs of anaphylactic shock/shock, narcolepsy, myocarditis, pericarditis, or thrombosis with thrombocytopenia syndrome were reported. In the naïve population, no evidence of VAED was found when analyzing severity, and the number and duration of symptoms in the vaccine and placebo groups.

2.3 Benefit/Risk Assessment

Neutralizing antibodies specific for the S protein of other coronaviruses have been shown to be associated with protection in humans. In animal models, neutralizing and IgG binding antibodies specific to the S protein of SARS-CoV-2 induced by vaccination have been shown to be associated with protection against challenge. Specifically, a recent investigation showed that adoptive transfer of purified IgG from convalescent macaques protects naïve recipient Rhesus macaques against SARS-CoV-2 challenge in a dose dependent fashion, with relatively low neutralizing antibody titers being sufficient to protect against SARS-CoV-2 in this model (52). High neutralizing antibody titers (500 with the assay utilized in the study) achieved full protection and low-moderate titers (50 with the assay utilized in the study) attained partial protection in macaques. These titers were described by the authors as readily achievable by vaccination in humans. These data suggest the sufficiency of neutralizing antibodies for protection in the absence of cellular and innate immune responses, although the role of other immune components in protection against SARS-CoV-2 continue to be elucidated. Other animal studies provide consistent evidence of the primary roles of humoral immune responses in protection against SARS-CoV-2 infection and/or disease, including in the evaluation of immunological biomarkers associated with protection in Rhesus macaques for DNA-based or Adenovirus-vectored-based reporting neutralizing antibody titers and other functional antibody responses as correlates of protective efficacy (53) (54), as well as studies showing that potent RBD-specific monoclonal antibodies can protect against SARS-CoV-2 challenge in macaques (55) (56).

Two COVID-19 mRNA vaccine candidates, BNT162b2 from Pfizer and BioNTech, and mRNA-1273 from Moderna, 2 viral vector vaccines, ChAdOx1-nCOV-19 from Oxford University/AstraZeneca and Ad26.COV2-S from Janssen; and 3 adjuvanted protein sub-unit vaccines (from Novavax, Clover and Medicago) have reported efficacy against COVID-19 illness and severe disease in their Phase III clinical studies (57) (58) (59) (60). Efficacy data on these vaccines from other manufacturers was collected during time periods of the COVID-19 pandemic that predated the Omicron variant wave and even the previous Delta variant wave.

Recent preliminary data have shown a decrease in vaccine efficacy in regions where the Beta (B.1.351) variant is prevalent. Data using an adjuvanted protein sub-unit vaccine (Novavax) and the ChAdOx1-nCoV-19 vaccine (AZD1222 [Oxford University/AstraZeneca]) showed lower efficacy against mild to moderate COVID-19 in South Africa where the Beta (B.1.351) predominates compared to efficacy in the UK (5) (6) (7). However, data from the Ad26.COV2.S vaccine (Janssen) show high efficacy against severe disease in South Africa. Sera from individuals immunized with COVID-19 vaccines show an ability to neutralize the variants but to a lesser extent than the prototype strain. This decrease in neutralization is highest against the South African Beta (B.1.351) variant which has a E484K mutation in the receptor-binding domain of the Spike (S) protein. Thus, there is a potential reduction in benefit of the D614 vaccines against newly emergent variants. The development of the bivalent vaccine with the D614 and B.1.351 variant is expected to provide greater benefit through protection against variants particularly in light of data showing improved cross-neutralization of the variants from Beta (B.1.351) convalescent sera compared to cross-neutralization of variants from D614 convalescent sera (57) (58) (59) (60).

Preclinical studies with AS03-adjuvanted CoV2 preS dTM monovalent (D614) vaccine in mice and NHPs showed an increase in magnitude of neutralizing antibody response and in NHPs protection against SARS-CoV-2 challenge compared to unadjuvanted vaccine along with a balanced Th1/Th2 profile. Interim data in humans from the Phase I/II study show that the neutralizing antibody titers observed after 2 doses of low dose antigen+AS03 were higher than following 2 doses of high-dose antigen without adjuvant demonstrating the benefit of the adjuvant in increasing the magnitude of immune response and potential dose-sparing effect. Interim data also showed induction of neutralizing and binding antibodies in adjuvanted vaccine groups with the highest responses induced following 2 injections of the high-dose+AS03 vaccine (35). Interim data from the Phase II study (VAT00002 Original Cohort) showed high proportion of participants with a 2-fold and 4-fold or greater rise in antibody titers after 2 injections in both younger and older naïve adults with similar proportions observed across the different antigen dose groups. The magnitude of neutralizing antibodies was comparable to a panel of human convalescent sera with neutralizing antibodies against D614G being generally consistent without clear evidence of a dose effect across treatment groups in the overall naïve study population. A pattern of higher levels of neutralizing antibody responses with higher antigen doses was observed in younger adults; this pattern was not observed in older adults. These observations were also observed with binding antibodies of the S-antigen.

A potential theoretical risk with coronavirus vaccines is the ability to potentiate immunopathology in vaccinees upon exposure to wild-type virus (37), called VAED. The potential for a coronavirus vaccine to exacerbate disease is a theoretical concern that has not been documented in humans to date, and hence will be explained as a theoretical risk in the Informed Consent document. The frequency and severity of COVID-19 among participants in the study will be actively surveilled for study halting rules. From the primary analysis of VAT00008 Stage 1 and Stage 2, no evidence of VAED was found.

Other potential risks, which apply to COVID-19 vaccines using other platforms than the study vaccines, are blood clotting, myocarditis, and pericarditis. Thrombosis with thrombocytopenia syndrome, myocarditis, and pericarditis represent AESIs in the study accordingly. However, these events were not included into the Risk Management Plan (RMP) as potential risks of the study

vaccines because, based on currently available evidence, no safety concern was identified for the CoV2 preS dTM vaccine.

Myocarditis and pericarditis have been reported following vaccination with mRNA COVID-19 vaccines, mainly in males under the age of 40 years within 14 days after a second dose. However, cases have also been reported in older males, in females, and following other doses. The observed risk is highest in males 12 to 17 years of age. While some cases required intensive care support, available data from short-term follow-up suggest that symptoms resolve in most individuals with conservative management. Information is not yet available about potential long-term sequelae (61) (62). Myocarditis and pericarditis events have also been detected in clinical studies and post-authorization surveillance of the Novavax COVID-19 vaccine, which is manufactured using a protein/adjuvant platform and a different adjuvant system than the CoV2 preS dTM vaccine (63). Based on this potential risk, participants will be advised to seek immediate medical attention and notify study site staff if symptoms compatible with myocarditis or pericarditis occur following vaccination. Participants with events of myocarditis and/or pericarditis will be discontinued from further vaccination and followed for subsequent visits as per the protocol for safety, immunogenicity, and efficacy endpoints.

AS03 is an oil-in-water emulsion containing α-tocopherol and squalene. To support the licensing of A/H1N1 pandemic influenza vaccines, Pandemrix® and Arepanrix®, in the elderly large clinical studies were carried out in participants aged 61 years and above (64). Additional clinical studies were conducted in adults ≥ 18 years of age, children from 6 months to 18 years of age, and older adults ≥ 65 years of age as well as post-licensure safety studies (32). All of these studies were conducted with vaccine antigens derived from the A/H1N1, H5N1, H7N1, and H9N2 strains. 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) (65). A Phase III efficacy study evaluated efficacy of AS03-adjuvanted TIV compared to unadjuvanted TIV among 43 695 volunteers 65 years of age or older (66). Furthermore, it is estimated that approximately 90 million doses of AS03-adjuvanted H1N1 vaccines were administered post-licensure in the context of H1N1 pandemic control (32). Taken together, these studies and post-licensure data showed that AS03 enhanced antibody and T cell responses with an acceptable safety profile.

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 (67) (68). 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 present in the influenza vaccines used at the time 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"* (69) (70) (71) (72) (73) (74) (75) (76) (77). The mechanism for this increased risk of narcolepsy remains to be fully understood. Current mechanistic hypotheses suggest that it is not likely linked directly to AS03, but more likely to the antigen and/or the circulating A/H1N1/pdm09 influenza virus. As a precautionary measure in the context of its COVID-19 vaccine candidate collaborations with other

companies using GSK's AS03 adjuvant, GSK expanded its research plan with Stanford University to evaluate whether the same potential mechanistic model hypothesized for influenza (potential antigen mimicry between proteins from the H1N1 pandemic virus itself and hypocretin) might apply in the context of COVID-19 vaccine candidates containing the SARS-CoV-2 spike protein. The research plan is currently ongoing, and the preliminary data currently available suggests that vaccination with spike protein does not evoke a cross-reactive anti-hypocretin (HCRT) response in COVID-19 convalescent subjects who carried the Human Leucocyte Antigen (HLA) DQB1*0602 (called DQ0602) gene. In the absence of clear evidence of functional cross-reactivity between spike protein and HCRT peptides, the possibility of molecular mimicry and its pathogenic consequences remains highly hypothetical. While the experiments and the conclusions drawn from the experiments conducted so far should not be considered as a predictive tool for narcolepsy pathogenesis, they are in line with the absence of any validated safety signal for narcolepsy following the mass COVID-19 vaccination worldwide and the absence of a reported increased incidence of narcolepsy following a SARS-CoV-2 infection.

Based on the theoretical concern that vaccination with an adjuvanted vaccine containing potent immunostimulants may interfere with immunological self-tolerance, potential Immune-Mediated Diseases (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 (see Table 10.4 for a full list).

Interim analysis for a 2-dose primary series of 10 µg CoV2 preS dTM-AS03 (D614) vaccine given 21 days apart from Stage I of the VAT00008 study showed efficacy in preventing symptomatic COVID-19, severe COVID-19, hospitalized COVID-19, and death associated with symptomatic COVID-19 in 18 to 59 years of age. Data available for participants aged 60 years and older were limited and therefore insufficient to establish efficacy in this age group. The CoV2 preS dTM-AS03 vaccine benefit/risk profile is expected to be positive based on available evidence. While study participants may or may not accrue any benefit from receiving the investigational/non-authorized vaccines in this study, study participation and study conduct is considered fundamental from the societal perspective towards the goal of demonstrating that the vaccine candidates will be useful tools 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-AS03 vaccines offer the potential of protection against SARS-CoV-2 infection, COVID-19 disease and its complications with a potential benefit of reduction of the associated burden of disease in the study population over 18 years of age. In addition, vaccination has the potential to reduce viral burden and viral shedding which may have potential indirect benefit in reduction of viral transmission and disease burden in the community.

More detailed information about the known and expected benefits and risks, reasonably expected AEs, the potential risks, and uncertainties of CoV2 preS dTM-AS03 may be found in the monovalent and bivalent CoV2 preS dTM-AS03 IB.

2.3.1 Risks from Study Participation

The potential risks of clinical significance and risk management are summarized in Table 2.2.

Table 2.2: 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-AS03		
Anaphylactic reactions	Class-effect for all vaccines (even non-adjuvanted).	Observation period after vaccination for early detection and treatment. Risk management includes also exclusion criterion E01 (see Section 5.2). No safety concern was identified with regards to anaphylactic reactions based on review of available study data (primary and booster vaccination).
Enhanced COVID-19/VAED	A theoretical concern with coronavirus vaccines is VAED. This is the potential (hypothetical) increased disease severity in vaccinees upon exposure to wild-type virus (37). This disease 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 (38) (39) (40). Available data from clinical and non-clinical studies, including from other COVID 19 vaccines from different platforms, do not indicate a risk of vaccine enhanced disease (78) (24) (27). However, considering limited long-term safety data and in the absence of effectiveness data, the available evidence is not yet sufficient to fully rule out VAED including	During the informed consent process, the participants enrolling in the study were informed of this potential risk. COVID-19 episodes and severity of illness are monitored with active and passive surveillance for the duration of the study. The candidate CoV2 preS dTM antigen selected for this study is expected to promote generation of robust neutralizing antibodies over binding (but non-neutralizing) antibodies, based on data generated with other coronavirus vaccine antigens (13) (30). The adjuvanted formulation is anticipated to further enhance the magnitude of neutralizing antibody responses and induce balanced Th1/Th2 cell responses (39) (49). Data from NHP studies and interim data from the Phase I/II study show induction of neutralizing antibody titers after 2 doses of antigen + AS03 adjuvant shows no evidence of Th2 bias and consistent IFNγ responses. Thus, these strategies (antigen design and adjuvant) mitigate by design the theoretical risks of immune enhancement of viral infection. No safety concern was identified with regards to VAED/VAERD based on review of available clinical study data (primary and booster vaccination).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
	VAERD as a safety concern. Thus, it remains an important potential risk. Risk not applicable for the booster vaccination: Vaccine Associated Enhanced Disease (VAED) including Vaccine Associated Enhanced Respiratory Disease (VAERD) is a risk in the naïve population as per Brighton Collaboration case definition. Since the booster dose is administered in already vaccinated individuals, this potential risk is not considered for the booster vaccination.	

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 adjuvanted vaccines. 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 over the duration of the study. No safety concern was identified with regards to pIMDs based on review of available study data (primary and booster vaccination).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
Myocarditis/pericarditis	An increased risk of myocarditis or pericarditis has been observed with mRNA COVID-19 vaccines, occurring mainly within 14 days after vaccination. Myocarditis and pericarditis have been reported in greatest numbers in males under the age of 40 years following a second dose of mRNA vaccines, but cases have been reported in older males and in females as well, and also following other doses. The observed risk is highest in males 12 to 17 years of age (age group not in the scope of this clinical study). While some cases required intensive care support, available data from short-term follow-up suggest that symptoms resolved in most individuals with conservative management. Information is not yet available about potential long-term sequelae of these events. Myocarditis and pericarditis events have also been detected in clinical studies and post-authorization surveillance of the Novavax COVID-19 vaccine, which is manufactured using a protein/adjuvant platform and a different adjuvant system than the CoV2 preS dTM vaccine. So far, no risk of myocarditis/pericarditis has been identified for either the monovalent or the bivalent study vaccine.	A history of myocarditis and/or pericarditis is a definitive contraindication for participants enrolled in the crossover/booster extension. During the informed consent process, participants enrolling in the crossover/booster extension will be informed of these potential risks and the need to seek immediate medical attention and notify the site study staff if they experience symptoms associated with myocarditis and/or pericarditis. The site will conduct an unscheduled visit and coordinate an appropriate diagnostic workup for participants who report symptoms which, in the judgement of the investigator, are consistent with a case of suspected myocarditis and/or pericarditis within 6 weeks after vaccination. If the diagnostic workup shows abnormal results, the participant will be referred to a cardiologist for evaluation and management. Participants with events of myocarditis and/or pericarditis will be discontinued from further vaccination and followed for subsequent visits as per the protocol for safety, immunogenicity, and efficacy endpoints. These events are AESIs and will be collected throughout the study.
Refer to monovalent and bivalent CoV2 preS dTM-AS03 IB Section 5 and Section 6 for more information regarding potential risks.	Refer to the monovalent and bivalent CoV2 preS dTM-AS03 IB Section 5 and Section 6 for more information regarding the data from previous experience with the adjuvants in the investigated vaccine.	

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
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 and blood sample collection for early detection and treatment
Theoretical risk that participant can be exposed to other SARS-CoV-2 infected individuals	SARS-CoV-2 virus is 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. Personal protective equipment (eg, masks for participants and site staff, clothing, goggles) to be used in sites. Home visit option for completion of study procedures in the setting of containment measures to minimize exposure. Participants will also be advised to adhere to local regulations and guidance (eg, self-isolation, social distancing) to minimize risk of exposure to SARS-CoV-2 infected individuals.

2.3.2 Benefits from Study Participation

Study participation and study conduct are considered fundamental from the societal perspective towards the goal of finding vaccines to help control the pandemic and decrease both the individual and public health burdens of COVID-19 illness and SARS-CoV-2 infection. In addition, interim analysis for a 2-dose primary series of 10 µg CoV2 preS dTM-AS03 (D614) vaccine given 21 days apart from Stage I of the VAT00008 study showed efficacy in preventing symptomatic COVID-19, severe COVID-19, hospitalized COVID-19, and death associated with symptomatic COVID-19 in 18 to 59 years of age. In a clinical study in booster vaccination (VAT00002 Booster Cohort), titers achieved post boosting with a Beta-variant containing Booster vaccine among both younger (18 to 55 years) and older adults (≥ 56 years) were higher than those achieved following a primary series in the population in VAT00008 Stage 1 in which efficacy was demonstrated (18 – 59 years).

Overall, the CoV2 preS dTM-AS03 (B.1.351) vaccine administered as a single booster dose in previously vaccinated individuals showed a benefit with a broad spectrum of activity eliciting

neutralizing antibodies against various variants, including Omicron BA.1, BA.2, and BA.4 subvariants. Findings of higher cross-neutralizing antibody titers to BA.1 with MV CoV2 preS dTM-AS03 (B.1.351) vaccine compared to D614 containing vaccines are consistent across both the VAT00002 and the VAT000013 studies. In the VAT00013 study, the neutralizing antibody response of CoV2 preS dTM-AS03 (B.1.351) vaccine against Omicron BA.1 variant at D28 was superior to the approved Pfizer/BioNTech vaccine which has shown to be effective against Omicron BA.1 variant. In addition, the neutralizing antibody responses against D614G, Beta, and Delta variants were higher compared to this approved mRNA vaccine. The VAT00002 - Supplemental Phase III Cohort 2 study demonstrated the ability of the CoV2 preS dTM-AS03 (B.1.351) vaccine to be a universal booster regardless of priming vaccine/priming platform. In addition, an increase in cross-neutralizing titers to Omicron BA.1, BA.2, and BA.4 were observed with CoV2 preS dTM-AS03 (B.1.351) with the fold-increase in titers and the magnitude of titers higher than those observed with CoV2 preS dTM-AS03 (D614) prototype booster vaccine. In the VAT00008 - Stage 2 efficacy study, the Beta strain-containing bivalent vaccine (BV CoV2 preS dTM-AS03 [D614 + B.1.351]) given as 2-dose primary series administered 21 days apart was evaluated during a predominantly Omicron (BA.1) period providing evidence for the efficacy of a Beta-strain containing vaccine against Omicron (BA.1 and BA.2).

2.3.3 Overall Benefit-Risk Conclusion

An increase in reactogenicity was observed in the vaccine group compared to the placebo group in VAT00008 Stage 1, as observed with other COVID-19 vaccines. This increased reactogenicity is not considered as a key risk due to the limited impact on the vaccine recipients. No other difference between the safety profile in the vaccine group and the placebo group was identified, with regard to SAEs, AESI, MAAEs and non-serious unsolicited AEs. The safety profile of the monovalent vaccine was similar when used for primary and for booster vaccination.

Efficacy and safety data from VAT00008 support a positive Benefit/Risk of primary vaccination in individuals aged 18 years to 59 years. At the time of primary analysis of VAT00008 Stage 1 and Stage 2, limited number of cases and sample size did not allow to demonstrate efficacy of primary vaccination in the older adult population.

Immunogenicity and Safety data from another clinical study performed with the monovalent D614 vaccine (VAT00002 Booster Cohort) support a positive Benefit/Risk of a booster vaccination in individuals 18 years of age and older: Antigen titers post boosting in VAT00002 were higher than those achieved following a primary series in VAT00008 Stage 1, in which efficacy was demonstrated. Given the epidemiological context with circulation of virus variants and non-clinical data on the beta variant (B.1.351) vaccine this variant vaccine formulation is chosen for booster vaccination in this study.

Available data showed that a single 5 µg dose of the CoV2 preS dTM AS03 (B.1.351) vaccine provides an effective boost with acceptable safety profile in younger and older adults primed with mRNA, adenovirus-vectored, and recombinant protein vaccine platforms. Neutralizing antibody titers after boost against a range of variants, including Omicron were higher than those observed after a booster dose of the approved Pfizer/BioNTech vaccine, Monovalent CoV2 preS dTM AS03 (D614) booster vaccine and after a 2-dose primary vaccine series with the CoV2 preS dTM AS03 (D614) vaccine.

The safety and efficacy results together with actions taken to minimize risk to participants enrolled in the study allow a positive benefit-risk assessment for study participants.

3 Objectives and Endpoints

The study objectives and the corresponding endpoints for the initial double-blind primary series design, prior to Crossover / Booster, are described in Table 3.1. The Crossover / Booster objectives and corresponding endpoints are described in Table 3.2.

Table 3.1: Objectives and Endpoints: Initial double-blind primary series design (These apply to Stage 1 and Stage 2 of the initial, double-blind, primary series study design, unless otherwise specified)

Objectives	Endpoints
Primary Efficacy (Stage 1 only)	
To assess, in participants who are SARS-CoV-2 naïve, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for the prevention of symptomatic COVID-19 occurring ≥ 14 days after the second injection.	• Occurrences of symptomatic COVID-19
Primary Efficacy (Stage 2 only)	
To assess, in all participants regardless of prior SARS-CoV-2 infection, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for prevention of symptomatic COVID-19 ≥ 14 days after the second injection.	• Occurrences of symptomatic COVID-19
Primary Safety	
To assess the safety of the CoV2 preS dTM-AS03 vaccines compared to placebo throughout the study.	For participants in the Reactogenicity Subset: • Presence of solicited (pre-listed in the participant's diary card / electronic diary card [DC/eDC] and [electronic] Case Report Form [CRF]) injection site reactions and systemic reactions occurring up to 7 days after each vaccination • Presence of non-serious unsolicited adverse events (AEs) reported up to 21 days after the last vaccination For all participants in the study: • Presence of unsolicited injection site and systemic AEs reported in the 30 minutes after each vaccination • Presence of medically-attended adverse events (MAAEs) throughout the study • Presence of serious adverse events (SAEs) throughout the study • Presence of adverse events of special interest (AESIs) throughout the study • Presence of virologically-confirmed SARS-CoV-2 infections and/or symptomatic COVID-19

Objectives	Endpoints
Key Secondary Efficacy Objective (Stage 1)	
1) To assess, in participants who are SARS-CoV-2 naïve, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for prevention of the following occurring ≥ 14 days after the second injection: • Prevention of SARS-CoV-2 infection • Prevention of severe COVID-19	Endpoints for secondary efficacy objective #1: • Occurrences of SARS-CoV-2 infection • Occurrence of severe COVID-19
Key Secondary Efficacy Objective (Stage 2)	
2) To assess: • Prevention of SARS-CoV-2 infection in participants who are SARS-CoV-2 naïve, occurring ≥ 14 days after the second injection • Prevention of severe COVID-19 in participants regardless of prior SARS-CoV-2 infection occurring ≥ 14 days after the second injection	Endpoints for secondary efficacy objective #2: • Occurrences of SARS-CoV-2 infection • Occurrence of severe COVID-19
Other Secondary Efficacy Objectives	
3) To assess, in participants who are SARS-CoV-2 naïve, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for the prevention of symptomatic COVID-19 occurring ≥ 14 days after the first injection.	Endpoint for secondary efficacy objective #3: • Occurrences of symptomatic COVID-19
4) Stage 1 only: To assess, in all participants regardless of prior SARS-CoV-2 infection, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for: • Prevention of symptomatic COVID-19 • Prevention of severe COVID-19	Stage 1 only: Endpoints for secondary efficacy objective #4: • Occurrences of symptomatic COVID-19 • Occurrence of severe COVID-19
5) To assess, in participants who are SARS-CoV-2 non-naïve, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for: • Prevention of symptomatic COVID-19 • Prevention of severe COVID-19	Endpoints for secondary efficacy objective #5: • Occurrences of symptomatic COVID-19 • Occurrence of severe COVID-19
6) To assess, in participants who are SARS-CoV-2 naïve, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for the prevention of asymptomatic SARS-CoV-2 infection.	Endpoint for secondary efficacy objective #6: • Occurrences of asymptomatic SARS-CoV-2 infection
7) To assess the impact of the CoV2 preS dTM-AS03 vaccines in the reduction of viral burden and shedding among participants with symptomatic COVID-19.	Endpoints for secondary efficacy objective #7: • Viral copies/mL in respiratory samples collected at each follow-up timepoint • Number of days with positive NAAT • Occurrences of positive NAAT in respiratory samples at each follow-up timepoint during symptomatic COVID-19
8) To assess, in all participants regardless of prior SARS-CoV-2 infection and in participants who are SARS-CoV-2 non-naïve and naïve, clinical efficacy of the CoV2 preS dTM-AS03 vaccines for: • Prevention of CDC-defined COVID-19 • Prevention of hospitalized COVID-19	Endpoints for secondary efficacy objective #8: • Occurrences of CDC-defined COVID-19 • Occurrences of hospitalized COVID-19 • Occurrences of symptomatic COVID-19 with severity of moderate COVID-19 or worse (composite endpoint of at least one of moderate or severe COVID-19)

Objectives	Endpoints
• Prevention of symptomatic COVID-19 with severity of moderate COVID-19 or worse (composite endpoint of moderate or severe COVID-19)	
9) To assess the durability of clinical efficacy of the CoV2 preS dTM-AS03 vaccines over time in SARS-CoV-2 naïve participants against: • SARS-CoV-2 infection • Asymptomatic SARS-CoV-2 infection	Endpoints for secondary efficacy objective #9: • Occurrences of SARS-CoV-2 infection • Occurrences of asymptomatic SARS-CoV-2 infection
10) To assess the durability of clinical efficacy of the CoV2 preS dTM-AS03 vaccines over time in all participants and by prior SARS-CoV-2 infection (naïve and non-naïve) for: • Prevention of symptomatic COVID-19 • Prevention of severe COVID-19 • Prevention of CDC-defined COVID-19 • Prevention of hospitalized COVID-19	Endpoints for secondary efficacy objective #10: • Occurrences of symptomatic COVID-19 • Occurrences of severe COVID-19 • Occurrences of CDC-defined COVID-19 • Occurrences of hospitalized COVID-19
11) To assess, in participants who are SARS-CoV-2 naïve, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for the prevention of symptomatic COVID-19 occurring ≥ 7 days after the second injection.	Endpoint for secondary efficacy objective #11: • Occurrences of symptomatic COVID-19
12) Stage 2 only: To assess, in participants who are SARS-CoV-2 naïve, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for: • Prevention of symptomatic COVID-19 • Prevention of severe COVID-19	Stage 2 only: Endpoint for secondary efficacy objective #12: • Occurrences of symptomatic COVID-19 • Occurrence of severe COVID-19
Secondary Immunogenicity	
1) To compare the neutralizing antibody response 21 days after last vaccination (D43) to the D614G variant between the monovalent and bivalent vaccines in SARS-CoV-2 naïve and non-naïve participants in the Random Immunogenicity Subcohort. 2) To compare the neutralizing antibody response 21 days after last vaccination (D43) to the Beta (B.1.351) variant between the monovalent and bivalent vaccines in SARS-CoV-2 naïve and non-naïve participants in the Random Immunogenicity Subcohort. 3) To compare the neutralizing antibody response 21 days after last vaccination (D43) to the Beta (B.1.351) variant in the bivalent vaccine group and the neutralizing antibody response to the D614G variant in the monovalent vaccine group in SARS-CoV-2 naïve and non-naïve participants in the Random Immunogenicity Subcohort.	Endpoints for secondary immunogenicity objectives #1 - 3: • Individual serum neutralizing titer at D01 and D43 • Responders, defined as participants who had baseline values below lower limit of quantification (LLOQ) with quantifiable neutralization titer above assay LLOQ at each pre-defined post-vaccination time point and participants with baseline values above LLOQ with a 4-fold increase in neutralizing antibody titers at each pre-defined post-vaccination time point • Seroresponse, defined as a 4-fold or greater rise in serum neutralization titer [pre/post] at D43 relative to D01
The following objectives will be assessed in participants regardless of prior SARS-CoV-2 infection and in SARS-CoV-2 non-naïve and naïve participants.	Endpoints for secondary immunogenicity objectives #4 - 9:

Objectives	Endpoints
4) To describe the neutralizing antibody profile at D01, D22, D43, D78, D134, D202, D292, and D387 in each study group for participants in the Random Immunogenicity Subcohort. 5) To describe the neutralizing antibody profile at D01, D22, D43, D78, D134, D202, D292, and D387 in each study group for participants aged 18-25 years in the Random Immunogenicity Subcohort. 6) To describe the association of neutralizing antibody responses and the risk of symptomatic COVID-19. 7) To describe the association of neutralizing antibody responses and the risk of SARS-CoV-2 infection. 8) To describe the association of neutralizing antibody responses and the risk of other COVID-19 disease endpoints. 9) To evaluate the immunological correlates of risk and correlates of protection against symptomatic COVID-19, SARS-CoV-2 infection, and other COVID-19 disease endpoints.	Neutralizing antibody titers will be measured in participants for each study group against the D614G and B.1.351 variants. • Individual serum neutralizing titer at each pre-defined time point • Individual serum neutralization titer fold-rise post-vaccination relative to D01 at each pre-defined time point • 2-fold rise and 4-fold-rise in serum neutralization titer [post/pre] (fold rise ≥ 2 and ≥ 4) at each pre-defined post-vaccination timepoint • Responders, defined as participants who had baseline values below LLOQ with quantifiable neutralization titer above assay LLOQ at each pre-defined post-vaccination time point and participants with baseline values above LLOQ with a 4-fold increase in neutralizing antibody titers at each pre-defined post-vaccination timepoint

Objectives	Endpoints
Secondary Safety	
1) To describe the frequency and spectrum of disease in episodes of symptomatic COVID-19 in SARS-CoV-2 non-naïve adults in each study group.	Endpoints for secondary safety objective #1: For SARS-CoV-2 non-naïve participants in the study: • Severity of symptoms associated with symptomatic COVID-19 episode • Occurrences of hospitalized COVID-19 • Occurrence of severe COVID-19 • Occurrences of COVID-19 in each severity rating on the 7-point ordinal scale • Death associated with COVID-19
2) To assess the safety of the CoV2 preS dTM-AS03 vaccines compared to placebo in participants aged 18-25 years throughout the study.	Endpoints for secondary safety objective #2: For participants in the Reactogenicity Subset: • Presence of solicited (pre-listed in the participant's diary card / electronic diary card [DC/eDC] and [electronic] Case Report Form [CRF]) injection site reactions and systemic reactions occurring up to 7 days after each vaccination • Presence of non-serious unsolicited adverse events (AEs) reported up to 21 days after the last vaccination For all participants in the study: • Presence of unsolicited injection site and systemic AEs reported in the 30 minutes after each vaccination • Presence of medically-attended adverse events (MAAEs) throughout the study • Presence of serious adverse events (SAEs) throughout the study • Presence of adverse events of special interest (AESIs) throughout the study • Presence of virologically-confirmed SARS-CoV-2 infections and/or symptomatic COVID-19
Exploratory Efficacy	
1) To assess in all participants regardless of prior SARS-CoV-2 infection and in SARS-CoV-2 non-naïve and naïve participants, clinical efficacy of the CoV2 preS dTM-AS03 vaccines for: • Reduction in duration of symptoms of symptomatic COVID-19 • Reduction in duration of hospitalization with symptomatic COVID-19 • Reduction in severity of symptomatic COVID-19 on the 7-point ordinal scale • Reduction in use of supplemental oxygen associated with symptomatic COVID-19 • Prevention of intensive care utilization associated with symptomatic COVID-19	Endpoints for exploratory efficacy objective #1: • Days with symptoms associated with symptomatic COVID-19 • Days of hospitalization associated with COVID-19 • Occurrences of symptomatic COVID-19 in each severity rating on the 7-point ordinal scale • Occurrences of symptomatic COVID-19 requiring supplemental oxygen • Days of use of supplemental oxygen over the course of symptomatic COVID-19 • Occurrences of intensive care utilization associated with symptomatic COVID-19 • Days of stay in an intensive care unit over the course of symptomatic COVID-19 • Occurrences of symptomatic COVID-19 requiring mechanical ventilation or ECMO

Objectives	Endpoints
• Reduction in use of mechanical ventilation or ECMO associated with symptomatic COVID-19 • Prevention of death associated with symptomatic COVID-19	• Days of use of mechanical ventilation or ECMO over the course of the symptomatic COVID-19 • Death associated with symptomatic COVID-19
2) To assess the clinical efficacy of the CoV2 preS dTM-AS03 vaccines in SARS-CoV-2 naïve participants by subgroups defined by age, high risk medical conditions, sex and race/ethnicity or a combination of those for: • Prevention of SARS-CoV-2 infection • Prevention of asymptomatic SARS-CoV-2 infection	<u>Endpoints for exploratory efficacy objective #2:</u> • Occurrences of SARS-CoV-2 infection • Occurrences of asymptomatic SARS-CoV-2 infection
3) To assess the clinical efficacy of the CoV2 preS dTM-AS03 vaccines in participants regardless of prior SARS-CoV-2 infection and by baseline prior SARS-CoV-2 infection (naïve and non-naïve) by subgroups defined by age, high risk medical conditions and race/ethnicity or a combination of those for: • Prevention of symptomatic COVID-19 • Reduction in duration of symptoms of COVID-19 • Prevention of severe COVID-19 • Prevention of hospitalized COVID-19 • Reduction in duration of hospitalization with symptomatic COVID-19 • Reduction in severity of symptomatic COVID-19 on the 7-point ordinal scale • Prevention of symptomatic COVID-19 with severity of moderate COVID-19 or worse (composite endpoint of moderate or severe COVID-19) • Reduction in use of supplemental oxygen associated with symptomatic COVID-19 • Prevention of intensive care utilization associated with symptomatic COVID-19 • Reduction in use of mechanical ventilation or ECMO associated with symptomatic COVID-19 • Prevention of death associated with symptomatic COVID-19	<u>Endpoints for exploratory efficacy objective #3:</u> • Occurrences of symptomatic COVID-19 • Days with symptoms associated with symptomatic COVID-19 • Occurrence of severe COVID-19 • Occurrences of CDC-defined COVID-19 • Occurrences of hospitalized COVID-19 • Days of hospitalization with symptomatic COVID-19 • Occurrences of symptomatic COVID-19 in each severity rating on the 7-point ordinal scale • Occurrence of symptomatic COVID-19 with severity of moderate COVID-19 or worse (composite endpoint of at least one of moderate or severe COVID-19) • Occurrences of symptomatic COVID-19 requiring intensive care utilization • Occurrences of symptomatic COVID-19 requiring supplemental oxygen • Days of supplemental oxygen use in participants with symptomatic COVID-19 • Occurrences of intensive care utilization associated with symptomatic COVID-19 • Days of stay in an intensive care unit associated with symptomatic COVID-19 • Occurrences of symptomatic COVID-19 requiring mechanical ventilation or ECMO • Days of use of mechanical ventilation or ECMO over the course of symptomatic COVID-19 • Deaths associated with symptomatic COVID-19
4) To assess the clinical efficacy of the CoV2 preS dTM-AS03 vaccines between the first and second injection in SARS-CoV-2 naïve participants for prevention of: • SARS-CoV-2 infection • Asymptomatic SARS-CoV-2 infection	<u>Endpoints for exploratory efficacy objective #4:</u> • Occurrences of SARS-CoV-2 infection • Occurrences of asymptomatic SARS-CoV-2 infection
5) To assess the clinical efficacy of the CoV2 preS dTM-AS03 vaccines between the first and second	<u>Endpoints for exploratory efficacy objective #5:</u> • Occurrences of symptomatic COVID-19 • Occurrences of hospitalized COVID-19

Objectives	Endpoints
injection in all participants and by baseline SARS-CoV-2 infection for prevention of: • Symptomatic COVID-19 • Hospitalized COVID-19 • Prevention of severe COVID-19	• Occurrence of severe COVID-19
6) To assess the clinical efficacy of the CoV2 preS dTM-AS03 vaccines against all COVID-19 events (including all events regardless of adjudication committee decision).	Endpoints for exploratory efficacy objective #6: • Occurrence of virologically-confirmed SARS-CoV-2 infections and COVID-19 events (including all events regardless of adjudication committee decision).
7) To assess the clinical efficacy of the CoV2 preS dTM-AS03 vaccines in prevention of all-cause death.	Endpoints for exploratory efficacy objective #7: • All-cause death
8) To describe the occurrence of the following events temporally associated with symptomatic COVID-19 in each study group: • Rates of new onset or exacerbation of pre-existing cardio-respiratory conditions • Rates of health care utilization (hospitalizations, ER visits, or non-routine medical office visits [including urgent care visits]) • antibiotic and antiviral use • work absenteeism within 30 days of illness	Endpoints for exploratory efficacy objective #8: • Episodes of new onset or exacerbation of pre-existing cardio-respiratory conditions • Occurrences of health care utilization events (hospitalizations, ER visits, or non-routine medical office visits [including urgent care visits]) • Instances of antibiotic or antiviral use • Occurrence and number of days of work absenteeism
9) To describe in each group the occurrence of events that may be classified as Long COVID syndrome.	Endpoints for exploratory efficacy objective #9: • Occurrence of Long COVID syndrome events
10) To assess impact of vaccination on asymptomatic SARS-CoV-2 NAAT positivity at the time of the crossover set of vaccinations in naïve participants	Endpoints for exploratory efficacy objective #10: • Occurrence of positive NAAT in respiratory samples at time of crossover
11) To describe in each group virologically-confirmed respiratory viral infections as ascertained by real-time polymerase chain reaction (RT-PCR) for other respiratory viruses (eg, Influenza, RSV).	Endpoints for exploratory efficacy objective #11: • Occurrences of respiratory viral infections (other than SARS-CoV-2) associated with COVID-19-like illness (by RT-PCR)
12) To assess clinical efficacy on prevention of symptomatic COVID-19 and SARS-COV-2 infection within the same residence of study participants.	Endpoints for exploratory efficacy objective #12: • Occurrences of symptomatic COVID-19 and SARS-CoV-2 infection among members in the same residence self-reported by the participant
13) To assess if and how vaccine efficacy for the prevention of virologically-confirmed symptomatic COVID-19 depends on genotypic or neutralization phenotypic characteristics of SARS-CoV-2 (sieve analysis for disease).	
14) To conduct exploratory analyses related to furthering the understanding of SARS-CoV-2 / COVID-19, including analyses related to immunology, virology, vaccines, and clinical conduct.	
15) To describe the relative efficacy against symptomatic COVID-19 by variants between the monovalent and bivalent vaccines.	Endpoints for exploratory efficacy objective #15: • Occurrences of symptomatic COVID-19

Objectives	Endpoints
Exploratory Immunogenicity	
The following objectives will be assessed in participants regardless of prior SARS-CoV-2 infection and in SARS-CoV-2 non-naïve and naïve participants. 1) To describe the binding antibody profile at D01, D22, D43, D78, D134, D202, D292, and D387 in each study group for participants in the Random Immunogenicity Subcohort. 2) To describe the association of binding antibody responses and the risk of symptomatic COVID-19. 3) To describe the association of binding antibody responses and the risk of SARS-CoV-2 infection. 4) To describe the association of binding antibody responses and the risk of other COVID-19 disease endpoints. 5) To describe the neutralizing antibody profile at D01, D22, D43, D78, D134, D202, D292, and D387 against newly emergent variant strains for participants in the Random Immunogenicity Subcohort.	<u>Endpoints for exploratory immunogenicity objectives #1 - 4:</u> Binding antibody concentration will be measured in participants for each study group against the homologous vaccine strains. • Individual antibody concentration at each pre-defined time point • Individual antibody fold-rise post-vaccination relative to D01 at each pre-defined post-vaccination time point • 2-fold-rise and 4-fold-rise (foldrise in antibody concentration [post/pre] ≥ 2 and ≥ 4) at each pre-defined post-vaccination time point • Responders, defined as participants who had baseline values below LLOQ with quantifiable antibody concentration above assay LLOQ at each pre-defined post-vaccination timepoints and participants with baseline values above LLOQ with a 4-fold increase in antibody concentrations at each pre-defined post-vaccination timepoint. • Individual antibody concentration (≥ 2xLLOQ or ≥ 4xLLOQ) at each pre-defined time point <u>Endpoints for exploratory immunogenicity objective #5:</u> Neutralizing antibody titers will be measured in participants against newly emergent variants of concern (VOCs). • Individual serum neutralization titer at each pre-defined time point • Individual serum neutralization titer fold-rise post-vaccination relative to D01 at each pre-defined time point • 2-foldrise and 4-fold-rise in serum neutralization titer [post/pre] (fold-rise ≥ 2 and ≥ 4) at each pre-defined post-vaccination timepoint • Responders, defined as participants who had baseline values below LLOQ with quantifiable neutralization titer above assay LLOQ at each pre-defined post-vaccination timepoint and participants with baseline values above LLOQ with a 4-fold increase in neutralizing antibody titers at each pre-defined post-vaccination timepoint.
6) To conduct exploratory analyses which may include (but are not limited to) testing of immune responses and other biomarkers in any subset of participants to inform further understanding of COVID-19 vaccines, including use as benchmarks for other studies.	

Table 3.2: Objectives and Endpoints: Crossover / Booster design

Objectives	Endpoints
Secondary Immunogenicity	
To describe the neutralizing antibody profile at D01 and at 21 days and 6 months after last crossover injection in the placebo group and booster injection in each study group for participants in the Random Immunogenicity Subcohort.	Endpoints for secondary immunogenicity objective: Neutralizing antibody titers will be measured in participants for each study group against the D614G and B.1.351 variants. • Individual serum neutralizing titer at each pre-defined time point • Individual serum neutralization titer fold-rise post-vaccination relative to D01 at each pre-defined time point • 2-fold rise and 4-fold-rise in serum neutralization titer [post/pre] (fold rise ≥ 2 and ≥ 4) at each pre-defined post-vaccination timepoint • Responders, defined as participants who had baseline values below LLOQ with quantifiable neutralization titer above assay LLOQ at each pre-defined post-vaccination time point and participants with baseline values above LLOQ with a 4-fold increase in neutralizing antibody
Secondary Safety	
1) To describe the frequency and spectrum of disease in episodes of symptomatic COVID-19 in SARS-CoV-2 non-naïve adults after the crossover or booster vaccinations with the CoV2 preSdTM-AS03 vaccines.	Endpoints for secondary safety objective #1: For SARS-CoV-2 non-naïve participants in the study: • Severity of symptoms associated with symptomatic COVID-19 episode • Occurrences of hospitalized COVID-19 • Occurrence of severe COVID-19 • Occurrences of COVID-19 in each severity rating on the 7-point ordinal scale • Death associated with COVID-19
2) To assess the safety of the CoV2 preS dTM-AS03 vaccines after the crossover or booster vaccinations	Endpoints for secondary safety objective #2: For all participants in the study: • Presence of unsolicited injection site and systemic AEs reported in the 30 minutes after each vaccination • Presence of non-serious unsolicited AEs reported up to 21 days after the booster vaccination • Presence of MAAEs throughout the study • Presence of SAEs throughout the study • Presence of AESIs throughout the study
Exploratory Efficacy	
1) To describe the relative efficacy ≥ 6 months after a booster dose among participants initially in the Vaccine group (earlier booster) versus the efficacy ≥ 14 days after a booster dose in participants initially in the Placebo group (later booster).	Endpoints for exploratory efficacy objective #1: • Occurrences of symptomatic COVID-19 • Occurrences of hospitalized COVID-19 • Occurrence of severe COVID-19

Objectives	Endpoints
2) To describe the relative efficacy ≥ 14 days after a booster dose among initial vaccine recipients versus ≥ 14 days after the primary series among initial placebo recipients.	Endpoints for exploratory efficacy objective #2: • Occurrences of symptomatic COVID-19 • Occurrences of hospitalized COVID-19 • Occurrence of severe COVID-19
3) To describe the relative efficacy ≥ 14 days after a booster dose among participants initially vaccinated with the monovalent CoV2 preS dTM-AS03 (D614) vaccine (Vaccine group Stage 1) versus the efficacy ≥ 14 days after a booster dose in participants initially vaccinated with the bivalent CoV2 preS dTM-AS03 (D614+B.1351) vaccine (Vaccine group Stage 2).	Endpoints for exploratory efficacy objective #3: • Occurrences of symptomatic COVID-19 • Occurrences of hospitalized COVID-19 • Occurrence of severe COVID-19
4) To describe the relative efficacy≥ 14 days after a booster dose among participants who received the CoV2 preS dTM-AS03 primary vaccination series versus the efficacy ≥ 14 days after a booster dose in participants who received authorized/approved vaccines primary vaccination series in the initial Placebo Group.	Endpoints for exploratory efficacy objective #4: • Occurrences of symptomatic COVID-19 • Occurrences of hospitalized COVID-19 • Occurrence of severe COVID-19
5) To describe the relative efficacy ≥ 14 days after a booster dose among participants with longer interval between primary series and booster (initial Vaccine group) versus the efficacy ≥ 14 days after a booster dose in participants with a shorter interval between primary series and booster (initial Placebo group).	Endpoints for exploratory efficacy objective #5: • Occurrences of symptomatic COVID-19 • Occurrences of hospitalized COVID-19 • Occurrence of severe COVID-19
Exploratory Immunogenicity	
1) To describe the immune response pre- and post-booster dose among participants initially vaccinated with the monovalent CoV2 preS dTM-AS03 (D614) vaccine (Vaccine group Stage 1) in the primary series versus participants initially vaccinated with the bivalent CoV2 preS dTM-AS03 (D614+B.1351) vaccine (Vaccine group Stage 2) in the primary series. 2) To describe the immune response pre- and post-booster dose among participants who received the CoV2 preS dTM-AS03 primary vaccination series versus participants who received authorized/approved primary vaccination series in the initial Placebo Group. 3) To describe the immune response pre- and post-booster dose among participants with longer interval between primary series and booster (initial Vaccine group) versus participants with a shorter interval between primary series and booster (initial Placebo group).	<u>Endpoints for exploratory immunogenicity objectives #1 - #3:</u> Neutralizing antibody titers will be measured in participants for each study group against the D614G and B.1.351 variants and other relevant VoCs. Binding antibody concentration will also be measured in participants for each study group. • Individual serum neutralizing titer and binding antibody concentration at each pre-defined time point • Individual serum neutralization titer and binding antibody concentration fold-rise post-vaccination relative to pre-booster at each pre-defined time point • 2-fold rise and 4-fold-rise in serum neutralization titer and binding antibody concentration [post/pre] (fold rise ≥ 2 and ≥ 4) at each pre-defined post-vaccination timepoint • Responders, defined as participants who had baseline values below LLOQ with quantifiable neutralization titer above assay LLOQ at each pre-defined post-vaccination time point and participants with baseline values above LLOQ with a 4-fold increase in antibody concentrations at each pre-defined post-vaccination timepoint

Objectives	Endpoints
4) To describe the association of neutralizing antibody responses and the risk of symptomatic COVID-19. 5) To describe the association of neutralizing antibody responses and the risk of other COVID-19 disease endpoints. 6) To evaluate the immunological correlates of risk and correlates of protection against symptomatic COVID-19, and other COVID-19 disease endpoints.	Endpoints for exploratory immunogenicity objectives #4 - #6: Neutralizing antibody titers will be measured in participants for each study group against the D614G and B.1.351 variants. • Individual serum neutralizing titer at each pre-defined time point • Individual serum neutralization titer fold-rise post-vaccination relative to pre-booster at each pre-defined time point • 2-fold rise and 4-fold-rise in serum neutralization titer [post/pre] (fold rise ≥ 2 and ≥ 4) at each pre-defined post-vaccination timepoint • Responders, defined as participants who had baseline values below LLOQ with quantifiable neutralization titer above assay LLOQ at each pre-defined post-vaccination time point and participants with baseline values above LLOQ with a 4-fold increase in neutralizing antibody titers at each pre-defined post-vaccination timepoint

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, multi-center, multi-country, multi-stage
Phase	III
Control method	Placebo-controlled
Study population	Adults 18 years of age and older
Level and method of blinding	Modified double-blind (observer-blind) for initial, double-blind, primary series design of study. Crossover / Booster study design details are as stated below in Crossover / Booster section: • Blinding for vaccine group assignment: participants, outcome assessors, Investigators, laboratory personnel, Sponsor study staff, those administering the study intervention if not involved in preparing study intervention

	• No blinding for vaccine group assignment: those preparing the study interventions
Study intervention assignment method	Participants will be screened for eligibility criteria at the time of inclusion and then randomized to either the investigational vaccine or placebo in a 1:1 ratio in each stage as shown below: • Stage 1: eligible participants will be randomized to receive either CoV2 preS dTM-AS03 (D614) vaccine or Placebo 1 (participants who receive the placebo as part of Stage 1) • Stage 2: eligible participants will be randomized to receive either CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine or Placebo 2 (participants who receive placebo as part of Stage 2) Randomization will be stratified by age groups (18-59 years of age and 60 years of age and older), baseline SARS-CoV-2 rapid serodiagnostic test positivity, and site. In the time period where the enrollment in Stage 1 overlaps with enrollment in Stage 2, participants will continue to be randomly allocated to one of the investigational vaccine groups and their matched placebo group in a 1:1 ratio. There will be no sharing of the placebo participants between the 2 stages.
Number of participants	A total of approximately 21 046 participants are planned to be enrolled (5080 per study intervention group in Stage 1 and 5443 per study intervention group in Stage 2). If the crossover is not implemented, recruitment will continue until the minimally required number of naïve participants to assess efficacy is enrolled (even if the overall enrollment target is reached). Participants who are SARS-CoV-2 non-naïve at baseline will be capped to approximately 30% of the total study population in Stage 1 (up to ~1524 participants/arm). The target for SARS-CoV-2 non-naïves is ~1633 participants/arm in Stage 2. The objective is to ensure a sufficient number of participants/arm who are SARS-CoV-2 naïve at baseline are enrolled to achieve the power of the study. The study will target enrollment of older adults (≥ 60 years of age) with a recruitment target of approximately 40% of the study population in each stage.

	Within the age group of 18-59 years, the study will target inclusion of approximately 35% of participants with high-risk medical conditions for COVID-19. The study will target recruitment of racial and ethnic diversity that will be representative of the countries in which the study will be conducted. See also Table 4.2 and Table 4.3.
Intervention groups	Stage 1: Participants in Stage 1 will be randomized in a 1:1 ratio to receive 2 injections 21 days apart of either CoV2 preS dTM-AS03 (D614) or Placebo 1. Stage 2: Participants in Stage 2 will be randomized in a 1:1 ratio to receive 2 injections 21 days apart of either CoV2 preS dTM-AS03 (D614 + B.1.351) or Placebo 2. See also Table 4.2 and Table 4.3.
Total duration of study participation	Initial, double-blind, primary series study design planned for 365 days post-last Initial injection (ie, approximately 386 days total) for each participant. Based on decisions of the Study OG, Stage 1 participants will be invited to participate in an unblinded Crossover / Booster study design with duration as follows: • For participants who initially received vaccine: 12 months post-booster (ie, approximately 18 to 24 months) • For participants who initially received placebo: 4 months post-last dose of the primary series + 12 months post-booster (ie, approximately 28 to 34 months) • For participants who do not consent to continue in the unblinded Crossover / Booster part of the study, all study procedures will be stopped and participants will be discontinued from the study.
Countries	Stage 1: United States, Honduras, Japan, Colombia, Kenya, India, Ghana, Nepal Stage 2: Colombia, Kenya, Uganda, India, Ghana, Nepal, Ukraine and Mexico
Use of an Independent Data Monitoring Committee, Dose Escalation Committee, or similar review group	Yes (see Section 10.1.5.1 for details)

Unblinded Crossover / Booster	All participants in Stage 1 and Stage 2 will be unblinded and informed of the results of the study. Study Investigators will discuss the possibility of receiving the (authorized/approved) vaccines available to them outside of the study. Based on decisions of the Study OG, participants will be invited upon consent to continue participation as part of an unblinded crossover / booster study design. The participant unblinding and consent will trigger the end of the initial double-blind primary series design and the start of the Crossover / Booster design, which includes a primary series vaccination for initial placebo recipients (ie, crossover vaccination) and a booster for both initial placebo and vaccine recipients (ie, booster vaccination). Non-naïve participants who initially received placebo and are 18-59 years of age will be offered the opportunity to receive the investigational CoV2 preS dTM-AS03 monovalent (D614) vaccine if authorized/approved vaccines are not available or if they choose not to receive an authorized/approved vaccine series. Naïve participants 18-59 years of age and all participants ≥ 60 years of age who initially received placebo will be recommended to receive an authorized/approved vaccination series. If initial placebo recipients of any age received the complete primary series of an authorized/approved vaccine outside of the study or the investigational study vaccine as a primary series, they will also be offered the opportunity to receive Sanofi's investigational Cov2 preS dTM-AS03 monovalent (B.1.351) booster vaccine ≥ 4 months post-last dose of the primary series or encouraged to receive an authorized/approved vaccine according to local guidance Participants who initially received the complete primary series of the CoV2 preS dTM-AS03 monovalent (D614) vaccine (Stage 1) or CoV2 preS dTM-AS03 bivalent (D614+B.1.351) vaccine (Stage 2) will be offered the opportunity to receive Sanofi's investigational CoV2 preS dTM-AS03 monovalent (B.1.351) booster vaccine ≥ 4 months post-last dose of the primary series or encouraged to

	receive an authorized/approved vaccine according to local guidance. If participants do not consent to continue with the unblinded crossover/booster, all study procedures will be stopped, and participants will be discontinued from the study and recommended to receive the authorized/approved vaccination series per local guidance.

Table 4.2: Planned sample size and approximate size of subsets in Stage 1

		Study Intervention Groups (Stage 1)	
		Vaccine 1	Placebo 1
		CoV2 preS dTM-AS03 (D614)	Placebo
Total Overall		5080	5080
Prior exposure to SARS-CoV-2	**SARS-CoV-2 naïves**	3556	3556
	SARS-CoV-2 non-naïves	Up to 1524	Up to 1524
Reactogenicity Subset		2000	2000
Random Immunogenicity Subset*		1415	559

Non-naive: Capped at approximately 30% of study population in this stage.
* Details of the random subset and subcohort are described below and in Appendix 10.6.

Table 4.3: Planned sample size and approximate size of subsets in Stage 2

		Study Intervention Groups (Stage 2)	
		Vaccine 2	Placebo 2
		CoV2 preS dTM-AS03 (D614 + B.1.351)	Placebo
Total Overall		5443	5443
Prior exposure to SARS-CoV-2	**SARS-CoV-2 naïves**	3810	3810
	SARS-CoV-2 non-naïves	1633	1633
Reactogenicity Subset		2000	2000
Random Immunogenicity Subset*		1415	559

If the crossover is not implemented, recruitment will continue until the minimally required number of naïve participants to assess efficacy is enrolled (even if the overall enrollment target is reached).
* Details of the random subset and subcohort are described below and in Appendix 10.6.

All participants will receive 2 injections given 3 weeks apart: the first injection will be at D01 (Vaccination [VAC] 1) and the second injection will be at D22 (VAC2).

Reactogenicity subset: A subset of participants (approximately 2000 per study group in each stage) will be allocated to the reactogenicity subset to collect solicited AEs for 7 days after each vaccination and non-serious unsolicited AEs up to 21 days after the last vaccination. In Stage 1, 25% of the first 8000 participants will be randomly allocated to the reactogenicity subset after which a capping system will be used to ensure a targeted number of participants are assigned to the reactogenicity subset. In Stage 2, the first 4000 participants along with all participants above 60 years of age will be allocated to the reactogenicity subset.

Random Immunogenicity Subset: A random subset of study participants in each stage stratified by treatment group, SARS-CoV-2 positivity on the rapid serodiagnostic test at enrollment, and age-group will be randomly allocated at enrollment (Step 1) with pre-identified allocation ratio in each stratum to enable immunogenicity assessments and for case-cohort analysis. This immunogenicity subset will potentially be supplemented by a random selection in Step 2 to form the Random Immunogenicity Subcohort. This additional supplemental random selection will occur, if needed, after the availability of results to define SARS-CoV-2 D01 and D22 naïve and non-naïve status of all enrolled participants. Details are included in Appendix 10.6.

The Random Immunogenicity Subcohort will be utilized to build a case-cohort, where the case cohort is comprised of all participants belonging to the random subcohort plus those participants who develop any efficacy endpoint events during study follow-up and were not already included in the corresponding random subcohort. This Random Immunogenicity Subcohort will be used for immunogenicity assessments, analysis of immunological correlates of risk, and correlates of protection.

Receipt of approved/authorized vaccines prior to the Crossover / Booster design

The statements below apply to study activities of participants prior to the unblinded Crossover / Booster design.

If an approved/authorized vaccine is available in the country or region where the study is conducted and the participant is eligible for receiving vaccine (based on the country prioritization strategy for vaccine deployment) at the time of enrollment, investigators will discuss this information with prospective study participants at the time of informed consent who will be encouraged to obtain the approved/authorized vaccine if applicable to them. Recruitment of eligible participants will proceed only if, despite encouragement, the candidate participant expresses no intention to seek an authorized or approved vaccine at the time of enrollment.

If the participant is enrolled and seeks vaccination of an authorized/approved vaccine outside of the study, he/she will be encouraged to discuss this intention proactively with the study investigator. The study Investigators will inform and discuss with these study participants the possibility of being unblinded to the study intervention to enable the participant to make decisions on receiving the available (authorized or approved) vaccine. The Sponsor will keep the study investigators updated on any new information related to the investigational products, so that such information can be provided to participants in discussions related to the potentially receiving the available authorized/approved vaccines. Participants should only request to be unblinded if they

decide to receive the approved/authorized vaccine. Participants who elect to be unblinded will have their code broken. Once unblinded, participants will be discontinued from study intervention administration.

If the participant is unblinded or receives the authorized/approved vaccine, this information would be collected. These study participants will be allowed to continue study participation if they choose to do so but will not be allowed to crossover; while continuation in the study will include all study procedures including safety follow-up, they will be censored from that point onward for efficacy and immunogenicity analysis for the primary vaccination/series.

Participants who decline the approved/authorized vaccine should remain blinded to treatment assignment for the entire duration of the study or until study discontinuation decisions are made with the appropriate regulatory agencies.

If at any time during study conduct it is determined that the vaccine candidates are not efficacious or that efficacy cannot be demonstrated, participants will be encouraged to seek vaccination of an authorized/approved vaccine if available to them.

Unblinded Crossover / Booster

All participants in Stage 1 and Stage 2 will be unblinded and informed of the results of the study. Study Investigators will discuss the possibility of receiving the (authorized/approved) vaccines available to them outside of the study.

Based on decisions of the Study OG, participants will be invited upon consent to continue participation as part of an unblinded crossover / booster study design. The participant unblinding and consent will trigger the end of the initial double-blind primary series design and the start of the Crossover / Booster design, which includes a primary series vaccination for initial placebo recipients (ie, crossover vaccination) and a booster for both initial placebo and vaccine recipients (ie, booster vaccination).

Non-naïve participants who initially received placebo and are 18-59 years of age will be offered the opportunity to receive the investigational CoV2 preS dTM-AS03 monovalent (D614) vaccine if authorized/approved vaccines are not available or if they choose not to receive an authorized/approved vaccine series.

Naïve participants 18-59 years of age and all participants ≥ 60 years of age who initially received placebo will be recommended to receive an authorized/approved vaccination series.

Placebo recipients	**18-59 years of age**	**≥ 60 years of age**
Non-naïves	CoV2 preS dTM-AS03 **MV(D614)** priming (if EUA vaccines not available or not preferred)	Priming with **EUA vaccines**
Naïves	Priming with **EUA vaccines**	Priming with **EUA vaccines**

Abbreviations: EUA: Emergency Use Authorization; MV monovalent

If initial placebo recipients of any age received the complete primary series of an authorized/approved vaccine outside of the study or the investigational study vaccine as a primary series, they will also be offered the opportunity to receive Sanofi's investigational CoV2 preS dTM-AS03 monovalent (B.1.351) booster vaccine ≥ 4 months post-last dose of the primary series or encouraged to receive an authorized/approved vaccine according to local guidance.

Participants who initially received the complete primary series of the CoV2 preS dTM-AS03 monovalent (D614) vaccine (Stage 1) or CoV2 preS dTM-AS03 bivalent (D614+B.1.351) vaccine (Stage 2) will be offered the opportunity to receive Sanofi's investigational CoV2 preS dTM-AS03 monovalent (B.1.351) booster vaccine ≥ 4 months post-last dose of the primary series or encouraged to receive an authorized/approved vaccine according to local guidance.

Primed participants with complete primary series	
Placebo recipients who received **EUA vaccines or investigational study vaccine**	CoV2 preS dTM-AS03 **MV(Beta)** (≥ 4 months post-last dose of the primary series)or **EUA** booster vaccination
Participants who received CoV2 preS dTM-AS03 **MV(D614)** or **bivalent** vaccine	CoV2 preS dTM-AS03 **MV(Beta)** (≥ 4 months post-last dose of the primary series) or **EUA** booster vaccination

Abbreviations: EUA, Emergency Use Authorization; MV, monovalent

If participants do not consent to continue with the unblinded crossover/booster, all study procedures will be stopped, and participants will be discontinued from the study and recommended to receive the authorized/approved vaccination series per local guidance.

All participants in the Placebo group will be eligible for crossover vaccination, regardless of whether they have previously experienced SARS-CoV-2 infection or COVID-19.

Participants who are terminated or choose to withdraw from the study will not be eligible for unblinded crossover / booster. Participants receiving any authorized/approved COVID-19 vaccine will not be eligible for crossover vaccination.

Participants in the Vaccine group who completed the primary series and did not receive an authorized/approved vaccine will be eligible for a booster ≥ 4 months post-last dose of the primary CoV2 preS dTM-AS03 vaccine.

Participants in the Placebo group who received the complete primary series of either an authorized/approved vaccine or CoV2 preS dTM-AS03 vaccine will be eligible for a booster ≥ 4 months post-last dose of the primary series.

Treatment: After obtaining consent for Crossover / Booster participation:

Crossover Injection(s) (Stage 1 and Stage 2): If initial injection was placebo (Stage 1 or Stage 2), primary injection(s) of an authorized/approved vaccine outside of the study (interval of doses

dependent on available vaccine and following local standard of care) or 2 primary series injections administered 21 days apart of CoV2 preS dTM-AS03 monovalent (D614) vaccine.

Booster Injection (Stage 1 and Stage 2): A booster injection of Sanofi's investigational CoV2 preS dTM-AS03 monovalent (B.1.351) booster vaccine ≥ 4 months post-last dose of the primary series.

Vaccine contraindications during the crossover period are described in Section 7.1.3 and Section 7.1.4.

Procedures:

At the time of Crossover / Booster, participants will be unblinded and Investigators will inform participants of the available results of the investigational vaccine, provide information on the Crossover / Booster, and discuss the availability of a locally-authorized/approved vaccine (outside of the study) for them prior to obtaining consent for participation in the Crossover / Booster.

If participants do not consent to participation in the Crossover / Booster and a locally-authorized authorized/approved vaccine is available outside of the study, they will be strongly encouraged to obtain the authorized/approved vaccine if available to them, clearly stating that obtaining an authorized/approved vaccines is expected to benefit them.

If participants do not consent to continue with the Crossover / Booster or are naïve participants 18-59 years of age or ≥ 60 years of age and do not receive an authorized/approved vaccine outside of the study, all study procedures will be stopped.

During the initial participant contact, the Investigator will provide the group assignment. After obtaining informed consent from participants to continue the study as part of the Crossover / Booster, participants will receive the primary series and booster injections, as described above.

- For those who initially received an investigational CoV2 preS dTM-AS03 vaccine (see also Table 1.5):
  - 3 blood sample visits: day of booster vaccination (pre-booster) and then 21 days and 6 months post-booster
  - Efficacy follow-up: 12 months post-booster
  - Safety follow-up phone call: 12 months post-booster
- For those who initially received placebo and then receive an authorized vaccine (outside of the study) or Sanofi's CoV2 preS dTM-AS03 monovalent (D614) vaccine (Stage 1) or CoV2 preS dTM-AS03 bivalent (D614+B.1.351) vaccine as primary series (see also Table 1.6):
  - 5 blood sample visits: day of first primary series vaccination (pre-vaccination 1)*, 21 days post-last dose of primary series*, day of the booster dose at ≥ 4 months post-last dose of primary series, 21 days post-booster, and 6 months post-booster
  - Efficacy follow-up: visit ≥ 4 months post-last dose of the primary series and phone call 12 months post-booster
  - Safety follow-up: visit ≥ 4 months post-last dose of the primary series and phone call 12 months post-booster

*Note for those who receive authorized vaccine (outside of the study) as primary series (Crossover vaccination): No protocol deviation will be considered if the corresponding blood sample is missed.

The blood samples will be collected for immunogenicity assessments, correlates of risk analysis and for the determination of naive/non-naive status at the time of the Crossover needed for evaluating durability of vaccine efficacy post-crossover in naive/non-naive individuals.

Unsolicited AEs will be collected up to 21 days after the booster vaccination. MAAEs, SAEs, and AESIs will be collected over the duration of the study including the Crossover / Booster (up to 12 months post-booster). Immediate adverse reactions (ie, occurring in the 30 minutes after vaccination) will be collected after CoV2 preS dTM-AS03 (D614) crossover injections and after booster injection; but immediate adverse reactions will not be collected after receipt of authorized/approved vaccine outside of the study for those who initially received placebo.

In the event that a participant develops symptoms which, based on the investigator's judgement, are consistent with a case of suspected myocarditis and/or pericarditis (eg, acute chest pain, shortness of breath, palpitations, or other signs or symptoms of myocarditis and/or pericarditis) within 6 weeks after vaccination, the site will conduct an unscheduled visit. The site will coordinate an appropriate diagnostic workup to make a determination of probable or confirmed myocarditis and/or pericarditis which may include, but is not limited to, an ECG and/or cardiac troponin testing (T or I). If the diagnostic workup shows abnormal results, the participant will be referred to a cardiologist for evaluation and management. The suspected myocarditis and/or pericarditis case should be reported immediately to the Sponsor within 24 hours as an AESI. Participants with events of myocarditis and/or pericarditis will be discontinued from further vaccination and followed for subsequent visits as per the protocol for safety, immunogenicity, and efficacy endpoints.

Following the Crossover and Booster injections, active and passive surveillance for COVID-19 symptoms will continue as described after the initial, double-blind, primary series study design set of vaccinations.

4.2 Scientific Rationale for Study Design

Rationale for Development Approach

The development approach for the CoV2 preS dTM-AS03 vaccine candidate is undergirded by the fact that it is taking place in the setting of a pandemic. The manufacturing platform is the same as is used to produce licensed recombinant HA influenza vaccine, commercialized in the US and EU. In the context of influenza vaccine development, thousands of younger and older adults have received proteins manufactured utilizing the same technology and similar process employed for this CoV2 preS dTM-AS03 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 dose to be used in the present study (quadrivalent recombinant influenza vaccine contains a total of 180 µg of HA protein; the protein dose of this CoV2 preS dTM vaccine is a maximum of 15 µg in the Phase II study and 10 µg in the Phase III 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, for a variety of different protein constructs and for the feasibility of developing a multivalent COVID-19 vaccine.

AS03 has been administered to many thousands of individuals (adults and elderly) as part of clinical studies of influenza vaccines as well as other vaccines (21). Notably, more than 20,000 older adults received AS03-adjuvanted influenza vaccine in a large, multi-country efficacy study (66). Furthermore, it is estimated that approximately 90 million doses of AS03-adjuvanted H1N1 vaccines were administered post-licensure in the context of H1N1 pandemic control (32). These studies and post-licensure data showed that AS03 enhanced antibody and T cell responses with an acceptable safety profile.

Recombinant proteins produced in the baculovirus manufacturing platform have been administered with AS03. 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 well tolerated with an acceptable safety profile and led to robust immune responses.

Sanofi initiated development of a recombinant protein vaccine consisting of a stabilized prefusion trimer of the SARS-CoV-2 S protein based on the work by Wrapp and colleagues (13) and using the AS03 adjuvant to optimize the immune response. A monovalent vaccine with the S protein sequence from the D614 variant (USA-WA1/2020 strain) was initially developed. Following the global spread of the D614 strain first identified in Wuhan, China, new, highly transmissible SARS-CoV-2 VOCs have emerged and are spreading globally. There has been particular emphasis on developing variant strain vaccines to protect against new variants emerge as current COVID-19 vaccines based on Spike protein from the D614 strains show modest levels of protection against new variants. To combat the emergence of variant strains, Sanofi is also developing a bivalent vaccine formulation with 2 recombinant prefusion delta TM proteins encoding the S protein sequence from the D614 strain and the Beta (B.1.351) variant (CoV2 preS dTM-AS03 [D614 + B.1.351]). This bivalent vaccine adjuvanted with AS03 is being tested in the Phase III efficacy study VAT00008 and Phase III Supplemental cohorts of study VAT00002. In this later study (VAT00002 - Supplemental Phase III Cohorts), Sanofi is developing a universal booster of the CoV2 preS dTM-AS03 vaccine as both monovalent vaccines containing either D614 strain or Beta (B.1.351) strain.

Nonclinical studies in multiple animal models with the monovalent D614 CoV2 preS dTM vaccine with adjuvant have demonstrated induction of immune responses and protection against viral challenge. This monovalent CoV2 preS dTM vaccine was evaluated with AS03 in the Phase I/II study (VAT00001) in healthy adults 18 years of age and older. A low-dose and a high-dose formulation corresponding to an effective dose of 1.3 µg and 2.6 µg of antigen were evaluated in the study (35). No related serious adverse events (SAEs) were observed in the study although higher than expected Grade 3 reactogenicity was observed after the second injection in the adjuvanted groups. Interim immunogenicity data showed that an antigen effective dose of 2.6 µg in a 2-injection schedule with the AS03 adjuvant induced the highest titers of neutralizing antibodies across all groups with no indication of a Th2 bias in the cell-mediated response with a

consistent elicitation of Interferon gamma responses (see Section 2.2). The interim data from this Phase I/II study showed a lower immune response in older adults and higher than expected reactogenicity.

A Phase II randomized, modified double-blind study (VAT00002 Original Cohort) in which safety, reactogenicity, and immunogenicity of 3 different doses of monovalent antigen (5 µg, 10 µg, and 15 µg) D614 CoV2 preS dTM-AS03 administered as 2 injections 21 days apart was initiated. Interim results from the Original Cohort this Phase II study showed a similar safety profile across antigen dose groups. A high proportion of 2-fold and 4-fold or greater rise in neutralizing antibody titers after 2 injections was observed in both younger and older naïve adults with similar proportions observed across the different antigen dose groups. Neutralizing antibody titers against D614G were generally consistent, comparable to a panel of human convalescent sera and without clear evidence of a dose effect across treatment groups in the overall study population (18 years and older). A pattern of higher neutralizing antibody titers with higher antigen doses was observed in the younger adult population; this was not evident in the older age group. These interim data on safety, reactogenicity, and immunogenicity from this Phase II study informed progression to Phase III and the dose of antigen to be used in the Phase III study (see Section 4.3).

VAT00008 is a Phase III, randomized, modified double-blind, placebo-controlled, multi-stage, multi-center, multi-country study to assess the efficacy, safety, and immunogenicity of two CoV2 preS dTM-AS03 vaccines (monovalent and bivalent) in adults 18 years of age and older with 2 stages. In Stage 1, the AS03 adjuvanted monovalent vaccine with the prefusion S protein from the prototype (D614) variant will be evaluated against a placebo control. In Stage 2, the AS03 adjuvanted bivalent vaccine with prefusion S protein from the prototype and South African Beta variant (D614 + B.1.351) will be assessed against a placebo control. Both stages are considered independent to enable generation of data to support licensure of each candidate vaccines (ie, the monovalent and bivalent vaccine). This bivalent vaccine adjuvanted with AS03 will be tested in this Phase III efficacy study without a safety lead-in based on the clinical data on safety, reactogenicity, and immunogenicity generated with the monovalent vaccine; similarity in manufacturing process for two CoV2 preS dTM components of the bivalent products compared to the monovalent product; similarity in construct design supporting a similar safety profile to the monovalent vaccine; and the total antigen content of the pre-S antigen in the bivalent vaccine (10 µg) is the same as the monovalent vaccine used in the Phase III study. The bivalent vaccine was tested in an immunogenicity study in naive NHPs assessing the bivalent formulation at at doses of 2.5, 5 and 10 µg per component adjuvanted with AS03 alongside the monovalent D614 and monovalent B.1.351 vaccines. Three weeks after the second vaccination, neutralizing and binding antibodies were observed in all macaques with all three antigen doses of the bivalent vaccine. The neutralizing antibody titers against the D614G strains induced by the bivalent vaccine were slightly lower to those induced by the monovalent D614 vaccine (2- to 3-fold lower and mainly in the low-dose group). Comparing the bivalent at 5 µg + 5 µg with monovalent D614 vaccine at 10 µg, the actual planned doses for VAT00008, the differences on D614 neutralizing antibody titers where not statistically significant suggesting limited immune interference at higher antigen doses and when comparing the same total antigen dose between the monovalent and bivalent vaccine. Neutralizing antibody titers against known VOCs (B.1.351, B.1.1.7, B.1.1.28, and B.1.617.2) were assessed in the study. Compared to the monovalent D614 vaccine, the bivalent vaccine induced much higher titers against the B.1.351 and B.1.1.28 variants, and comparable neutralization of the currently 2 most widely circulating B.1.1.7 and B.1.617.2

variants. Compared to the monovalent B.1.351 vaccine, the bivalent vaccine induced much higher neutralizing antibody titers against the parental D614 and D614G strains, as well as against B.1.1.7 and B.1.617.2 variants. These data generated in naïve NHPs showing balanced neutralization of all known VOCs to date with the bivalent vaccine (D614+B.1.351), limited interference against the D614G variant compared to the monovalent D614 vaccine support the evaluation of the bivalent vaccine in VAT00008 Stage 2. Preliminary data on efficacy in hamsters demonstrated that all AS03-adjuvanted vaccine formulations (D614, B.1.351 and D614+B.1.351) conferred protection against body weight loss caused by infection with the B.1.351 (Beta) variant.

Justification for primary and key secondary endpoints

Efficacy against symptomatic COVID-19 (confirmed by NAAT) is the proposed primary endpoint as it is clinically meaningful, and illness endpoints are generally preferred and accepted by regulatory bodies for other vaccines against COVID-19. The primary endpoint includes symptomatic COVID-19 disease of any severity (Section 8.2.1.1), which is consistent with other authorized vaccines.

In addition to the primary endpoint, hypothesis testing will be performed for assessing vaccine efficacy against SARS-CoV-2 infection and against severe COVID-19.

Prevention of severe COVID-19 is relevant as it represents the spectrum of disease generating the largest burden of illness associated with SARS-CoV-2 infection related to loss of function or life.

Prevention of SARS-CoV-2 infection as determined by a positive antibody test against the SARS-CoV-2 Nucleoprotein or a positive NAAT on respiratory sample is proposed as a key secondary endpoint for demonstrating vaccine efficacy. The high proportion of asymptomatic infections (30% to 50%) and evidence of asymptomatic transmission makes prevention of infection, independent of development of symptoms, a clinically relevant outcome in the context of the pandemic (24) (79) (26) (43). Assessment of serological SARS-CoV-2 infection would detect antibodies against a non-S protein of SARS-CoV-2 virus that would enable differentiation of antibodies induced by infection and vaccination (because vaccination is only expected to generate antibody responses to the S protein, while infection is expected to generate antibodies against non-S proteins as well). The ascertainment of serological infection will be performed on samples collected prior to vaccination (D01), 21 days after the last vaccination, and at 2 months, 4 months, 6 months, 9 months, and 12 months post-last vaccination timepoints. Samples collected prior to first vaccination and 21 days after last vaccination would serve as baseline measurements to assess antibody seroconversion in samples collected at later timepoints during the study.

Justification for the age range and study population

The study will be conducted in adults 18 years of age and older with stratification by 2 age groups: 18-59 years of age and 60 years and older. The study targets recruitment of approximately 40% of the study population above 60 years of age and stratification of this age-group ensures the benefits of randomization within this age-strata. The incidence of disease is higher in adults compared to children, with older adults at highest risk of severe disease, hospitalizations, and death compared to younger adults. No upper age-range is specified and participants with medical conditions associated with higher risk of COVID-19 disease (detailed in Section 5.3) will not be excluded from the study.

The first analyses from Stage 1 showed that the number of participants older than 60 years recruited in the study was limited to 8% because they were the priority eligible population for vaccination at the time the study was conducted. For this reason, the number of cases observed in this population was limited and vaccine efficacy in this age group could not be accurately estimated. However, the high antibody titers obtained after booster administration in the VAT02 study are supportive of booster vaccination in this age group.

Moreover, to ensure evaluation of vaccine performance in high-risk groups, the study will target enrollment of approximately 35% of participants enrolled in the 18-59 years age group with at least one of the high-risk medical conditions. Participants with well-controlled human immunodeficiency virus (HIV) infection will not be excluded from the study. All sites will target to have community outreach programs to ensure that ethnic and racial diversity will be, at a minimum, representative of the population of the country in which the study is being conducted.

Justification for modified double-blind (observer-blind) design during the entire study

The study is a modified double blind (observer-blind) study. Designated site staff involved in preparing the vaccine will be unblinded because the vaccine formulation will be prepared by mixing the recombinant protein and adjuvant at the study site out of sight of the participant while the placebo does not require mixing, and the appearance of the vaccine formulation is different to the placebo. Study staff involved in administering the vaccine may be blinded to the vaccine formulation if they are not involved in preparing the vaccine. The Investigator/Sub-investigator/staff involved in the safety assessment and surveillance will be blinded in order to decrease the risk of potential bias in safety and efficacy assessments. Laboratories performing the assays evaluating immunogenicity and efficacy endpoints will be blinded to study intervention.

Rationale for placebo

Placebo will be used for comparison to vaccine to allow safety comparisons. 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 study intervention group and is the most scientifically rigorous way to assess absolute efficacy of the candidate vaccine. Randomized, placebo-controlled trials provide unbiased estimates of vaccine safety and efficacy with absolute vaccine efficacy determined by comparing the reduction in the incidence of disease in groups receiving vaccine compared to groups receiving a placebo control. The comparison to a placebo group allows the unbiased evaluation of safety and clinical outcomes related to COVID-19-like illness and SARS-CoV-2 infection by study intervention group and is the most scientifically rigorous way to assess absolute efficacy of the candidate vaccine.

A consultation organized by the WHO concluded that in settings where vaccine supplies are limited, where vaccines remain investigational and/or where public health recommendations for use of these vaccines have not been made, a placebo-controlled study is ethically appropriate and remains the most robust scientific approach to generate data on efficacy of new vaccines (1). A recent commentary from an ethics committee that approved the conduct of a placebo-controlled trial provide similar rationale for their approval (80). While in the context of deployment of currently authorized COVID-19 vaccines which have demonstrated high efficacy in some regions a head-to-head randomized efficacy trial may be considered, such a non-inferiority efficacy trial would be very large and operationally challenging to conduct in a timely manner. Therefore, it is

proposed to conduct this Phase III placebo-controlled efficacy study in regions and in subgroups of populations where the conditions outlined above are met at the time of conduct of the study.

The recommendations and guidance have been deliberated and taken into consideration in the development and conduct of this study. Key aspects of the protocol are highlighted below, which operationalize the considerations into protocol-defined strategies to minimize risk to participants, particularly those receiving placebo, during study conduct.

- Before the enrollment in the study:
  In regions where an approved/authorized vaccine is available, and the participant is eligible for receiving vaccine (based on the prioritization strategy for vaccine deployment) at the time of enrollment, investigators will encourage prospective participants to obtain the approved/authorized vaccine if applicable to them as stated in the synopsis and Section 6.6.

  This ensures that investigators take the opportunity to educate participants about authorized/available vaccines in the region, discuss the appropriateness of this study for the participant and offer a health-information resource to participants regarding COVID-19 vaccines. It may also be the case that individuals would like to access approved vaccines but they are not locally available, or are only available to select groups within the population. In those cases, participants may be enrolled in the study but will continue to be informed about their options to receive an approved vaccine should it become available at some point during the trial.

- While the participant is enrolled in the study:
  There is no prohibition to receive the authorized/approved COVID-19 vaccine. The participant can decide any time during the study to get an authorized/approved COVID-19 vaccine.

  All participants can request being unblinded to the study intervention to enable making the decisions on receiving the available (authorized or approved) vaccine at any time during the trial. The trial protocol responds to the recommendation mentioned above to extend the request for unblinding to ALL participants regardless of their risk status as described in Section 6.6.

  Participants who receive the authorized/available vaccine will be offered the opportunity to continue participation in the trial, if they wish to do so. This provision enables continued monitoring of safety for participants, generating data on the safety, immunogenicity and efficacy of an authorized/available vaccine.

- Access to the study vaccine for placebo recipients:
  An unblinded crossover design is planned to ensure all participants obtain the benefit of vaccination. Unblinding will allow participants to make an informed decision and study Investigators to customize the best option for each participant. For non-naïve participants who initially received placebo and are 18-59 years of age, the study Investigators will inform

participants and discuss the possibility of receiving the available (authorized or approved) vaccines or, the investigational CoV2 preS dTM-AS03 monovalent (D614) vaccine. Naïve participants 18-59 years of age and all participants ≥ 60 years of age who initially received placebo will be recommended to receive an authorized/approved vaccine. Regardless of the vaccine chosen for the primary series as part of Crossover, participants will also be offered to receive Sanofi's investigational CoV2 preS dTM-AS03 monovalent (B.1.351) booster vaccine ≥ 4 months post-last dose of the primary vaccination schedule or encouraged to receive an authorized/approved vaccine according to local guidance. A booster vaccination with Sanofi's investigational CoV2 preS dTM-AS03 monovalent (B.1.351) booster vaccine ≥ 4 months post-last dose of the primary vaccination schedule will also be offered to participants who initially received the vaccine, to optimize the immune response in both Placebo and Vaccine group participants.

4.3 Justification for Dose

The dose of the monovalent and bivalent vaccines and dosing schedule chosen in this study are based on results from nonclinical studies in animal models, manufacturing capacity limitations, and results from the Phase I/II safety and immunogenicity study (VAT00001) and Phase II safety and immunogenicity study (VAT00002). Interim data from the Phase I/II study showed that a single injection did not generate meaningful neutralizing titers above background and that a 2-injection schedule of the adjuvanted protein was necessary to induce neutralizing antibodies.

The effective dose of antigen administered in the Phase I/II study were 1.3 µg and 2.6 µg of functional SARS-CoV-2 S protein. Lower than expected immunogenicity was observed in the Phase I/II study, particularly in the older adults, indicating the need for evaluation of higher antigen doses. In a nonclinical study in NHPs using an effective dose of 4 µg and 12 µg of recombinant protein with AS03 adjuvant to assess efficacy against SARS-CoV-2 viral challenge, both doses conferred robust protection against viral replication in the lower and upper airways after a challenge with a virulent viral stock (NR-53780 BEI stock). Strong reduction of viral replication was demonstrated on D02 and D04, with a trend for a higher reduction in the high dose vaccine group. The pathology and inflammation in the lungs induced by infection 7 days post-challenge was clearly reduced in the immunized Rhesus macaques, and no increase in inflammatory cytokines or chemokines was observed. At both low and high doses, the AS03-adjuvanted vaccine elicited high humoral (binding, functional and neutralizing antibodies) and cellular (Th1/Th2 balanced S-specific cytokine responses and Tfh cells 2 weeks post-boost) responses. These data provide support to the hypothesis that improved formulation with higher antigen doses might improve vaccine performance.

In addition to the data generated with the vaccine candidate in NHPs and in the clinical Phase I/II study, historical data generated with vaccines for pathogens different than SARS-CoV-2 as well as other SARS-CoV-2 protein vaccines candidates further inform the desirable dose range being assessed in the Phase II study to inform Phase III dose selection:

- 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. AS03 adjuvanted arms demonstrated robust responses even with the lowest antigen level (81).

- 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. In this study, robust humoral immune responses were observed in the AS03 adjuvanted arms against homologous and heterologous H7 influenza strains. 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.
- A recombinant prefusion stabilized SARS-CoV-2 S protein vaccine manufactured in baculovirus expression system adjuvanted with Matrix-M1 adjuvant has shown high immune responses against SARS-CoV-2, and an adjuvanted protein dose of 5 µg administered in a 2-injection schedule has advanced to Phase III studies (82).
- A stabilized prefusion form of the SARS-CoV-2 spike protein produced by transient expression in *Nicotiana benthamiana* and displayed as a viral-like particle demonstrated promising immune responses when administered in a 2-dose regimen with adjuvants in an early clinical study. A dose of 3.75 µg adjuvanted with AS03 has advanced to late stage clinical trials (36).
- A protein subunit vaccine candidate composed of a stabilized trimeric form of the S-protein produced in CHO cells showed promising responses when administered with adjuvants. A dose of 9 µg adjuvanted with AS03 administered in a 2-injection scheduled has been selected to advance to late stage clinical studies (83).

The total antigen dose of S protein used in the monovalent and bivalent vaccines in Phase III are based on the Phase II (VAT00002 Original Cohort) clinical data, nonclinical data, and manufacturing supply considerations. Interim data on safety, reactogenicity, and immunogenicity from the Phase II study informed the selection of antigen dose for the Phase III study.

In the Phase II study (VAT00002), pre-defined criteria were proposed in interaction with regulatory authorities for all antigen dose groups to be considered for selection for the Phase III study. All the antigen dose groups in the study met all the following criteria and accordingly can be considered for selection for the Phase III study.

Safety:

- An observed frequency of < 20% of participants in the vaccine group with any Grade 3 systemic reaction up to 7 days after any injection
- An observed frequency of < 10% of participants in the vaccine group with Grade 3 injection site pain within 7 days after any injection
- An observed frequency of < 5% of participants in the vaccine group with any Grade 3 unsolicited Adverse Reactions up to 21 days after the last injection
- No other safety concerns deemed unacceptable based on review of SAEs, AESIs and MAAEs

Immunogenicity

- Seroconversion rate of ≥ 90% in younger adults (18-59 years of age) based on neutralizing antibodies in SARS-CoV-2 naïve adults

- Seroconversion rate of ≥ 75% in older adults (≥ 60 years of age, including those with high risk conditions) based on neutralizing antibodies in SARS-CoV-2 naïve adults

The reactogenicity and safety profile was similar across antigen dose groups and therefore the choice of antigen dose is largely dependent on the observed immunogenicity profile in the naïve adults.

The neutralizing antibody responses to D614G were generally consistent without clear evidence of a dose effect across treatment groups in the overall naive population (18 years and older). A pattern of higher neutralizing antibody titers with higher antigen doses was observed in the younger adults age group; this pattern was not evident in the older age group.

The ratio of neutralizing antibody responses in vaccinees compared to human convalescent sera have been modeled to correlate with observed vaccine efficacy against the homologous variants. In these models, ratios of 1 correlate to vaccine efficacy of ~80-90% and ratios of 0.8 correlate to vaccine efficacy of ~70-80% (84) (85). This relationship is modeled for neutralizing antibody responses and efficacy against the homologous variants and it may be expected that against heterologous variants, the predicted vaccine efficacy will be lower for a similar ratio of vaccine-induced antibody response to human convalescent sera (HCS).

In the VAT00002 study, the GMTs observed at D36 in the overall study population were comparable to GMTs observed in a panel of human convalescent sera (GMT 2140; 95% CI: 1543, 2967; N=79) measured in the same pseudovirus neutralizing assay, laboratory and time frame. In younger adults, the ratio of neutralizing antibody titers to HCS was > 1 (ie, 1.37, 1.85, and 2.25, respectively) in the younger naïve adults; and in the older adults, the ratio was 0.7 - 0.75 (for all 3 doses). Based on these pseudovirus neutralizing ratios (vaccine induced/HCS) there is expected to be little difference in vaccine protection between antigen dose levels. However, this conclusion is applicable to homologous variants or variants associated with only small drifts in neutralizing activity. Based on available preclinical data with the vaccine candidates tested in this study and additional data from other vaccines, neutralizing antibody titers against B.1.351 and P.1 variants are likely to be lower. In the context of changing epidemiology, selection of 10 µg antigen dose for the D614 monovalent vaccine for the Phase III study is expected to mitigate the potential impact of variant circulation as it may provide greater cross-reactive antibody titers against variant strains. It is also likely that a higher antigen dose would provide greater durability of response and improve the avidity of antibody responses over time. The predicted vaccine efficacy curve based on vaccine induced/HCS antibodies begins to plateau at ratios close to 2. Increasing the ratio from 1.85 for the 10 µg dose to 2.25 for the 15 µg dose is only expected to marginally increase vaccine efficacy based on these models. Importantly, in the context of a pandemic, a lower antigen dose would translate into a significant increase in vaccine supply.

Therefore, the 10 µg dose for the monovalent D614 vaccine was selected to be tested in Stage 1 of the Phase III trial. This selection mitigates the risk of having lower titers against variants that would be circulating at the time of the efficacy trial with potential to result in lower observed vaccine efficacy for the monovalent D614 vaccine than predicted by the above-mentioned models.

For Stage 2 of the Phase III trial with the bivalent, D614 + B.1351adjuvanted vaccine, a 5 µg (D614 component) + 5 µg (B.1.351 component) antigen dose was selected. The 5 µg antigen dose with the D614 vaccine provides homologous neutralizing antibody responses comparable to convalescent sera in the overall naïve population. It is reasonable to expect that similar

homologous responses would be elicited by the B.1.351 component of the bivalent vaccine. Thus, by design, the inclusion of the B.1.351 antigen with the D614 antigen in the bivalent vaccine mitigates the risk of lower antibody responses against circulating variants anticipated with the monovalent D614 vaccine.

Supplemental Phase III Cohorts are being tested as part of VAT00002 study to allow the evaluation of the potential use of CoV2 preS dTM-AS03 to boost responses in individuals previously vaccinated with other platforms; for this purpose, the study is assessing the safety and immunogenicity of different formulations of the CoV2 preS dTM-AS03 vaccine, including monovalent (D614 and B1.351) and bivalent (D614 + B.1.351) formulations, for use as a universal late booster. The study will also further evaluate the safety and immunogenicity of Beta (B.1.351) variant-containing vaccine formulation (CoV2 preS dTM-AS03 [B.1.351]) in the context of primary immunization of naïve, previously unvaccinated individuals. Interim analysis results from Supplemental Phase III Cohort 1, Cohort 2 (protein primed group), and comparator group of VAT00002 study showed that a single 5 µg dose of the CoV2 preS dTM-AS03 (D614) vaccine provided an effective boost to the neutralizing Ab response among individuals primed with one of the four widely deployed priming vaccines (heterologous vaccine) or primed with homologous vaccine CoV2 preS dTM-AS03 (D614). Overall, no safety concerns were identified, nor any specific risk group identified for whom safety was of concern. Among participants receiving a 5 µg booster dose of the CoV2 preS dTM-AS03 (D614) vaccine, there was a favorable safety profile. The safety profile is consistent across all priming groups, except for an increase of reactogenicity with the homologous primed group. No safety issues were identified in subgroups (defined by age or the presence of a high-risk medical condition). These safety data are supportive of the use of a CoV2 preS dTM-AS03 vaccine as a 5 µg booster, regardless of priming vaccine.

Conclusions on dose selection for Phase III trial:

- Monovalent D614 vaccine: 10 µg D614 antigen + AS03 selected for Stage 1
- Bivalent D614 + B.1.351 vaccine: 5 µg D614 antigen + 5 µg B.1.351 antigen + AS03 selected for Stage 2

Justification for crossover vaccination with CoV2 preS dTM-AS03 monovalent (D614) vaccine

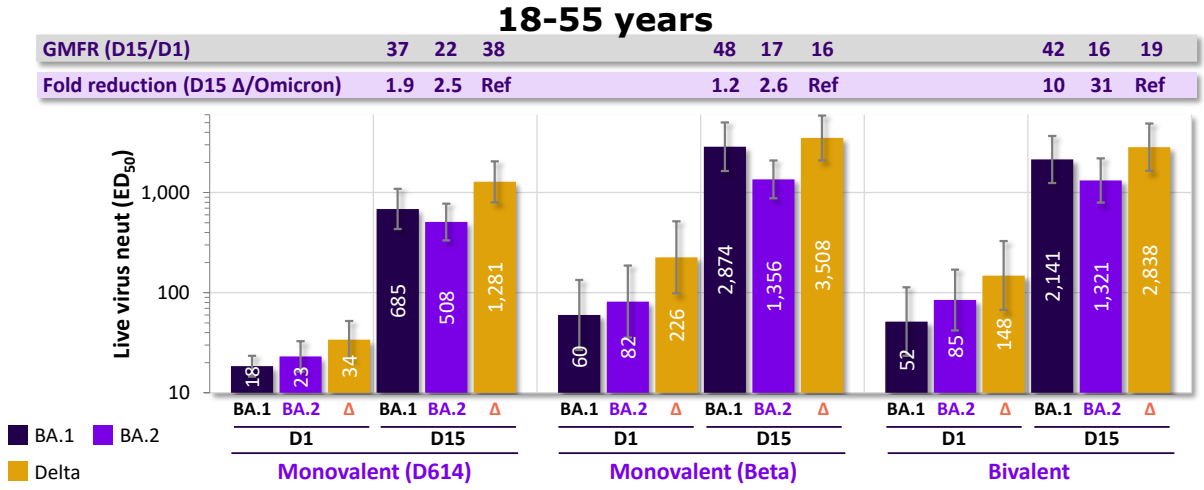
The use of the CoV2 preS dTM-AS03 monovalent (D614) vaccine for crossover vaccinations of non-naïve participants aged 18-59 years is proposed because both the monovalent D614 and bivalent (D614+B.1.351) vaccines demonstrated efficacy against Omicron in non-naïve participants, with evidence of durability after monovalent D614. In fact, the efficacy of the bivalent vaccine against Omicron in non-naïve participants was 73.8% [95% CI: 53.9; 85.9] at 2 months post-vaccination (based on sensitivity analysis) and the efficacy of the monovalent D614 against Omicron at 4-6 months post-vaccination was 53.4% [95% CI: 13.2; 76.0]; however, the durability of the efficacy of the bivalent formulation has not yet been established. The results of the primary analyses on efficacy in Stage 1 of the VAT00008 study showed that the efficacy against symptomatic COVID-19 in SARS-CoV-2 naïve adults, 14 days after the second injection was 57.9% [95.86% CI: 26.5; 76.7]. Although the vaccine efficacy point estimate was over 55%, the lower bound of the adjusted confidence interval was not above 30%; therefore, the primary endpoint of the study was not met. The clinical data show that the product is well tolerated with an acceptable safety profile.

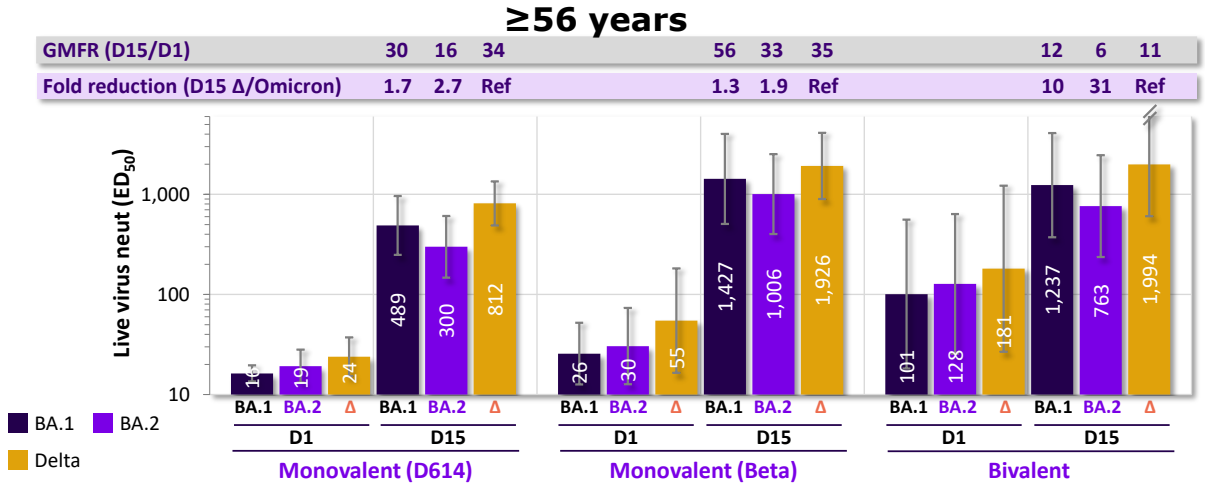
In addition, the more rapid availability of monovalent D641 will expedite the onset of the crossover/booster vaccination and decrease the time participants may be at risk.

Justification for booster vaccination with CoV2 preS dTM-AS03 monovalent (B.1.351) vaccine

The benefit of a booster dose with non-adjuvanted CoV2 preS dTM (B.1.351) or AS03-adjuvanted CoV2 preS dTM (D614), (B.1.351) or (D614+B.1.351) was demonstrated in mRNA-primed and subunit-primed macaques, as described in Section 2.2. The booster vaccines induced very high and durable neutralizing antibodies against the 4 VOC Alpha, Beta, Gamma and Delta and robust neutralization of the more antigenically distant Omicron and SARS-CoV-1 (31). In addition, boosting with the CoV2 preS TM vaccine candidates expanded the S-specific memory B cell population generated post primary vaccination, especially in animals with low responses after the prime, to same levels as those reported after mRNA immunization in NHPs (86). The recall response was observed whatever the vaccine formulation used (homologous D614, heterologous B.1.351 or bivalent, with or without adjuvant).

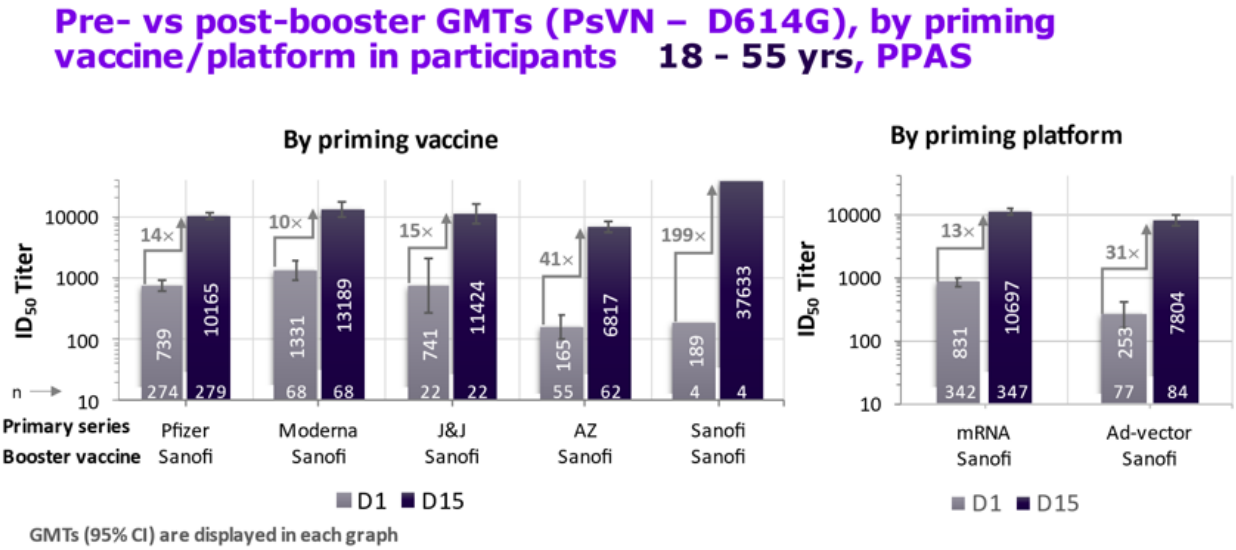
In addition to the non-human primate data, preliminary data was generated from a subset of participants in the VAT00002 clinical trial who received a single injection of the Monovalent Beta Booster vaccine, the Monovalent D614 booster and Bivalent booster (D614+B.1.351 strains) 4-10 months after receiving a primary series of the Pfizer BNT162b2 vaccine. Participants were 18 years of age or older, not pregnant and provided written informed consent prior to enrolment. Individuals receiving the monovalent D614 booster were enrolled in Cohort 1 between July and August 2021 while individuals in Cohort 2 were randomly allocated in a 1:1 ratio to receive either the monovalent Beta or Bivalent booster vaccine and enrolled between November and December 2021. These studies are ongoing. In this preliminary dataset, a convenience sample of 20 participants 18-54 years of age and 10 participants 55 years and older provided sera samples prior and 15 days after boost. Neutralizing antibodies using a live-virus neutralization assay were measured against Delta VOC, BA.1 and BA.2 VOC.





These results show the magnitude of cross-reactive neutralizing antibodies against both Omicron sublineages (BA.1 and BA.2) were observed with all three booster vaccine candidates in younger and older adults. In this small subset of participants, it was observed that the Beta booster candidate was similar in performance to the Monovalent D614 booster vaccine providing early clinical evidence for use of the monovalent beta booster in this study.

Additional data show that the Beta booster induces high antibody titers after homologous (investigational monovalent D614 vaccine) and heterologous (authorized/approved vaccines) primary series and titers do not differ if the booster is a monovalent B.1.351 or bivalent (D614+B.1.351) vaccine. In the VAT00002 study, the monovalent B.1.351 booster responses were comparable to those induced by bivalent (D614+B.1.351) booster after heterologous boosting. In addition, the monovalent B.1.351 booster following monovalent D614 prime generated ~ 3 times higher neutralizing titers compared to heterologous boosting (see below).



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 (CSR) 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. This study is designed to be pragmatic to maximize representation of the broader population by minimizing exclusionary eligibility criteria and allowing the participation of individuals with a broad range of medical conditions, including controlled HIV infection, Hepatitis B and Hepatitis C, and conditions associated with an increased risk of severe COVID-19. It is also designed to be inclusive of other subpopulations affected by COVID-19, including older adults as well as ethnic and racial minorities.

If an approved/authorized vaccine is available in the country or region where the study is conducted and the participant is eligible for receiving vaccine (based on the country prioritization strategy for vaccine deployment) at the time of enrollment, investigators will discuss this information with prospective study participants at the time of informed consent who will be encouraged to obtain the approved/authorized vaccine if applicable to them. Recruitment of eligible participants will proceed only if, despite encouragement, the candidate participant expresses no intention to seek an authorized or approved vaccine at the time of enrollment.

5.1 Inclusion Criteria

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

Age

I01: Aged 18 years or older on the day of inclusion

Type of participant and disease characteristics

I02: For persons living with HIV, stable HIV infection determined by participant currently on antiretrovirals with CD4 count > 200/mm^3

I03: SARS-CoV-2 rapid serodiagnostic test performed at the time of enrollment to detect presence of SARS-CoV-2 antibodies

I04: Does not intend to receive an authorized/approved COVID-19 vaccine despite encouragement by the Investigator to receive the authorized vaccine available to them at the time of enrollment[a]

Sex, contraceptive/barrier method and pregnancy testing requirements

I05: A female participant is eligible to participate if she is not pregnant or breastfeeding and one of the following conditions applies:

- Is of non-childbearing potential. To be considered of non-childbearing potential, a female must be post-menopausal for at least 1 year or surgically sterile.
  -
  - OR
  -
- Is of childbearing potential and agrees to use an effective contraceptive method or abstinence from at least 4 weeks prior to the first study intervention administration until at least 12 weeks after the second study intervention administration.

A participant of childbearing potential must have a negative highly sensitive pregnancy test (urine or serum as required by local regulation) within 25 hours before any dose of study intervention.

Informed Consent

I06: Informed consent form has been signed and dated

Other Inclusions

I07: Able to attend all visits and to comply with all study procedures

I08: Covered by health insurance, only if required by local, regional or national regulations

5.2 Exclusion Criteria

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

Medical conditions

E01: 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[b]

E02: Dementia or any other cognitive condition at a stage that could interfere with following the study procedures based on Investigator's judgment

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[a] While recruitment of eligible participants will proceed only if the candidate participant expresses no intention to seek an authorized or approved vaccine at the time of enrollment, if the participant is enrolled and seeks vaccination of an authorized/approved vaccine outside of the study, he/she will be encouraged to discuss this intention proactively with the trial investigator and will be permitted to receive the authorized vaccine at any time. 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 efficacy and safety. Participants will continue to be followed for the duration of the study as per scheduled visits and procedures. Participants will not receive the second vaccination if they have received the authorized/approved vaccine between the first and second scheduled vaccination (see Section 7.1.2 : Definitive Contraindications).

[b] The components of SARS-CoV-2 Recombinant Protein vaccines are listed in Section 6.1 and in the monovalent and bivalent CoV2 preS dTM Investigator's Brochures and the AS03 adjuvant Investigator's Brochure.

E03: Self-reported thrombocytopenia, contraindicating intramuscular (IM) vaccination based on Investigator's judgment

E04: Bleeding disorder, or receipt of anticoagulants in the past 21 days preceding inclusion, contraindicating IM vaccination based on Investigator's judgment

E05: Unstable acute or chronic illness that in the opinion of the Investigator or designee poses additional risk as a result of participation or that could interfere with the study procedures

E06: 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

Prior/concomitant therapy

E07: Receipt of any vaccine in the 30 days preceding or on the day of the first study vaccination or planned receipt of any vaccine between the first study vaccination and in the 30 days following the second study vaccination except for influenza vaccination, which may be received at any time in relation to study intervention.

E08: Prior administration of a coronavirus vaccine (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2], SARS-CoV, Middle East Respiratory Syndrome [MERS-CoV])

E09: Receipt of solid-organ or bone marrow transplants in the past 180 days

E10: Receipt of anti-cancer chemotherapy in the last 90 days

Prior/concurrent clinical study experience

E11: 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 study investigating a vaccine, drug, medical device, or medical procedure

Other exclusions

E12: Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily

E13: 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

Depending on country regulations and feasibility, if the participant has a primary physician who is not the Investigator, the site may contact this physician with the participant's consent to inform him / her of the participant's participation in the study. In addition, the site may ask this primary physician to verify exclusion criteria including but not limited to previous therapies, such as previous vaccines.

5.3 High-Risk Medical Conditions

High-risk conditions are conditions considered to be associated with an increased risk of severe COVID-19 (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/evidence-table.html) and include:

- cancer
- chronic kidney disease
- chronic obstructive pulmonary disease (COPD)
- immunocompromised state from solid organ transplant
- immunocompromised state from other causes (blood or bone marrow transplant, immune deficiencies, HIV, use of corticosteroids, or use of immunosuppressors)
- obesity (body mass index of 30 or higher)
- heart conditions such as heart failure
- coronary artery disease or cardiomyopathies
- sickle cell disease
- thalassemia
- type 1 or type 2 diabetes mellitus
- moderate-to-severe asthma
- cerebrovascular disease
- cystic fibrosis
- hypertension/high blood pressure
- neurologic conditions
- hepatic disease
- pulmonary fibrosis
- smoking

The study will seek to maximize enrollment of participants with high-risk medical conditions. Specifically, it is planned to target recruitment of approximately 35% of participants 18-59 years of age with at least one of the high-risk medical conditions listed above.

5.4 Representation of Study Subpopulations

The study targets representation of specific study subpopulations by capping or targeting the number of participants in specific subpopulations.

Participants who are SARS-CoV-2 non-naïve at baseline will be capped to approximately 30% of the total study population in Stage 1 (up to ~1524 participants/arm). The target for SARS-CoV-2 non-naïves is ~1633 participants/arm in Stage 2. The objective is to ensure a sufficient number of participants/arm who are SARS-CoV-2 naïve at baseline are enrolled to achieve the power of the study. To achieve this, all participants will be tested for antibodies to SARS-CoV-2 at Visit 1 (V01) using a rapid serodiagnostic test to determine enrollment in the study. Participants with antibodies to SARS-CoV-2 as determined by rapid serological test at the time of enrollment will be included in the study until the study reaches a pre-defined size triggering the need to restrict further recruitment to individuals testing negative on the rapid serological test, in order to secure that a maximum of ~30% of the total study population will be SARS-CoV-2 non-naive.

The Stage 1 cap of 30% serodiagnostic test positive participants may not be reached before completion of enrollment, but if it is reached, then from that point on only candidate study participants who test negative on the rapid serodiagnostic test will be enrolled. If the crossover is

not implemented, recruitment will continue until the minimally required number of naïve participants to assess efficacy is enrolled (even if the overall enrollment target is reached).

The study will target enrollment of older adults (≥ 60 years of age) with a recruitment target of approximately 40% of the study population in each stage. Within the age group of 18-59 years of age, the study will target inclusion of approximately 35% of participants with high-risk medical conditions for COVID-19. The study will target recruitment of racial and ethnic diversity that will be representative of the countries in which the study will be conducted.

In addition, it may be necessary to cap the number of participants in specific age-groups in particular countries based on availability and deployment of an authorized/approved vaccine. Prospective study candidates belonging to any of the capped subpopulations may be excluded once the cap is reached for the corresponding category.

5.5 Lifestyle Considerations

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

5.6 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.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria not met, capping condition reached, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) can be rescreened if the exclusionary condition is considered to be temporary in nature by the investigator.

6 Study Interventions and Concomitant Therapy

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.

Note: Vaccines or products administered outside of study protocol are not considered as study interventions and are reported in the CRF as reportable medications (see Section 6.9). Study procedures (eg, blood sampling) are also not considered as study interventions.

6.1 Study Interventions Administered

Study interventions are described in Table 6.1.

Table 6.1: Identity of study interventions

CoV2 preS dTM-AS03 (D614) (recombinant, adjuvanted)	
Intervention Names	**COVID-19 vaccine (recombinant, adjuvanted) or CoV2 preS dTM-AS03 (D614)**
Use	Experimental
IMP and NIMP	IMP
Type	Vaccine
Dose Form	Solution and emulsion for injection, mix pre-injection according to dose preparation protocol. The solution (Antigen) and emulsion (AS03 Adjuvant), once mixed, form a multi-dose vaccine in a vial. CoV2 preS dTM antigen is a sterile, clear, colorless solution (with possible presence of endogenous particles) of SARS-CoV-2 prefusion S proteins for IM injection. The antigen solution can contain endogenous particles. If present, these light-colored particles are slow sinking and suspended in solution. AS03 adjuvant is a whitish to yellowish homogenous milky liquid emulsion. After mixing, the vaccine is a whitish to yellowish homogeneous milky liquid emulsion.
Unit Dose Strengths	Each 0.5 mL dose of Study Intervention will contain the following: • preS-delta TM D614: prefusion S delta TM D614 COVID-19 antigen, (10 µg) • AS03 adjuvant is an oil-in-water emulsion containing squalene (10.69 milligrams), DL-α-tocopherol (11.86 milligrams) and polysorbate 80 (4.86 milligrams).
Excipients/Diluent	Excipients: *Solution vial (Antigen):* • Sodium phosphate monobasic monohydrate • Sodium phosphate dibasic dodecahydrate • Sodium chloride • Polysorbate 20 *Emulsion vial (AS03):* • Sodium chloride • Disodium hydrogen phosphate • Potassium dihydrogen phosphate • Potassium chloride Water for injection

Dosage Level	0.5 mL per dose
Number of Doses / Dosing Interval	2 injections / 21 days apart
Route of Administration	IM injection
Site of Administration	Deltoid muscle in the upper arm
Sourcing	CoV2 preS dTM (D614): Provided by the Sponsor AS03: Provided by GSK
Packaging and Labeling	Each study intervention component will be provided in a separate, individual box (ie, box for antigen and box for adjuvant). Each study intervention (vial) will bear one fixed label and each box will bear one fixed label containing the vial identification (treatment) number. All will be labeled in accordance with local Health Authority requirements.
Batch Number	TBD
Storage Conditions	2ºC to 8ºC (35°F to 46°F) and protected from light
CoV2 preS dTM-AS03 (D614 + B.1.351) (recombinant, adjuvanted)	
Intervention Names	**COVID-19 vaccine (recombinant, adjuvanted) or CoV2 preS dTM-AS03 (D614 + B.1.351)**
Use	Experimental
IMP and NIMP	IMP
Type	Vaccine
Dose Form	Solution and emulsion for injection, mix pre-injection according to dose preparation protocol. The solution (bivalent formulated Antigen containing D614 and B.1.351) and emulsion (AS03 Adjuvant), once mixed, form a multi-dose vaccine in a vial. CoV2 preS dTM bivalent antigen is a sterile, clear, colorless solution (with possible presence of endogenous particles) of SARS-CoV-2 prefusion S proteins (D614 and B.1.351) for IM injection. The antigen solution can contain endogenous particles. If present, these light-colored particles are slow sinking and suspended in solution. AS03 adjuvant is a whitish to yellowish homogenous milky liquid emulsion. After mixing, the vaccine is a whitish to yellowish homogeneous milky liquid emulsion.
Unit Dose Strengths	Each 0.5 mL dose of Study Intervention will contain the following: • preS-delta TM D614: prefusion S delta TM D614 COVID-19 antigen, (5 µg)

	• preS-delta TM B.1.351: prefusion S delta TM B.1.351 COVID-19 antigen, (5 µg) • AS03 adjuvant is an oil-in-water emulsion containing squalene (10.69 milligrams), DL-α-tocopherol (11.86 milligrams) and polysorbate 80 (4.86 milligrams).
Excipients/Diluent	Excipients: *Solution vial (bivalent Antigen):* • Sodium phosphate monobasic monohydrate • Sodium phosphate dibasic dodecahydrate • Sodium chloride • Polysorbate 20 *Emulsion vial (AS03):* • Sodium chloride • Disodium hydrogen phosphate • Potassium dihydrogen phosphate • Potassium chloride Water for injection
Dosage Level	0.5 mL per dose
Number of Doses / Dosing Interval	2 injections / 21 days apart
Route of Administration	IM injection
Site of Administration	Deltoid muscle in the upper arm
Sourcing	CoV2 preS dTM (D614 + B.1.351): Provided by the Sponsor AS03: Provided by GSK
Packaging and Labeling	Each study intervention component will be provided in a separate, individual box (ie, box for antigen and box for adjuvant). Each study intervention (vial) will bear one fixed label and each box will bear one fixed label containing the vial identification (treatment) number. All will be labeled in accordance with local Health Authority requirements.
Batch Number	TBD
Storage Conditions	2ºC to 8ºC (35°F to 46°F) and protected from light
Placebo	
Intervention Names	**Placebo**
Use	Placebo - comparator
IMP and NIMP	IMP
Type	Vaccine

Dose Form	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	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 those used for other study interventions. Each study intervention (vial) will bear one fixed label and each box will bear one fixed label containing the vial identification (treatment) number. All will be labeled in accordance with local Health Authority requirements.
Batch Number	TBD
Storage Conditions	2 ºC to 8ºC (35°F to 46°F)
CoV2 preS dTM-AS03 (B.1.351) (recombinant, adjuvanted)	
Intervention Names	**Monovalent (B.1.351) CoV2 preS dTM (5 µg antigen) + AS03 (full-dose adjuvant)**
Use	Experimental
IMP and NIMP	IMP
Type	Vaccine
Dose Form	Solution and emulsion for injection, mix pre-injection according to dose preparation protocol. The solution (Antigen) and emulsion (AS03 Adjuvant), once mixed, form a multi-dose vaccine in a vial. CoV2 preS dTM antigen is a sterile, clear, colorless solution (with possible presence of endogenous particles) of SARS-CoV-2 prefusion S proteins for IM injection. The antigen solution can contain endogenous particles. If present, these light-colored particles are slow sinking and suspended in solution. AS03 adjuvant is a whitish to yellowish homogenous milky liquid emulsion. After mixing, the vaccine is a whitish to yellowish homogeneous milky liquid emulsion.
Unit Dose Strengths	Each 0.5 mL dose of Study Intervention will contain the following: • preS-delta TM B.1.351: prefusion S delta TM B.1.351 COVID-19 antigen, (5 µg)

	AS03 adjuvant (full-dose) is an oil-in-water emulsion containing squalene (10.69 milligrams), DL-α-tocopherol (11.86 milligrams) and polysorbate 80 (4.86 milligrams).
Excipients / Diluent	Excipients: *Solution vial (Antigen):* • Sodium phosphate monobasic monohydrate • Sodium phosphate dibasic dodecahydrate • Sodium chloride • Polysorbate 20 • Water for injection *Emulsion vial (AS03):* • Sodium chloride • Disodium hydrogen phosphate • Potassium dihydrogen phosphate • Potassium chloride • Water for injection
Dosage Level	0.5 mL per dose
Number of Doses / Dosing Interval	1 injection (booster)
Route of Administration	IM injection
Site of Administration	Deltoid muscle in the upper arm
Sourcing	CoV2 preS dTM (B.1.351): 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 one fixed label containing the dose number. All will be labeled in accordance with local Health Authority requirements.
Batch Number	TBD
Storage Conditions	2ºC to 8ºC (35°F to 46°F) and protected from light

IMP: Investigational Medicinal Product; NIMP: Non-Investigational Medicinal Product; TBD: to be determined

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 multi-dose vial of CoV2 preS dTM antigen, either monovalent or bivalent antigen, will be mixed with the multi-dose vial of the AS03 adjuvant at the site prior to administration. The vaccine formulation will be prepared in the CoV2 preS dTM antigen vials by adding an equal volume of AS03 adjuvant. Further details of the mixing protocol will be provided in the Operating Guidelines.
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 before Crossover / Booster

6.3.1 Randomization and Allocation Procedures

On the day of enrollment, participants will be tested for presence of SARS-COV-2 antibodies using a rapid serodiagnostic test. Participants who meet the inclusion/exclusion criteria and sign the informed consent form (ICF) will be randomly assigned to one of the study groups (vaccine versus placebo) with randomization ratio 1:1 in either Stage 1 only or Stage 2 only.

In the time period where the enrollment in Stage 1 overlaps with enrollment in Stage 2, participants will continue to be randomly allocated to one of the investigational vaccine groups and their matched placebo group in a 1:1 ratio. There will be no sharing of the placebo participants between the 2 stages.

Stratified permuted block randomization will be applied for study group randomization where strata are age group (18-59 years and ≥ 60 years), baseline SARS-CoV-2 rapid serodiagnostic test positivity (Positive/Negative), and sites. Participants who are positive by the rapid serodiagnostic test will be included in the study until a trigger is reached indicating an anticipated proportion of SARS-COV-2 non-naïve individuals of approximately 30% at the end of enrollment.

An independent randomization will be applied to assign participants to the reactogenicity subset versus not in the subset with allocation ratio 1:3 in Stage 1. This randomization will be applied to the first 8000 participants in the study. Randomization to the reactogenicity subset will be stratified by intervention group, age-group, and country in participants who are SARS-CoV-2 rapid serodiagnostic test negative. Randomization to the reactogenicity subset will be stratified by intervention group and age-group in those participants who are SARS-CoV-2 rapid serodiagnostic test positive. The proportion of participants in each age-group and in each stratum determined by SARS-CoV-2 rapid serodiagnostic positivity in the reactogenicity subsets will be reflective of the overall study population.

After 8000 participants are recruited in Stage 1, a capping system will be used to ensure a targeted number of participants are assigned to the reactogenicity subset.

In Stage 2, the first 4000 participants along with all participants above 60 years of age will be allocated to the reactogenicity subset.

Another independent randomization will be applied to assign all participants to the Random Immunogenicity Subset. Approximately 15% of all participants will be assigned to the Immunogenicity subset at enrollment (Step 1) with pre-identified allocation ratio in each stratum. The Random Immunogenicity Subset assigned at enrollment will be stratified by intervention group, SARS-CoV-2 positivity on the rapid serodiagnostic test, and age-group. The allocation at enrollment to the Random Immunogenicity Subset will be supplemented, if needed, by randomly selected participants in pre-identified strata to complete the Random Immunogenicity Subcohort (Step 2). This additional random selection will occur after the availability of results to define SARS-CoV-2 D01 and D22 naïve and non-naïve status of all enrolled participants. Details are described in Appendix 10.6.

Site staff will connect to the IRT system, enter the identification and security information, and confirm a minimal amount of data in response to IRT prompts. The IRT will collect information on age-group, high risk medical conditions, ethnicity/race, and result of SARS-CoV-2 rapid serodiagnostic test to enable monitoring of enrollment and capping of study population groups (Section 5.4). 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 consisting of a 12-digit string (a 3-digit country identifier, a 4-digit study center identifier, and a 5-digit participant identifier). The first digit for the last 5-digit participant identifier will indicate the stage of enrollment (eg, 1 for Stage 1, 2 for Stage 2). The second digit of last 5-digit participant identifier will be designed as the indication of Reactogenicity Subset, Random Immunogenicity Subset, and indication of enrollment.

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

Randomization lists are constructed by a list of random vial numbers and a list of random dose numbers. Both lists are used to record product information for either single--dose vials (placebo) or multi-dose vials (active antigen and adjuvant). Vial numbers are unblinded which are used for packaging purpose and in IRT system to track product information. Dose numbers are blinded which are used in IRT system and in the CRF. Each participant will be vaccinated with the study interventions corresponding to the group mentioned on the randomization list. If the vial initially taken for vaccination is broken or cannot be used, the IRT will re-assign another dose number from the same vaccine/placebo (but not necessarily from the same vial).

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 monitoring for efficacy and the participant will not know which vaccine is administered in order to decrease the risk

of potential bias. Study site staff who administer the vaccine may also be blinded if they are not involved in preparation of the vaccine.

- 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 and kept only by the independent unblinded statistical group for each of the planned interim analyses. The final codebreaking will occur at the primary analyses when all efficacy data are available. Code will be kept by the Sponsor until all primary analyses and results are available. Global Clinical Immunology (GCI) will be kept blinded until all immunogenicity results are released. If the primary objectives are met during an interim analysis, further decision of the study continuity and blinding will be determined by the Sponsor while preparing the analyses and outputs required for Regulatory actions.

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.

If the participant is enrolled and seeks vaccination of an authorized/approved vaccine outside of the study, he/she will be encouraged to discuss this intention proactively with the study investigator. The study investigators will inform and discuss with these study participants the possibility of being unblinded to the study intervention to enable the participant to make decisions on receiving the available (authorized or approved) vaccine. The Sponsor will keep the study investigators updated on any new information related to the investigational products, so that such information can be provided to participants in discussions related to the potentially receiving the available authorized/approved vaccines. Participants should only request to be unblinded if they decide to receive the approved/authorized vaccine. Participants who elect to be unblinded will have their code broken. Once unblinded, participants will be discontinued from study intervention administration.

The blind 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. In the event that the unblinding occurs due to a medical emergency, once the emergency has been addressed by the site, the Investigator or a delegate must notify the Sanofi Responsible Medical Officer (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 Independent Ethics Committee / Institutional Review Board (IEC / IRB) 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 the Sanofi 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 unexpected SAE considered causally

related, as described in International Council for Harmonisation (ICH)[a]. E2A. 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.
- by the Independent DSMB if needed to facilitate their assessment of safety.

The code-breaking procedures are described in the Operating Guidelines and in the DSMB charter.

6.4 Study Intervention Compliance

The following measures will ensure that the study intervention is administered as planned (see Table 6.1), and that any non-compliance is documented so that it can be accounted for in the data analyses:

- All study interventions 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 Dose Modification

Not applicable.

6.6 Access to Authorized/Approved Vaccine during the Initial, Double-Blinded, Primary Series Design Phase of the Study

If an approved/authorized vaccine is available in the country or region where the study is conducted, investigators will discuss this information with prospective study participants at the time of informed consent who will be encouraged to obtain the approved/authorized vaccine if applicable to them. Recruitment of eligible participants will proceed only if, despite encouragement, the candidate participant expresses no intention to seek an authorized or approved vaccine at the time of enrollment.

If the participant is enrolled and seeks vaccination of an authorized/approved vaccine outside of the study, he/she will be encouraged to discuss this intention proactively with the study investigator. The study investigators will inform and discuss with these study participants the possibility of being unblinded to the study intervention to enable the participant to make decisions on receiving the available (authorized or approved) vaccine. The Sponsor will keep the study investigators updated on any new information related to the investigational products, so that such information can be provided to participants in discussions related to the potentially receiving the available authorized/approved vaccines. Participants should only request to be unblinded if they

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

decide to receive the approved/authorized vaccine. Participants who elect to be unblinded will have their code broken. Once unblinded, participants will be discontinued from study intervention administration.

6.7 Continued Access to Study Intervention After the End of the Initial, Double-Blinded, Primary Series Design Phase of the Study

Based on decisions of the Study OG, Stage 1 and Stage 2 participants will be invited to continue participation as part of an unblinded Crossover / Booster study design.

After unblinding and upon consent to participate in the unblinded Crossover / Booster study part of the study:

Participants who initially received the complete primary series of the CoV2 preS dTM-AS03 monovalent (D614) vaccine (Stage 1) or CoV2 preS dTM-AS03 bivalent (D614+B.1.351) vaccine (Stage 2) will be offered to receive Sanofi's investigational CoV2 preS dTM-AS03 monovalent (B.1.351) booster vaccine or encouraged to receive an authorized/approved vaccine according to local guidance ≥ 4 months post-last dose of the primary series.

Participants who initially received placebo will be informed the interim results of the study. Non-naïve participants who initially received placebo and are 18-59 years of age will be offered the opportunity to receive the investigational CoV2 pre-S dTM-AS03 monovalent (D614) vaccine if authorized/approved vaccines are not available or if they choose not to receive an authorized/approved vaccine. Naïve participants 18-59 years of age and all participants ≥ 60 years of age who initially received placebo will be recommended to receive an authorized/approved vaccination series. If initial placebo recipients receive authorized/approved vaccine outside of the study or the investigational study vaccine as a primary series, they will also be offered to receive Sanofi's investigational CoV2 preS dTM-AS03 monovalent (B.1.351) booster vaccine or encouraged to receive an authorized/approved vaccine according to local guidance ≥ 4 months post-last dose of the primary series.

If participants do not consent to continue with the unblinded crossover/booster or are naïve participants 18-59 years of age or all participants ≥ 60 years of age and do not receive an authorized/approved vaccine outside of the study, all study procedures will be stopped.

Participants who are terminated or choose to withdraw from the trial will not be eligible for unblinded crossover / booster. Participants receiving any authorized/approved COVID-19 vaccine will not be eligible for crossover vaccination.

Participants in the Vaccine group who completed the full primary series and did not receive an authorized/ approved vaccine will be eligible for a booster ≥ 4 months post-last dose of the primary CoV2 preS dTM-AS03 vaccine.

Participants in the Placebo group who completed a full vaccination schedule of either an authorized/approved vaccine or CoV2 preS dTM-AS03 vaccine will be eligible for a booster ≥ 4 months post-last dose of the primary series.

6.8 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) Evaluate the participant to determine, in consultation with the RMO, whether study intervention should be interrupted.
3) Closely monitor the participant for any AE/SAE.
4) Document the quantity of the excess of the overdose in the source documents.

6.9 Concomitant Therapy

Reportable medications include medications that may affect the interpretation of safety data (eg, an antipyretic or analgesic that could have reduced the intensity or frequency of an adverse event) or may interfere with the development or measurement of the immune response (eg, the use of immune-suppressors, immune-modulators, or some antibiotics that can affect certain bioassays). Some medications such as steroids can affect both the evaluation of the safety and the immune response to a vaccine.

This may include medications of interest that were started prior to the day of vaccination, and even stopped prior to enrollment if there is a reasonable possibility that they may have an impact on safety and / or immune assessment during study participation.

The following 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], anticoagulants, antithrombotics) Note: Topical analgesics should NOT be applied at the injection site of study intervention; however, if they are applied inadvertently, they should be recorded.
- Category 2: medications impacting or that may have an impact on the immune response (eg, hydroxychloroquine, other vaccines, blood products, immunoglobulins, monoclonal antibodies, convalescent plasma, antivirals and antiretrovirals, 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)

In addition to the above, some therapies or vaccines are to be collected even if they were taken before study vaccination or are stopped prior to enrollment, or if they are taken after the solicited period and at any time during the study. In this regard, information on use of influenza vaccines in the 6 months prior to enrollment is to be collected; information on immunoglobulins, plasma and other blood products, monoclonal antibodies, antineoplastics, immunomodulators (including high-

dose corticosteroids utilized for more than 10 days) administered up to 90 days before vaccination will be collected.

Reportable medications/vaccinations will be collected in the CRF from the day of each Initial study vaccination only to the end of the solicited and unsolicited follow-up period after each Initial study vaccination in all participants, with the exception of influenza and COVID-19 vaccination which will be collected throughout the study in all participants. In addition, any medications used for COVID-19 treatment or prophylaxis (eg, SARS-CoV-2 antivirals, monoclonal or polyclonal antibodies or plasma) will be collected throughout the study in all participants.

Dosage and administration route, homeopathic medication, topical and inhaled steroids, as well as topical, ophthalmic, and ear treatments will not be recorded (except topical analgesics applied at the injection site of study intervention).

Medications given in response to an AE will be captured in the "Action Taken" section only. Medications administered during a COVID-19-like illness episode will be captured in the appropriate CRF but will not be considered as concomitant medications. Medications will be coded. No details will be recorded in the concomitant medication Form of the CRF unless the medication(s) received belongs to one of the pre-listed categories.

6.9.1 Rescue Medicine

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

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

7.1.1 Temporary Contraindications (Initial)

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) in the 30 days prior to the first study vaccination except for influenza vaccine which may be received at any time with respect to study intervention

TCI03: Receipt of any vaccine (other than the study vaccine[s]) in the 21 days preceding or on the day of the second study vaccination or planned receipt of any vaccine in the

30 days following the second study vaccination except for influenza vaccine, which may be received at any time with respect to study intervention.

7.1.2 Definitive Contraindications (Initial)

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 and other study assessments/procedures. Additional unscheduled visits may be performed for safety reasons and information will be reported in the source documents.

Should a participant experience at least one of the conditions listed below, the Investigator will discontinue vaccination:

DCI01: Pregnancy, as indicated by a positive urine or serum test

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

DCI03: AE assessed as related to the study vaccine following the previous dose of vaccine which may place the participant at unreasonable or significant risk of injury or illness following repeat exposure to study vaccine, based on Investigator's judgment

DCI04: Positive NAAT at V01 or Symptomatic COVID-19 or asymptomatic SARS-CoV-2 infection confirmed by NAAT after V01 and before V02

DCI05: Receipt of COVID-19 vaccine (other than the study vaccine) or anti-SARS-CoV-2 monoclonal or polyclonal antibody in the period between the first study vaccination and the day corresponding to the second study vaccination

If the participant is enrolled and seeks vaccination of an authorized/approved vaccine outside of the study, he/she will be encouraged to discuss this intention proactively with the study investigator and will be permitted to receive the authorized vaccine at any time. 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 efficacy and safety. Participants will be invited to a visit prior to receiving the vaccine and invited to provide a blood sample for immunological assessment. Participants will continue to be followed for the duration of the study as per scheduled visits and procedures except for receipt of the second vaccination as detailed above.

7.1.3 Temporary Contraindications (Crossover / Booster design)

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 Crossover 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: Pregnancy, as indicated by a positive urine or serum test[a]

TCI03: Breastfeeding

7.1.4 Definitive Contraindications (Crossover / Booster design)

Should a participant experience at least one of the conditions listed below, the Investigator will discontinue vaccination:

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

DCI03: AE assessed as related to the study vaccine following the previous dose of vaccine which may place the participant at unreasonable or significant risk of injury or illness following repeat exposure to study vaccine, based on Investigator's judgment

DCI06: For participants originally assigned to the vaccine group, receipt of COVID-19 vaccine (other than the study vaccine) at any time during the study- Does not apply to participants originally randomized in the Placebo group

DCI07: Terminated or have chosen to withdraw from the study prior to the time of the crossover

DCI08: Booster vaccination only: Did not receive the complete primary series vaccination or received a booster vaccination with an authorized/approved vaccine

DCI09: History of myocarditis and/or pericarditis prior to vaccination

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 or designee for safety, behavioral, or compliance reasons.
- The reason for withdrawal should be clearly documented in the source documents and in the CRF: Adverse Event, 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 biological samples taken (unless local law required not to destroy them), and the Investigator must document this in the site study records.
- Withdrawn participants will not be replaced.

[a] If a participant is of childbearing potential, an effective contraceptive method or abstinence should be recommended until at least 12 weeks after the last crossover study intervention administration.

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). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered lost to follow-up.

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 tables. 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.

Blood and 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 (for the initial, double-blind, primary series study design), including any extra assessments that may be required, is not planned to exceed 160 mL (see Table 8.1). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

In addition, if a participant seeks an authorized/approved vaccine, they will be invited to a visit prior to receiving the vaccine and invited to provide a blood sample for immunological assessment.

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

Table 8.1: Samples collected per visit (initial, double-blind, primary series study design)

	D01	D22	D43	D78	D134	D202	D292	D387
Vaccination	X	X						
	BL0001	BL0002	BL0003	BL0004	BL0005	BL0006	BL0007	BL0008
Anti-S IgG ELISA*	X	X	X	X	X	X	X	X
SARS-CoV-2 Pseudovirus Neutralization Assay* / ††	X	X	X	X	X	X	X	X
SARS-CoV-2 Virus Neutralization Assay*	X	X	X	X	X	X	X	X
ECLIA Multiplex Assay*	X	X	X					
Anti-N Immunoassay†	X	X	X	X	X	X	X	X
Anti-S Immunoassay	X							
SARS-CoV-2 NAAT on nasopharyngeal sample‡	X	X						
SARS-CoV-2 NAAT and pan-Respiratory panel NAAT on respiratory sample during COVID-19-like illness §	Illness visit (see Section 8.2.1.2)							
Rapid SARS-CoV-2 serodiagnostic Test**	X							

* These assays will be done on the Random Immunogenicity Subcohort as well as in those participants with any of the efficacy endpoints.

† The anti-N immunoassay will be tested on samples from all participants.

‡NAAT for SARS-CoV-2 will be performed based on Section 8.1.5.

§Respiratory specimens will be collected at the first illness visit, 2-4 days later in all participants with COVID-19-like illness. In participants who have virologically-confirmed SARS-CoV-2 infection, anterior nasal swabs samples will be collected 7-9 days and 12-14 days after the first illness visit.

** Test at site prior to enrollment (see Section 8.1.4).

†† BL1-BL3 samples for all US participants only will be tested in the D614G Pseudovirus neutralization assay at Monogram.

For those who participate in the Crossover / Booster, sample collection will be as shown in Table 8.2 and Table 8.3.

Table 8.2: Booster sample collection (for those who initially received vaccine)

	BV01	BV02	BV03
Booster Vaccination	X		
	BL1003	BL1004	BL1005
Anti-N Immunoassay*	X		
Anti-S IgG ELISA†	X	X	X
SARS-CoV-2 Pseudovirus Neutralization Assay D614G†	X	X	X
SARS-CoV-2 Pseudovirus Neutralization Assay B.1.351†	X	X	X
SARS-CoV-2 Virus Neutralization Assay†	X	X	X
ECLIA Multiplex Assay†	X	X	X

*Tested only in subjects determined to be previously naive at baseline

†These assays will be done on the Random Immunogenicity Subcohort as well as in those participants with any of the efficacy endpoints
Additional exploratory testing to be defined at a later date may be performed on crossover samples.

Table 8.3: Crossover / Booster blood sampling (for those who initially received placebo)

	CRV01	CRV02	CRV03	BV01	BV02	BV03
Vaccination	X	X		X		
	BL1001		BL1002	BL1003	BL1004	BL1005
Anti-N Immunoassay*	X			X		
Anti-S IgG ELISA†	X		X	X	X	X
SARS-CoV-2 Pseudovirus Neutralization Assay D614G†	X		X	X	X	X
SARS-CoV-2 Pseudovirus Neutralization Assay B.1.351†	X		X	X	X	X
SARS-CoV-2 Virus Neutralization Assay†	X		X	X	X	X
ECLIA Multiplex Assay†	X		X	X	X	X

*Tested only in subjects determined to be previously naive at baseline and/or naive at CRV01 visit

†These assays will be done on the Random Immunogenicity Subcohort as well as in those participants with any of the efficacy endpoints

Additional exploratory testing to be defined at a later date may be performed on crossover samples.

For those who receive authorized vaccine (outside of the study) as primary series (Crossover vaccination), no protocol deviation will be considered if the corresponding blood sample is missed.

8.1 Baseline Assessments at the Time of Vaccination

8.1.1 Demographic Information and Risk Factor Data

All participants will be asked to provide information on demographic information such as age, sex, race, and ethnicity at the time of enrollment. Race and ethnicity data will be collected from participants as these are factors found to be associated with an increased risk of severe COVID-19.

In addition, information on factors associated with increased risk of exposure to SARS-CoV-2 and increased risk of infection will be collected at the time of enrollment. This may include type of occupation, workplace, type of residence, household/residence members, use of public transport, social interactions and known history of contact with positive individuals. These risk factors will also be collected at each scheduled visit.

8.1.2 Physical Examination and Vital Signs

At the time of enrollment, height, weight, vital signs, and a targeted physical examination will be performed. For further details on these safety assessments, see Section 8.3.1 and Section 8.3.2.

8.1.3 Medical History

Prior to enrollment, participants will be assessed for pre-existing conditions and illnesses, both past and ongoing with specific details regarding medical conditions associated with high risk of COVID-19 (Section 5.3). Any such conditions will be documented in the source document including the date of diagnosis. 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 repetitive outpatient care will be collected in the CRF. In addition, any prior history of COVID-19 will be collected.

8.1.4 Baseline SARS-CoV-2 Antibody Screening

A blood sample will be obtained before study enrollment to ascertain evidence of SARS-CoV-2 antibodies using a SARS-CoV-2 rapid serodiagnostic test that will be done at the site.

8.1.4.1 Assure COVID-19 IgG/IgM Rapid Test

The Assure COVID-19 IgG/IgM Rapid Test will be performed at the clinical site by trained personnel. The Rapid Diagnostic Test will be used according to the product insert provided by the manufacturer. The Assure COVID-19 IgG/IgM Rapid Test Device is a lateral flow immunochromatographic assay for the detection of SARS-CoV-2 antibodies in venous whole blood, serum or plasma. This test uses anti-human IgM antibody (test line IgM), anti-human IgG (test line IgG) and goat anti-mouse IgG (control line C) immobilized on a nitrocellulose strip. The conjugate pad contains recombinant SARS-CoV-2 antigen (antigen is recombinant Nucleocapsid Protein and Spike Protein [S1]) conjugated with colloid gold. During testing, the specimen binds

with SARS-CoV-2 antigen-conjugated gold colloid coated particles in the test cassette. When a specimen followed by assay buffer is added to the sample well, IgM and/or IgG antibodies if present, will bind to COVID-19 conjugates making antigen antibodies complex. This complex migrates through nitrocellulose membrane by capillary action. When the complex meets the line of the corresponding immobilized antibody (anti-human IgM and/or anti-human IgG) the complex is trapped forming a red line which confirm a reactive test result. Absence of a red line in the test region indicates a non-reactive test result. To serve as a procedural control, a red line will always appear in the control line region, indicating that the proper volume of specimen has been added and membrane wicking has occurred. The presence of a red band(s) on the test region(s) indicates a positive result for the particular IgG and/or IgM antibodies, while its absence indicates a negative result. A red band at the control region (C) serves as a procedural control, indicating that membrane wicking is working.

The results of this test will be used for determining the randomization strata and to cap/target the enrollment of SARS-CoV-2 non-naïve participants but not for the determination of whether participants are SARS-CoV-2 naïve or non-naïve. The study will cap/target the representation of SARS-CoV-2 non-naïve individuals to approximately 30% of all study participants to secure the sample size needed in the SARS-CoV-2 naïve population to demonstrate vaccine efficacy (see Section 9.2 for sample size details and Section 6.3.1). While this serodiagnostic test will be utilized to provide real-time information about proportion of participants enrolled who may have been previously infected with or immunized against SARS-CoV-2 and therefore critical for study capping decisions, classification of naïve and non-naïve status will be based on other assays (specifically, the combination of information from the N ELECSYS, S ELECSYS, and NAAT at baseline).

Other local tests could be used if the Assure COVID-19 IgG/IgM Rapid Test is not allowed for use in the country where the study is conducted.

At the time of enrollment, participants will be directed not to get an antibody test outside the study because of the risk of vaccine-induced seropositivity which would make the interpretation of the antibody test difficult and raise the potential for unintentional unblinding**.**

8.1.4.2 ELECSYS Anti-SARS-CoV2 Anti-N ECLIA

SARS-CoV-2 anti-nucleocapsid antibodies will be measured using the Roche ELECSYS anti-SARS-CoV-2 ECLIA on the following blood samples:

- BL0001-BL0008 in all participants
- BL1001 in placebo subjects and BL1003 in vaccine participants determined to be naive at the time of crossover enrollment
- BL1003 on placebo participants determined to be naive at the time of crossover booster vaccination. Details will be provided in the Operating Guidelines and PPD laboratory manual. This test may be used on D01 and D22 samples and on samples from the unblinded phase of the study in all participants to determine naïve and non-naïve status at the time of initial study enrollment and at Crossover / Booster, respectively.

ELECSYS Anti SARS CoV 2 is an immunoassay intended for qualitative detection of antibodies to SARS-CoV-2 in human serum. The ELECSYS anti-SARS-CoV-2 assay uses a recombinant

protein representing the nucleocapsid (N) antigen for the determination of antibodies against SARS-CoV-2. Sample, biotinylated SARS-CoV-2 specific recombinant antigen and SARS-CoV-2 specific recombinant antigen labeled with a ruthenium complex are first incubated and form a sandwich complex. After addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin. The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell/ProCell M/ProCell II M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier. Results are determined automatically by the software by comparing the electrochemiluminescence signal obtained from the reaction product of the sample with the signal of the cutoff value previously obtained by calibration.

8.1.4.3 ELECSYS Anti-SARS-CoV-2 Anti S ECLIA

This test will be used on BL0001 samples in all participants to determine naïve and non-naïve status at initial study enrollment; details will be provided in the Operating Guidelines and the PPD laboratory manual.

ELECSYS Anti SARS CoV 2 is an immunoassay intended for qualitative detection of antibodies to SARS-CoV-2 in human serum. The ELECSYS anti-SARS-CoV-2 assay uses a recombinant protein representing the S antigen for the determination of antibodies against SARS-CoV-2. Sample, biotinylated SARS-CoV-2 specific recombinant antigen and SARS-CoV-2 specific recombinant antigen labeled with a ruthenium complex are first incubated and form a sandwich complex. After addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin. The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell/ProCell M/ProCell II M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier. Results are determined automatically by the software by comparing the electrochemiluminescence signal obtained from the reaction product of the sample with the signal of the cutoff value previously obtained by calibration.

8.1.5 NAAT Assessment Prior to Vaccination

All participants will have a single bilateral nasopharyngeal swab collected at the enrollment visit and at the second vaccination visit for confirmation of SARS-CoV-2 infection at the initial study enrollment. This will be used for the determination of whether the individual is SARS-CoV-2 naïve or non-naïve (see Section 9.3).

Symptoms/conditions of COVID-19-like-illness may overlap with potential solicited systemic reactogenicity events that are expected after vaccination (eg, myalgia, headache, fever, chills, malaise, fatigue, and arthralgia) during the reactogenicity period (until 7 days after study injection). For instances in which study participants meet the COVID-19-like-illness definition during the reactogenicity period based solely on these systemic symptoms that overlap with vaccine reactogenicity, investigators should use their clinical judgment to decide if a COVID-19-like-illness visit (see Section 8.2.1.2) is necessary or not. Regardless of whether a COVID-19-like-illness visit is triggered, the investigator should report the COVID-19-like-illness occurrence

in the CRF and the results of the nasopharyngeal swab collected at the time of vaccination visit tested by protocol-defined NAAT will be used to ascertain whether the symptoms correspond to a SARS-CoV-2 infection. Any study participant reporting any of other COVID-19-like-illness definitory symptoms during the 7-day period after each vaccination should be evaluated for COVID-19 with COVID-19-like-illness visits and procedures completed.

8.2 Efficacy and Immunogenicity Assessments

Planned time points for all efficacy and immunogenicity assessments are provided in the SoA.

8.2.1 Efficacy Assessments

8.2.1.1 Definitions

COVID-19-like illness

Symptoms/conditions of COVID-19-like illness are as listed below, along with an accompanying tabulation of terms used in the CRFs versus DC/eDC memory aids (Table 8.4). COVID-19-like illness symptoms will be graded by the intensity grade (see Section 10.3.5.1.3).

New onset or exacerbation of any ONE of the following:

- Fever (measured temperature ≥ 100.4ºF OR ≥ 38.0ºC)
- Difficulty breathing or shortness of breath
- Altered level of consciousness
- Myocarditis, myocardial infarction
- Thromboembolic event (blood clots [eg, pulmonary embolism, deep vein thrombosis, stroke])
- Purpura fulminans
- Clinical or radiographic evidence of pneumonia
- Chilblains (COVID-toes)

OR

New onset or exacerbation of ANY ONE of the following (that persists for a period of at least 24 hours or reoccurs after a 12-hour period):

- Cough (dry or productive)
- Anosmia or partial loss of smell
- Ageusia or dysgeusia (loss or disturbance of taste)

OR

New onset of any TWO of the following symptoms that are present at the same time (both symptoms that persist for a period of at least 24 hours or reoccur after a 12-hour period):

- Sore throat
- Chills
- Myalgia
- Fatigue

- Malaise
- Headache
- Rhinorrhea or nasal congestion
- Abdominal pain
- At least one of nausea, diarrhea, vomiting

Table 8.4: COVID-19-like illness symptoms/conditions: CRF and Diary Card/electronic Diary Card / Memory Aid terms

CRF term	Diary Card / electronic Diary Card / Memory Aid term
Cough	Cough
Fever	Temperature measured as 38.0ºC (100.4ºF) or higher
Anosmia	Loss or disturbance of smell
Ageusia	Loss or disturbance of taste
Chilblains	Pain, redness, sores in your fingers and toes exposed to cold
Shortness of breath	Difficulty breathing or feeling short winded
Altered level of consciousness	Altered consciousness or altered behavior
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
Malaise	Feeling unwell
Headache	Headache
Rhinorrhea	Runny nose
Nasal congestion	Stuffy nose
Abdominal Pain	Belly pain
Nausea	Feeling queasy
Diarrhea	Loose stools
Vomiting	Throwing up
Fatigue	Tiredness

Virologically-confirmed SARS-CoV-2 infection

Virologically-confirmed SARS-CoV-2 infection is defined as a positive result for SARS-CoV-2 by NAAT on at least one respiratory sample. This includes positive results by any NAAT including tests performed outside the study protocol if confirmed by the adjudication committee.

Serologically-confirmed SARS-CoV-2 infection

Serologically-confirmed SARS-CoV-2 infection is defined as a positive result in a serum sample for antibodies specific to the Nucleocapsid of SARS-CoV-2 detected by ELECSYS Anti-SARS-CoV-2 Anti-N ECLIA.

SARS-CoV-2 infection

SARS-CoV-2 infection is defined as a serologically-confirmed SARS-CoV-2 infection OR virologically-confirmed SARS-CoV-2 infection.

Symptomatic COVID-19

Symptomatic COVID-19 is defined as virologically-confirmed SARS-CoV-2 infection accompanied by protocol-defined COVID-19-like illness.

Asymptomatic SARS-CoV-2 infection

Asymptomatic SARS-CoV-2 infection is defined as SARS-CoV-2 infection, with no reported COVID-19-like illness episodes between enrollment and 14 days after the timepoint at which SARS-CoV-2 infection is ascertained.

CDC-defined COVID-19

Virologically-confirmed SARS-CoV-2 infection with at least one of:

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

Hospitalized COVID-19

Hospitalized COVID-19 is defined as an episode of Symptomatic COVID-19 that requires inpatient hospitalization.

Moderate COVID-19

Moderate COVID-19 is defined as Symptomatic COVID-19 with:

- Shortness of breath that persists for at least 12 hours
  OR
- Clinical signs of moderate illness measured at least on two occasions separated by 30 mins (respiratory rate [RR] ≥ 20 breaths per minute at rest AND heart rate [HR] ≥ 90 beats per minute at rest)

AND

- No clinical signs indicative of Severe COVID-19

Severe COVID-19

Severe COVID-19 is defined as COVID-19 with any one of the following:

- Any clinical signs of severe illness measured at least on 2 occasions separated by 30 minutes (saturation of oxygen [SpO2] ≤ 93% on room air (corrected for altitude), PaO2/FiO2 < 300 mm Hg, RR ≥ 30 breaths per minute at rest, HR ≥ 125 beats per minute at rest)
- Supplemental oxygen administration for > 1 hour
- Use of invasive or non-invasive ventilation or Extracorporeal Membrane Oxygenation
- Clinical diagnosis of respiratory failure (ie, clinical need for one of the preceding therapies, but preceding therapies not able to be administered in setting of resource limitation)
- Significant acute renal, hepatic, or neurologic dysfunction
- Shock (defined by systolic blood pressure < 90 mm Hg, or diastolic blood pressure < 60 mm Hg or requiring vasopressors)
- Admission to an ICU
- Death

COVID-19 severity scale

The COVID-19 severity scale is based on the ordinal scale of clinical assessment:

1) Death
2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation
3) Hospitalized, on non-invasive ventilation or high flow oxygen devices
4) Hospitalized, requiring supplemental oxygen
5) Hospitalized, not requiring supplemental oxygen – discharged but requiring ongoing medical care (COVID-19 related or otherwise)
6) Hospitalized, not requiring supplemental oxygen – discharged without ongoing medical care
7) Not hospitalized

Death associated with COVID-19

Death associated with COVID-19 is defined as death in a participant with COVID-19 who died within 28 days of the first positive specimen date if association confirmed by adjudication committee OR died more than 28 days after the first specimen date and COVID-19 is mentioned as an immediate or underlying cause of death on the death certificate if association confirmed by the adjudication committee.

An adjudication committee will be assembled for the purpose of reviewing potential cases to determine if the criteria for the safety and efficacy endpoints have been met (see Section 10.1.5.4).

8.2.1.2 Schedule of Activities for COVID-19-like Illness

Surveillance for COVID-19

Participants will be contacted once a week over the entire duration of the study to inquire about the development of symptoms of COVID-19-like-illness and to remind participants to contact study staff if they experience symptoms of COVID-19-like illness. Active surveillance can be completed directly by study staff or through the use of the eDC. If there is no response to the contact, site staff will try and contact the study participant by other means. In addition to this active surveillance, 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 or if they have a positive COVID-19 test from any other source.

To surveil for COVID-19, symptoms for COVID-19-like-illness (Section 8.2.1.1) will be elicited weekly from the participants and presence of COVID-19-like-illness would result in the site arranging a COVID-19-like-illness visit to collect respiratory specimens as soon as possible.

Schedule of visits

During the surveillance for symptoms of COVID-19-like illness, participants will notify investigators about the onset of COVID-19-like symptoms or if they had a positive COVID test from any other source. Sites will contact participants to verify the symptoms meet the COVID-19-like illness definition. Participants with verified COVID-19-like illness will be asked to visit the site as soon as possible for the collection of respiratory samples as detailed below and reminded to complete daily reporting of their symptoms in the electronic or paper diary and to inform the site if they seek medical care. In instances in which study participants meet the COVID-19-like-illness definition during the reactogenicity period based solely on systemic symptoms that overlap with vaccine reactogenicity (eg, myalgia, headache, fever, chills, malaise, fatigue, and arthralgia), Investigators should use their clinical judgment to decide if a COVID-19-like-illness visit is necessary or not. Regardless of whether a COVID-19-like-illness visit is triggered, the Investigator should report the COVID-19-like-illness occurrence in the CRF and the nasopharyngeal swab collected at the time of vaccination visit will be analyzed by protocol-defined NAAT to ascertain whether the symptoms correspond to a SARS-CoV-2 injection; if positive on the nasopharyngeal swab collected at study vaccination visit, participants will have subsequent visits to collect respiratory specimens as defined below. Any study participant reporting any of the other COVID-19-like-illness definitory symptoms during the 7-day period

after each vaccination should be evaluated for COVID-19 with COVID-19-like-illness visits and procedures completed.

The start of the illness episode is the date of the first symptom onset corresponding to the COVID-19-like-illness. The last date of the COVID-19-like-illness is the last day of the last symptom provided that such date is followed by an asymptomatic period of at least 3 days; if symptoms reoccur earlier than the completion of the 3-day asymptomatic period, then the reoccurring symptoms are to be considered part of the same illness rather than a new illness. If symptoms reoccur after an asymptomatic period of at least 3 days, then those symptoms are to be considered a new COVID-19-like-illness.

In the event of an illness with a positive NAAT for SARS-CoV-2, exacerbation/worsening of COVID-19-like-illness symptoms or occurrence of new symptoms during the ongoing illness will be considered part of the ongoing COVID-19 illness episode and a new COVID-19-like-illness visit and subsequent schedule of events is generally discouraged although it may be triggered at the investigator's discretion.

In the event of exacerbation/worsening of COVID-19-like-illness symptoms or occurrences of new symptoms during an ongoing COVID-19-like-illness which is not associated with a positive NAAT for SARS-CoV-2 (missing or negative test), a new COVID-19-like-illness visit and subsequent schedule of events should be generally triggered if the new symptom or exacerbation of symptom occurs more than 7 days from the onset of the initial COVID-19-like-illness. In these cases, the onset of illness will correspond to the date of onset of the new symptom(s) or the date of the worsening of the pre-existing symptom(s).

At the site visit, a nasopharyngeal and anterior nasal swab will be collected from the participant at the site. If a participant cannot come to the site for a sample collection and the site has the capacity to conduct remote visits, a member of the site staff can collect at the participant's current location. The DC/eDC will be reviewed by a site clinician. Vital signs (Respiratory Rate and heart rate) and SpO2 by pulse oximetry will also be collected to determine severity of COVID-19 illness. Participants will be provided with a pulse oximeter for at least twice daily reporting of SpO2 including after exercise and provided instructions on how to use the pulse oximeter. Participants will be informed that if the readings are repeatedly (on at least 2 readings separated by 5 minutes) below the predefined threshold (eg, 93% at sea level or corresponding value adjusted for altitude), they should contact the site who may require the participant to visit the site and/or visit their local health care provider.

For the collection of subsequent respiratory samples (as detailed below), participants will be offered the choice of either visiting the site, home visit, or self-collection. Participants may be provided a self-sampling kit and provided instructions on how to self-collect nasal swabs and return them to the sites.

Investigators will be encouraged to collect an additional respiratory specimen at the first CLI visit for local clinical laboratory testing to enable medical management and early diagnosis of participants with COVID-19 if deemed necessary.

All participants with symptoms will be informed by investigators of the local guidance and advice for suspected COVID-19 and be advised to follow local health guidelines regarding COVID-19

prevention (eg, quarantine, avoidance of use of public transportation) until the availability of the results of the local or protocol-defined NAAT test.

Collection of respiratory samples for NAAT

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 8.2.1.1 and the "Schedule of Visits" subsection immediately above).

The following respiratory samples will be collected triggered by the development of COVID-19-like illness:

- First samples: The first respiratory sample will be obtained as soon as possible from the onset of symptoms of COVID-like illness. This sample will be a single bilateral nasopharyngeal swab collected by study site clinicians. In addition, a bilateral anterior nasal swab will also be collected at this time, after collection of the nasopharyngeal swab. This bilateral anterior nasal swab could be collected by the study site clinicians or by self-sampling by the participant. For participants who meet the COVID-19-like-illness definition during the post-vaccination reactogenicity period solely based on symptoms that overlap with systemic reactogenicity symptoms, the nasopharyngeal sample obtained at the time of study injection will be considered as the first sample for confirmation of virologically-confirmed SARS-CoV-2 infection. Investigators will be encouraged to collect an additional respiratory specimen at the first CLI visit for local clinical laboratory testing to enable medical management and early diagnosis of participants with COVID-19 if deemed necessary.
- Second sample: A second respiratory sample will be collected 2-4 days after the first sample. This sample will be an anterior nasal swab that could be collected by the study site clinicians or by self-sampling by the participant. This sample may or may not be collected in participants who meet the COVID-19-like illness definition during the post-vaccination reactogenicity period solely based on symptoms that overlap with systemic reactogenicity symptoms, based on Investigator's judgment (see Section 8.1.4).
- Third sample: If a swab collected on D01 or D02-D04 is positive or results are pending (either by a local test or protocol-defined NAAT) an additional anterior swab will be obtained 7-9 days after the first sample that could be collected by the study site clinicians or by self-sampling by the participant.
- Fourth sample: In participants who are determined to have virologically-confirmed SARS-CoV-2 infection by NAAT on either the first nasopharyngeal swab or the second anterior nasal swab (if applicable), an anterior nasal swab will be collected 12-14 days after the first sample by the study site clinicians or by self-sampling by the participant.

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

All participants will be required to record their symptoms and severity of symptoms on a daily basis at least until the result of all their protocol-defined (nasopharyngeal swab at Visit 1 and anterior nasal swab at Visit 2) NAAT or local clinical test (if taken) is available.

All participants seen for suspected COVID-19 will be notified of their swab results. Participants who are determined to be negative for SARS-CoV-2 by both the protocol-defined NAAT and any local clinical test, if done, will be asked to stop recording daily symptoms and only record the maximum severity of each symptom over the duration of the illness episode as well as the total duration of the illness episode. Any medications, hospitalizations, and health care visits will be collected, and outcome of the illness will be collected.

In individuals who are positive either by the protocol-defined NAAT on nasopharyngeal sample or the local NAAT taken at the first visit or the protocol-defined NAAT on an anterior nasal sample collected 2-4 days later, participants will be asked to continue recording of their symptoms daily until the end of the illness if illness duration is less than 30 days. Participants who are positive or whose results are pending will have a subsequent respiratory sample (an anterior nasal swab) collected 7-9 days after the first specimen collection. Participants who are positive will have an anterior nasal swab 12-14 days after the first specimen collection. Investigators will provide local health care details, inform participants of the need for twice daily SpO2 recording including post-exercise, and reinforce the need for daily recording of symptoms and collection of information as detailed below. Participants will be asked to record symptoms daily until the end of their illness (if shorter than 30 days) or up to 30 days. After 30 days, if symptoms continue, they will be required to report the end date for their symptoms.

In addition, information on healthcare utilization events (hospitalizations, emergency room visits, and non-routine office visits [including urgent care visits]) occurring within 30 days of the start of the illness episode, reason for the health care visit, diagnosis, outcome of the health care visit, and prescribed medication including duration of medication (eg, antibiotics, antivirals) will be collected.

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 (eg, Chest x-ray, computerized tomography), use of mechanical ventilation and other 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 follow-up telephone call 30 days after the onset of symptoms. If symptoms are ongoing at the 30-day telephone call, a second telephone call 30 days later will be arranged.

The intensity scale for the COVID-19-like illness symptoms is presented in Section 10.3.5.1.3.

Safety monitoring of COVID-19-like illness

In all participants with a COVID-19-like illness, symptoms and the intensity of symptoms will be recorded daily and monitored by study staff. Study investigators will contact the participants at least daily until the results of the NAAT test (both protocol-defined NAAT and local clinical test, if performed) are reported as negative. If any of the NAAT test results are reported as positive, study investigators will continue at least daily contact with participants until 30 days after illness onset or until illness resolution if illness duration is $\leq$ 30 days. If illness continues beyond 30 days, frequency of contact will be as per Investigator judgment. In the event of a Grade 3 intensity of symptom, study staff will be automatically alerted through the e-diary system. In participants using a paper diary, daily recording of the symptoms by study staff will be performed

and additional contacts may be performed as per Investigator judgment. Additional investigations or procedures (eg, Chest x-ray) for medical and safety monitoring of the participant may be performed as judged necessary by the Investigator.

In individuals who are SARS-CoV-2 negative (ie, negative on both protocol-defined NAAT tests at CLI01 and CLI02 and local clinical test if performed), daily contact need not to continue unless judged necessary by the investigator for medical monitoring of the participant.

Participants will be encouraged to visit the site as soon as possible upon verification of a COVID-like illness. If a participant cannot come to the site for a sample collection and the site has the capacity to conduct remote visits, a member of the site staff can visit the participant at their location. Study investigators will be encouraged to collect additional respiratory specimens for local clinical laboratory testing to enable medical management and early diagnosis of participants with COVID-19. Results of such local laboratory testing outside the study protocol assays will be recorded in the CRF along with available details of such local NAAT.

Participants will be provided a pulse oximeter, trained in its use and informed of the need to contact study staff or visit a health care provider as detailed above. In participants using an e-diary, an automatic alert will notify study staff of pulse oximeter readings below the defined threshold to trigger contact with the participant. Participants will also be informed of the danger signs and symptoms of COVID-19 at the time of the visit.

Laboratory testing for the confirmation of symptomatic COVID-19, viral burden and other respiratory viruses

The ascertainment of whether a participant has COVID-19 will be based on a positive NAAT in the first nasopharyngeal swab or the second anterior nasal swab collected 2-4 days after the first nasopharyngeal swab.

In participants determined to have a virologically-confirmed case of COVID-19, a quantitative assessment of viral burden will be performed on all the protocol-defined respiratory samples, ie, the nasopharyngeal swab and the 4 anterior nasal swabs.

Positive polymerase chain reaction (PCR) samples may undergo additional testing (eg, genetic sequencing) to identify the strain which caused the infection and for additional correlates and sieve analysis.

The anterior nasal sample collected upon the first illness visit only will also be tested for other respiratory viruses (eg, influenza, RSV) (see Section 8.2.2.8).

Notification of test results

All participants seen for suspected COVID-19 will be notified of their swab results within 24 hours of the result becoming available to the Investigator. This will include results of any local testing as well as protocol-defined NAAT results.

The first test results, either from the nasopharyngeal swab or local test (if taken), will be notified to participants to enable them to follow the local coronavirus guidelines. In individuals who are negative, participants will be informed that further test results may be available (eg, anterior nasal swab), and there is a possibility that subsequent samples may be positive.

In individuals who are positive, investigators will inform participants of local guidelines and requirements for COVID-19 cases, provide local health care details, inform participants of the need for twice daily SpO2 recording and reinforce the need for further procedures as detailed in the protocol.

In the event that a participant was diagnosed with virologically-confirmed SARS-CoV-2 infection, the study investigators will report the result to the Public Health body as per local guidelines. The study investigator may also inform the primary care provider.

8.2.1.3 Nucleic Acid Amplification Test (NAAT) for Detection of Virologically-Confirmed SARS-CoV-2 Infection

The Abbott RealTime SARS-CoV-2 assay will be used for the detection of virologically-confirmed SARS-CoV-2 infection by the central laboratory; details will be provided in the Operating Guidelines and PPD laboratory manual. Testing will be performed on:

- Nasopharyngeal swabs collected at baseline in all participants
- Nasopharyngeal swabs collected at D22 in all participants
- Nasopharyngeal swab collected at initial COVID-19-like illness visit
- Anterior nasal swab collected 2-4 days after initial COVID-19-like illness visit
- Anterior nasal swab collected 7-9 days after initial COVID-19-like illness visit in virologically-confirmed SARS-CoV-2 infected participants as defined above
- Anterior nasal swab collected 12-14 days after initial COVID-19-like illness visit in virologically-confirmed SARS-CoV-2 infected participants as defined above

The Abbott RealTime SARS-CoV-2 assay is a dual target assay for the RNA-dependent RNA polymerase (RdRp) and N genes. An RNA sequence that is unrelated to SARS-CoV-2 target sequence is introduced into each specimen at the beginning of sample preparation. This unrelated RNA sequence is simultaneously amplified by RT-PCR and serves as an internal control (IC) to demonstrate that the process has proceeded correctly for each sample.

The assay detects the SARS-CoV-2 virus and IC target sequences by using target-specific fluorescent-labeled oligonucleotide probes. The probes do not generate a signal unless they are specifically bound to the amplified product. The two SARS-CoV-2-specific probes are labeled with the same fluorophore, and the IC-specific probe is labeled with a different fluorophore, thus allowing for simultaneous detection of both SARS-CoV-2 and IC amplified products in the same reaction well.

8.2.1.4 ELECSYS Anti-SARS-CoV2 Anti-N ECLIA

SARS-CoV-2 anti-nucleocapsid antibodies will be measured using the Roche ELECSYS anti-SARS-CoV-2 ECLIA on all blood samples in participants for ascertainment of serologically-confirmed SARS-CoV-2 infection. In addition, this test will be used on D01 and D22 samples at initial enrollment and at the unblinded phase of the study in all participants to determine naïve and non-naïve status (see Section 8.1.4.2). Details will be provided in the Operating Guidelines and the PPD laboratory manual.

8.2.2 Immunological and Virological Assessments

Assays will be performed by Sanofi laboratory (Swiftwater, PA, USA), an external testing laboratory under Sanofi laboratory responsibility, or other US Government-designated laboratories. The address is provided in the Operating Guidelines.

8.2.2.1 SARS-CoV-2 Pseudovirus Neutralization Assay (Monogram laboratory)

SARS-CoV-2 neutralizing antibodies will be measured using a pseudovirus neutralization assay on blood samples BL0001-BL0008 for participants in the Random Immunogenicity Subcohort (for immunogenicity assessments) and in participants with efficacy endpoints for analysis of correlates of risk and protection. The pseudovirus neutralization assay will assess responses against the D614G variant of the Wuhan-1 strain (VRC7480) and the B.1.351 variant in the bivalent vaccine on blood samples BL1001-BL1005. Additional assays against other emergent VOCs (eg, B.1.1.7, P.1.) may be undertaken.

The PhenoSense (PS) CoV neutralizing antibody Assay has been developed by leveraging the proprietary PS Assay platform that was developed to evaluate antiretroviral drug susceptibility and later adapted to evaluate entry inhibitors, neutralizing antibody activity and co-receptor tropism. The production of luciferase is dependent on virus entry and the completion of a single round of virus replication. Agents that inhibit pseudovirus entry or replication reduce luciferase activity in a dose-dependent manner, providing a quantitative measure of drug and antibody susceptibility. Over time, the PS assay platform has been successfully adapted to evaluate vaccines and entry inhibitors that target a variety of enveloped viruses, including Influenza, RSV and most recently SARS-CoV-2.

The measurement of neutralizing antibody activity using the PhenoSense SARS-CoV-2 neutralizing antibody assay is performed by generating HIV-1 pseudovirions that express the SARS-CoV-2 spike protein. The pseudovirus is prepared by co-transfecting HEK293 producer cells with an HIV-1 genomic vector and a SARS-CoV-2 envelope expression vector. Neutralizing antibody activity is measured by assessing the inhibition of luciferase activity in HEK293 target cells expressing the ACE2 receptor following pre-incubation of the pseudovirions with serial dilutions of the serum specimen. The expression of luciferase activity in target cells is inhibited in the presence of anti-SARS CoV-2 neutralizing antibody. Data are displayed by plotting the percent inhibition of luciferase activity vs. log10 reciprocal of the serum/plasma dilution and neutralizing antibody titers are reported as the reciprocal of the serum dilution conferring 50% inhibition (ID50) of pseudovirus infection.

$$\%\text{Inhibition} = 100\% - (\text{RLU(Vector+Sample+Diluent)} \div \text{RLU(Vector+Diluent)}) \times 100\%)$$

To insure that the measured nAb activity is SARS-CoV-2 neutralizing antibody specific, each test specimen is also assessed using a non-specific pseudovirus (specificity control) that expresses a non-reactive envelope protein of one or more unrelated viruses (eg, avian influenza virus)

Additional pseudovirus neutralization assays may be utilized at a future date, pending acceptance of data demonstrating the applicability of the test for SARS-CoV-2 immunogenicity.

8.2.2.2 SARS-CoV-2 Pseudovirus Neutralization Assay (Nexelis)

The SARS-CoV-2 Pseudovirus Neutralization Assay (Nexelis) evaluates the level of neutralizing SARS-CoV-2 pseudovirus antibodies present in the human serum samples. on blood samples BL0001-BL0008 and BL1001-BL1005 for participants in the Random Immunogenicity Subcohort (for immunogenicity assessments) and in participants with efficacy endpoints for analysis of correlates of risk and protection.

Pseudotyped virus particles are made from a modified Vesicular Stomatitis Virus (VSVΔG) backbone and bear the S glycoprotein of the SARS-CoV-2 from which the last 19 amino acids of the cytoplasmic tail were removed. The pseudoparticles contain a Luciferase reporter used for detection. Seven 2-fold serial dilutions of heat-inactivated human serum samples are prepared in 96-well transfer plate(s). The SARS-CoV-2 pseudovirus is added sequentially to the serum dilutions at a target working dilution (to obtain approximately 75◦000-300◦000 relative luminescence units [RLU]/well) and incubated at 37°C with 5% CO_2 supplementation for 60◦±◦5◦minutes. Serum-virus complexes are then transferred onto plates, previously seeded overnight with Vero E6 cells, and incubated at 37°C and with 5% CO_2 supplementation for 20◦±◦2 hours. Following this incubation, the luciferase substrate is added to the cells in order to assess the level of luminescence per well. The plate(s) are then read on a luminescence plate reader and the intensity of the luminescence is quantified in RLUs and is inversely proportional to the level of neutralizing antibodies present in the serum. The neutralizing titer of a serum sample is calculated as the reciprocal serum dilution corresponding to the 50% neutralization antibody titer (NT50) for that sample.

This assay may be used to assess antibody responses against the parent D614G and other variant strains (eg, B.1.17, P1, B.1.617.2).

8.2.2.3 SARS-CoV-2 Virus Neutralization Assay (USG)

SARS-CoV-2 Virus Neutralization Assay will be measured on blood samples BL0001-BL0008 and BL1001-BL1005 in the Random Immunogenicity Subcohort (for immunogenicity assessments) and in participants with efficacy endpoints for analysis of correlates of risk and protection.

The SARS-CoV-2 microneutralization assay quantifies neutralizing antibodies in human serum samples to SARS-CoV-2. In the assay, serial dilutions of heat-inactivated sera are prepared and mixed with an equal volume of SARS-CoV-2 virus. The diluted serum and virus mixtures are incubated for 1 hour (neutralization step). Following this incubation, the serum/virus mixtures are inoculated onto confluent VERO E6 cell monolayers in 96-well microplates. The inoculated VERO E6 monolayers are then incubated at 37℃ with CO_2 for 40-46 hours, at which time the monolayers are fixed with acetone. The fixative is removed, the plates are washed, and the *in situ* Enzyme Linked Immunosorbent Assay (ELISA) is conducted.

For the *in situ* ELISA, the fixed VERO E6 monolayers are incubated with commercial anti-coronavirus protein antibodies for 1 hour. The plate is washed, and then a commercial horseradish peroxidase secondary antibody is added, and the plate is incubated for 1 hour. The plate is washed, and a commercial substrate and stop solution are used per manufacturer's instructions and the optical density is obtained to determine the reportable value.

8.2.2.4 SARS-CoV-2 Spike Protein Antibody Serum IgG ELISA (Nexelis laboratory)

SARS-CoV-2 anti-S protein IgG antibodies will be measured using an ELISA on blood samples BL0001-BL0008 and BL1001-BL1005 in the Random Immunogenicity Subcohort (for immunogenicity assessments) and in participants with efficacy endpoints for analysis of correlates of risk and protection.

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.

8.2.2.5 Detection of Binding Antibody Levels by ECLIA (Nexelis laboratory)

SARS-CoV-2 binding antibodies will be measured using an electrochemiluminescence immunoassay (ECLIA) on blood samples BL0001-BL0003 and BL1001-BL1005 for participants in the Random Immunogenicity Subcohort for immunogenicity assessments.

The 4-plex SARS-CoV-2 assay (detecting serum IgG binding to SARS-CoV-2 antigens Spike Protein (S-2P), Receptor Binding Domain (RBD), and Nucleocapsid (N), with a BSA control) is intended for use to aid in identifying volunteers with an immune response to SARS-CoV-2 S-2P after vaccination with experimental SARS-CoV-2 vaccines.

MSD SECTOR® plates are precoated by MSD with SARS-CoV-2 spike (S-2P), receptor binding domain (RBD) protein, Nucleocapsid (N) protein and a Bovine Serum Albumin (BSA) control in each well in a specific spot-designation for each antigen. The assay will be performed with a Beckman Coulter Biomek based automation integration platform including the Biotek 405TS Plate Washer. Serum samples will be heat-inactivated for 30 minutes at 56ºC prior to assay. Plates are blocked for 60 minutes at room temperature (RT) with MSD blocker A solution without shaking. Plates are washed and MSD reference standard (calibrator), QC test sample (pool of COVID-19 convalescent sera) and human serum test samples are added to the precoated wells in duplicates in an 8-point dilution series. Reference standard is added in triplicates. MSD Control sera (low, medium and high) are added undiluted in triplicates as per validated assay format. Additional assay controls might be added in triplicates. Samples are incubated at RT for 4 hours

with shaking on a Titramax Plate shaker (Heidolph) at 1500 rpm. SARS-CoV-2 specific antibodies present in the sera or controls bind to the coated antigens. Plates are washed to remove unbound antibodies. Antibodies bound to the SARS-CoV-2 viral proteins are detected using an MSD SULFO-TAGTM anti-human IgG detection antibody incubated for 60 minutes at RT and with shaking. Plates are washed and a read solution (MSD GOLDTM read buffer) containing electrochemiluminescence (ECL) substrate is applied to the wells, and the plate is entered into the MSD MESO Sector S 600 detection system. An electric current is applied to the plates and areas of well surface which form antigen-anti human IgG antibody SULFO-TAGTM complex will emit light in the presence of the ECL substrate.

The MSD MESO Sector S 600 detection system quantitates the amount of light emitted and reports the ECL unit response as a result for each test sample, control sample and reference standard of each plate. Analysis is performed with the MSD Discovery Workbench software, Version 4.0. Calculated ECLIA parameters to measure binding antibody activities will include interpolated concentrations or assigned international units (IU/mL) read from the standard curve. Only SARS-CoV-2 Spike (S-2P) values will be reported.

8.2.2.6 SARS-CoV-2 Viral Burden Assessment

The Abbott RealTime SARS-CoV-2 assay done at University of Washington will be used for the quantitation of viral burden on respiratory samples collected during illness visits which are confirmed as virologically-confirmed SARS-CoV-2 in the Sanofi assays.

The Abbott RealTime SARS-CoV-2 assay is a dual target assay for the RNA-dependent RNA polymerase (RdRp) and N genes. An RNA sequence that is unrelated to SARS CoV-2 target sequence is introduced into each specimen at the beginning of sample preparation. This unrelated RNA sequence is simultaneously amplified by RT-PCR and serves as an internal control (IC) to demonstrate that the process has proceeded correctly for each sample.

The assay detects the SARS-CoV-2 virus and IC target sequences by using target-specific fluorescent-labeled oligonucleotide probes. The probes do not generate a signal unless they are specifically bound to the amplified product. The two SARS-CoV-2-specific probes are labeled with the same fluorophore, and the IC-specific probe is labeled with a different fluorophore, thus allowing for simultaneous detection of both SARS-CoV-2 and IC amplified products in the same reaction well.

8.2.2.7 SARS-CoV-2 Viral Sequencing

Genome sequencing of SARS-CoV-2 virus will be performed on respiratory samples collected during the study which are confirmed as virologically-confirmed SARS-CoV-2 in the Sanofi assays from study participants using the Swift Biosciences v2 single tube, SARS-CoV-2 multiplex amplicon sequencing panel for the recovery of genomes from low viral loads samples. The resulting libraries are sequenced on an Illumina NextSeq. Resulting raw read files, consensus whole genome sequence, and summary variant allele frequencies will be returned, consistent with FDA guidelines.

8.2.2.8 Pan Respiratory PCR Method

This will be performed on the first anterior swab collected at the illness visit in all participants in whom the anterior nasal swab is collected.

The Bio Fire FilmArray® Respiratory Panel 2 (RP2) PCR pouch is a closed system disposable that stores all the necessary reagents for sample preparation, reverse transcription, PCR, and detection in order to isolate, amplify, and detect nucleic acid from multiple respiratory pathogens within a single nasopharyngeal swab specimen. After sample collection, the user injects hydration solution and sample combined with sample buffer into the pouch, places the pouch into a FilmArray instrument, and starts a run.

During a run, the FilmArray system: 1) lyses the sample by agitation (bead beading); 2) extracts and purifies all nucleic acids from the sample using magnetic bead technology; 3) performs nested multiplex PCR by first performing reverse transcription and a single, large volume, massively multiplexed reaction (PCR1) then performs multiple singleplex second-stage PCR reactions (PCR2) to amplify sequences within the PCR1 products; and 4) uses endpoint melting curve data to detect and generate a result for each target on the FilmArray RP2 array.

The Bio Fire FilmArray® Respiratory Panel 2 PCR will be performed on the first anterior nasal swab collected during the illness visit.

8.3 Safety Assessments

This section presents clinical and safety assessments other than adverse events 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 Physical Examinations

At the time of enrollment, height and weight will be collected and a targeted physical examination including vital signs based on the participant's medical history may be performed. At designated visits, the Investigator or a designee may 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.

8.3.2 Vital Signs

Oral pre-vaccination temperature will be systematically collected by the investigator on the source document. Tympanic, skin, and temporal artery thermometers must not be used. Respiratory rate, heart rate, and pulse oximetry SpO2 will be recorded by study investigators at COVID-like-illness visits during a COVID-19-like illness episode. The Investigator may collect other vital signs they consider necessary based on medical judgment during any participant visit and record it in the source document.

8.3.3 Clinical Safety Laboratory Assessments

See Appendix 10.2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.

8.3.4 Pregnancy Testing

Urine or serum pregnancy testing will be performed in females of childbearing potential before each vaccination.

8.4 Adverse Events, Serious Adverse Events, and Other Safety Reporting

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).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 10.3.

A dedicated Sponsor's Safety Team composed of RMOs, Biostatistics, and Pharmacovigilance will ensure the safety monitoring by reviewing all SAEs immediately and all safety data at regular intervals to identify any new safety signals or safety concerns during the conduct of the study.

A Protocol Safety Review Team (PSRT) will review interim and cumulative blinded safety data on a regular basis with a remit to recommend DSMB escalation to the Sponsor.

All safety data will be reviewed on a regular basis by the Sponsor's Safety PSRT and the DSMB, in order to identify any new safety signals or potential safety concerns during the conduct of the study. The data will remain blinded for the Sponsor and the PSRT, while the DSMB can receive blinded and unblinded data.

SAEs and AESIs will be reviewed immediately by the Sponsor's Safety Team and shared on an expedited basis with the DSMB and the PSRT. Those data will remain blinded for the review. Unblinding of the treatment code for a patient may be requested by the Sponsor for regulatory reporting purpose (IND safety reports / suspected unexpected serious adverse reactions [SUSARs]) or by the DSMB.

Further details on the composition and frequency of meetings are provided in the Sponsor's Safety Management Team and PSRT charters.

On the basis of this review, and especially on SAEs assessed as related by Investigator and Sponsor, the Sponsor will decide whether further vaccine administration should be temporarily halted as a precautionary measure while investigating the safety signal.

Safety will be evaluated through:

- Assessment of the reactogenicity profile of each study intervention for participants in the Reactogenicity Subset in each age group up to 21 days after the last vaccination overall (regardless of prior SARS-CoV-2 infection at baseline) and in SARS-CoV-2 naïve and non-naïve subgroups:

- Presence of solicited (prelisted in the participant's DC/eDC and CRF) injection site reactions and systemic reactions occurring up to 7 days after each vaccination
- Presence of non-serious unsolicited AEs reported up to 21 days after the last vaccination

Note: For the Crossover / Booster: Unsolicited AEs will be collected up to 21 days after the booster vaccination. MAAEs, SAEs, and AESIs will be collected over the duration of the study including the Crossover / Booster (up to 12 months post-booster). Immediate adverse reactions (ie, 30 minutes after vaccination) will be collected after Crossover receipt of CoV2 preS dTM-AS03 (D614) as primary series for those who initially received placebo and after Booster receipt of CoV2 preS dTM-AS03 (B.1.351) for all participants; but immediate adverse reactions will not be collected after receipt of authorized/approved vaccine outside of the study for those who initially received placebo.

- Assessment of safety of each study intervention for participants in each age group overall (regardless of prior SARS-CoV-2 infection at baseline) and in SARS-CoV-2 naïve and non-naïve subgroups:
  - Presence of unsolicited injection site and systemic AEs reported in the 30 minutes after each vaccination
  - Presence of MAAEs throughout the study
  - Presence of SAEs throughout the study
  - Presence of AESIs throughout the study
  - Presence of virologically-confirmed SARS-CoV-2 infection and/or symptomatic COVID-19
- Monitoring for harm will be undertaken on a continuous basis by the DSMB for imbalance of frequency of COVID-19 and severe COVID-19 (see Section 9.5)
- Assessment of frequency and spectrum of disease in episodes of virologically-confirmed COVID-19 illness in each study group:
  - Severity of symptoms associated with symptomatic COVID-19 episode
  - Occurrences of hospitalized COVID-19
  - Occurrences of severe COVID-19
  - Occurrence of COVID-19 in each severity rating on the 7-point ordinal scale
  - Death associated with COVID-19

Halting Rules

Blinded safety data will be reviewed by the Sponsor's Safety Team (RMO, Biostatistics, and PV) and PSRT at regular intervals to identify any new safety signals or safety concerns during the conduct of the study. A pause in either recruitment and/or further vaccination might be recommended by the Sponsor or the DSMB while it investigates any safety signal or concern. The Sponsor has the responsibility to make the decision to pause the study.

Enrollment and vaccination will be paused during the review and the data will be examined if any of the following conditions occur:

- Any death assessed as related to the vaccine by the Investigator and the Sponsor are reported in the study
- Any safety signal raised by the DSMB upon unblinded review of the data (which may include SUSARS, AESIs, MAAEs, unsolicited or solicited AEs)

- An unfavorable imbalance of severe or serious conditions is identified by the DSMB between vaccine and placebo, including harm monitoring for COVID-19 (Section 9.5)

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

All 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 DCs/eDCs 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 adverse events 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 Initial vaccination (up to D387). However, before the first study intervention administration, only SAEs related to study procedures are to be collected in the CRF (eg, SAEs related to blood sampling).

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 information on AEs or SAEs 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.

COVID-19 Events

All virologically-confirmed SARS-CoV-2 infections (including tests conducted outside study procedures and protocols) (Section 8.2.1.1) will be recorded in the CRF. The date of positive results, duration of illness (if any) and symptoms during the illness episode including hospitalization will be recorded. This will enable any COVID-19 events that are not collected as part of the study procedures or study tests to be collected for evaluation of safety and efficacy. An adjudication committee will be assembled for the purpose of reviewing potential cases to determine if the criteria for the primary, secondary, or exploratory safety and efficacy endpoints have been met.

Medically-Attended Adverse Events (MAAEs)

MAAEs will be collected throughout the study.

Adverse Events of Special Interest (AESIs)

AESIs will be collected throughout the study.

See Section 8.4.6 for the list of AESIs.

8.4.2 Method of Detecting AEs and SAEs

Individual DCs/eDCs, 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 DCs/eDCs 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 DC/eDC 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 DC/eDC 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 (or over the telephone if the visit cannot be performed in-person) using a questionnaire to capture SAEs and AESIs, if applicable.

For the Crossover / Booster:

- follow-up will be done by interviewing participants as part of safety follow-up call 12 months post-booster.

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, SAEs and AESIs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts, unless a participant refuses further contact. All AEs that are considered by the Investigator as serious, or related to the study intervention administered, or that led to study or vaccination discontinuation, or AESIs (as defined in Section 8.4.6), will be followed during the conduct of the study until resolution, stabilization, or the participant is lost to follow-up (as defined in Section 7.3). For related SAEs ongoing at last study visit, such follow-up may need to continue after the end of the study.

Further information on follow-up procedures is provided in Appendix 10.3.

8.4.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of an 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, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- 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.
- 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.

8.4.5 Pregnancy

Pregnant women are not eligible to participate in the study and females of childbearing potential agree to use an effective contraceptive method during a period starting 4 weeks prior to the first vaccination and ending 12 weeks after the last vaccination, as defined in the inclusion criteria. However, a participant could potentially become pregnant during her participation.

If the pregnancy starts during the period of contraception or abstinence:

- Details of all pregnancies in female participants will be collected after the start of study intervention and until the pregnancy outcome.
- When pregnancy exposure is reported, the investigator should promptly inform the Sponsor and will record pregnancy information together with the contraceptive method on the appropriate form and submit it to the Sponsor within 1 month of learning of the pregnancy.
- 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.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- 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. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- The offspring will be followed for up to 12 months by the pharmacovigilance department. This follow-up period will apply also to pregnancy exposures reported after blinded crossover in this study would be initiated. Any data collected after CRF lock will be transmitted to the pharmacovigilance department on the paper form.

If the pregnancy starts after the period of contraception or abstinence:

- The data collection will be the same during the period of the study. It will end at the last visit of the participant. This will apply also to pregnancy exposures reported after blinded crossover in this study would be initiated.
- 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 8.4.4. 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.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention until delivery or until delivery and end of lactation. However, the participant will be followed for safety assessment (and may be followed for efficacy/immunogenicity assessments, if applicable).

8.4.6 Adverse Events of Special Interest

AESIs will include (see Appendix 10.5):

- Anaphylactic reactions[a]
- Generalized convulsion[a]
- Thrombocytopenia[a]
- Thrombosis with Thrombocytopenia Syndrome[a,b]
- Myocarditis[c]
- Pericarditis[c]
- New onset and worsening of pIMDs (listed in Table 10.4)

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 Pharmacokinetics

Pharmacokinetics parameters are not evaluated in this study.

8.6 Genetics

Genetics are not evaluated in this study.

[a] For case definition, please refer to https://brightoncollaboration.us/category/pubs-tools/case-definitions/.

[b] Due to safety signals detected after the use of other COVID-19 vaccine platforms from other manufacturers, Thrombosis with Thrombocytopenia Syndrome (87) (88) is also considered AESI.

[c] For case definitions of myocarditis and pericarditis, please refer to https://www.cdc.gov/mmwr/volumes/70/wr/mm7027e2.htm.

8.7 Biomarkers

It is possible that as understanding of SARS-CoV-2 virus develops, biomarkers other than those specifically described in the immunogenicity assessments section (Section 8.2.2) may be evaluated in this study in exploratory analyses.

8.8 Immunogenicity Assessments

See Section 8.2.2.

8.9 Medical Resource Utilization and Health Economics

Medical Resource Utilization will be collected as part of COVID-illness in this study (see Section 8.2.1.1) as well as for SAE narrative preparation and categorization. In the context of a COVID-19-like illness, information on hospital stays, emergency room visits, non-routine medical office visits (including urgent care visits), and administered or prescribed antivirals and antibiotics will be collected from the subject for the purposed of healthcare utilization assessment (regardless of whether or not the medical event, healthcare contact or the use of medications is considered to be directly linked to the illness). Data collection will cover the period from the start to the end of the COVID-19-like illness. Medically-confirmed data, where available, will be considered the primary information source. Routine health care visits for pre-existing conditions, routine check-ups, medication prescription renewals, as well as medical office/health care visits procedures and hospitalizations planned prior to the start of the respiratory illness will not be recorded as part of the assessment of these endpoints.

8.10 Leftover Biological Samples and Use of Data

Any unused part of the serum or respiratory samples collected for this study 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.

In addition, participants will be asked to indicate in the ICF whether they will permit the future use of any unused stored serum samples, by Sanofi or one of its research partners, for other tests and the corresponding data, unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of any unused biological samples will not be included in the site-specific ICF). If they refuse permission, the biological samples will not be used for any testing other than that directly related to this study. If they agree to this future use, they will not be paid for giving permission. Data and samples will be used in compliance with the information provided to participants in the ICF Part 2 (future research). 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 and their mechanism of action, the knowledge of infectious diseases, or to improve existing tests or develop new tests to assess vaccines, or to help identify new vaccine targets or biomarkers that predict participant response to the vaccine. Such research may also include, but is not limited to, performing assessments on DNA, RNA, proteins or metabolites. If future research on human genetic material is performed, a specific individual consent will be obtained.

All study participant data and biological samples will be coded such that no direct identifiers will be linked to participants. Coded data and biological samples may be transferred to a Sponsor site (or a subcontractor site), which may be located outside of the country where the study is conducted. The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 10.1.4).

The biological samples will be securely stored at the Sanofi laboratory (GCI) or Contract Research Laboratory up to 25 years after the end of the study. Unused samples may also be sent to another long-term repository at the NIH, BARDA, as well as other US Government (USG)-designated laboratories. Any samples remaining at the end of retention period will be destroyed. If a participant requests destruction of his/her samples before the end of the retention period, the Investigator must notify the Sponsor (or its contract organization) in writing. In such case, samples will be destroyed, and sample related coded data will be anonymized unless otherwise required by applicable laws.

Study participant coded data will be stored for future research for up to 25 years after the end of the study. If data are still considered of important scientific value after this period, coded data already available will be anonymized unless otherwise required by applicable laws (the same will apply to the data of a study participant who has requested the destruction of his/her samples).

Participant's coded data sets provided to researchers for a specific research project will be available to the researchers for a maximum of 2 years after the end of their specific project (end of project is defined by publication of the results or finalization of the future research project report).

Note: The other biological samples collected to qualify the participant for inclusion in the study or to monitor his/her health during the study are dedicated for immediate use. If any of these biological samples 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.

9 Statistical Considerations

All statistical analysis described in this section will be applied for each stage based on the same methodology independently, unless otherwise specified. No formal multiplicity adjustment will be done in the statistical analysis of vaccine efficacy between the 2 stages. The analysis for each vaccine will be conducted against placebo controls enrolled contemporaneously. Analysis for cross-over / booster will be detailed in SAP.

9.1 Statistical Hypotheses

Hypothesis testing will be conducted for the primary efficacy objectives and the 2 key secondary efficacy objectives. Analyses of the primary safety objectives, other secondary objectives, and exploratory objectives will be descriptive.

Primary objective

The hypothesis testing of vaccine efficacy (VE) against the primary endpoint of symptomatic COVID-19 in each stage is as follows:

H0: VE $\leq$ 30%

HA: VE > 30%

The point estimate of VE is calculated by the incidence rate ratio (IRR):

$$\widehat{VE} = 1 - \frac{C_V/PY_V}{C_P/PY_P} \qquad \text{(Formula 1)}$$

where C_V and C_P represent the cases in vaccine group and placebo group respectively;

PY_V and PY_P represent total # of 1000 person-years in vaccine group and placebo group respectively;

The CI for VE will be calculated by an exact method assuming a binomial distribution of the number of cases in vaccine group conditional on the total number of cases in the study:

Let $q = \frac{C_V}{C_V+C_P}$ represent the proportion of cases belonging to vaccine group among the total number of cases, and let $\theta = \frac{E(C_V)}{E(C_V)+E(C_P)} = \frac{1-VE}{1-VE+PY_P/PY_V}$. Given the total number of cases, C_V has a binomial distribution (C_V+C_P, θ). Thus, a CI for θ may be constructed using the exact Clopper-Pearson method for binomial proportions (exact method) (17).

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

$$\widehat{VE} = 1 - \frac{C_V/PY_V}{C_P/PY_P} = 1 - \frac{PY_P}{PY_V} \times \frac{q}{1-q},$$

which is a strictly decreasing function of q.

Finally, for the primary endpoint, a CI of the VE will be constructed based on the CI of θ.

Secondary objectives

Other hypothesis testing with a different LB will be applied to the key secondary objectives: SARS-CoV-2 infection (defined in Section 8.2.1) and severe COVID-19:

H0: VE ≤ 0%

HA: VE > 0%

The point estimate of VE for severe COVID-19 is based on IRR (Formula 1) above with same methods to calculate the CI.

The point estimate of VE for SARS-CoV-2 infection is based on relative risk (RR) of COVID-19 case occurrence shown below:

$$\widehat{VE} = 1 - \frac{C_V/N_V}{C_P/N_P} \qquad \text{(Formula 2)}$$

where C_V and C_P represent the cases in vaccine group and placebo group respectively;

N_V and N_P represent total # of participants in vaccine group and placebo group respectively;

The CI of VE by RR is calculated with the same method as described above for the CI of VE by IRR by replacing the 1000 person-years to number of participants in the denominators, respectively. It is proposed to use RR for evaluating SARS-CoV-2 infection as the ascertainment of serological infection using blood samples collected at serial intervals does not enable robust assessments of person-time at risk for each individual.

For participants experiencing multiple events of symptomatic COVID-19, SARS-CoV-2 infection, or severe COVID-19 during the duration of the study, the first event will be counted for the analyses of VE of the primary and key secondary efficacy endpoints.

9.2 Sample Size Determination

A total of 10 160 participants in Stage 1 and 10 886 participants in Stage 2 are planned to be enrolled and randomized with allocation ratio (1:1) into vaccine group and placebo group. Among those, participants who are SARS-CoV-2 non-naïve at baseline will be capped to approximately 30% of the total population in Stage 1 (up to ~3048 participants [~1524/arm]). The target for SARS-CoV-2 non-naïves is ~3266 participants (~1633/arm) in Stage 2. If the crossover is not implemented, recruitment will continue until the minimally required number of naïve participants to assess efficacy is enrolled (even if the overall enrollment target is reached).To that end, the sample size of at least 7112 SARS-CoV-2 naïve participants in Stage 1 and 7620 SARS-CoV-2 naïve participants in Stage 2 is powered independently to demonstrate the primary objective of VE against symptomatic COVID-19 in SARS-CoV-2 naïve adults in each stage. Of note, the primary endpoint for Stage 2, including both naïve and non-naïve participants, was changed after enrollment of Stage 2 was already completed; therefore, all sample size calculations were based on a primary endpoint that considered only naïve participants. The power of primary efficacy analysis is driven by the total number of symptomatic COVID-19 events.

Assumptions for sample size calculation are listed as follows [a]:

- The LB of adjusted CI for the VE estimate is > 30% for both stages
- The expected true VE for symptomatic COVID-19 is 70%
- The 1-sided type I error for each stage is 0.025 with the sample size calculated based on adjusted alpha of 1-sided 0.02276 for final analysis including one interim at 70% data
- Power = 90% for each stage

Each stage is considered as independent of the other so that the type I error is controlled for each stage but not for the study. While the above assumptions remain the same for each stage of the

[a] Assumptions were made before the primary objective change was made in the protocol. Enrollment was already completed before the change in the primary endpoint; however, the power calculations are still the same.

study, the following assumptions are different for both stages because Stage 2 is expected to start after Stage 1.

- The incidence rate of symptomatic COVID-19 in Placebo is assumed as 2.25% illness rate in Stage 1 and 2.25% illness rate in Stage 2, per 2-months follow-up period
- Attrition rate = 25% in Stage 1 and 30% in Stage 2

The attrition rate is assumed to be higher for Stage 2 as larger parts of the population are eligible to receive vaccine.

For each stage, the type I error of hypothesis testing is controlled as 1-sided 0.025, and O'Brien Fleming (OBF) spending function is applied to adjust for multiplicity of interim analysis for efficacy with one potential interim analysis when accrual of approximately 50%-70% of the total number of events is reached (see Section 9.5). The sample size calculated based on the adjusted final alpha of 0.02276 will ensure at least 90% power to conclude on primary objective when the interim analysis is conducted between 50% - 70% range of data. Adjusted alpha by OBF alpha spending function is applied and the corresponding adjusted CI will be used for hypothesis testing (by exact method as described in Section 9.1) at each interim and at final analysis against symptomatic COVID-19 in each stage independently.

In each stage, with assumptions described above, a total of approximately 78 symptomatic COVID-19 events are required. The expected follow-up time to accrue the required number of events for 90% power is approximately 2 months post-second dose, given the incidence rate assumption in each stage respectively. However, the number of events may be reached earlier or later than the assumed 2-month period.

Because Omicron is the prevalent variant during case accrual for Stage 2 and the unexpected vaccine efficacy against Omicron is expected to be lower than the original assumption of 70%, the expected true VE for symptomatic COVID-19 for Stage 2 was estimated at 60%. Therefore, a total of approximately 125 symptomatic COVID-19 events are required to achieve 80% power with 1-side type I error rate of 0.025, assuming no interim analysis. If any interim analysis is planned for Stage 2, type I error rate will be adjusted appropriately.

It is considered success for the key secondary endpoints if the LB of the CI for the corresponding VE is > 0% against either the SARS-CoV-2 infection endpoint, or severe COVID-19. The Holm's procedure (18) will be applied to control the overall 1-sided alpha 0.025 against key secondary objectives. Assuming the VE against SARS-CoV-2 infection endpoint is at least 40%, a total of 162 infections will have at least 80% power to conclude at 0% LB. Assuming the VE against severe COVID-19 is 80%, a total of 22 events will provide at least 80% power to conclude at 0% LB.

The study is planned to have 5080 participants in the vaccine group in Stage 1 which will provide at least 92.1% probability to detect an event with 0.05% rate. In Stage 2, 5443 participants in vaccine group will provide at least 93.4% probability to detect an event with 0.05% rate.

9.3 Analysis Sets

The prior SARS-CoV-2 infection status of all randomized participants for the initial, double-blind, primary series design will be defined as following:

Prior SARs-CoV-2 infection status	Description
SARS-CoV-2 Naïve at baseline (Naïve-D01)	• Negative by the anti-S immunoassay (Roche Elecsys) on D01 serum sample AND • Negative by the anti-N immunoassay on D01 serum sample AND • Negative NAAT for SARS-CoV-2 on respiratory sample collected on D01 (see Section 8.1.5)
SARS-CoV-2 Non-Naïve at baseline (Non-Naïve-D01)	• Positive by the anti-S immunoassay (Roche Elecsys) on D01 serum sample OR • Positive by the anti-N immunoassay on D01 serum sample OR • Positive NAAT for SARS-CoV-2 on respiratory sample collected on D01 (see Section 8.1.5)
SARS-CoV-2 Naïve at second injection (Naïve-D01+D22)	• Negative by the anti-S immunoassay (Roche Elecsys) on D01 serum sample AND • Negative by anti-N immunoassay on D01 and D22 serum samples AND • Negative NAAT for SARS-CoV-2 on respiratory samples collected on D01 and D22 (see Section 8.1.5)
SARS-CoV-2 Non-Naïve at second injection (Non-Naïve - D01/D22)	• Positive by the anti-S immunoassay (Roche Elecsys) on D01 serum sample OR • Positive by the anti-N immunoassay on D01 or D22 serum samples OR • Positive NAAT for SARS-CoV-2 on respiratory samples collected on D01 or D22 (see Section 8.1.5)

The following analysis sets are defined and will be applied for each stage in the initial double-blind primary series design:

Population	Description
Screened	All participants screened for potential study enrollment will be included regardless of being enrolled or not being enrolled. The screening includes the SARS-CoV-2 rapid serodiagnosis test results, demographic information (age, ethnic/racial population, high-risk medical conditions), and inclusion/exclusion criteria. The participants reaching the enrollment cap identified in IRT will be excluded from the study enrollment and will have no participant ID assigned.
Randomized	All participants with a randomized group that has been allocated by IRT
Safety Analysis Set (SafAS)	All randomized participants who have received at least one dose of the study vaccine or placebo. All participants will have their safety analyzed after each dose according to the intervention they actually received, and after any dose according to the intervention received at the first dose. Safety data recorded for participants not administered a study intervention will be excluded from the analysis (and listed separately).
Reactogenicity Safety Analysis Subset (RSafAS)	Subset of the SafAS and comprising all participants who receive at least one study injection and are randomized into the reactogenicity subset.
Full Analysis Set	All randomized participants who receive at least one study injection. Participants will be analyzed according to the intervention to which they were randomized.
Modified Full Analysis Set post-dose 1 (mFAS-PD1)	Subset of the FAS excluding: • Participants with onset of symptomatic COVID-19 episode between the date of the first injection and 14 days after the first injection • Participant discontinued from study before 14 days after the first injection
Modified Full Analysis Set post-dose 2 (mFAS-PD2)	Subset of the FAS excluding: • Participants who did not complete the vaccination schedule (2 injections) • Participants with onset of symptomatic COVID-19 episode between the date of the first injection and before 14 days after the second injection • Participant received the second injection despite meeting any of the definitive contraindication criteria • Participant discontinued from study before 14 days after the second injection
Per-Protocol Analysis Set (PPAS)	Subset of the mFAS-PD2. Participants presenting with at least one of the following relevant protocol deviations 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 received a vaccine / placebo other than the one that he / she was randomized to receive

	• Preparation and / or administration of vaccine was not done as per-protocol • Participant did not receive vaccine / placebo in the proper time window The definition may be complemented with additional criteria for exclusion after the blinded review of protocol deviations reported on site.
Immunogenicity Analysis Set (IAS)	All randomized participants assigned to the Random Immunogenicity Subcohort (either allocation at enrollment OR supplemental selection after enrollment [see Appendix 10.6 for details]). Participants not compliant with the protocol will be excluded from IAS: • Participants who did not complete the vaccination schedule (2 doses) • Participant did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria • Participant received a vaccine / placebo other than the one that he / she was randomized to receive • Preparation and / or administration of vaccine was not done as per-protocol • Participant did not receive vaccine / placebo in the protocol-defined time window • Participants who did not collect D43 blood sample • Participant received the second injection despite meeting any of the definitive contraindication criteria • Participant receives an authorized/approved COVID-19 vaccine prior to D43 The definition may be complemented with additional criteria for exclusion after the blinded review of protocol deviations reported on site.
Case-cohort immunogenicity analyses set (ccIAS)	ccIAS includes all participants in the IAS or those have been determined to meet the efficacy endpoints. More details about ccIAS will be defined in the SAP or supplementary SAP.

The following analysis sets are defined and will be applied for Crossover phase receiving primary vaccine series among initial placebo recipients at each stage:

Crossover-Safety Analysis Set (CR-SafAS)	All participants who have received at least one dose of CoV2 preS dTM-AS03 vaccine during crossover study phase. All participants will have their safety analyzed after each dose, and after any dose. Safety data recorded from participants not administered CoV2 preS dTM-AS03 vaccines will be excluded from the analysis (only listed separately).

Crossover – Full analysis set (CR-FAS)	All participants who received at least one dose of primary vaccination series (either CoV2 preS dTM-AS03 vaccine or external approved COVID vaccine) during the crossover study phase
Crossover - Modified Full Analysis Set post-primary series	Subset of the CR-FAS excluding: • Participants with onset of symptomatic COVID-19 episode between the date of the first injection and 14 days after the last primary injection • Participant discontinued from study before 14 days after the last primary injection • Participant received the 2nd injection despite meeting any of the definitive contraindication criteria (only for CoV2 preS dTM-AS03 vaccine)
Crossover - Immunogenicity Analysis Set (CR-IAS)	All randomized participants assigned to the Random Immunogenicity Subcohort (either allocation at enrollment OR supplemental selection after enrollment [see Appendix 10.6 for details]). Participants not compliant with the protocol will be excluded from CR-IAS: • Participants who did not complete the primary series vaccination schedule (CoV2 preS dTM-AS03 vaccine or external approved vaccine) • Preparation and / or administration of vaccine was not done as per-protocol (only for CoV2 preS dTM-AS03 vaccine) • Participant did not receive vaccine in the protocol-defined time window (only for CoV2 preS dTM-AS03 vaccine) • Participants who did not collect any blood sample post primary series and before Booster • Participant received the second injection despite meeting any of the definitive contraindication criteria (only for CoV2 preS dTM-AS03 vaccine) The definition may be complemented with additional criteria for exclusion after the review of protocol deviations reported on site.
Crossover - Case-cohort immunogenicity analyses set (CR-ccIAS)	CR-ccIAS includes all participants in the CR-IAS or those have been determined to meet the efficacy endpoints in the crossover study phase. More details about CR-ccIAS will be defined in the SAP or supplementary SAP.

The following analysis sets are defined and will be applied for booster phase at each stage:

Booster - Safety Analysis Set (BS-SafAS)	All participants who have received one dose of CoV2 preS dTM-AS03 vaccine during booster study phase.
Booster - Modified Full Analysis Set (BS-mFAS)	Subset of the BS-SafAS excluding: • Participants with onset of symptomatic COVID-19 episode between the date of the booster injection and 14 days after the booster injection • Participant discontinued from study before 14 days after the booster injection

	• Participant received the booster injection despite meeting any of the definitive contraindication criteria
Booster - Immunogenicity Analysis Set (BS-IAS)	All participants assigned to the Random Immunogenicity Subcohort (either allocation at enrollment OR supplemental selection after enrollment [see Appendix 10.6 for details]). Participants not compliant with the protocol will be excluded from BS-IAS: • Participants who did not receive one dose of CoV2 preS dTM-AS03 vaccine during booster study phase. • Preparation and / or administration of the booster vaccine was not done as per-protocol • Participant did not receive booster vaccine in the protocol-defined time window • Participants who did not collect any blood sample after the booster • Participant received the booster injection despite meeting any of the definitive contraindication criteria The definition may be complemented with additional criteria for exclusion after the review of protocol deviations reported on site.
Booster - Case-cohort immunogenicity analyses set (BS-ccIAS)	BS-ccIAS includes all participants in the BS-IAS or those have been determined to meet the efficacy endpoints in booster study phase. More details about BS-ccIAS will be defined in the SAP or supplementary SAP.

9.4 Statistical Analyses

The statistical analysis plan (SAP) will be finalized prior to either breaking the study blind from Sponsor or prior to the database lock for the first interim analysis, whichever occurs first; 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. All analyses described in this section will be applied for each stage based on the same methodology independently. Populations applied will be further specified for each stage in the document of tables, listings, figures (TLFs).

The endpoints for efficacy, immunogenicity, and safety are as shown in Table 3.1.

9.4.1 General Considerations

Hypothesis testing will be conducted for the primary efficacy objectives and the 2 key secondary objectives. Analyses of other secondary objectives and exploratory objectives will be descriptive. Exploratory objectives will be included in either SAP or supplementary SAP.

9.4.2 Primary Endpoint

9.4.2.1 Efficacy

For the primary objective in each stage, the point estimate of VE in the SARS-CoV-2 naïve for Stage 1 population and in all participants regardless of prior SARS-CoV-2 infection status for Stage 2 is calculated based on the incidence rate per 1000 person-year (Formula 1) and the corresponding adjusted CIs for VE estimates based on adjusted alpha will be calculated by an exact method assuming a binomial distribution of the number of cases in vaccine group conditional on the total number of cases as described in Section 9.1. Details of alpha adjustments are explained in Section 9.2. For the presentation of the overall results of the study an unadjusted 95% CI for VE will also be calculated for each analysis.

The primary objective in each stage will be considered demonstrated if the point estimate of VE is > 50% and the LB of the adjusted CI is > 30% at the planned interim analysis or at the final analysis.

The analyses of the primary efficacy endpoints will be conducted in the mFAS-PD2 Naïve-D01+D22 analysis set for Stage 1 and in the mFAS-PD2 analysis set for Stage 2 to conclude on demonstration of the primary objective.

Sensitivity Analysis 1:

Sensitivity analysis against symptomatic COVID-19 will be conducted with VE calculated by RR (Formula 2) in addition to person-year approach in the mFAS-PD2 Naïve-D01+D22 analysis set for Stage 1 and in the mFAS-PD2 analysis set for Stage 2.

Sensitivity Analysis 2:

Sensitivity analysis against symptomatic COVID-19 will be conducted in the PPAS Naïve-D01+D22 analysis set for Stage 1 and in the PPAS analysis set for Stage 2.

Sensitivity Analysis 3 (Stage 1 only):

Sensitivity analysis against symptomatic COVID-19 will be conducted in the mFAS-PD2 in participants determined to be seronegative by the rapid diagnostic testing for SARS-CoV2 at enrollment.

In addition, survival analyses of symptomatic COVID-19 endpoints will be conducted using a stratified Cox proportional hazard model with separate baseline strata of age group, sex, and high-risk medical condition groups for Stage 1, serostatus at D01+D22 will also be included in the Cox proportional hazard model for Stage 2. If informative censoring is observed in the study, a Cox model adjusting for this informative censoring may be conducted.

Survival analysis will be conducted in the mFAS-PD2 Naïve-D01+D22 and PPAS Naïve-D01+D22 analysis sets for Stage 1 (both key secondary endpoints) and for Stage 2 SARS-COV-2 infection endpoint. Survival analysis will be conducted in the mFAS-PD2 and PPAS analysis sets for severe COVID-19 endpoint for Stage 2.

9.4.2.2 Safety

The main parameter will be described for all safety endpoints. The percentage of participants (denominator of number of participants) will be provided for all safety endpoints. In addition, incidence rate with denominator of 1000 person-years will also be provided for analysis of SAEs, AESIs, MAAEs, and virologically-confirmed SARS-CoV-2 infection and/or symptomatic COVID-19 throughout the study. This analysis to calculate incidence rate of events using person-time as a denominator for the safety endpoints listed above will be complementary analysis to the primary safety analysis using cumulative frequency. This analysis is planned as participants in this study are given the option of unblinding to receive approved/authorized COVID-19 vaccines during the conduct of the study. In this situation, it is possible that the safety follow-up of the placebo group may be shorter than the one of the vaccine group. In this situation, the duration of follow-up should ideally be integrated in the presentation of the safety data, ie, using the person-time denominator to calculate the incidence rate of the events in addition to the cumulative frequency analysis (number of events with the number of participants as the denominator). This minimizes the likelihood of biased assessment given the potential for shorter duration of follow-up for the participants in the placebo group.

The corresponding 95% CIs for incidence rates will be calculated based on the Poisson method, and 95% CI for percentages or proportions will be calculated based on Person-Clopper method. Subgroup analyses will be performed for at least age group and baseline SARS-CoV-2 serostatus (Naïve-D01 or Non-Naïve-D01) as defined in Section 9.3 for main safety analyses.

RSafAS will be used for safety analyses for the following endpoints:

- Presence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (pre-listed in the participant's DC/eDC and CRF) injection site reactions and systemic reactions occurring up to 7 days after each vaccination.
- Presence, nature (MedDRA SOC and PT), time of onset, duration, intensity, relationship to vaccination and whether the event led to early termination from the study of non-serious unsolicited AEs reported up to 21 days after the last vaccination.

SafAS will be used for the safety analysis for the following endpoints:

- Presence, and relationship of unsolicited (immediate) injection site and systemic AEs reported in the 30 minutes after each vaccination.
- Presence, nature (MedDRA SOC and PT), time of onset, seriousness criteria, relationship to vaccination, outcome, and whether the event led to early termination from the study, of SAEs.
- Presence, nature (MedDRA SOC and PT), relationship to vaccination of all protocol-specified AESIs from the time of the first study vaccination throughout the study.
- Presence of virologically-confirmed SARS-CoV-2 infections and/or symptomatic COVID-19
- Presence, nature (MedDRA SOC and PT), relationship to vaccination of MAAEs throughout the study.

9.4.3 Secondary Endpoints

9.4.3.1 Efficacy

Key Secondary Endpoints

Hypothesis testing for key secondary objectives in the SARS-CoV-2 naïve population will be performed for the SARS-CoV-2 infection endpoint and severe COVID-19 occurring ≥ 14 days after the second vaccination. This hypothesis testing of the 2 secondary endpoints is conditional to the success of the primary objective. The Holms procedure is applied to the 2 endpoints to control for the study wise error rate of 1-sided 0.025 (18).

The same statistical methods by IRR (Formula 1) will be applied for the endpoint of severe COVID-19. Statistical method by RR (Formula 2) for the SARS-CoV-2 infection endpoint will be applied due to the unknown time of infection onset. Hypothesis testing is described in the Section 9.1 for each of the key secondary endpoints. Survival analysis using a Cox proportional hazard model will also be applied for severe COVID-19 endpoint only.

The conclusions of efficacy against each of the key secondary endpoints will be based on mFAS-PD2 Naïve-D01+D22 analysis set by hypothesis testing for Stage 1; SARS-COV-2 infection endpoint based on mFAS-PD2 Naïve-D01+D22, and severe COVID-19 endpoint based on mFAS-PD2 for Stage 2. Sensitivity analysis for key secondary efficacy endpoints will be conducted on PPAS Naive-D01+D22 analysis set for Stage 1; SARS-COV-2 infection based on PPAS Naïve-D01+D22 and severe COVID-19 based on PPAS for Stage 2. Survival analysis will be conducted in the mFAS-PD2 Naïve-D01+D22 analysis set for Stage 1 (both key secondary endpoints), and for Stage 2 SARS-CoV-2 infection endpoint; survival analysis will be conducted in mFAS-PD2 analysis set for Stage 2 severe symptomatic COVID-19 endpoint.

Hypothesis testing for key secondary objectives will be conducted when both of the following conditions are met:

- The primary objective is demonstrated
- 22 severe cases and 162 infections are collected

The criteria of 22 severe COVID-19 and 162 SARS-CoV-2 infections are calculated based on 80% of power with assumed VEs (80% for VE against severe COVID-19 and 40% for VE against SARS-CoV-2 infection) and one-side alpha 0.0125.

If both of the criteria are met, the hypothesis testing of the key secondary endpoints will be done in the same timeframe as the efficacy analysis for the primary endpoint.

If either criteria are not met, hypothesis testing for the key secondary endpoints will be performed with final data available in comparison to a placebo control, (ie, at the time of the analysis with data prior to the cross-over) if at least a minimum of 11 severe events or 70 infections are collected. In this case, if only the minimum number of events are met for only one of the key secondary endpoints, the corresponding hypothesis testing will be performed without alpha splitting. If the minimum numbers of events are met for both key secondary endpoints, the Holm's procedure will be applied for the testing of the 2 key secondary endpoints.

For planning of situation that not meeting the number of planned number of cases upon the availability of final data described above, a base case is planned for the minimum numbers of severe COVID-19 (11) and SARS-CoV-2 infections (70), which are calculated based on at least 70% of power and assumed VEs (90% for VE against severe COVID-19 and 50% for VE against SARS-CoV-2 infection) and one-side alpha 0.0125.

More details will be described in the SAP.

Other Secondary Endpoints

The VE of symptomatic COVID-19 disease occurring 14 days post dose 1 will also be assessed by IRR (Formula 1) and survival analysis with mFAS-PD1 Naïve-D01 analysis set.

The point estimates of VE with CIs (by exact method) will be calculated for other secondary efficacy endpoints defined by occurrence of events. For secondary endpoints defined by symptomatic events with onset of time available (eg, symptomatic COVID-19 of at least moderate severity), the point estimate of VE will be calculated by IRR (Formula 1). For secondary endpoints without onset of time available (eg, asymptomatic infection or SARS-CoV-2 infection), the point estimate of VE will be calculated by RR (Formula 2).

The objectives defined by number of days as endpoints will be analyzed with summary statistics (min, max, mean, median, Q1, Q3) by study intervention groups. Analysis will be displayed separately for each symptom (eg, hospitalization, stay in an intensive care unit, use of supplemental oxygen, use of mechanical ventilation) by study group.

For the secondary endpoint defined with severity of symptomatic COVID-19 on a 7-point ordinal scale, VE will be calculated for each level or worse using IRR (Formula 1) with corresponding 95% CI calculated (by exact method).

To assess the durability of VE over time, point estimates of VE with 95% CI will be described for different time periods (eg, events occurring every 2 months depending on the availability of the data).

For objectives applicable to all participants, the secondary efficacy endpoints will be analyzed in mFAS-PD1 and mFAS-PD2 analysis sets. For objectives applicable to naïve participants, the secondary efficacy endpoints will be analyzed in the mFAS-PD1 Naïve-D01 and mFAS-PD2

Naïve-D01+D22 analysis sets. For objectives applicable to non-naïve participants, the secondary efficacy endpoints will be analyzed in the mFAS-PD1 Non-Naïve-D01 and mFAS-PD2 Non-Naïve-D01/D22 analysis sets.

More details will be described in the SAP.

9.4.3.2 Immunogenicity

The percentage of participants defined as responders, having a 2-fold rise (2FR), 4-fold rise (4FR) and ≥ 2x LLOQ or ≥ 4x LLOQ (for binding antibodies by ELISA) will be provided against each endpoint with the corresponding 95% CIs using the Clopper-Pearson method. Geometric mean titers (GMTs) or geometric mean value of concentrations (GMCs), and fold-rise (FR) in each injection group will be summarized along with their 95% CIs using the normal approximation of log-transformed titers. GMT ratios or GMC ratios (95% CI calculated by normal approximation of log-transformed titers) and differences of percentages of responders (95% CI calculated by Newcombe-Wilson score method (89) without continuity correction) will be provided for some main immunogenicity analyses. Geometric mean titer ratios (GMTRs) or geometric mean concentrations ratios (GMCRs) defined as geometric mean of individual titers/concentration ratios (post-vaccination/pre-vaccination) will also be summarized. Additional parameters may be displayed as appropriate.

All immunogenicity analyses will be conducted in the IAS in all, Naïve-D01, and Non-Naïve-D01 participants. Subgroup analyses will be performed at least by age-group for main immunogenicity analyses.

For objectives post-Crossover / Booster, analyses will be conducted in the CR-IAS and BS-IAS.

9.4.3.3 Safety

For severity of symptoms associated with symptomatic COVID-19 episode, percentages with 95% CI (by Clopper-Pearson methods) will be described for presence of symptoms, intensity, duration in all symptomatic COVID-19. Details of endpoint definitions will be defined in the SAP.

SafAS population will be used for analysis of severity of symptoms.

All other secondary safety endpoints will be described by incidence rates (denominator with 1000 person-years) as well as percentages with 95% CI with the 95% CI calculated by the Clopper-Pearson method. Subgroup analyses will be performed for at least age group, high-risk conditions, and country/region for main safety analyses.

SafAS Non-Naïve-D01 population will be utilized for the following endpoints:

- Occurrences of hospitalized COVID-19
- Occurrence of severe COVID-19
- Occurrences of COVID-19 in each severity rating on the 7-point ordinal scale
- Death associated with COVID-19

Symptomatic COVID-19 will be analyzed in each rating or worst on the 7-point ordinal scale.

Participants with active SARS-CoV-2 infection at baseline (as determined by positive NAAT at D01) will be listed separately, if applicable. More analyses will be described in the SAP.

For objectives post-Crossover / Booster, analyses will be conducted in the CR-SafAS and BS-SafAS.

9.4.4 Exploratory Endpoints

9.4.4.1 Efficacy

Estimation of each observational efficacy endpoint will be described with 95% CI calculated. The mFAS-PD2 will be the main population used for efficacy exploratory endpoints, but it may be complemented with analysis in other populations. Estimation and statistical methods on the observational efficacy endpoints for Crossover / Booster study will be as appropriate to the data collected. Details will be provided in the SAP or supplementary SAP.

9.4.4.2 Immunogenicity

The IAS or ccIAS will be applied for exploratory immunogenicity analyses. Details will be provided in the SAP or supplementary SAP.

9.5 Interim Analyses

The monitoring plan for interim efficacy, futility, and harm described in this section will be performed with data collected in each stage, respectively.

An interim analysis will be triggered with the criteria listed below (applied independently to each of the 2 study stages). At the interim analysis, planned analyses of efficacy, futility, and safety will be performed by an independent statistical group and evaluated by the DSMB. The database will be cleaned and locked for the interim analysis.

1) Observed cases are within the range of 40 to 55 symptomatic COVID-19 cases (from 50% to 70% data)
2) All participants enrolled have a median 2-month follow-up after 2 injections
3) Injection site and systemic reactogenicity data after the second vaccination is available on at least 50% participants assigned in the reactogenicity subset.
4) A minimum of 5 severe COVID-19 cases
5) A minimum of 3000 vaccine recipients have been followed for at least 1 month after the second vaccination for collection of safety data on MAAEs, AESIs, and SAEs

The Sponsor, in collaboration with independent committees, as well as the study OG, may decide to accelerate the interim analysis or skip the interim analysis before unblinding (eg, based on Regulatory considerations of emerging knowledge about expectations related to vaccine approval). In either case of skipping the planned interim analysis, or if the information fraction is different than planned (not within the range of 50% to 70% data), alpha splitting will be adjusted

based on Lan-DeMets OBF approximation spending function approach for interim and final efficacy analysis, if applicable.

In the event that the interim analysis of the Stage 1 is reached prior to the initiation of enrollment of Stage 2, the protocol may be amended based on the recommendations of the DSMB and discussion with the regulatory authorities.

Monitoring for Efficacy

At either interim or final analysis for efficacy, the point estimate of vaccine efficacy and associated 2-sided CI for the primary efficacy endpoint will be provided. The confidence level of the CI is determined by the OBF type alpha spending function with one-sided adjusted nominal level 0.025 at corresponding information time. The primary analysis population is the mFAS-PD2 Naïve-D01+D22 analysis set for Stage 1 and in the mFAS-PD2 analysis set for Stage 2. The success criteria for demonstration of efficacy include: 1) the LB of CI is > 30%, and 2) the point estimate of VE is > 50%.

The DSMB may also consider supportive data such as secondary endpoints and other key information described above, to aid the assessment of totality of safety and efficacy data at the interim analysis.

Monitoring for Futility

At each interim analysis, a non-binding futility analysis may be performed. Hypothesis testing is used for futility analysis at each interim based on 95% CI (one-sided unadjusted alpha of 0.025):

H0: VE ≥ 50%

HA: VE < 50%

Futility or low probability of having a positive study outcome may be concluded if the upper bound of the CI < 50%, based on the PPAS Naïve-D01+D22 analysis set for Stage 1 and in the PPAS analysis set for Stage 2. The Sponsor will carefully evaluate the DSMB recommendation and take appropriate action for the study.

The DSMB may also monitor the study for operational futility (eg, based on enrollment progression, event accrual rate, drop-out rate, magnitude of censoring) and make related recommendations to study conduct.

Monitoring for Harm

Continuous monitoring for harm will be conducted by assessing the frequency of symptomatic COVID-19 cases (primary endpoint) and severe COVID-19 separately. For each endpoint, the number of cases will be examined comparing vaccine group versus placebo group as each case accrues. Once a case occurs, a one-sided conditional exact binomial test is applied as follows:

H0: $p \leq 0.5$

HA: $p > 0.5$

Where p is the binomial probability that a case participant is assigned to the vaccine group conditional on the total observed number of cases at that moment. Each test is performed at the same one-sided nominal unadjusted alpha of 0.05. The non-binding harm monitoring for symptomatic COVID-19 will start when at least 10 symptomatic COVID-19 cases are observed.

The non-binding harm monitoring for severe COVID-19 will start when the first severe COVID-19 case is observed.

The population used for harm monitoring will be the SafAS in all participants. Once the results of testing of the D01 samples are available to determine the participants prior SARS-CoV-2 infection status, harm monitoring will also be evaluated in the SafAS Naïve-D01 analysis set and the SafAS Non-Naïve-D01 analysis set respectively for each endpoint.

If a null hypothesis is rejected for any one of the endpoints in any one of the population tested (based on the availability of baseline serostatus information), the DSMB will be notified immediately of the potential harm signal and will carefully review all unblinded case information to make recommendations on study conduct.

Monitoring for Operational Futility

The DSMB monitors the study for operational futility. The objective is to monitor the projected number of treatment arm-pooled symptomatic COVID primary endpoints by each of a set of calendar dates to aid ascertainment of whether the study is on target to meet the study objective regarding the evaluation of VE.

The operational futility monitoring report is based on treatment-blinded data and is provided to the DSMB as well as to the Study OG and the Trial Leadership Group starting at the second data review DSMB meeting to be held in September 2021. The report will include the following:

a) The enrollment rate
b) The accrual rate of symptomatic COVID-19 cases for the primary efficacy endpoint
c) The right censoring rate to date, including participants early terminated and received approved COVID-19 vaccine
d) The mean projected number of treatment arm-pooled primary symptomatic COVID-19 endpoints in the mFAS-PD2 naive D01+D22 cohort for Stage 1 and in the mFAS-PD2 cohort for Stage 2, with a Wald 95% CI for the mean by each calendar date 15 October 2021, 15 December 2021, and 15 February 2022
e) The estimated distribution of the total treatment arm-pooled number of primary symptomatic COVID-19 endpoints in the mFAS-PD2 naïve D01+D22 cohort, with corresponding power to reject H0: VE $\leqslant$ 30% using a 1-sided 0.025-level Wald test from a Cox model under the alternative hypotheses VE = 70%, 80%, and 90% by each calendar date 15 October 2021, 15 December 2021, and 15 February 2022.

The estimation procedures in (d) and (e) above will be conducted under each of the following 3 scenarios:

1) The treatment arm-pooled symptomatic COVID-19 endpoint rate in (d) and (e) used for generating future data are based on a Bayesian model and the prior assumption that VE=70% (the design alternative)
2) The treatment arm-pooled symptomatic COVID-19 endpoint rate in (d) and (e) used for generating future data are based on a Bayesian model and the prior assumption that VE= 30% (the null hypothesis)

3) The treatment arm-pooled symptomatic COVID-19 endpoint rate in (d) and (e) used for generating future data is based on a Bayesian model and the prior assumption that the COVID-19 endpoint rate equals to the observed-to-date symptomatic COVID-19 endpoint rate.

The Bayesian model in (d) and (e) will be conditioned on the observed data to-date, more specifically, to-date data in (a), (b), and (c). Right censoring in (c) occurs due to a variety of events including early termination, unblinding for any reason and receipt authorized/approved COVID-19 vaccine.

While it is the primary responsibility of the Study OG with the Trial Leadership Group to make decisions regarding trial operations and modifications based on the monitoring of the treatment-blinded primary endpoints, given the resource issues involved, DSMB review is also needed because issues of scientific integrity are also involved. Upon request, the statisticians will provide the DSMB and the Study OG with additional information, as appropriate, for use in their consideration of whether to recommend early trial completion.

A full description of the operational futility statistical analysis is available in the Operational Futility Monitoring SAP.

Other Supportive Information

Monitoring for potential disease enhancement will be conducted by the evaluation of the 7-point ordinal scale analysis at each interim analysis by the DSMB.

Other efficacy analysis stated in Section 9.4.3.1 as well as safety analyses described in Section 9.4.3.3 will be conducted as supportive information at each interim analysis based on available data such as efficacy against symptomatic COVID-19 caused by variants matched to those in the vaccine.

The SAP will describe the DSMB monitoring in greater detail.

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 (eg, data protection law as General Data Protection Regulation [GDPR])

- The protocol, informed consent form (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
  - Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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
  - Determining whether an incidental finding (as per Sanofi policy) should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:

    The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and

    The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.

    The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.

    In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- 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), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

As applicable, according to Directive 2001/20/EC, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical study that are deemed as "substantial" (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical study participants or on the scientific value of the study) prior to their implementation.

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 or his/her legally authorized representative and answer all questions regarding the study.
- If an approved/authorized vaccine is available in the country or region where the study is conducted and the participant is eligible for receiving vaccine (based on the country prioritization strategy for vaccine deployment) at the time of enrollment, investigators will discuss this information with the prospective study participant at the time of informed consent who will be encouraged to obtain the approved/authorized vaccine if applicable to them. Recruitment of eligible participants will proceed only if, despite encouragement, the candidate participant expresses no intention to seek an authorized or approved vaccine at the time of enrollment. Participants will be encouraged to receive the authorized/approved vaccine if they are eligible and the vaccine is available.
- 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 ICFs during their participation in the study.
- A copy of the ICF(s) 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 prior to submission to the IEC / IRB for approval.

10.1.4 Data Protection

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy & Data Protection laws and regulations, including the GDPR (General Data Protection Regulation). The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including Investigators, nurses, experts, service providers, Ethics Committee members, etc.

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.

Protection of participant data

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, if permitted by local (or country) regulations, because these data are required by regulatory agencies (90) and specific race and ethnicity categories are associated with a higher risk of COVID-19.
- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers will be identifiable only by the unique identifier; 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 applicable 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.
- Participants must be informed that their study-related data will be used for the whole "drug development program", ie, for this study as well as for the following steps necessary for the

development of the investigational product, including to support negotiations with payers and publication of results.

Protection of data related to professionals involved in the study

- Personal data (eg, contact details, affiliation(s) details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or pre-contractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.
- Personal data can be processed for other studies and projects.
- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agency's disqualification list.
- Personal data can be communicated to the following recipients:
    - Personnel within Sanofi or partners or service providers involved in the study
    - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency
- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:
    - The standard contractual clauses of the European Commission for transfers towards our partners and service providers,
    - Sanofi's Binding Corporate Rules for intra-group transfers.
- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to thirty (30) years, unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of Investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the Transcelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry/). Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members

of the Transcelerate project. This sharing allows Investigators to keep their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the Transcelerate project.

- Professionals have the right to object to the processing, to request for access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 54 rue La Boétie - 75008 PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.5 Committees Structure

10.1.5.1 Data and Safety Monitoring Board (DSMB) and Study Oversight Group

Study oversight is provided by an independent DSMB and by the study OG. While the OG is specific to the study, the DSMB is common across the harmonized COVID-19 vaccine efficacy studies funded by the USG. The DSMB applies pre-defined, OG- and DSMB-approved interim monitoring criteria, and reviews unblinded data on safety, efficacy, and study integrity. Recommendations for early vaccination termination, study termination, or design modifications are made to the OG. The OG determines adaptations in study design not predefined in the protocol, based on treatment-blinded data and DSMB recommendations.

10.1.5.2 Cardiac Adjudication Committee

Suspected cases of myocarditis and/or pericarditis will be referred to an external cardiac adjudication committee (common with influenza mRNA vaccine clinical studies sponsored by Sanofi) for assessment and confirmation.

10.1.5.3 Protocol Safety Review Team

A PSRT will be formed to review interim and cumulative blinded safety data on a regular basis with a remit to recommend DSMB escalation to the Sponsor. Further details on the composition and frequency of meetings are provided in the PSRT charter.

10.1.5.4 Adjudication Committee

An Adjudication Committee (AC) composed of members who are independent from the Sponsor and the Principal Investigators will be assembled for the purpose of reviewing potential cases to determine if the criteria for the safety and efficacy endpoints have been met. The AC will remain blinded to treatment assignment. The AC composition, its remit, and frequency of data review will be further defined in an AC Charter.

10.1.6 Dissemination of Clinical Study Data

Study participants

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.
- Guidance on completion of CRFs will be provided in the CRF completion instructions.
- 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 in as separate study document.
- 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).
- 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.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- 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.

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. It is to be noted that participants will have the choice to use either a paper DC provided by the site or an eDC. For eDCs, participants will use an app to be installed either on their own personal device or on a device loaned to them as a part of study supplies. Details on eDCs (including "terms of use", if applicable) will be included 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 or 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:

- For study termination:
    - Discontinuation of further study intervention development
    - Information on the study intervention leads to doubt as to the benefit/risk ratio
- For site termination:

- 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 or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

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 or serum human chorionic gonadotropin (hCG) pregnancy test (as needed for females 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.

Table 10.1: Protocol-required laboratory tests

Laboratory Tests	Time period for assessment	Parameters
Screening Tests	For initial primary series study design: pre-injections 1 and 2 at D01 and V02 (D22), respectively For Crossover / Booster: pre-injection at CRV01, CRV02, and BV01	Highly sensitive urine or serum human chorionic gonadotropin (hCG) pregnancy test (as needed for females 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

Participants, outcome assessors, Investigators, laboratory personnel, sponsor study staff, and those administering the study intervention if not involved in preparing the study intervention will be blinded to intervention group; and those preparing/administering the study interventions will be unblinded.

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: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of 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 intervention-intervention 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. • 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:

An adverse reaction (AR) is any noxious and unintended response to a study intervention related to any dose.

Immediate Event/Reaction:

Immediate events are recorded to capture medically relevant unsolicited injection site and systemic AEs which occur within the first 30 minutes after vaccination.

Reactogenicity / Solicited Reactions

The **reactogenicity** of a vaccine refers to the property of such vaccine to be able to produce common "expected" adverse reactions (either systemic or at the injection site) and its associated signs and symptoms.

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 corresponding IMP administered.

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

Injection / Administration Site Reactions:

An injection/administration site reaction is an AR at and around the injection/administration site of the IMP. Injection/administration site reactions are commonly inflammatory reactions.

Solicited injection / administration site reactions are reactions at and around the injection / administration site of the IMP observed and reported under the conditions (nature and onset) pre-listed in the protocol and CRF. It is considered by default as being related to the IMP administered at that site.

Note: « Administration site reaction » term is only to be used for vaccines that are not intended to be administered by injection.

Systemic AR:

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

Solicited systemic reactions are systemic AEs observed and reported under the conditions (nature and onset) pre-listed in the protocol and CRF. Solicited systemic reactions occurring during the specified collection period are always considered related to the IMP even if there is evidence of alternative etiology.

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 onset window post-vaccination. For example, varicella or a solicited term such as headache starting after the solicited observation period (eg, 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 an IMP.

Unsolicited AEs includes both serious (SAEs) and non-serious unsolicited AEs.

All unsolicited AEs occurring at and around the IMP injection/administration site are to be considered by default as related to the IMP administered at that site and are therefore referred as unsolicited injection/administration site ARs.

All unsolicited AEs which are not at and around the IMP injection/administration site, are referred as systemic unsolicited AE. For each unsolicited systemic AE, the investigator assesses the relationship to the IMP. Systemic AEs assessed as related to IMP are referred as systemic ARs.

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.

Medically Attended AE (MAAE)

An MAAE is a new onset or a worsening of a condition that prompts the participant or participant's parent/legally acceptable representative 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.

Potential Immune-Mediated Diseases (pIMDs):

pIMDs are a subset of adverse events that include autoimmune diseases and other inflammatory and/or neurological disorders of interest which may or may not have an autoimmune aetiology. pIMDs AEs that need to be recorded and reported as pIMDs include those listed in Appendix 10.5: Adverse Events of Special Interest.

10.3.2 Definition of SAE

An SAE is defined as any adverse event 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 admitted (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 or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Is other medically important event • The term "Other medically important events" refers to events which do not meet any of the above seriousness criteria, but which are considered as serious based on investigator medical judgment • Medical or scientific judgment should be exercised by the Investigator in deciding whether expedited reporting is appropriate in other situations such as significant medical events that 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 include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse, new-onset diabetes or autoimmune disease, or suspected transmission of any infectious agent via an authorized medicinal product.

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.
- 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 (either solicited or unsolicited) and all solicited systemic AEs are considered to be related to the IMP (see definition in Section 6) 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 (except for injection site reactions which will be related by default). 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 as either not related or related, based on the following definitions:
  - Not related – The AE is clearly / most probably caused by other etiologies such as participants' 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
  - Related – There is a "reasonable possibility" that the AE was caused by the study intervention administered, meaning that there are facts (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 makes 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 an 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 submitted documents.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.
- Serious adverse events likely to be related to the study intervention, 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) 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

Using a Verbal Autopsy Questionnaire to Aid in Determining the Cause of Death

In case of the absence or inadequacy of health information that would allow a thorough evaluation of the causes of the death of a study participant, the verbal autopsy procedure may be triggered by either the Investigator or the Sponsor. Detailed instructions on the use of the verbal autopsy questionnaire, as well as the questionnaire itself, are provided in the Operating Guidelines.

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 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 – Adults

CRF term (MedDRA lowest level term [LLT])	Injection site pain	Injection site erythema	Injection site swelling
Diary Card / electronic 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 / electronic 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 pain, the scale will be provided in the CRF and the intensity will be transcribed from the diary card. For other injection site reactions (erythema and swelling), the classification as Grades 1, 2, or 3 will be applied at the time of statistical analysis; the scale is provided for information purposes only. The actual size of the reaction will be reported in the CRF.

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

CRF term (MedDRA lowest level term [LLT])	Fever	Headache	Malaise	Myalgia	Arthralgia	Chills
Diary Card / electronic Diary Card	Temperature	Headache	Feeling unwell	Muscle aches and pains	Joint pain	Chills
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.	Pain in a joint or joints	Sensation of cold

CRF term (MedDRA lowest level term [LLT])	Fever	Headache	Malaise	Myalgia	Arthralgia	Chills
Intensity scale*	Grade 1: ≥ 38.0°C to ≤ 38.4°C, **or** ≥ 100.4°F to ≤ 101.1°F	Grade 1: A type of adverse event (AE) that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.	Grade 1: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.	Grade 1: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.	**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 2: A type of AE 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 2: A type of AE 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 2: A type of AE 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 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 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.

CRF term (MedDRA lowest level term [LLT])	Fever	Headache	Malaise	Myalgia	Arthralgia	Chills
	Grade 3: ≥ 39.0°C or ≥ 102.1°F	Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	Grade 3: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.	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 / electronic Diary Card:** Grade 1: No interference with usual activities Grade 2: Some interference with usual activities Grade 3: Significant; prevents usual activities	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 / electronic 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 (except fever), the scale will be provided in the CRF and the intensity will be transcribed from the diary card. For fever, the body temperature will be recorded, 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 DC, 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 AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
  - DC/eDC: No interference with usual activities.
- Grade 2
  - CRF: A type of AE 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.
  - DC/eDC: Some interference with usual activities.
- Grade 3
  - CRF: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
  - DC/eDC: Significant; prevents usual activities.

10.3.5.1.3 COVID-19 Symptoms Intensity Grading Scale

COVID-19 symptoms (except for loss of taste and loss of smell) will be classified according to the following intensity scale:

- Grade 1
  - CRF: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
  - DC: No interference with usual activities.
- Grade 2
  - CRF: A type of AE 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.
  - DC: Some interference with usual activities.

- Grade 3
  - CRF: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
  - DC: Significant; prevents usual activities.

For sense of smell and sense of taste, the following grading will apply:
- Grade 0 – sense of smell/sense of taste is the same as usual
- Grade 1 – sense of smell/sense of taste is less than usual
- Grade 2 – no sense of smell/sense of taste

10.4 Appendix: Contraceptive and Barrier Guidance

10.4.1 Definitions

Females of Childbearing Potential

A female 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.

Females in the following categories are not considered to be of childbearing potential

1) Premenarchal
2) Premenopausal female with 1 or more 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.

10.4.2 Contraception Guidance

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• **Highly Effective Methods[b] That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] – oral – injectable
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
• **Effective Methods[d] That Are Not Considered Highly Effective** *Failure rate of ≥ 1% per year when used consistently and correctly.*
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
• Male or female condom with or without spermicide
• Cervical cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
b) Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
c) Considered effective, but not highly effective - failure rate of ≥1% per year. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception.
d) Male condom and female condom should not be used together (due to risk of failure from friction).

10.5 Appendix: Adverse Events of Special Interest (AESIs)

AESIs considered potentially applicable to coronavirus vaccine

- Anaphylactic reactions
- Generalized convulsion
- Thrombocytopenia
- Thrombosis with Thrombocytopenia Syndrome
- Myocarditis
- Pericarditis

The definitions below are intended to serve as a guide to help in the reporting of suspected cases of myocarditis and/or pericarditis; however, the diagnosis of suspected cases is left to the investigator's clinical judgement.

Probable case of myocarditis

Presence of ≥ 1 new or worsening of the following clinical symptoms:

- Chest pain/pressure/discomfort
- Dyspnea/shortness of breath/pain with breathing
- Palpitations
- Syncope

AND

Presence of ≥ 1 new finding of the following:

- Troponin level above upper limit of normal (any type of troponin)
- Abnormal electrocardiogram (ECG or EKG) or rhythm monitoring findings consistent with myocarditis, which includes at least one of the following:
    - ST segment or T-wave abnormalities
    - Paroxysmal or sustained atrial, supraventricular, or ventricular arrhythmias
    - AV nodal conduction delays or intraventricular conduction defects
- Abnormal cardiac function or wall motion abnormalities on echocardiogram
- Cardiac magnetic resonance imaging (cMRI) finding consistent with myocarditis (91)

AND

- No other identifiable cause of the symptoms and findings

Confirmed case of myocarditis

Meets the case definition of probable case

AND

- Histopathologic confirmation of myocarditis (using Dallas criteria) (92)

OR

- cMRI findings consistent with myocarditis in the presence of troponin level above upper limit of normal (any type of troponin)

AND

- No other identifiable cause of the symptoms and findings

Acute pericarditis case definition

Presence of ≥ 2 new or worsening of the following clinical features (93):

- Acute chest pain (typically described as pain made worse by lying down, deep inspiration, or cough and relieved by sitting up or leaning forward, although other types of chest pain may occur)
- Pericardial rub on examination
- New ST-elevation or PR-depression on ECG
- New or worsening pericardial effusion on echocardiogram on magnetic resonance imaging

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

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 10.4.

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 10.4, 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 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 participant, the Investigator (or designate) must complete, date and sign an electronic Expedited Adverse Events Report.

Table 10.4: List of potential immune-mediated diseases (version: January 2022)

Blood disorders and coagulopathies	**Cardio-pulmonary inflammatory disorders**	**Endocrine disorders**
- Antiphospholipid syndrome - Autoimmune aplastic anemia - Autoimmune hemolytic anemia, including: o Warm antibody hemolytic anemia o Cold antibody hemolytic anemia - Autoimmune lymphoproliferative syndrome (ALPS) - Autoimmune neutropenia - Autoimmune pancytopenia - Autoimmune thrombocytopenia* o Frequently used related terms include: “autoimmune thrombocytopenic purpura”, “idiopathic thrombocytopenic purpura (ITP)”, “idiopathic immune thrombocytopenia”, “primary immune thrombocytopenia”. - Evans syndrome - Pernicious anemia - Thrombosis with thrombocytopenia syndrome (TTS) - Thrombotic thrombocytopenic purpura o Also known as “Moschcowitz-syndrome” or “microangiopathic hemolytic anemia”	- Idiopathic Myocarditis/Pericarditis, including: o Autoimmune / Immune-mediated myocarditis o Autoimmune / Immune-mediated pericarditis o Giant cell myocarditis - Idiopathic pulmonary fibrosis, including: o Idiopathic interstitial pneumonia (Interstitial lung disease, Pulmonary fibrosis, Immune-mediated pneumonitis) o Pleuroparenchymal fibroelastosis (PPFE) - Pulmonary alveolar proteinosis (PAP) o Frequently used related terms include: “pulmonary alveolar lipoproteinosis”, “phospholipidosis”	- Addison’s disease - Autoimmune / Immune-mediated thyroiditis, including: o Hashimoto thyroiditis (autoimmune hypothyroidism, lymphocytic thyroiditis) o Atrophic thyroiditis o Silent thyroiditis o Thyrotoxicosis - Autoimmune diseases of the testis and ovary, including: o Autoimmune oophoritis o Autoimmune ovarian failure o Autoimmune orchitis - Autoimmune hyperlipidemia - Autoimmune hypophysitis - Diabetes mellitus type I - Grave's or Basedow’s disease, including: o Marine Lenhart syndrome o Graves' ophthalmopathy, also known as thyroid eye disease (TED) or endocrine ophthalmopathy - Insulin autoimmune syndrome - Polyglandular autoimmune syndrome, including: o Polyglandular autoimmune syndrome type I, II and III
Eye disorders	**Gastrointestinal disorders**	**Hepatobiliary disorders**
- Ocular Autoimmune / Immune-mediated disorders, including:	- Autoimmune / Immune-mediated pancreatitis - Celiac disease	- Autoimmune cholangitis - Autoimmune hepatitis - Primary biliary cirrhosis

o Acute macular neuroretinopathy (also known as acute macular outer retinopathy) o Autoimmune / Immune-mediated retinopathy o Autoimmune / Immune-mediated uveitis, including idiopathic uveitis and sympathetic ophthalmia o Cogan's syndrome: an oculo-audiovestibular disease o Ocular pemphigoid o Ulcerative keratitis o Vogt-Koyanagi-Harada disease	- Inflammatory Bowel disease, including: o Crohn's disease o Microscopic colitis o Terminal ileitis o Ulcerative colitis o Ulcerative proctitis	- Primary sclerosing cholangitis
Musculoskeletal and connective tissue disorders	**Neuroinflammatory/neuromuscular disorders**	**Renal disorders**
- Gout, including: o Gouty arthritis - Idiopathic inflammatory myopathies, including: o Dermatomyositis o Inclusion body myositis o Immune-mediated necrotizing myopathy o Polymyositis - Mixed connective tissue disorder - Polymyalgia rheumatica (PMR) - Psoriatic arthritis (PsA) - Relapsing polychondritis - Rheumatoid arthritis, including: o Rheumatoid arthritis associated conditions o Juvenile idiopathic arthritis o Palindromic rheumatism o Still's disease o Felty's syndrome - Sjögren's syndrome - Spondyloarthritis, including: o Ankylosing spondylitis	- Acute disseminated encephalomyelitis (ADEM)* and other inflammatory-demyelinating variants, including: o Acute necrotising myelitis o Bickerstaff's brainstem encephalitis o Disseminated necrotizing leukoencephalopathy (also known as Weston-Hurst syndrome, acute hemorrhagic leuko-encephalitis, or acute necrotizing hemorrhagic encephalomyelitis) o Myelin oligodendrocyte glycoprotein antibody-associated disease o Neuromyelitis optica (also known as Devic's disease) o Noninfective encephalitis / encephalomyelitis / myelitis o Postimmunization encephalomyelitis - Guillain-Barré syndrome (GBS)*, including:	- Autoimmune / Immune-mediated glomerulonephritis, including: o IgA nephropathy o IgM nephropathy o C1q nephropathy o Fibrillary glomerulonephritis o Glomerulonephritis rapidly progressive o Membranoproliferative glomerulonephritis o Membranous glomerulonephritis o Mesangioproliferative glomerulonephritis o Tubulointerstitial nephritis and uveitis syndrome

o Juvenile spondyloarthritis o Keratoderma blenorrhagica o Psoriatic spondylitis o Reactive Arthritis (Reiter's Syndrome) o Undifferentiated spondyloarthritis - Systemic Lupus Erythematosus, including: o Lupus associated conditions (e.g. Cutaneous lupus erythematosus, Lupus nephritis, etc.) o Complications such as shrinking lung syndrome (SLS) - Systemic Scleroderma (Systemic Sclerosis), including: o Reynolds syndrome (RS) o Systemic sclerosis with diffuse scleroderma o Systemic sclerosis with limited scleroderma (also known as CREST syndrome)	o Variants such as Miller Fisher syndrome and the acute motor and sensory axonal neuropathy (AMSAN) - Idiopathic cranial nerve palsies/paresis and inflammations (neuritis), including: o Cranial nerve neuritis (e.g. Optic neuritis) o Idiopathic nerve palsies/paresis (e.g. Bell's palsy) o Melkersson-Rosenthal syndrome o Multiple cranial nerve palsies/paresis - Multiple Sclerosis (MS), including: o Clinically isolated syndrome (CIS) o Malignant MS (the Marburg type of MS) o Primary-progressive MS (PPMS) o Radiologically isolated syndrome (RIS) o Relapsing-remitting MS (RRMS) o Secondary-progressive MS (SPMS) o Uhthoff's phenomenon - Myasthenia gravis, including: o Ocular myasthenia o Lambert-Eaton myasthenic syndrome - Narcolepsy* (with or without presence of unambiguous cataplexy) - Peripheral inflammatory demyelinating neuropathies and plexopathies, including o Acute Brachial Radiculitis (also known as Parsonage-Turner Syndrome or neuralgic amyotrophy) o Antibody-mediated demyelinating neuropathy	

	o Chronic idiopathic axonal polyneuropathy (CIAP) o Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP), including atypical CIDP variants (e.g. multifocal acquired demyelinating sensory and motor neuropathy also known as Lewis-Sumner syndrome) o Multifocal motor neuropathy (MMN) - Transverse myelitis (TM), including: o Acute partial transverse myelitis (APTM) o Acute complete transverse myelitis (ACTM)	
Skin and subcutaneous tissue disorders	**Vasculitis**	**Other (including multisystemic)**
- Alopecia areata - Autoimmune / Immune-mediated blistering dermatoses, including: o Bullous Dermatitis o Bullous Pemphigoid o Dermatitis herpetiformis o Epidermolysis bullosa acquisita (EBA) o Linear IgA-mediated bullous dermatosis (LABD), also known as Linear IgA disease o Pemphigus - Erythema multiforme - Erythema nodosum - Lichen planus, including: o Liquen planopilaris - Localised Scleroderma (Morphoea) o Eosinophilic fasciitis (also called Shulman syndrome) - Psoriasis	- Large vessels vasculitis*, including: o Arteritic anterior ischemic optic neuropathy (AAION or arteritic AION) o Giant cell arteritis (also called temporal arteritis) o Takayasu's arteritis - Medium sized and/or small vessels vasculitis*, including: o Anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified) o Behcet's syndrome o Buerger's disease (thromboangiitis obliterans) o Churg–Strauss syndrome (allergic granulomatous angiitis) o Erythema induratum (also known as nodular vasculitis) o Henoch-Schonlein purpura (also known as IgA vasculitis)	- Anti-synthetase syndrome - Capillary leak syndrome o Frequently used related terms include : "systemic capillary leak syndrome (SCLS)" or "Clarkson's Syndrome" - Goodpasture syndrome o Frequently used related terms include: "pulmonary renal syndrome" and "anti-Glomerular Basement Membrane disease (anti-GBM disease)" - Immune-mediated enhancement of disease, including: o Vaccine associated enhanced disease (VAED and VAERD). Frequently used related terms include "vaccine-mediated enhanced disease (VMED)", "enhanced respiratory disease (ERD)", "vaccine-induced

- Pyoderma gangrenosum - Reactive granulomatous dermatitis, including : o Interstitial granulomatous dermatitis o Palisaded neutrophilic granulomatous dermatitis - Stevens-Johnson Syndrome (SJS), including: o Toxic Epidermal Necrolysis (TEN) o SJS-TEN overlap - Sweet's syndrome, including: o Acute febrile neutrophilic dermatosis - Vitiligo	o Microscopic polyangiitis o Necrotizing vasculitis o Polyarteritis nodosa o Single organ cutaneous vasculitis, including leukocytoclastic vasculitis, hypersensitivity vasculitis and acute hemorrhagic edema of infancy (AHEI) o Wegener's granulomatosis	enhancement of infection", "disease enhancement", "immune enhancement", and "antibody-dependent enhancement (ADE) - Immunoglobulin G4 related disease - Langerhans' cell histiocytosis - Multisystem inflammatory syndromes, including: o Kawasaki's disease o Multisystem inflammatory syndrome in adults (MIS-A) o Multisystem inflammatory syndrome in children (MIS-C) - Overlap syndrome - Raynaud's phenomenon - Sarcoidosis, including: o Loefgren syndrome - Susac's syndrome

*Adverse events of special interest (AESI) considered potentially applicable to COVID-19 vaccines as defined by the Safety Platform for Emergency Vaccines (SPEAC), based on known association with vaccination in general (see https://brightoncollaboration.us/wp-content/uploads/2021/01/SO2_D2.1.2_V1.2_COVID-19_AESI-update-23Dec2020-review_final.pdf). SPEAC list extended with additional potential immune-mediated diseases.

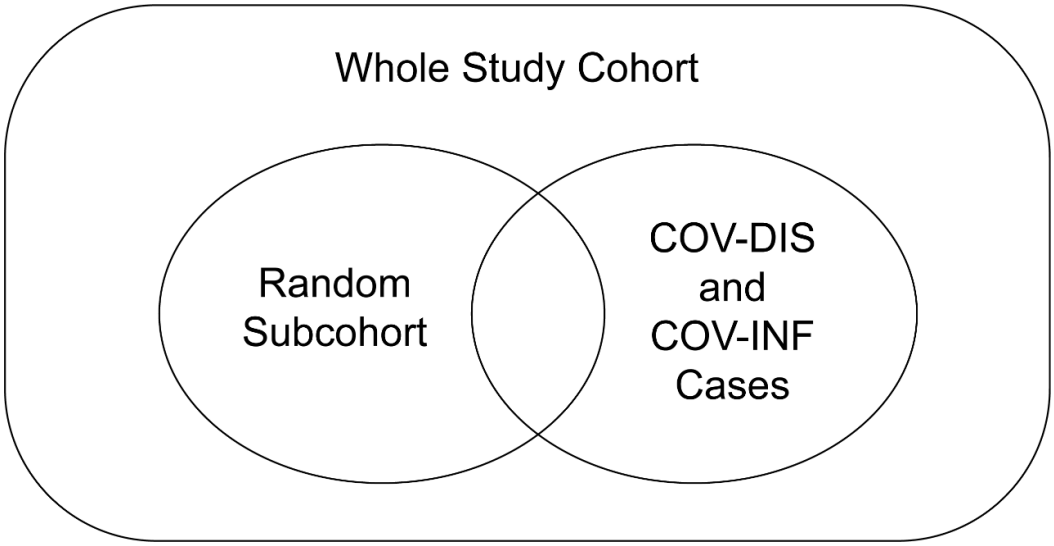
10.6 Appendix: Random Immunogenicity Subcohort for Measuring Antibody Markers for Assessment of Immunogenicity, Immunological Correlates of Risk, and Immunological Correlates of Protection

In this study, the 2-phase sampling design are embedded to the IRT system at enrollment (Step 1 randomization). A 2-phase sampling design is used for measuring antibody markers in a case-cohort defined as a selected subset of all study participants and from endpoint cases (both COVID-19 primary endpoints and secondary SARS-CoV-2 infection endpoints, including both protocol-specified SARS-CoV-2 naïve at D01 and D22 [D01+D22] and non-naïve at D01+D22 participants) at each stage of the study, for assessing vaccine immunogenicity, immunological correlates of risk, and various types of immunological correlates of protection. This set of participants selected for antibody marker measurement is referred to as the 'Case Cohort'. A 2-phase sampling design is an extension of Prentice's (1986) case-cohort sampling design (Figure 10.1), which instead of employing simple random sampling of the whole study cohort (as in Prentice, 1986), draws a separate random sample from each of multiple strata defined by a set of baseline participant covariates (94). Use of a 2-phase sampling case-cohort design enables generation of antibody marker data for the Random Immunogenicity Subcohort participants during early study follow-up through the shipment of periodic batches of samples (also including available samples from endpoint cases outside of the Random Immunogenicity Subcohort) to the labs, enabling conduct of antibody marker correlates analyses shortly after the time of the primary analysis. As well, this 2-phase design allows use of the same Random Immunogenicity Subcohort for assessing correlates of risk and protection against each of multiple study endpoints. The Case Cohort is the union of the 2 sub-regions in Figure 10.1.

10.6.1 Eligibility Criteria for Case Cohort Sampling

Only participants with available baseline stratification information (Section 10.6.2) are eligible for sampling into the Random Immunogenicity Subcohort. For sampling of endpoint cases into the Case Cohort, all vaccine recipient cases and all SARS-CoV-2 non-naïve D01+D22 placebo recipient cases are included, whereas SARS-CoV-2 naïve D01+D22 placebo recipient cases are not included, because almost all of the antibody responses at D43 will be negative given the naïve status. All vaccine recipient cases and all SARS-CoV-2 non-naïve D01+D22 placebo recipient cases are included regardless of the time of their failure event date, even if it occurred before or near D43 (this is done for simplicity). However, in the correlates data analyses of D43 antibody markers, the set of endpoint cases only includes individuals with endpoint event date occurring at least 7 days after the D43 visit, to account for the fact that endpoints occurring shortly after D43 may have acquired SARS-CoV-2 prior to the D43 time point, and hence could complicate the interpretation of the correlates results.

Figure 10.1: Case Cohort



Note: Case Cohort. Schema for the two-phase sample for measuring antibody markers and enabling assessment of immunological correlates of risk and protection. The Whole Study Cohort refers to the mFAS-PD2 cohort defined in Section 9.3. Antibody markers are measured from all participants sampled into the Random Immunogenicity Subcohort (labeled Random Subcohort in the diagram) in Step 1 and 2 described in Section 10.6.2 and from all vaccine recipients and SARS-CoV-2 D01+D22 non-naïve placebo recipients who experience a COVID-19 primary endpoint (denoted COV-DIS) and/or experience the secondary infection endpoint (denoted COV-INF). Case Cohort = Random Immunogenicity Subcohort selected in Step 1 and 2 + specified COV-DIS and COV-INF endpoint cases.

10.6.2 Sampling Plan for Selecting the Random Immunogenicity Subcohort

Separately for Stage 1 and 2 of the study, we consider a 2-step sampling plan for selection of the Random Immunogenicity subset. Step 1 of the random sampling is performed at enrollment by the IRT system. At this step, a 2-phase sampling design will be employed to random sample of all participants into the Random Immunogenicity subset within 8 baseline covariate strata defined by cross-classification of (vaccine, placebo) x (baseline SARS-CoV-2 positive vs. negative status by rapid serodiagnostic test) x (18-59 years, ≥ 60 years).

Step 2 of the random sampling is performed after the SARS-CoV-2 D01+D22 naïve/non-naive status available for all enrolled participants. All participants in US country not sampled into the Random Immunogenicity Subcohort in Step 1 and with available stratification information are eligible for sampling in Step 2. At this step, sampling without replacement will be employed to meet the minimum sample size requirement (pooling Step 1 and Step 2) for each of the 8 strata specified in Table 10.5. Note that sampling in Step 2 is stratified by the D01+D22 naïve/non-naïve status (a post-baseline covariate), whereas sampling in Step 1 is stratified by the baseline negative/positive rapid serodiagnostic test result. All other stratification covariates are the same in Steps 1 and 2. A single sampling list will be generated in Step 2.

10.6.3 Stratum-specific Sample Sizes in the Random Immunogenicity Subcohort

Table 10.5 specifies approximate allocation ratio in each pre-identified stratum for the Random Immunogenicity Subcohort in Step 1, for each of the 8 baseline covariate status, and separately for Stage 1 and Stage 2 of the study. The allocation ratio in each pre-identified stratum is fixed.

Table 10.5: Step 1 Allocation ratio (Random vs non-Random) in each stratum of the Random Immunogenicity Subcohort for measuring antibody markers for assessment of immunogenicity and immunological correlates of risk and protection at each stage of the study

Approximate Numbers of Participants (with allocation ratios in each stratum) Sampled in Step 1 Into 16 Baseline Covariate Strata, Separately for Stage 1 and 2 of the Study				
Region	**Negative SARS-CoV-2 Rapid Test†**		**Positive SARS-CoV-2 Rapid Test†**	
Age (Years)	**18–59**	**≥ 60**	**18–59**	**≥ 60**
	Study Stage 1			
Monovalent Vaccine	**1:4**	**1:4**	**1:3**	**1:3**
Placebo	**1:19**	**1:19**	**1:3**	**1:3**
	Study Stage 2			
Bivalent Vaccine	**1:4**	**1:4**	**1:3**	**1:3**
Placebo	**1:19**	**1:19**	**1:3**	**1:3**

† Baseline SARS-CoV-2 rapid serodiagnostic test positivity

The vaccine-arm baseline seronegative strata are assigned large sample sizes because the correlates of risk and protection analyses focus on these subgroups. The placebo-arm baseline seronegative strata are assigned small sample sizes given the expectation that almost all antibody marker values will be negative/zero (at the lower quantitation limit of the assay) given the absence of prior exposure to SARS-CoV-2 antigens. Equal stratum sizes are assigned for the vaccine-arm and placebo-arm baseline seropositive strata in order to compare responses of antibody markers induced by prior infection alone versus induced by the combination of prior infection and vaccination.

For each study stage, Table 10.6 specifies approximate target stratum-specific sample size requirements for the Random Immunogenicity subcohort. If the samples from Step 1 do not meet the target, then supplemental sampling will be needed in Step 2. Step 2 is designed to make sure that participants have enough samples in each stratum.

Table 10.6: Approximate stratum-specific sample sizes for the Random Immunogenicity subset

	Approximate Stratum-specific Sample Sizes to Determine Supplemental Sampling			
Naïve Status	**SARS-CoV-2 Naïve at D01+D22 †**		**SARS-CoV-2 Non-Naïve at D01/D22 †**	
Age (Years)	**18–59**	**≥ 60***	**18–59**	**≥ 60***
	Study Stage 1 (N ≈ 1415 Vaccinees, N ≈ 559 Placebos)			
Monovalent Vaccine	750	284	**229**	**152**
Placebo	107	71	229	152
	Study Stage 2 (N ≈ 1415 Vaccinees, N ≈ 559 Placebos)			
Bivalent Vaccine	750	284	**229**	**152**
Placebo	107	71	229	152

† SARS-CoV-2 naïve/non-naïve at D01+D22 status is defined using the anti-N immunoassay on the D01 and D22 serum samples and NAAT for SARS-CoV-2 on the D01 and D22 nasopharyngeal swabs

*the sample size for ≥ 60 will change depending on the actual enrollment

If a stratum has the required minimal sample size after completion of Step 1, then no random sampling will be performed for that stratum in Step 2. If a stratum has fewer participants than the required minimal sample size, then supplemental random sampling will be performed in Step 2. In the special case that sampling in Step 2 is carried out for a given stratum but fewer participants in the stratum are eligible for sampling than the required minimal sample size, then all eligible participants in that stratum will be selected into the Random Immunogenicity Subcohort.

10.6.4 Antibody Marker Measurements from Participants in the Case Cohort

Antibody markers are measured from Case Cohort participants in USG labs at all available sampling time points (Days 1, 22, 43, 78, 134, 202, 292, and 387). The measurements are made in two stages. Stage 1 includes the D01, D22, and D43 time points, and Stage 2 includes all other time points for the entire Case Cohort. Specifically, Stage 1 includes all vaccine-arm and D01+D22 non-naïve placebo-arm endpoint cases (both COVID-19 primary endpoints and secondary infection endpoints) measured through to the time of the primary analysis as well as additional vaccine-arm and D01+D22 non-naïve placebo-arm endpoint cases that occur between the primary analysis and finalization of the data set for transfer to the CoVPN for the initial assessment of D43 antibody marker correlates of risk and protection. Stage 1 focuses on D43 antibody markers because, in general, accepted immunological surrogate endpoints are defined based on an approximate peak time point antibody marker.

Stage 2 also includes antibody marker data from all additional vaccine-arm and D01+D22 non-naïve placebo-arm endpoint cases (both COVID-19 primary endpoints and secondary infection endpoints) through to the end of the follow-up period of the study, including all available sampling time points. The Stage 2 endpoint data and antibody marker data enable assessment of longitudinal antibody markers as case-proximal correlates of risk and protection.

10.7 Appendix: Country-specific Requirements

10.7.1 VAT00008 Sub-study in Japan

A VAT00008 Sub-study will be conducted in Japan based on regulatory authority feedback. Details will be included as a separate annex to the main VAT00008 study protocol.

10.7.2 Serious Adverse Event Reporting Period

Refer to the national expedited/periodic reporting requirements in the countries where this study is conducted. Details on country-specific requirements are available in the Operating Guidelines.

10.8 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 RMP.

10.9 Appendix: Abbreviations

Ab	Antibody
ACE2	Angiotensin converting enzyme-related peptidase 2
AE	Adverse Events
AESI	Adverse events of special interest
AN	Anterior nasal
AR	Adverse reactions
CI	Confidence interval
CLI	COVID-19-like illness
cMRI	Cardiac magnetic resonance imaging
CoV2 preS dTM	CoV2 prefusion Spike delta TM
CR	Crossover
CRF	Case report form
DC	Diary Card
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eDC	electronic Diary Card
ELISA	Enzyme-linked immunosorbent assay
FAS	Full analysis set
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
GPV	Global Pharmacovigilance
GSK	GlaxoSmithKline
HCP	Host cell protein
HCRT	Hypocretin
HCS	Human convalescent sera
HRT	Hormonal replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation

IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committees
IM	Intramuscular
IMP	Investigational Medicinal Product
IRB	Institutional Review Boards
IRR	Incidence rate ratio
IRT	Interactive Response Technology
LB	Lower bound
LLOQ	Lower limit of quantification
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
mFAS	modified Safety Analysis Set
mRNA	Messenger ribonucleic acid
NAAT	Nucleic acid amplification test
NHP	Non-human primate
NIMP	Non- Investigational Medicinal Product
NP	Nasopharyngeal
OBF	O'Brien Fleming
OG	Oversight Group
pIMD	Potentially immune-mediated disease
PPAS	Per-protocol analysis set
PSRT	Protocol Safety Review Team
PT	Preferred term
PV	Pharmacovigilance
RBD	Receptor binding domain
RMO	Responsible Medical Officer
RMP	Risk Management Plan
RNA	Ribonucleic acid
rSafAS	Reactogenicity Safety Analysis Set
RR	Relative risk
S	Spike

SAE	Serious adverse events
SafAS	Safety Analysis Set
SAP	Statistical analysis plan
SoA	Schedule of Activities
SOC	System organ class
TBD	To be determined
TIV	Trivalent influenza vaccine
USG	United States Government
VAC	Vaccination
VAED	Vaccine-associated enhanced disease
VAERD	Vaccine-associated enhanced respiratory disease
VE	Vaccine efficacy
VOC	Variant of concern
WHO	World Health Organization

10.10 Appendix: Protocol Amendment History

The Protocol Amendment Rationale for the current amendment is located directly before the Table of Contents.

Protocol Update from Version 1.0 (30 March 2021) to Version 2.0 (16 April 2021):

The main reason for updating the protocol from Version 1.0 to Version 2.0 was due to Center for Biologics Evaluation and Research feedback for study design. The main updates were as shown below:

Revision	Rationale
Text revised throughout to describe no overlap for placebo in Stage 1 and Stage 2: "In the event that the enrollment in Stage 1 overlaps with enrollment of Stage 2, participants will continue to be randomly allocated to one of the investigational vaccine groups and their matched placebo group in a 1:1 ratio. There will be no sharing of the placebo participants between the 2 stages."	The availability of the bivalent vaccine for Stage 2 is scheduled for September while the monovalent vaccine (Stage 1) is scheduled to start in May/June. We expect to complete recruitment of Stage 1 by the middle of August and therefore do not anticipate any significant overlap in enrollment between the 2 stages. It is also necessary to undertake formal multiplicity adjustment in statistical analysis if there is a sharing of the placebo group between the 2 stages. To avoid this issue even in the unlikely event that there is overlap in enrollment between the 2 stages, the protocol has been amended to clarify that no sharing of the placebo participants will occur between the 2 stages. The randomization plan will be a 1:1 allocation between the treatment groups in each stage.
Secondary efficacy objective #6 deleted: "To assess the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for the prevention of symptomatic COVID-19 by the variant and genotypic characteristics of the viral strains causing symptomatic COVID-19."	We have deleted this secondary objective as it is a duplicate of exploratory objective #11. Assessment of clinical vaccine efficacy by the variant strains is considered an exploratory objective and it is not proposed to make claims or hypothesis testing based on efficacy against matched strains or a particular variant strain. Methods for accurate classification of variants are yet to be standardized and accepted. As such, efficacy by potential variant and any genotypic characteristics will be performed under the exploratory objective referring to Sieve Analysis (Exploratory Objective #11). Moreover, we do not have a validated assay for viral sequencing, do not have accepted methodologies for

	classification of virus sequences and mutations into variant categories and do not have accepted methodologies for antigenicity based categorization of virus sequences for determination of matched and mismatched viruses. Therefore, it is proposed to maintain this as an exploratory objective using sieve analysis.
Secondary Immunogenicity Objectives: Specifying that immunogenicity assessments will be against the D614G variant. 1) To compare the neutralizing antibody response 21 days after last vaccination (D43) to the D614G variant between the monovalent and bivalent vaccines in SARS-CoV-2 naïve and non-naïve participants in the Random Immunogenicity Subcohort. 3) To compare the neutralizing antibody response 21 days after last vaccination (D43) to the B.1.351 strain in the bivalent vaccine group and the neutralizing antibody response to the D614G variant in the monovalent vaccine group in SARS-CoV-2 naïve and non-naïve participants in the Random Immunogenicity Subcohort.	Clarifying that the immunogenicity assessments will be performed against the D614G variant.
Sample size is modified for the study.	Based on CBER feedback recommending a minimum of 7500 vaccine recipients who have received the 2-dose regimen the sample size for Stage 1 has been increased to 8000 participants in the vaccine group and 8000 participants in the placebo group for a total of 16 000 participants. The sample size assumptions have been modified accordingly and have been modified for Stage 2 as well.
Analysis Sets tables Split into 2 separate tables: - One for definitions of prior SARS-CoV-2 infection - One for analysis sets	In line with SAP revisions, for clarity on definitions for prior infection status versus analysis sets used for biostatistical analyses.

Statistical considerations / Statistical Analyses (Primary Safety Endpoints): Text revised as shown below: The main parameter will be described for all safety endpoints. The percentage of participants (denominator of number of participants) will be provided for all safety endpoints as the main analysis. In addition, incidence rate with denominator of 1000 person-years will be provided for analysis of SAEs, AESIs, MAAEs, and SARS-CoV-2 infection and/or symptomatic COVID throughout the study. This analysis to calculate incidence rate of events using person-time as a denominator for the safety endpoints listed above will be complementary analysis to the primary safety analysis using cumulative frequency. This analysis is planned as participants in this study are given the option of unblinding to receive approved/authorized COVID-19 vaccines during the conduct of the study. In this situation, it is possible that the safety follow-up of the placebo group may be shorter than the one of the vaccine group. In this situation the duration of follow-up should ideally be integrated in the presentation of the safety data, ie, using the person-time denominator to calculate the incidence rate of the events in addition to the cumulative frequency analysis (number of events with the number of participants as the denominator). This minimizes the likelihood of biased assessment given the potential for shorter duration of follow-up for the participants in the placebo group.	The changes are made to clarify that the primary safety endpoint analyses will be based on using percentages as per CBER feedback. Incidence rates will be used as complementary analyses, and the paragraph provides rationale for the proposal to use incidence rates as complementary analysis.
Section 8.4 / Section 10.1.5.2: Text revised as shown below: A Protocol Safety Review Team (PSRT) will review interim and cumulative blinded safety data on a regular basis with a remit to ~~escalate concerns to the~~ recommend DSMB escalation to the Sponsor.	This change has been made to reflect the PSRT Charter.

Section 8.4: Modification to study halting rule • An unfavorable imbalance of severe or serious conditions is identified by the DSMB between vaccine and placebo, including harm monitoring for COVID-19 (Section 9.5)	Based on CBER feedback, made it clear that the DSMB can recommend a study halting based on the harm monitoring plan detailed in Section 9.5 for COVID-19.
Section 9.5: Addition of condition to criteria for triggering interim efficacy analysis. The following criterion #5 has been added. A minimum of 3000 vaccine recipients have been followed for at least 1 month after the second vaccination for collection of safety data on MAAEs, AESIs, and SAEs	The following additional criterion has been added to trigger the interim analyses based on CBER feedback.
Section 9.5: <u>Monitoring for Harm:</u> <u>Text revised as shown below:</u> Where p is the binomial probability that a case participant is assigned to the vaccine group conditional on the total observed number of cases at that moment. Each test is performed at the same one-sided nominal unadjusted alpha of 0.05. The non-binding harm monitoring for symptomatic COVID-19 will start when at least 10 symptomatic COVID-19 cases are observed. The non-binding harm monitoring for severe COVID-19 will start when ~~at least 5~~ <u>the first s</u>evere COVID-19 case~~s are~~ <u>is</u> observed.	Text revised due to CBER feedback to perform analyses regularly based on accumulating case counts.

Protocol Update from Version 2.0 (16 April 2021) to Version 3.0 (18 May 2021):

The main reason for updating the protocol from Version 2.0 to Version 3.0 was due to availability and addition of Phase II (Study VAT00002) Day 01 – Day 43 Key Interim Data that informed antigen dose selection for the monovalent vaccine and bivalent vaccine used in the study. The main updates are as shown below:

Revision	Rationale
Synopsis: Rationale: Added new text for new variant of concern (ie, B.1.617.2)	Most current updates on epidemiology and variants of concern added. On 11 May 2021, WHO declared the B.1.617.2 variant as a "variant of concern".
Synopsis: Rationale Added manufacturing information as shown below: Following VAT00001 study, the manufacturing process had been further developed increasing the purity of the vaccine candidate to > 90% for the Phase II and Phase III clinical materials.	Product text added in line with Investigator's Brochure update.
Data and dose decision from Phase II (Study VAT00002) added throughout.	<u>Conclusions on dose selection for Phase III trial</u> • Monovalent D614 vaccine: 10 µg D614 antigen + AS03 selected for Stage 1 • Bivalent D614 + B.1.351 vaccine: 5 µg D614 antigen + 5 µg B.1.351 antigen + AS03 selected for Stage 2 The rationale for dose-selection based on data from the interim results of the Phase II study is presented in the protocol.
Countries changed from "TBD" to text below: Stage 1: United States and others TBD Stage 2: TBD	Added United States for initial Stage 1 start, but other country selection is still TBD. Stage 2 is still TBD.
Synopsis and Section 4.1: Text added as shown below: The Sponsor will maintain the study investigators updated on any new	Further clarification on Sponsor on maintaining investigators update on new information to inform participant decision on unblinding and receipt of authorized/approved vaccine.

information related to the investigational products, so that such information can be provided to participants in discussions related to the potentially receiving the available authorized/approved vaccines.	
Synopsis and Sections 4.1 / 6.3.2 / 6.6: Text added as shown below: If at any time during study conduct it is determined that a vaccine candidate is not efficacious or that efficacy cannot be demonstrated, participants will be encouraged to seek vaccination of an authorized/approved vaccine if available to them.	Further clarification on investigators encouraging participants to get the vaccine available to them at the time the study vaccine is shown to be not efficacious or that efficacy cannot be demonstrated.
Synopsis: Sensitivity Analysis 3 / Section 9.4.2.1 Text added as shown below: In addition, survival analyses of symptomatic COVID-19 endpoints will be conducted using a stratified Cox proportional hazard model with separate baseline strata of age group, sex, and high-risk medical condition groups. <u>If informative censoring is observed in the trial, a Cox model adjusting for this informative censoring may be conducted.</u>	Text added to accommodate if informative censoring observed during the trial conduction that may influence the planned statistical analyses.

Sample Size Calculation text revised as below: Assumptions for sample size calculation are listed as follows: • The LB of adjusted CI for the VE estimate is > 30% for both stages • The expected true VE for symptomatic COVID-19 is 70% • The 1-sided type I error for each stage is 0.025 with sample size calculated based on adjusted alpha of 1-sided 0.02276 for final analysis including one interim at 70% data • Power = 90% for each stage Each stage is considered as independent of the other so that the type I error is controlled for each stage but not for the study.	The update is to further clarify how we calculate the sample size. Details of interim data fraction is specified so that the sample size calculation can be easily replicated. Each stage is considered as 2 independent sub-studies so the type I error is not controlled for study but stage.
Sample Size Calculation text added as below: The sample size calculated based on the adjusted final alpha of 0.02276 will ensure at least 90% power to conclude on primary objective when the interim analysis is conducted between 50% - 70% range of data.	The update is to add the rationale about the power and sample size to support our proposal. Since 70% data fraction provides the most conservative sample size (highest sample size) so doing interim within the range of 50% ~ 70% can also maintain appropriate power.
Rationale / Section 2.2 / Section 4.2: Nonclinical Studies (monovalent vaccine with the prefusion S protein from the D614 prototype) text added.	Additional data added at time of this protocol update, in line with text in the Investigator's Brochure update.
Exploratory immunogenicity objective #6 added as shown below: To conduct exploratory analyses which may include (but are not limited to) testing of immune responses and other biomarkers in any subset of participants to inform further understanding of COVID-19 vaccines, including use as benchmarks for other studies.	Additional objective will enable utilization of these Phase III data as potential benchmarks for booster, variant priming studies, and other COVID-19 vaccine studies.

Section 8.4.6: Added AESI • Thrombosis with Thrombocytopenia Syndrome*	Due to thrombo-embolic events reported after the use of Adenovirus-vectored COVID-19 vaccines from other manufacturers, Thrombosis with Thrombocytopenia Syndrome is included as an AESI.
Section 9.5 (Monitoring for Futility): Added sentence as shown below: The DSMB may also monitor the study for operational futility (eg, based on enrollment progression, event accrual rate, drop-out rate, magnitude of censoring) and make related recommendations to study conduct.	Operational futility monitoring text added per Data Safety Monitoring Board recommendations.
Section 10.1.3: Following text added for Informed Consent: The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.	This is included to be less restrictive in our inclusion of participants and enable participants with legally approved representatives to participate in the study.

Protocol Update from Version 3.0 (18 May 2021) to Version 4.0 (11 August 2021):

The main reasons for updating the protocol were:

- Version 3.0 (dated 18 May 2020) to version 4.0 (dated 11 August 2021):
    - Addition of blinded crossover study design, as well as other new information at the time of the update (eg, additional bivalent product information, assay testing known at the time)
    - Version submitted to Independent Ethics Committees / Institutional Review Boards but not used in the study

The main updates are as shown below:

Revision	Rationale
Throughout: Greek strain/variant naming conventions added.	To align with the World Health Organization naming convention of COVID-19 variants (see https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/).
Throughout (at mention of VAT00002): Added text for booster study and added "Original Cohort of VAT00002"	Study VAT00002 has been amended to include supplemental Phase III booster cohorts. Initial portion of study ("Original Cohort of VAT00002", Phase II) is ongoing.
Synopsis: Rationale / Section 2.2 / Section 4.2: Nonclinical Studies text added for bivalent vaccine data.	Additional nonclinical data added at time of this protocol update, in line with text in the Investigator's Brochure update.
Objectives: Synopsis and Table 3.1: Added secondary efficacy objectives #11 and #12, with accompanying endpoints: #11: "To assess the durability of vaccine efficacy post crossover in all participants and by prior SARS-CoV-2 infection (naïve and non-naïve)." #12: "To assess the durability of vaccine efficacy post-crossover, in participants who are SARS-CoV-2 naïve."	Additional objectives related to crossover design added to assess the long-term vaccine efficacy in all participants including in those vaccinated through crossover.
Objectives: Synopsis and Table 3.1: Added secondary immunogenicity objective #5: #5:	Additional objective added to analyze immunogenicity data in younger adults (18-25 years). This age-group is the comparator

"To describe the neutralizing antibody profile at D01, D22, D43, D78, D134, D202, D292, and D387 in each study group for participants aged 18-25 years in the Random Immunogenicity Subcohort."	group for pediatric population and the data generated will support the pediatric development plan.
Objectives: Synopsis and Table 3.1: Added secondary safety objective #2: "To assess the safety of the CoV2 preS dTM-AS03 vaccines compared to placebo in participants aged 18-25 years throughout the study."	Additional objective added to analyze safety data in younger adults (18-25 years). This age-group is the comparator group for pediatric population and the data generated will support the pediatric development plan.
Table 3.1 only: Exploratory efficacy objectives #9 and #10 added, with accompanying endpoints: #9: "To describe in each group the occurrence of events that may be classified as Long COVID syndrome." #10: "To assess impact of vaccination on asymptomatic SARS-CoV-2 NAAT positivity at the time of the crossover set of vaccinations" in naïve participants."	#9: Additional exploratory efficacy objective to assess occurrence of Long COVID syndrome. #10: Additional exploratory efficacy objective related to crossover design added.
Throughout: Blinded crossover text/tables added	Description of blinded crossover design including additional study visits and procedures was added throughout the protocol.
Analysis Sets: Synopsis Table and Section 9.3: Added bullet for modified full analysis set Post dose 1 and post-dose 2 text: - (Section 9.3 only) Post-dose 1: "Participant discontinued from study before 14 days after the first injection" - (Synopsis and Section 9.3) Post-dose 2: "Participant discontinued from study before 14 days after the second injection"	Definition of mFAS-PD1 and mFAS-PD2 revised to match revised SAP text. Vents accrued only after D14 post-vaccination will be evaluated for the efficacy endpoints and therefore participants censored prior to 14 days post-vaccination will not be included in the modified FAS.

Synopsis and Section 9.4.3.1: Added for key secondary endpoints: (**Bold** is synopsis and 9.4.3.1 only, normal is 9.4.3.1 only) "**Hypothesis testing for key secondary objectives will be conducted when both of the following conditions are met:** • **The primary objective is demonstrated** • **22 severe cases and 162 infections are collected** The criteria of 22 severe COVID-19 and 162 SARS-CoV-2 infections are calculated based on 80% of power with assumed VEs (80% for VE against severe COVID-19 and 40% for VE against SARS-CoV-2 infection) and one-side alpha 0.0125. **If both of the criteria are met, the hypothesis testing of the key secondary endpoints will be done in the same timeframe as the efficacy analysis for the primary endpoint.** **If either criteria are not met, hypothesis testing for the key secondary endpoints will be performed with final data available in comparison to a placebo control, (ie, at the time of the analysis with data prior to the cross-over) if at least a minimum of 11 severe events or 70 infections are collected.** In this case, if only the minimum number of events is met are met for only one of the key secondary endpoints, the corresponding hypothesis testing will be performed without alpha splitting. If the minimum numbers of events are met for both key secondary endpoints, the Holm's procedure will be applied for the testing of the two key secondary endpoints. For planning of situation that not meeting the number of planned number of cases upon the availability of final data described above, a base case is planned for the minimum numbers of severe COVID-19 (11) and SARS-CoV-2 infections (70), which are calculated based on at least 70% of power and assumed VEs (90% for VE against severe COVID-19 and 50% for	Added details of the strategy of hypothesis testing of the 2 key secondary endpoints with consideration of the crossover process to clarify scenarios considering the criteria of hypothesis testing and the timing of planned analyses prior to cross-over.

VE against SARS-CoV-2 infection) and one-side alpha 0.0125."	
Table 6.1: Dose Form text updated and placeholder bivalent text replace by actual text	Bivalent information available at the time of this amendment to support Stage 2.
Section 8.2.2.2 and 8.2.2.3: Previous testing Section 8.2.2.2 (SARS-CoV-2 Neutralizing Antibody Assessment [Sanofi Pasteur]) deleted and replaced by 2 new sections: - Section 8.2.2.2: SARS-CoV-2 Pseudovirus Neutralization Assay (Nexelis) - Section 8.2.2.3: SARS-CoV-2 Virus Neutralization Assay (USG)	To reflect actual testing known at the time of this amendment.
Section 9.5: Text added for Monitoring of Operational Futility: "The DSMB monitors the study for operational futility. The objective is to monitor the projected number of treatment arm-pooled symptomatic COVID primary endpoints by each of a set of calendar dates to aid ascertainment of whether the study is on target to meet the study objective regarding the evaluation of VE. The operational futility monitoring report is based on treatment-blinded data and is provided to the DSMB as well as to the Oversight Group and the Trial Leadership Group starting at the second data review DSMB meeting to be held in September 2021. The report will include the following: a) The enrollment rate b) The accrual rate of symptomatic COVID-19 cases for the primary efficacy endpoint c) The right censoring rate to date, including participants early terminated and received approved COVID-19 vaccine	To provide guidance to regulatory agencies and study staff on operational futility.

d) The mean projected number of treatment arm-pooled primary symptomatic COVID-19 endpoints in the mFAS-PD2 naive D01+D22 cohort, with a Wald 95% CI for the mean by each calendar date 15 October 2021, 15 December 2021, and 15 February 2022 e) The estimated distribution of the total treatment arm-pooled number of primary symptomatic COVID-19 endpoints in the mFAS-PD2 naïve D01+D22 cohort, with corresponding power to reject H0: VE $\leqslant$ 30% using a 1-sided 0.025-level Wald test from a Cox model under the alternative hypotheses VE = 70%, 80%, and 90% by each calendar date 15 October 2021, 15 December 2021, and 15 February 2022. The estimation procedures in (d) and (e) above will be conducted under each of the following 3 scenarios: 1) The treatment arm-pooled symptomatic COVID-19 endpoint rate in (d) and (e) used for generating future data are based on a Bayesian model and the prior assumption that VE=70% (the design alternative) 2) The treatment arm-pooled symptomatic COVID-19 endpoint rate in (d) and (e) used for generating future data are based on a Bayesian model and the prior assumption that VE= 30% (the null hypothesis) 3) The treatment arm-pooled symptomatic COVID-19 endpoint rate in (d) and (e) used for generating future data is based on a Bayesian model and the prior assumption that the COVID-19 endpoint rate equals to the observed-to-date symptomatic COVID-19 endpoint rate.	

The Bayesian model in (d) and (e) will be conditioned on the observed data to-date, more specifically, to-date data in (a), (b), and (c). Right censoring in (c) occurs due to a variety of events including early termination, unblinding for any reason and receipt authorized/approved COVID-19 vaccine. While it is the primary responsibility of the Oversight Group with the Trial Leadership Group to make decisions regarding trial operations and modifications based on the monitoring of the treatment-blinded primary endpoints, given the resource issues involved, DSMB review is also needed because issues of scientific integrity are also involved. Upon request, the statisticians will provide the DSMB and the Oversight Group with additional information, as appropriate, for use in their consideration of whether to recommend early trial completion. A full description of the operational futility statistical analysis is available in the Operational Futility Monitoring SAP.”	

Protocol Update from Version 4.0 (11 August 2021) to Version 5.0 (08 September 2021):

The main reasons for updating the protocol from version 4.0 to version 5.0 (dated 08 September 2021) were to revise sample sizes for Stage 1 and Stage 2 and capping percentages for non-naive and for older adult strata. The main updates are as shown below:

Revision	Rationale
Throughout: Overall sample size reduced for each stage	The assumed incidence rate for the study was revised based on monitoring available epidemiological data in the public domain in VAT08 countries. The assumed incidence rate over 2 months was increased from 1.25% to 2.25% which reduces the sample size of the study and for each stage. This decreases the proposed sample size of the study from 37 430 to 21 046.
Throughout: For Stage 2: Reactogenicity subset sample size reduced to match Stage 1	Despite reducing sample size of the study, kept subsets as-is for Stage 1. This maintains the proposed number of 2000 participants in each intervention arm to provide reactogenicity data. Reduced Reactogenicity subset and Random Immunogenicity subset sample size for Stage 2 to be consistent with Stage 1 as Stage 2 sample size is similar to Stage 1.
Throughout: For Stage 2: Random Immunogenicity subset sample size reduced to match Stage 1	
Throughout: Cap for participants who are SARS-CoV-2 non-naive at baseline changed from a maximum of approximately 20% to 30%	This reflects the observed increase in SARS-CoV-2 seropositivity rates in the study and decreases the number of screen failures while maintaining sufficient number of SARS-CoV-2 naïve adults for demonstration of the primary objective.
Throughout: Target recruitment enrollment for older adults (≥ 60 years of age) changed from “at least 40%” to “approximately 40%”	The target to recruit older participants in the study is maintained; however, as there is widespread global COVID-19 vaccination campaigns with prioritization of vaccination of older adults, recruitment and retention of older adults in the trial is unlikely to be higher than 40% of the entire study population.

Throughout: Within the age group of 18-59 years, the study target for recruitment of participants with high-risk medical conditions for COVID-19 changed from "35%" (and "at least 35%") to "approximately 35%".	This modification has been made to be consistent with the wording through the document stating that the recruitment targets are approximates.
Section 7.1.4: Renumbered definitive contraindications for crossover	To maintain consistency with numbering for contraindications that are the same between initial and crossover and to avoid the same numbering for 2 different items between initial and crossover.

Protocol Update from Version 5.0 (08 September 2021) to Version 6.0 (11 April 2022):

The main reasons for updating the protocol were to add design and procedures for unblinded Crossover / Booster design, to add data available from clinical and nonclinical studies to support Crossover / Booster, and to revise primary efficacy objective to be applicable to Stage 1 and/or Stage 2. Further details are described in the table below:

Revision	Rationale
Throughout: Added Unblinded Crossover / Booster study design, objectives/endpoints, justification, new booster vaccine study intervention Stage 1 participants will be invited upon consent to continue participation as part of an unblinded crossover / booster study design. The participant unblinding and consent will trigger the end of the initial double-blind primary series design and the start of the Crossover / Booster design, which includes a primary series vaccination for initial placebo recipients (ie, crossover vaccination) and a booster for both initial placebo and vaccine recipients (ie, booster vaccination). Initial Stage 1 and Stage 2 design is now referred to as "initial, double-blind, primary series study design" Based on an interim/final efficacy analysis and the recommendation of the Study OG, primary series followed by a booster dose will be offered to initial	Crossover/Booster design added for Stage 1 based on decisions of the Study Oversight Group (OG). After unblinding, participants who were initially in the placebo group will be offered vaccination. In addition, a booster vaccination will be available participants in both placebo and vaccine groups to provide additional protection. Similar procedures are proposed for participants in Stage 2 based on OG recommendations when results from Stage 2 are available.

placebo recipients and a booster will be offered to initial vaccine recipients to participants in Stage 2. The investigational product to be in used in the Stage 2 unblinded crossover vaccinations will be determined based on available efficacy data.	
Version numbering history table: Added text as below for protocol version 4.0 row: Submitted to Independent Ethics Committees / Institutional Review Boards and Health Authorities, but not used in the study <u>in most countries. However, enrollment needed to start in India and version 4.0 was used while waiting for Ethics Committee review of version 5.0.</u>	Protocol version 4.0 was to be the first amendment of the study; however, protocol version 5.0 needed to be created soon after version 4.0 approval and became labelled as the new amendment #1. However, after version 5.0 was approved internally within Sanofi, the study needed to be started in India but had to wait for Ethics Committee review of version 5.0. Therefore, it was decided to start in India by using version 4.0.
Document History and Protocol Amendment Rationale: Added text as shown below: "This amendment is considered to be **substantial** based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union."	Text added to follow Common Protocol Template requirements. Considered as substantial due to primary efficacy objective/endpoint revisions and addition of crossover/booster design after OG decision.
Synopsis: Rationale Updated variants of concern text	Update according to most recent epidemiology and variants of concern circulation.
Efficacy Objectives/Endpoints: <u>Primary Efficacy:</u> Original primary efficacy objective now specified as Stage 1 only, and a new primary efficacy added specific to Stage 2 as below: "To assess, in all participants regardless of prior SARS-CoV-2 infection, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for prevention of symptomatic COVID-19 ≥ 14 days after the second injection." <u>Key Secondary and Other Secondary Efficacy Objectives (tables and body text)</u>:	Given the current global epidemiological situation where most of the population has already been infected, the primary population for the assessment of vaccine efficacy in Stage 2 was changed from naïve participants to all participants who meet per-protocol defined criteria. Therefore, an additional secondary objective for the assessment of vaccine efficacy in the naïve population in Stage 2 was incorporated. Objectives for each of the stages were specified for clarity.

Clarified as to which stage they applied, where necessary Added objective #12 as shown below: "Stage 2 only: To assess, in participants who are SARS-CoV-2 naïve, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for the prevention of symptomatic COVID-19 occurring ≥ 14 days after the second injection."	
Exploratory Efficacy Objectives/Endpoints: Added exploratory efficacy objective #15: To describe the relative efficacy against symptomatic COVID-19 by variants between the monovalent and bivalent vaccines	Additional analyses planned to be able to compare the two vaccines within the same study.
Countries: Synopsis and Table 4.1: - Stage 1: removed Uganda and Sri Lanka - Stage 2: removed Sri Lanka and Nigeria; and added Ukraine and Mexico	Updated list since previous protocol version.
Tables 1.1 and 1.2 and Tables 4.1 and 4.2: Revised sample size for Random Immunogenicity Subset	Corrected error to align with Table 10.6
Sample size determination: Added text as shown below: "Because Omicron is the prevalent variant during case accrual for Stage 2 and the expected vaccine efficacy against Omicron is expected to be lower than the original assumption of 70%, the expected true VE for symptomatic COVID-19 for Stage 2 was estimated at 60%. Therefore, a total of approximately 125 symptomatic COVID-19 events will be required to achieve 80% power with 1-side type I error rate of 0.025, assuming no interim analysis. If any interim analysis is planned for Stage 2, type I error rate will be adjusted appropriately."	Changes made to adjust for the most prevalent circulation of the Omicron variant during Stage 2 study conduct and the expected lower vaccine efficacy against this strain.
Synopsis, Section 4.1, and Section 8.4:	No changes in safety assessment made for the study initial schedule. Additional detail is

Text revised as shown below: "For the Crossover / Booster: Unsolicited AEs will be collected up to 21 days after the booster vaccination. MAAEs, SAEs, and AESIs will be collected over the duration of the study including the Crossover / Booster (up to 12 months post-booster for those who initially received CoV2 preS dTM-AS03 [D614] and up to 6 months post-booster for those who initially received placebo).Immediate adverse reactions (ie, 30 minutes after vaccination) will be collected after Crossover receipt of CoV2 preS dTM-AS03 (D614) as primary series for those who initially received placebo and after Booster receipt of CoV2 preS dTM-AS03 (B.1.351) for all participants; but immediate adverse reactions will not be collected after receipt of authorized/approved vaccine outside of the study for those who initially received placebo."	provided to describe safety follow up for unblinded crossover and booster vaccinations.
Synopsis and Section 9.3: Modified Full Analysis Set post-dose 2 (mFAS-PD2) row: Text added as shown below for bullet #2: Participants with onset of symptomatic COVID-19 episode between the date of the first injection and <u>before</u> 14 days after the second injection	Text revised to add clarity and to be consistent with the primary objective.
Synopsis and Section 9.4.2.2: Primary Safety Endpoints: "The corresponding 95% CIs for incidence rates will be calculated based on the Poisson method, and 95% CI for percentages or proportions will be calculated based on Person-Clopper method"	Poisson method is more accurate due to shortened follow-up time.
Throughout: AESIs: include myocarditis and pericarditis	Myocarditis and pericarditis have been detected as safety signals for other COVID-19 vaccine platforms. They have been added as AESIs to the VAT00002 study protocol. To keep the list of AESIs aligned across the different clinical studies in the project these adverse events are added to the list of AESIs for VAT00008 as well.

Section 2.2: Updated previous experience in humans for the monovalent D614 vaccine and nonclinical studies with the bivalent D614+B.1.351 vaccines and the monovalent D614 and monovalent B.1.351 vaccines	Updates made with data available at the time of this amendment to support Crossover / Booster study design and use of Beta Booster.
Section 2.3: - Updated Benefit risk with new data from VAT00008 and VAT00002 - Updated VAED text - Updated narcolepsy text	Updates made with data available at the time of this amendment in line with updates also to the CoV2 preS dTM-AS03 IB as well as GSK's most recent AS03 adjuvant IB.
Section 2.3: Added text as shown below: "Other potential risks, which apply to COVID-19 vaccines using other platforms than the study vaccines, that are mentioned in the Informed Consent document are blood clotting, myocarditis, and pericarditis. Thrombosis with thrombocytopenia syndrome, myocarditis, and pericarditis represent AESIs in the study accordingly. However, these events were not included into the Risk Management Plan (RMP) as potential risks of the study vaccines because based on currently available evidence they apply to other vaccine platforms."	Added wording into this section mentioning blood clotting, myocarditis and pericarditis and why they were included into ICF but not into RMP. The wording in ICF reflects that these potential risks pertain to other COVID-19 vaccine technologies.
Section 4.2: Updated rationale for development approach for variants, VAT00008, and VAT00002 Supplemental cohorts	Development approach updated with data available at the time of this amendment.
Section 4.2: Justification for the age range and study population: added paragraph for cases in VAT00008 Stage 1 and VAT00002 booster data surrounding participants ≥ 60 years.	Justification expanded incorporating updated information available at the time of this amendment.
Section 4.3: Justification for dose: Added VAT00002 Supplemental Cohort 1 data	Data added to support booster study design and booster study intervention of a beta booster at 5 µg antigen dose

Section 5.4: Deleted text as shown below: "~~Given the nearly optimal sensitivity and specificity of the rapid diagnostic test utilized in this study (99% and 100% respectively for the rapid serodiagnostic test described in Section 8 for assessment of seropositivity and capping of non-naïve participants, it is expected that the seropositivity rate obtained with the rapid diagnostic test will closely mirror the true prevalence of prior SARS-CoV-2 infection in prospective study participants and will therefore be an adequate surrogate for the proportion of non-naïve participants enrolled at any given time in the study.~~"	To allow for assessment of naïve and non-naïve participants to be done using the tests that will be used for analyses instead of the RDT.
Section 6.9: Revised text as shown below: Reportable medications/vaccinations will be collected in the CRF from the day of each Initial study vaccination only to the end of the solicited and unsolicited follow-up period after each Initial study vaccination in all participants, with the exception of influenza and COVID-19 vaccination which will be collected throughout the study in all participants. In addition, any medications used for COVID-19 treatment or prophylaxis (eg, SARS-CoV-2 antivirals, monoclonal or polyclonal antibodies or plasma) will be collected throughout the study in all participants.	Text revised to provide clarity on reportable medications/vaccinations during the initial study vaccination and those to be reported throughout the duration of the study.
Table 8.1: Added note as shown below: "†† BL1-BL3 samples for all US participants only will be tested in the D614G Pseudovirus neutralization assay at Monogram"	To provide clarity on testing for all BL1-BL3 samples from US subjects.
Section 8.1.4.1: Added text:	To give flexibility for countries where the Assure test is not allowed for use.

"Other local tests could be used if the Assure COVID-19 IgG/IgM Rapid Test is not allowed for use in the country where the study is conducted."	
Section 8.2.1.1: Definition for COVID-19-like-illness: Previous text: • Fever (measured temperature > 100.4ºF OR 38.0ºC) Revised text: • Fever (measured temperature ≥ 100.4ºF OR ≥ 38.0ºC)	Revised to "≥" to align with measurement used in the Case Report Forms and intensity grading scales.
Section 8.2.1.1: Reversed order of COVID-19 severity scale as shown below: 1) Death 2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation 3) Hospitalized, on non-invasive ventilation or high flow oxygen devices 4) Hospitalized, requiring supplemental oxygen 5) Hospitalized, not requiring supplemental oxygen – discharged but requiring ongoing medical care (COVID-19 related or otherwise) 6) Hospitalized, not requiring supplemental oxygen – discharged without ongoing medical care 7) Not hospitalized	Order reversed to match order of presentation in the blank Case Report Forms.
Section 9.5: "Stage 1", "Stage 2", or "each stage" specified as appropriate for analysis sets.	Text revised to align with efficacy objectives changes noted above.
Section 10.5 / Table 10.4 List of potential immune-mediated diseases Table replaced with an updated table; date updated in table title to "version: January-2022"	Updated for consideration of emerging possible immune-mediated pIMDs of interest in the context of COVID-19 vaccine safety monitoring.
Table 10.6: Bivalent Vaccine row	Administrative error corrected.

Data for 18-59 years changed from “75” to “750”	

Protocol Update from Version 6.0 (11 April 2022) to Version 7.0 (02 August 2022):

The main reasons for updating the protocol were to add design and procedures for unblinded Crossover / Booster design, to add data available from clinical and nonclinical studies to support Crossover / Booster, and to revise primary efficacy objective to be applicable to Stage 1 and/or Stage 2. Further details are described in the table below:

Revision	Rationale
Throughout: Updated Unblinded Crossover / Booster study design for Stage 1 and added same design for Stage 2. “All participants in Stage 1 and Stage 2 will be unblinded and informed of the results of the study. Study Investigators will discuss the possibility of receiving the (authorized/approved) vaccines available to them outside of the study. Based on decisions of the Study Oversight Group (OG), participants will be invited upon consent to continue participation as part of an unblinded crossover / booster study design. The participant unblinding and consent will trigger the end of the initial double-blind primary series design and the start of the Crossover / Booster design, which includes a primary series vaccination for initial placebo recipients (ie, crossover vaccination) and a booster for both initial placebo and vaccine recipients (ie, booster vaccination). Non-naïve participants who initially received placebo and are 18-59 years of age will be offered the opportunity to receive the investigational CoV2 preS dTM-AS03 monovalent (D614) vaccine if authorized/approved vaccines are not available or if they choose not to receive an authorized/approved vaccine series. Naïve participants 18-59 years of age and all participants ≥ 60 years of age who initially received	Crossover/Booster design revised for Stage 1 and same procedures added for Stage 2 based on available data and decisions of the Study Oversight Group (OG). Recommendations from the OG were based on the latest available results, where efficacy was demonstrated in non-naïve participants 18-59 years of age. Data were limited in other populations which precluded any valid conclusion and subsequent recommendation. Text changed: - From: “…at least 1 dose of primary series…” - To: “…the complete primary series…” - Reason: To ensure the booster dose is administered to participants who have completed their primary series vaccination schedule to ensure best protection.

placebo will be recommended to receive an authorized/approved vaccination series. If initial placebo recipients of any age received the complete primary series of an authorized/approved vaccine outside of the study or the investigational study vaccine as a primary series, they will also be offered the opportunity to receive Sanofi Pasteur's investigational Cov2 preS dTM-AS03 monovalent (B.1.351) booster vaccine ≥ 4 months post-last dose of the primary series or encouraged to receive an authorized/approved vaccine according to local guidance. Participants who initially received the complete primary series of the CoV2 preS dTM-AS03 monovalent (D614) vaccine (Stage 1) or CoV2 preS dTM-AS03 bivalent (D614+B.1.351) vaccine (Stage 2) will be offered the opportunity to receive Sanofi Pasteur's investigational CoV2 preS dTM-AS03 monovalent (B.1.351) booster vaccine ≥ 4 months post-last dose of the primary series or encouraged to receive an authorized/approved vaccine according to local guidance. If participants do not consent to continue with the unblinded Crossover / Booster, all study procedures will be stopped, and participants will be discontinued from the study and recommended to receive the authorized/approved vaccination series per local guidance."	
Version numbering history table: Added text as below for protocol version 6.0 row: "Amendment #2: Substantial amendment submitted and used in some countries but not others"	Added text due to new Amendment #3 (version 7.0).
Document History and Protocol Amendment Rationale: Added text as shown below: "This amendment is considered to be **non-substantial** based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European	Text revised to be non-substantial to follow Common Protocol Template requirements.

Parliament and the Council of the European Union **because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study**."	
Other Secondary Efficacy Objectives/Endpoints (Synopsis and Table 3.2): Revised Objectives #4 and #12 as shown below: Objective #4: Stage 1 only: To assess, in all participants regardless of prior SARS-CoV-2 infection, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for: • Prevention of symptomatic COVID-19 • Prevention of severe COVID-19 Endpoints for #4: Specified as Stage 1 only. Objective/endpoints #12: Added severe COVID-19 Stage 2 only: To assess, in participants who are SARS-CoV-2 naïve, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for: • Prevention of symptomatic COVID-19 • Prevention of severe COVID-19	Assessment of efficacy against symptomatic COVID-19 in all participants regardless of baseline status is now the primary endpoint for Stage 2 and assessment of efficacy against severe cases in all participants regardless of baseline status is now a key secondary endpoint for Stage 2; therefore, they were removed from Objective 4. Efficacy against severe cases was added in objective/endpoint to cover this endpoint for Stage 2.
Throughout: Efficacy/Safety follow-up for those who initially received placebo changed from 6 months post-booster to 12 months post-booster. Therefore, 12-month post-booster phone call added. With new study duration as specified below: "For participants who initially received placebo: ≥ 4 months post-last dose of the primary series + ~~6~~ 12 months post-booster (ie, approximately ~~22~~28 to ~~28~~34 months"	No changes in safety assessment made for the study initial schedule. Additional detail is provided to describe safety follow up for unblinded crossover and booster vaccinations and to ensure the 12-month safety follow-up period after booster for both initial vaccine and placebo recipients, per CBERs request.
Section 2: Introduced an investigator sponsored study, VAT00013 - COVIBOOST	Introduced in Section 2 before presenting data in Section 2.3.2 to support benefit of the study

	vaccine, particularly against the omicron variant.
Section 2.2: Background updated with new sub-section for Clinical data for the CoV2 preS dTM-AS03 bivalent (D614+B.1.351) vaccine.	New efficacy and safety data for VAT00008 Stage 2 available at the time of this amendment to support crossover.
Table 2.2: Updated Risk Table with new disclaimer note in the "Enhanced COVID-19/VAED" row as shown below: "Risk not applicable for the booster vaccination: Vaccine Associated Enhanced Disease (VAED) including Vaccine Associated Enhanced Respiratory Disease (VAERD) is a risk in the naïve population as per Brighton Collaboration case definition. Since the booster dose is administered in already vaccinated individuals, this potential risk is not considered for the booster vaccination."	Added clarity of known risks based on data from Stage 1 and Stage 2.
Section 2.3.2 and 2.3.3: Added benefits of Beta booster vaccination, specifically for omicron variant.	Summary added to support benefits of Beta Booster to be used for the Booster vaccination in the study.
Section 4.2: Text revised as below: The AS03 adjuvanted H7 recombinant protein vaccine was found to be ~~safe and~~ well tolerated with an acceptable safety profile and led to robust immune responses.	No need to state "safe", there is no vaccine 100% safe, and in the text is already mentioned "well tolerated and with acceptable safety profile", which was clear as-is.
Section 4.3: Justification for crossover vaccination with CoV2 preS DTM-AS03 monovalent (D614) vaccine: Added subsection for justification of monovalent (D614) vaccine for crossover vaccination	Data added to support Crossover design.
Section 4.3:	Data added to support Booster design.

Justification for booster vaccination with CoV2 preS DTM-AS03 monovalent (B.1.351) vaccine: Revised subsection for justification of monovalent (B.1.351) vaccine for booster vaccination	
Section 7.1.4 (Definitive Contraindication #8 for Crossover/Booster Design) and throughout: Definitive Contraindication #8 and throughout: Previous text required at least 1 dose of primary vaccination. New text changed to require the complete primary series before booster vaccination.	To ensure participants complete primary series before receiving the booster vaccination.
Section 8.2.2.5: Blood sampling revised as shown below: "SARS-CoV-2 binding antibodies will be measured using an electrochemiluminescence immunoassay (ECLIA) on blood samples BL0001-~~BL0008~~BL0003 and…"	Sample numbers changed from "BL0008" to "BL0003" to align with plan in Table 8.1.

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