NCT Number: NCT04762680

Title Page

Protocol Title:

Immunogenicity and Safety of SARS-CoV-2 Recombinant Protein Vaccines with AS03 Adjuvant in Adults 18 Years of Age and Older as a Primary Series and Immunogenicity and Safety of a Booster Dose of SARS-CoV-2 Adjuvanted Recombinant Protein Vaccines (two Monovalent and one Bivalent)

Study Code: VAT00002

Amendment Number: Amendment 6

Compounds:

Original Phase II Cohort:

SARS-CoV2 prefusion Spike delta TM (CoV2 preS dTM), monovalent D614

AS03: Oil-in-water based adjuvant System containing α-Tocopherol and Squalene

Supplemental Phase III Cohorts:

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, monovalent B.1.351 (CoV2 preS dTM-AS03 [B.1.351]): monovalent vaccine with the S protein sequence from the B.1.351 variant

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

Brief Title:

Study of Recombinant Protein Vaccines with Adjuvant as a Primary Series and as a Booster Dose against COVID-19 in Adults 18 Years of Age and Older

Study Phase: Phase II/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: U1111-1251-4616

EudraCT: 2020-003370-41

NCT: NCT04762680

Protocol Version Number: 10.0

Approval Date: 20 January 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

Previous Version	Date	Comments
1.0	05 October 2020	Original, Phase III design submitted to Health Authorities for IND review
2.0	15 January 2021	Design with Phase II only was submitted to the IRB, but was not submitted to Health Authorities
3.0	04 February 2021	Original protocol version used in the study
4.0	08 April 2021	Update due to CBER non-hold comment
5.0	10 June 2021	Study design updated to add Supplemental Phase III Cohorts for Booster Study 1, version not submitted
6.0	02 August 2021	Added conditional co-primary objectives for Supplemental Cohort 1 and relevant nonclinical non-human primate (NHP) study result, not submitted to Health Authorities
7.0	31 August 2021	Updated with minor changes to inclusion and exclusion criteria
8.0	12 October 2021	Study design updated to remove bivalent vaccine candidate for protein-primed dosing groups, AESIs updated to include myocarditis and pericarditis, and a pooled primary series cohort added as possibility for the Cohort 1 and 2 Comparator Group
9.0	19 November 2021	Study design updated to remove the bivalent vaccine candidate arm from Variant Prime Cohort 3

Amendment 6 (20 January 2022)

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.

Overall Rationale for the Protocol Amendment:

The major protocol revisions and rationale for revisions from Version 9.0 to Version 10.0 are as shown below:

Revision	Rationale
Throughout: Removed Supplemental Variant Prime Cohort 3	1) Operational feasibility of enrolling SARS-CoV-2 naïve participants has become significantly more challenging 2) While data would be supportive of the planned indication, data are not required for regulatory purposes
Throughout: Total participant numbers changed to 3660 (was 4238)	Total changed for removal of Variant Prime Cohort 3 participants

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.

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1 Protocol Summary

1.1 Synopsis

Protocol Title:

Immunogenicity and Safety of SARS-CoV-2 Recombinant Protein Vaccines with AS03 Adjuvant in Adults 18 Years of Age and Older as a Primary Series and Immunogenicity and Safety of a Booster Dose of SARS-CoV-2 Adjuvanted Recombinant Protein Vaccines (two Monovalent and one Bivalent)

Brief Title:

Study of Recombinant Protein Vaccines with Adjuvant as a Primary Series and as a Booster Dose 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 on 20 January 2020 of a Public Health Emergency of International Concern, followed by the declaration on 11 March 2020 of a pandemic (1). The virus has been detected in 222 countries/regions and led to significant morbidity, mortality, and economic impact (2).

The clinical profile of COVID-19, the illness caused by SARS-CoV-2, is variable. In the majority of cases, the manifestations are mild or individuals may be asymptomatic (4). 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 up to 2 months after illness onset despite viral clearance (5). Based on early data, age over 50 years, chronic medical conditions, and race/ethnicity are important risk factors for severe outcomes and death due to COVID-19 (4) (6). A number of vaccine candidates in clinical development including viral vector-based vaccines, messenger ribonucleic acid (mRNA), protein subunit, and inactivated vaccines encoding the Spike (S)-protein of SARS-CoV-2 induce neutralizing antibodies. These include:

- 2 COVID-19 mRNA vaccine candidates:
  - BNT162b2: International Non-Proprietary Name (INN)- COVID-19 mRNA vaccine (nucleoside-modified) from Pfizer/BioNTech (hereafter called Pfizer/BioNTech)
  - mRNA-1273: INN- COVID-19 mRNA vaccine (nucleoside modified) from Moderna (hereafter called Moderna)
- 2 adenovirus-vectored vaccine candidates:
  - ChAdOx1-nCOV-19: INN- COVID-19 vaccine (ChAdOx1-S [recombinant]) vaccine from Oxford University/AstraZeneca (hereafter called Oxford University/AstraZeneca)

- Ad26.COV2-S: INN- COVID-19 vaccine (Ad26.COV2-S [recombinant]) from Johnson & Johnson/Janssen (hereafter called J&J/Janssen)

These vaccine candidates have demonstrated efficacy against COVID-19 illness and severe disease in their Phase III clinical studies (7) (8) (9). Emergency authorization or other forms of regulatory approval have been granted in multiple countries for these as well as a number of other vaccines against COVID-19.

To address the urgent medical need caused by this outbreak, Sanofi Pasteur is developing a candidate vaccine consisting of a stabilized prefusion trimer of the SARS-CoV-2 S protein based on the work by Wrapp and colleagues (10). Sanofi Pasteur is applying the manufacturing technology used to produce recombinant influenza vaccine, which is commercialized in the United States (US) and the European Union (EU), to develop a vaccine that can be supplied at a large multi-national scale. The recombinant protein vaccine will be used in combination with an adjuvant system to optimize the immune response. AS03, an oil-in-water based adjuvant supplied by GlaxoSmithKline, will be utilized for this vaccine development.

The safety and immunogenicity of the recombinant SARS-CoV-2 prefusion Spike delta TM (CoV2 preS dTM) vaccine adjuvanted with the AS03 or AF03 adjuvants was evaluated in the Phase I/II study (VAT00001) in healthy adults 18 years of age and older. The objective of the Phase I/II study was to inform dose selection, formulation choice and injection schedule selection for progression to Phase III. A low-dose and a high-dose antigen formulation, corresponding to an effective dose of 1.3 µg and 2.6 µg of CoV2 preS dTM antigen were evaluated in the study in combination with a fixed dose of either AS03 or AF03 adjuvant systems. 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 recombinant protein 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 of age and older, 62.5% in 60 years of age and older). The magnitude of neutralizing antibody responses was also lower in adults 50 years of age and older compared to that in the younger adult age group indicating the need for further optimization of the antigen formulation and dose (doses higher than the effective high dose of 2.6 µg of CoV2 preS dTM antigen are being evaluated in this Phase II study). In adjuvanted groups with the 2-injection schedule, there was no indication of a T-helper (Th)2 bias in the cell-mediated response with a

consistent elicitation of Interferon-gamma responses. At the interim analysis, no serious adverse events (SAEs) considered related to the vaccine were observed in any of the groups. Higher than expected Grade 3 reactogenicity was observed after the second injection in the adjuvanted groups. This reactogenicity profile was transient, self-limiting, non-serious, and did not lead to study withdrawal of any participant. This higher than expected reactogenicity is hypothesized to be due to higher than targeted content of Host-Cell Protein (HCP) in the Phase I/II clinical material. The lower than expected immunogenicity in combination with the higher than expected reactogenicity observed in the Phase I/II study indicates that assessment of optimized antigen formulations (with higher antigen dose and lower HCP content) is necessary to select a formulation to progress to Phase III evaluation.

In addition, a nonclinical study in non-human primates (NHPs) (CoV2-04_NHP) using formulations with an effective antigen dose of 4 µg or 12 µg with AS03 adjuvant to assess efficacy against SARS-CoV-2 viral challenge was performed (11). 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). Marked reduction of viral replication was demonstrated on D2 and D4, 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 T follicular helper (Tfh) cells 2 weeks post-boost) responses. The high immunogenicity and efficacy demonstrated in rhesus macaques using 4 and 12 µg effective doses in this study supported the Original Phase II Cohort in this VAT00002 dose-ranging clinical study assessing 5, 10, and 15 µg of CoV2 preS dTM vaccine antigen adjuvanted with AS03.

Original Phase II Cohort

The Original Phase II Cohort enrolled in VAT00002 corresponds to a Phase II, randomized, modified double-blind, multi-center, dose-finding study conducted in adults 18 years of age and older to evaluate the safety, reactogenicity, and immunogenicity of 2 injections of CoV2 preS dTM-AS03 adjuvanted vaccine (hereafter referred to as CoV2 preS dTM-AS03) administered by intramuscular (IM) route. In this study, 3 different antigen doses (effective doses of 5 µg, 10 µg, and 15 µg of CoV2 preS dTM monovalent D614 antigen) with a full dose of AS03 adjuvant are being evaluated. A 2-injection schedule with doses administered 21 days apart, as supported by data from the VAT00001 study, is being evaluated in the Original Phase II Cohort.

Reactogenicity was assessed in all participants in this cohort by collecting solicited adverse events (AEs) for 7 days after each vaccination and unsolicited AEs through 21 days after the last vaccination. All participants are to provide information on SAEs, medically-attended adverse events (MAAEs), and adverse events of special interest (AESIs) for the duration of the study. Neutralizing and binding antibodies are to be assessed in all participants over multiple time points over the duration of the study. Cellular and mucosal responses are being assessed in a subset of participants. In addition, all episodes of COVID-19 will be collected over the duration of the study.

Interim safety, reactogenicity, and immunogenicity data from this Original Phase II Cohort informed the decisions to progress to a Phase III study and to select an antigen dose formulation for use in the Phase III. This interim analysis occurred after availability of reactogenicity data up to 21 days post-injection 2 and neutralizing antibody responses 14 days post-injection 2.

Participants were to 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 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 time of enrollment.

The immunogenicity and early safety of the candidate vaccine formulations has been established in the preliminary interim analysis recently completed. In naïve adults, a high proportion of 2-fold and 4-fold or greater rise in neutralizing antibody titers was observed after 2 injections in both younger and older adults with similar proportions observed across the different antigen dose groups. The magnitude of neutralizing antibody responses was higher in the 18 to 59 year old age groups compared to the ≥ 60 year old age groups at all antigen dosages. An increase in titers with an increase in antigen dose was observed in the 18 to 59 year old age group. A single injection in naïve adults did not generate meaningful neutralizing titers above background consistent with previous results in the Phase I/II study.

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. Based on these results, a total dose of ≤ 5 µg of S protein antigen was selected to be evaluated as booster vaccine candidates in the supplemental cohorts in this VAT00002 study.

Supplemental Phase III Cohorts

New, highly transmissible SARS-CoV-2 variants of concern have emerged and are spreading globally. The United Kingdom (UK) first identified a Variant of Concern called Alpha (B.1.1.7), which has been shown to be more transmissible and has since been detected in many other countries around the world (12). Other variants have emerged first identified in South Africa (Beta [B.1.351] variant), Brazil (Gamma [B.1.1.28 or P.1] variant), and India (Delta [B.1.617] variant) 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 or no efficacy against mild to moderate COVID-19 in South Africa where Beta (B.1.351) predominated compared to higher efficacy observed for these vaccines in studies conducted in the UK (13) (14) (15) (9) (16). In a Phase III study of the Ad26CoV2.S vaccine (Johnson & Johnson/Janssen [J&J/Janssen]), significant efficacy was reported against moderate to severe-critical COVID-19 in South Africa where Beta (B.1.351) predominated during the surveillance period. These findings indicate that some prototype vaccines can confer meaningful protection against the Beta (B.1.351) variant, albeit lower than in settings where D614G and other variants predominated. 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 most notable against the 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. 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 (17). 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 variants of concern.

To address the emergence of variant strains, Sanofi Pasteur is developing monovalent and bivalent vaccines for use as a universal late booster and/or variant prime vaccines containing prototype D614 and/or the Beta (B.1.351) variants.

Nonclinical studies were performed in NHP to document the CoV2 preS dTM-AS03 (D614) and variant vaccine formulations (monovalent B.1.351 and bivalent D614 + B.1.351) when used as a booster 7 months after a primary vaccination with different vaccine platforms. The role of AS03 in potentiating the immune response was also evaluated as it is unknown if the adjuvant will be necessary in a boosting scenario.

Vaccine encoding the Beta (B.1.351) variant was developed and the immunogenicity of a monovalent vaccine based on the B.1.351 Spike and a bivalent vaccine (D614 + B.1.351) was evaluated. A third immunization (booster) with monovalent (D614), monovalent (B.1.351) or bivalent (D614 + B.1.351) formulations, 7 months after a priming immunization with messenger ribonucleic acid (mRNA) or subunit vaccine, adjuvanted with AS03, was also evaluated (CoV2-07_NHP and CoV2-08_NHP). In order to address the risk of lower vaccine efficacy due to variants of concerns, vaccines containing the variant CoV2 preS dTM antigen (B.1.351) as a monovalent or bivalent (D614 + B.1.351) formulation were evaluated for immunogenicity and efficacy in a primary series given to naïve animals, and as a late booster given to NHPs previously vaccinated with subunit or mRNA COVID-19 vaccine candidates.

In addition, the ability of the vaccine to elicit cross-neutralizing antibodies against Alpha (B.1.1.7), Beta (B.1.351), Gamma (B.1.1.28 or P.1), Delta (B.1.617.2), and Epsilon (B.1.429), SARS-CoV-2 virus variants was evaluated in NHP samples using the lentivirus-based pseudo-neutralization assay.

The nonclinical studies showed that the bivalent CoV2 preS dTM-AS03 (D614 + B.1.351) induced strong neutralizing antibody responses against the 4 variants of concern known to date: Alpha (B.1.1.7), Beta (B.1.351), Gamma (B.1.1.28 or P.1),and Delta (B.1.617.2) in naïve macaques. The benefit of a late 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. The booster vaccine induced very high neutralizing antibodies against the 4 variants of concern and robust neutralization of the distant SARS-CoV-1. Finally, preliminary data on efficacy in hamsters demonstrated that 2 doses of AS03-adjuvanted vaccine formulations (D614, B.1.351, and D614 + B.1.351) conferred protection against body weight loss caused by infection with the Beta (B.1.351) variant.

The Supplemental Phase III Cohorts of the VAT00002 study will be structured as follows:

- **Supplemental Cohort 1**: adults 18 years of age and older who were vaccinated 4 to ≤ 10 months prior with an authorized/approved mRNA or adenovirus-vectored COVID-19 vaccine will be given Monovalent (D614) CoV2 preS dTM-AS03 (CoV2 preS dTM-AS03 [D614]) as a single booster injection.
- **Supplemental Cohort 2, Main Arms:**
  - Adults 18 years of age and older who were vaccinated 4 to ≤ 10 months prior with an authorized/approved mRNA or adenovirus-vectored COVID-19 vaccine will be randomized to receive a single booster injection of one of the following:
    - Monovalent (B.1.351) CoV2 preS dTM-AS03 (CoV2 preS dTM-AS03 [B.1.351])
    - Bivalent (D614 + B.1.351) CoV2 preS dTM-AS03 (CoV2 preS dTM-AS03 [D614 + B.1.351])
  - Adults 18 years of age and older who were vaccinated 4 to ≤ 10 months prior with the protein-based vaccine in the Original Phase II Cohort will be randomized to receive a single booster injection of one of the following:
    - CoV2 preS dTM-AS03 (D614)
    - CoV2 preS dTM-AS03 (B.1.351)
- **Supplemental Cohort 2 Exploratory B.1.351 Arms:** in these arms, different antigen doses of CoV2 preS dTM, monovalent B.1.351 (CoV2 preS dTM [B.1.351]) with and without adjuvants will be evaluated. Adults 18 years of age and older who received the Pfizer/BioNTech vaccine 4 to ≤ 10 months prior will be randomized to receive a single booster injection of one of the following CoV2 preS dTM-AS03 (B.1.351) formulations:
  - 2.5 µg antigen with AS03 adjuvant
  - 2.5 µg antigen with half-dose AS03[a] adjuvant
  - 5 µg antigen with half-dose AS03 adjuvant
  - 5 µg antigen with no adjuvant
- **Supplemental Cohorts Comparator Group:** SARS-CoV-2-naïve, unvaccinated, adults who are 18-55 years of age will be given CoV2 preS dTM-AS03 (D614) as a primary series vaccination of 2 injections given 21 days apart.
- **Supplemental Cohorts Subsets and Assessment of Immunogenicity to Emerging Variants of Concern:** A randomized subset of 70 participants in Cohort 1 will be tested for additional SARS-CoV-2 variants of concern including Delta. No additional sample collection, procedures, or visits are required for this subset. A randomized subset of 82 participants in Cohort 2 comprised of younger adults (18 to 55 years of age) will provide samples for cellular immune response and mucosal antibody assessments and will also be tested for additional variants of concern including Delta.

[a] The half dose of AS03 and the full dose of AS03 contain amounts of tocopherol of 5.93 mg and 11.86 mg, respectively

Objectives and Endpoints:

Primary Safety (applicable to Original Phase II Cohort as well as Supplemental Phase III Cohorts)	
To assess the safety profile of all participants in each age group and in each study Intervention Group.	• Presence of unsolicited systemic AEs reported in the 30 minutes after each vaccination • Presence of solicited (pre-listed in the participant's diary card [DC] and [electronic] Case Report Form [CRF]) injection site reactions and systemic reactions occurring up to 7 days after each vaccination • Presence of unsolicited AEs reported up to 21 days after the last vaccination • Presence of serious adverse events (SAEs) throughout the study • Presence of AESIs throughout the study • Presence of MAAEs throughout the study
Primary Immunogenicity-Original Phase II Cohort	
To assess the neutralizing antibody profile 14 days after the last vaccination (D36) in SARS-CoV-2-naïve adults in each study Intervention Group.	Neutralizing antibody titers will be measured in SARS-CoV-2-naïve participants for each study Intervention Group against the D614G variant. • Individual serum neutralizing titer at D01 and D36 • Individual serum neutralization titer fold-rise post-vaccination relative to D01 at D36 • 2-fold-rise and 4-fold-rise in serum neutralization titer [post/pre] (fold-rise ≥ 2 and ≥ 4) at D36 relative to D01 • Responders in SARS-CoV-2 naive, defined as participants who had baseline values below lower limit of quantification (LLOQ) with quantifiable neutralization titer above assay LLOQ at D36
Primary Immunogenicity-Supplemental Cohort 1	
Co-primary objectives: 1) To demonstrate in adults 18-55 years of age and previously vaccinated with the Pfizer/BioNTech vaccine that a booster dose of CoV2 preS dTM-AS03 (D614) vaccine induces an immune response that is non-inferior to the response induced by a two‑dose priming series with the CoV2 preS dTM-AS03 (D614) vaccine in naïve, previously unvaccinated individuals. 2) To demonstrate in adults 18-55 years of age and previously vaccinated with the Pfizer/BioNTech vaccine that a booster dose of CoV2 preS dTM-AS03 (D614) vaccine induces an immune response that is superior to that observed immediately before booster.	Neutralizing antibody titers will be measured for each study Intervention Group against the D614G strain. • Individual serum neutralizing titer at D01 and D15 (Intervention Group) • Individual serum neutralizing titer at D36 (Comparator Group)
Primary Immunogenicity-Supplemental Cohort 2	
Co-primary objectives: 1) To demonstrate in adults 18-55 years of age and previously vaccinated with the Pfizer/BioNTech vaccine that a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351)	• Individual serum neutralizing titer at D01 and D15 against the B.1.351 variant for the CoV2 preS dTM-AS03 (B.1.351) vaccine and the CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine Intervention Groups.

vaccine induces an immune response that is non-inferior to the response induced by a two-dose priming series with the CoV2 preS dTM-AS03 (D614) vaccine in naïve, previously unvaccinated individuals. 2) To demonstrate in adults 18-55 years of age and previously vaccinated with the Pfizer/BioNTech vaccine that a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine induces an immune response that is superior to that observed immediately before booster.	• Individual serum neutralizing titer at D01 and D15 against the D614G strain for the CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine Intervention Group. • Individual serum neutralizing titer against the D614G strain at D36 (Comparator Group)
Secondary Immunogenicity-Original Phase II Cohort	
1) To assess the neutralizing antibody profile at D22, D78, D134, D202, D292, and D387 in SARS-CoV-2 naïve adults in each study Intervention Group. 2) To assess the neutralizing antibody profile at D01, D22, D36, D78, D134, D202, D292, and D387 in each study Intervention Group for SARS-CoV-2 non-naïve participants. 3) To assess the binding antibody profile at D01, D22, D36, D78, D134, D202, D292, and D387 in each study Intervention Group in SARS-CoV-2 naïve and non-naïve participants.	<u>Endpoints for secondary immunogenicity objectives #1 and #2:</u> Neutralizing antibody titers will be measured in participants for each study Intervention Group against the D614G variant. • 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 timepoint and participants with baseline values above LLOQ with a 4-fold increase in neutralizing antibody titers at each pre-defined post-vaccination timepoint <u>Endpoints for secondary immunogenicity objective #3:</u> Binding antibody concentrations will be measured in participants for each study Intervention Group against the D614G variant. • 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 (fold-rise 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 pre-defined post-vaccination timepoints and participants with baseline values above LLOQ with a 4-fold increase in binding antibody concentration at each pre-defined post-vaccination timepoint

Secondary Immunogenicity-Supplemental Cohort 1	
Conditional secondary objectives: conditional on meeting the primary objectives for Supplemental Cohort 1: 1) To demonstrate, in adults 18-55 years of age, previously vaccinated with the CoV2 preS dTM-AS03 (D614) vaccine, that a booster dose of CoV2 preS dTM-AS03 (D614) vaccine induces an immune response that is noninferior to the response induced by a two-dose priming series with CoV2 preS dTM-AS03 (D614) vaccine in naïve, previously unvaccinated, individuals. 2) To demonstrate, in adults 18-55 years of age, previously vaccinated with CoV2 preS dTM-AS03 (D614) vaccine, that a booster dose of CoV2 preS dTM-AS03 (D614) vaccine induces an immune response that is superior to that observed immediately before booster. Conditional secondary objectives: conditional on meeting the conditional secondary objectives (1) and (2) for Supplemental Cohort 1: 3) To demonstrate in adults 18-55 years of age and previously vaccinated with an mRNA COVID-19 vaccine, that a booster dose of CoV2 preS dTM-AS03 (D614) vaccine induces an immune response that is non-inferior to the response induced by a two-dose priming series with CoV2 preS dTM-AS03 (D614) vaccine in naïve, previously unvaccinated individuals. 4) To demonstrate in adults 18-55 years of age and previously vaccinated with an mRNA COVID-19 vaccine, that a booster dose of CoV2 preS dTM-AS03 (D614) vaccine induces an immune response that is superior to that observed immediately before booster. Conditional secondary objectives: conditional on meeting the conditional secondary objectives (3) and (4) for Supplemental Cohort 1: 5) To demonstrate, in adults 18-55 years of age previously vaccinated with an adenovirus-vectored COVID-19 vaccine, that a booster dose of CoV2 preS dTM-AS03 (D614) vaccine induces an immune response that is non-inferior to the response induced by a two-dose priming series with CoV2 preS dTM-AS03 (D614) vaccine in naïve, previously unvaccinated, individuals. 6) To demonstrate, in adults 18-55 years of age previously vaccinated with adenovirus-vectored COVID-19 vaccines, that a booster dose of CoV2 preS dTM-AS03 (D614) vaccine induces	Endpoints for conditional secondary objectives #1 and #2: • Individual serum neutralizing titer against the D614G strain at D01 and D15 (group primed with CoV2 preS dTM-AS03 [D614] vaccine) • Individual serum neutralizing titer against the D614G strain at D36 (Comparator Group) Endpoints for conditional secondary objectives #3 and #4: • Individual serum neutralizing titer against the D614G strain at D01 and D15 (groups primed with mRNA COVID-19 vaccines) • Individual serum neutralizing titer against the D614G strain at D36 (Comparator Group) Endpoints for conditional secondary objectives #5 and #6: • Individual serum neutralizing titer against the D614G strain at D01 and D15 (group primed with adenovirus-vectored COVID-19 vaccine) • Individual serum neutralizing titer against the D614G strain at D36 (Comparator Group) Endpoints for secondary objectives #7 - #10: • Seroresponse rate, defined as a 4-fold or greater rise in serum neutralization titer [post/pre] against the D614G strain, at D15 relative to D01, in each study Intervention Group • Seroresponse rate, defined as a 4-fold or greater rise in serum neutralization titer [post/pre] against the D614G strain, at D36 relative to D01 (Comparator Group) Endpoints for secondary objectives #11 - #14: • Individual serum neutralizing titer at D01 and D15 against the D614G strain in each Intervention Group • Individual serum neutralization titer fold-rise post-vaccination relative to D01 at D15 against the D614G strain in each Intervention Group • ≥ 2-fold-rise and ≥ 4-fold-rise in serum neutralization titer [post/pre] (fold-rise ≥ 2 and ≥ 4) at D15 relative to D01 against the D614G strain in each study Intervention Group • Seroresponse rate, defined as a 4-fold or greater rise in serum neutralization titer [post/pre] at D15 relative to D01, against the D614G strain in each study Intervention Group Endpoints for secondary objective #15: • Individual serum neutralizing titer at D01 and D15 to the B.1.351 variant in each Intervention Group • Individual serum neutralizing titer at D01 and D36 to B.1.351 variant in the Comparator Group Endpoints for secondary objective #16: • Individual serum neutralizing titer at D01 and D15 to the B.1.351 variant in each Intervention Group

an immune response that is superior to that observed immediately before booster. Conditional secondary objective: conditional on meeting the conditional secondary objectives (5) and (6) for Supplemental Cohort 1, the following objectives will be sequentially tested: 7) To demonstrate in adults 18-55 years of age and previously vaccinated with the Pfizer/BioNTech vaccine that a booster dose of CoV2 preS dTM-AS03 (D614) vaccine induces a seroresponse that is non-inferior to the seroresponse induced by a two‑dose priming series with the CoV2 preS dTM-AS03 (D614) vaccine in naïve, previously unvaccinated individuals. 8) To demonstrate, in adults 18-55 years of age previously vaccinated with the CoV2 preS dTM-AS03 (D614) vaccine, that a booster dose of CoV2 preS dTM-AS03 (D614) vaccine induces a seroresponse that is noninferior to the seroresponse induced by a two-dose priming series with CoV2 preS dTM-AS03 (D614) vaccine in naïve, previously unvaccinated, individuals. 9) To demonstrate in adults 18-55 years of age and previously vaccinated with an mRNA COVID-19 vaccine, that a booster dose of CoV2 preS dTM-AS03 (D614) vaccine induces a seroresponse that is non-inferior to the seroresponse induced by a two-dose priming series with CoV2 preS dTM-AS03 (D614) vaccine in naïve, previously unvaccinated individuals. 10) To demonstrate, in adults 18-55 years of age previously vaccinated with an adenovirus-vectored COVID-19 vaccine, that a booster dose of CoV2 preS dTM-AS03 (D614) vaccine induces a seroresponse that is noninferior to the seroresponse induced by a two-dose priming series with CoV2 preS dTM-AS03 (D614) vaccine in naïve, previously unvaccinated, individuals. Secondary objectives: 11) To describe, in adults 18-55 years of age previously vaccinated with the Moderna vaccine, the immune response to a booster dose of CoV2 preS dTM-AS03 (D614) vaccine. 12) To describe, in adults 18-55 years of age previously vaccinated with the Oxford/AstraZeneca vaccine, the immune response to a booster dose of CoV2 preS dTM-AS03 (D614) vaccine.	• Individual serum neutralizing titer at D01 and D36 against the D614G strain in the Comparator Group Endpoints for secondary objective #17: • Individual serum neutralizing titer to the D614G strain and B.1.351 variant in each Intervention Group at each pre-defined timepoint • Individual serum neutralization titer fold-rise post-vaccination to the D614G strain and B.1.351 variant at each pre-defined timepoint relative to D01 in each Intervention Group • ≥ 2-fold-rise and ≥ 4-fold-rise in serum neutralization titer [post/pre] (fold-rise ≥ 2 and ≥ 4) to the D614G strain and B.1.351 variant at each pre-defined timepoint relative to D01 in each study Intervention Group Endpoints for secondary objective #18: • Individual serum neutralizing titer at D01 and D15 against the D614G strain in each Intervention Group • Individual serum neutralization titer fold-rise post-vaccination relative to D01 at D15 against the D614G strain in each Intervention Group • ≥ 2-fold-rise and ≥ 4-fold-rise in serum neutralization titer [post/pre] (fold-rise ≥ 2 and ≥ 4) at D15 relative to D01 against the D614G strain in each study Intervention Group • Seroresponse rate, defined as a 4-fold or greater rise in serum neutralization titer [post/pre] at D15 relative to D01, against the D614G strain in each study Intervention Group • Individual serum neutralizing titer at D01 and D15 profile to the B.1.351 variant in each Intervention Group • Individual serum neutralization titer fold-rise post-vaccination relative to D01 at D15 profile to the B.1.351 variant in each Intervention Group • ≥ 2-fold-rise and ≥ 4-fold-rise in serum neutralization titer [post/pre] (fold-rise ≥ 2 and ≥ 4) at D15 relative to D01 profile to the B.1.351 variant in each study Intervention Group • Seroresponse rate, defined as a 4-fold or greater rise in serum neutralization titer [post/pre] at D15 relative to D01, profile to the B.1.351 variant in each study Intervention Group Endpoints for secondary objective #19: • 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 (fold-rise in antibody concentration [post/pre] ≥ 2 and ≥ 4) at each pre-defined post-vaccination time point relative to D01 • Responders, defined as participants who had baseline values below LLOQ with quantifiable antibody concentration above assay LLOQ at pre-defined post-

13) To describe, in adults 18-55 years of age previously vaccinated with the J&J/Janssen vaccine, the immune response to a booster dose of CoV2 preS dTM-AS03 (D614) vaccine. 14) To describe, in adults 18-55 years of age previously vaccinated with any COVID-19 vaccine, the immune response to a booster dose of CoV2 preS dTM-AS03 (D614) vaccine. 15) To compare the neutralizing antibody profile to the B.1.351 variant at D01 and D15 in the booster groups and at D36 in the Comparator group. 16) To compare the neutralizing antibody profile to the B.1.351 variant at D01 and D15 in the booster groups and neutralizing antibody profile to the D614G strain at D36 in the Comparator Group. 17) To assess the neutralizing antibody profile to the D614G strain and to the B.1.351 variant at D29, D91, D181, and D366 overall, and by age group, by priming platform, and by priming vaccine. 18) To describe the neutralizing antibody profile to the B.1.351 variant and to the D614G strain at D01 and D15 in adults older than 55 years of age in the booster group, overall, by priming platform, and by priming vaccine. 19) To assess the binding antibody profile at D01, D15, D29, D91, D181, and D366 after booster immunization in adults previously vaccinated with COVID-19 vaccines, overall and by age group, by priming platform, and by priming vaccine.	vaccination timepoints and participants with baseline values above LLOQ with a 4-fold increase in binding antibody concentration at each pre-defined post-vaccination timepoint
Secondary Immunogenicity-Supplemental Cohort 2	
<u>Conditional co-secondary objectives: conditional on meeting the primary immunogenicity objectives for Supplemental Cohort 2</u>: 1) To demonstrate in adults 18-55 years of age and previously vaccinated with an mRNA COVID-19 vaccine, that a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine induces an immune response that is non-inferior to the response induced by a two-dose priming series with CoV2 preS dTM-AS03 (D614) vaccine in naïve, previously unvaccinated individuals. 2) To demonstrate in adults 18-55 years of age and previously vaccinated with an mRNA COVID-19 vaccine, that a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine induces an immune response that is superior to that observed immediately before booster.	<u>Endpoints for conditional secondary objectives #1 and #2:</u> • Individual serum neutralizing titer at D01 and D15 against the B.1.351 variant for the CoV2 preS dTM-AS03 (B.1.351) vaccine and the CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine Intervention Groups. • Individual serum neutralizing titer at D01 and D15 against the D614G strain for the CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine Intervention Group. • Individual serum neutralizing titer against the D614 strain at D36 (Comparator Group) <u>Endpoints for conditional secondary objectives #3:</u> • Individual serum neutralizing titer at D15 against the B.1.351 variant for the CoV2 preS dTM-AS03 (B.1.351) vaccine and the CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine Intervention Groups • Individual serum neutralizing titer at D36 against the B.1.351 variant for the Comparator Group <u>Endpoints for secondary objectives #4 - #5:</u> • Seroresponse rate, defined as a 4-fold or greater rise in serum neutralization titer [post/pre] at D15 relative to

Conditional secondary objective: conditional on meeting the primary immunogenicity objectives (1) and (2) and the co-secondary objectives for Supplemental Cohort 2: 3) To demonstrate in adults 18-55 years of age and previously vaccinated with the Pfizer/BioNTech vaccine, that a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine induces an immune response against the B.1.351 variant at D15 that is superior to that against the B.1.351 variant at D36 in the Comparator Group. Conditional secondary objectives: conditional on meeting the conditional secondary objective (3) for Supplemental Cohort 2, the following objectives will be sequentially tested: 4) To demonstrate in adults 18-55 years of age and previously vaccinated with the Pfizer/BioNTech vaccine that a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine induces a seroresponse that is non-inferior to the seroresponse induced by a two-dose priming series with the CoV2 preS dTM-AS03 (D614) vaccine in naïve, previously unvaccinated individuals. 5) To demonstrate in adults 18-55 years of age and previously vaccinated with an mRNA COVID-19 vaccine, that a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine induces a seroresponse that is non-inferior to the seroresponse induced by a two-dose priming series with CoV2 preS dTM-AS03 (D614) vaccine in naïve, previously unvaccinated individuals. Secondary objectives: 6) To describe, in adults 18-55 years of age and previously vaccinated with an adenovirus-vectored COVID-19 vaccine, the immune response to a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine compared to the response induced by a two dose priming series with CoV2 preS dTM-AS03 (D614) vaccine in naïve, previously unvaccinated individuals. 7) To describe, in adults 18-55 years of age and previously vaccinated with an adenovirus-vectored COVID-19 vaccine, the immune response to a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-	D01, against the B.1.351 variant for the CoV2 preS dTM-AS03 (B.1.351) vaccine and the CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine Intervention Groups • Seroresponse rate, defined as a 4-fold or greater rise in serum neutralization titer [post/pre] at D15 relative to D01, against the D614G strain for the CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine Intervention Group • Seroresponse rate, defined as a 4-fold or greater rise in serum neutralization titer [post/pre] against the D614G strain at D36 relative to D01 (Comparator Group) Endpoints for secondary objectives #6 - #11: • Individual serum neutralizing titer at D01 and D15 against the D614G strain and to the B.1.351 variant in each Intervention Group • Individual serum neutralization titer fold-rise post-vaccination relative to D01 at D15 against the D614G strain and to the B.1.351 variant in each Intervention Group • ≥ 2-fold-rise and ≥ 4-fold-rise in serum neutralization titer [post/pre] (fold-rise ≥ 2 and ≥ 4) at D15 relative to D01 against the D614G strain and to the B.1.351 variant in each study Intervention Group • Seroresponse rate, defined as a 4-fold or greater rise in serum neutralization titer [post/pre] at D15 relative to D01, against the D614G strain and to the B.1.351 variant in each study Intervention Group Endpoints for secondary objective #12: • Individual serum neutralizing titer at D01 and D15 to the B.1.351 variant in each Intervention Group • Individual serum neutralizing titer at D01 and D36 to the B.1.351 variant in the Comparator Group Endpoints for secondary objective #13: • Individual serum neutralizing titer at D01 and D15 against the D614G strain in each Intervention Group • Individual serum neutralizing titer at D01 and D36 against the D614G strain in the Comparator Group Endpoints for secondary objective #14: • Individual serum neutralizing titer at D01 and D15 against the D614G strain in each Intervention Group • Individual serum neutralization titer fold-rise post-vaccination relative to D01 at D15 against the D614G strain in each Intervention Group • ≥ 2-fold-rise and ≥ 4-fold-rise in serum neutralization titer [post/pre] (fold-rise ≥ 2 and ≥ 4) at D15 relative to D01 against the D614G strain in each study Intervention Group • Seroresponse rate, defined as a 4-fold or greater rise in serum neutralization titer [post/pre] at D15 relative to D01, against the D614G strain in each study Intervention Group • Individual serum neutralizing titer at D01 and D15 profile to the B.1.351 variant in each Intervention Group

AS03 (D614 + B.1.351) vaccine compared to that observed immediately before booster. 8) To describe, in adults 18-55 years of age previously vaccinated with the Moderna vaccine, the immune response to a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine. 9) To describe, in adults 18-55 years of age previously vaccinated with the Oxford/AstraZeneca vaccine, the immune response to a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine. 10) To describe, in adults 18-55 years of age previously vaccinated with the J&J/Janssen vaccine, the immune response to a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine. 11) To describe, in adults 18-55 years previously vaccinated with any COVID-19 vaccine, the immune response a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine. 12) To compare the neutralizing antibody profile to the B.1.351 variant at D15 in each study Intervention Group and D36 in the Comparator Group, overall, by priming platform, and by priming vaccine. 13) To compare the neutralizing antibody profile against the D614G strain at D15 following a booster dose of CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine and at D36 in the Comparator Group. 14) To describe, among adults previously primed with CoV2 preS dTM-AS03 (D614) vaccine, the immune response induced by a booster dose of CoV2 preS dTM-AS03 (D614) vaccine or CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine, overall, by priming dose, and by age. 15) To assess the neutralizing antibody profile to the D614G strain at D29, D91, D181, and D366 in each study Intervention Group, overall, by age group, by priming platform, and by priming vaccine. 16) To assess the neutralizing antibody to the B.1.351 variant at D29, D91, D181, and D366 in each study Intervention Group, overall, by age group, by priming platform, and by priming vaccine. 17) To describe, in adults over 55 years of age, the neutralizing antibody profile to the B.1.351 variant and to the D614G strain at D01 and	• Individual serum neutralization titer fold-rise post-vaccination relative to D01 at D15 profile to the B.1.351 variant in each Intervention Group • ≥ 2-fold-rise and ≥ 4-fold-rise in serum neutralization titer [post/pre] (fold-rise ≥ 2 and ≥ 4) at D15 relative to D01 profile to the B.1.351 variant in each study Intervention Group • Seroresponse rate, defined as a 4-fold or greater rise in serum neutralization titer [pre/post] at D15 relative to D01, profile to the B.1.351 variant in each study Intervention Group <u>Endpoints for secondary objectives #15 and #16: neutralizing responses to be evaluated against the D614G strain and to the B.1.351 variant</u> • Individual serum neutralizing titers in each Intervention Group at each pre-defined timepoint • Individual serum neutralization titer fold-rise post-vaccination at each pre-defined timepoint relative to D01 in each Intervention Group • ≥ 2-fold-rise and ≥ 4-fold-rise in serum neutralization titer [post/pre] (fold-rise ≥ 2 and ≥ 4) at each pre-defined timepoint relative to D01 in each study Intervention Group <u>Endpoints for secondary objective #17:</u> • Individual serum neutralizing titer at D01 and D15 against the D614G strain in each Intervention Group • Individual serum neutralization titer fold-rise post-vaccination relative to D01 at D15 against the D614G strain in each Intervention Group • ≥ 2-fold-rise and ≥ 4-fold-rise in serum neutralization titer [post/pre] (fold-rise ≥ 2 and ≥ 4) at D15 relative to D01 against the D614G strain in each study Intervention Group • Seroresponse rate, defined as a 4-fold-or greater rise in serum neutralization titer [pre/post] at D15 relative to D01, against the D614G strain in each study Intervention Group • Individual serum neutralizing titer at D01 and D15 profile to the B.1.351 variant in each Intervention Group • Individual serum neutralization titer fold-rise post-vaccination relative to D01 at D15 profile to the B.1.351 variant in each Intervention Group • ≥ 2-fold-rise and ≥ 4-fold-rise in serum neutralization titer [post/pre] (fold-rise ≥ 2 and ≥ 4) at D15 relative to D01 profile to the B.1.351 variant in each study Intervention Group • Seroresponse rate, defined as a 4-fold-or greater rise in serum neutralization titer [pre/post] at D15 relative to D01, profile to the B.1.351 variant in each study Intervention Group

D15 by Intervention Group, overall, by priming platform, and by priming vaccine. 18) To describe in adults previously vaccinated with the Pfizer/BioNTech vaccine the immune response (as assessed by pseudovirus neutralization assay geometric mean titers and geometric mean titer ratios) to a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine exploratory formulations, overall and by age stratum. 19) To assess the binding antibody profile at D01, D15, D29, D91, D181, and D366 after booster immunization in adults previously vaccinated with COVID-19 vaccines, overall and by age group, by priming platform, and by priming vaccine.	<u>Endpoints for secondary objective #18:</u> • Individual serum neutralizing titer at D01 and D15 against the D614G strain in each Intervention Group • Individual serum neutralization titer fold-rise post-vaccination relative to D01 at D15 against the D614G strain in each Intervention Group • ≥ 2-fold-rise and ≥ 4-fold-rise in serum neutralization titer [post/pre] (fold-rise ≥ 2 and ≥ 4) at D15 relative to D01 against the D614G strain in each study Intervention Group • Seroresponse rate, defined as a 4-fold-or greater rise in serum neutralization titer [pre/post] at D15 relative to D01, against the D614G strain in each study Intervention Group • Individual serum neutralizing titer at D01 and D15 profile to the B.1.351 variant in each Intervention Group • Individual serum neutralization titer fold-rise post-vaccination relative to D01 at D15 profile to the B.1.351 variant in each Intervention Group • ≥ 2-fold-rise and ≥ 4-fold-rise in serum neutralization titer [post/pre] (fold-rise ≥ 2 and ≥ 4) at D15 relative to D01 profile to the B.1.351 variant in each study Intervention Group • Seroresponse rate, defined as a 4-fold or greater rise in serum neutralization titer [pre/post] at D15 relative to D01, profile to the B.1.351 variant in each study Intervention Group <u>Endpoints for secondary objective #19:</u> • 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 (fold-rise 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 pre-defined post-vaccination timepoints and participants with baseline values above LLOQ with a 4-fold increase in binding antibody concentration at each pre-defined post-vaccination timepoint

Secondary Safety-Original Phase II Cohort	
1) To describe the occurrences of laboratory-confirmed symptomatic COVID-19 in all participants in each study Intervention Group. 2) To describe the occurrences of serologically-confirmed SARS-CoV-2 infection in each study Intervention Group.	Endpoints for secondary safety objective #1: • Occurrences of laboratory-confirmed symptomatic COVID-19 (based on locally-confirmed or protocol-defined NAAT) • Occurrences of symptomatic COVID-19 episodes associated with hospitalization. • Occurrences of severe symptomatic COVID-19 • Death associated with symptomatic COVID-19 Endpoints for secondary safety objective #2: • Occurrences of serologically-confirmed SARS-CoV-2 infection
Secondary Safety-Supplemental Cohorts 1 and 2	
To describe the occurrences of laboratory-confirmed symptomatic COVID-19, overall and in each study Intervention Group	• Occurrences of laboratory-confirmed symptomatic COVID-19 (based on locally-confirmed or protocol-defined NAAT) • Occurrences of symptomatic COVID-19 episodes associated with hospitalization. • Occurrences of severe symptomatic COVID-19 • Death associated with symptomatic COVID-19
Exploratory Immunogenicity-Original Phase II Cohort	
1) To describe the ratio between neutralizing antibodies and binding antibodies. 2) To assess the T-cell cytokine profile at D01, D22 and D36 in a subset of participants. 3) To further assess the cellular immune response at D01, D22, D36, D134 and D387 in a subset of participants. 4) To assess the mucosal antibody response at D01, D22, D36, and D134 in a subset of participants. 5) To describe the neutralizing antibody response to emergent SARS-CoV-2 variant strains	Endpoint for exploratory immunogenicity objective #1: • Ratio between binding antibody (enzyme-linked immunosorbent assay [ELISA]) concentration and neutralizing antibody titer Endpoint for exploratory immunogenicity objective #2: • T-helper cell (Th)1 and Th2 cytokines measured in whole blood following stimulation with full-length S protein at D01, D22 and D36. Endpoint for exploratory immunogenicity objective #3: • Other cellular-mediated immunity (CMI) assessments may be performed by Intracellular Cytokine Staining or/and enzyme-linked immunospot (ELISpot) assays. Endpoints for mucosal antibody responses (objective #4) will be specified in a supplemental analysis plan. Endpoints for exploratory immunogenicity objective #5: • Neutralizing antibody responses to emergent variant strains will be measured in participants for each study Intervention Group: • 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 timepoint and participants with baseline values above

	LLOQ with a 4-fold increase in neutralizing antibody titers at each pre-defined post-vaccination timepoint
Exploratory Immunogenicity-Supplemental Cohorts	
Supplemental Cohorts 1 and 2: 1) To describe the neutralizing antibody response to emergent SARS-CoV-2 variant strains 2) To further describe humoral immune responses based on relevant emerging assays, if applicable Supplemental Cohort 2: 3) To assess the cellular immune response at D01, D15, D29, D91, and D366 in a subset of participants. 4) To assess the mucosal antibody response at D01, D15, and D91 in a subset of participants. 5) To describe the neutralizing antibody response to emergent SARS-CoV-2 variant strains 6) To further describe humoral immune responses based on relevant emerging assays, if applicable Supplemental Cohorts 1 and 2: 7) To describe the neutralizing antibody response, by presence or absence of baseline high-risk medical conditions	Endpoints for exploratory immunogenicity objective #1 and #5: Neutralizing antibody responses to emergent variant strains will be measured: • 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] 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 Endpoint for exploratory immunogenicity objective #2 and #6: • Biomarker measurement at baseline and/or post-vaccination visits Endpoint for exploratory immunogenicity objective #3: • Other CMI assessments may be performed by Intracellular Cytokine Staining or/and enzyme-linked immunospot (ELISpot) assays. Endpoint for mucosal antibody responses (objective #4) will be specified in a supplemental analysis plan Endpoints for exploratory immunogenicity objective #7: Neutralizing antibody responses to D614G and B.1.351 strains will be measured: • 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] 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

Overall Design

Type of design	Parallel, multi-center
Phase	II/III
Control method (for Supplemental Phase III Cohorts only)	active comparator (comparator = CoV2 preS dTM-AS03 [D614] administered as a 2-injection primary series)
Study population	Adults 18 years of age and older
Countries	Original Phase II Cohort: United States, Honduras Supplemental Phase III Cohorts: to be determined (TBD)
Level and method of blinding	**Original Phase II Cohort**: Modified double-blind (observer-blind) • 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 **Supplemental Phase III Cohorts:** • Supplemental Cohorts Comparator Group will be open-label. • Supplemental Cohort 1 Booster Group will be open-label. • Supplemental Cohort 2 will involve sequential randomization to main arms (CoV2 preS dTM-AS03 [D614], CoV2 preS dTM-AS03 [B.1.351], and CoV2 preS dTM-AS03 [D614 + B.1.351]) followed by randomization to exploratory CoV2 preS dTM-AS03 (B.1.351) arms after filling the former. Intervention and exploratory groups will be modified double-blind (observer-blinded) as described
Study intervention assignment method	Participants will be screened for eligibility criteria at the time of inclusion. **Original Phase II Cohort:** The randomization was stratified by age groups (18-59 years of age and 60 years of age and older), baseline SARS-CoV-2 rapid serodiagnostic test positivity (Positive/Negative), and high-risk medical conditions (Yes/No). Eligible participants were randomly assigned to one of 3 study groups in a 1:1:1 ratio, corresponding to one of 3 formulations of CoV2 preS dTM-AS03 vaccine (with different antigen doses). **Supplemental Phase III Cohorts:** • Supplemental Cohort 1: previously-vaccinated participants will be stratified based on the priming vaccine received 4 to ≤ 10 months prior and by age group (18-55 years of age and 56 years of age and older) and will receive a single booster dose of CoV2 preS dTM-AS03 (D614). • Supplemental Cohort 2, Main Arms: Participants previously vaccinated with an authorized/approved mRNA or adenovirus-vectored

	COVID-19 vaccine will be stratified based on the vaccine received 4 to ≤ 10 months prior and by age group (18-55 years of age and 56 years of age and older) and randomly assigned to 1 of the following booster formulations in a 1:1 ratio: o CoV2 preS dTM-AS03 (B.1.351) o CoV2 preS dTM-AS03 (D614 + B.1.351) Participants previously vaccinated with CoV2 preS dTM-AS03 (D614) as a primary series in the Original Phase II Cohort will be stratified by age group (18-55 years of age and 56 years of age and older) and randomly assigned to 1 of the following booster formulations in a 9:1 ratio for younger adults (D614:B.1.351) and a 1:1 ratio for older adults: o CoV2 preS dTM-AS03 (D614) o CoV2 preS dTM-AS03 (B.1.351) • Supplemental Cohort 2 Exploratory B.1.351 Arms: Participants previously vaccinated with the Pfizer/BioNTech mRNA vaccine will be enrolled after completion of enrollment of the above booster arms in Cohort 2 and will be stratified by age group (18-55 years of age and 56 years of age and older) and randomly assigned to receive 1 of the following CoV2 preS dTM (B.1.351) formulations in a 1:1:1:1 ratio: o 2.5 µg antigen with AS03 adjuvant o 2.5 µg antigen with half-dose[a] AS03 adjuvant o 5 µg antigen with half-dose AS03 adjuvant o 5 µg antigen with no adjuvant • Supplemental Cohorts Comparator Group: SARS-CoV-2-naïve, unvaccinated, adults who are 18-55 years of age will be given CoV2 preS dTM-AS03 (D614) as a primary series vaccination of 2 injections given 21 days apart. • Supplemental Cohort Subsets and Assessment of Immunogenicity to Emerging Variants of Concern: A randomized subset of 70 participants in Cohort 1 will be tested for additional SARS-CoV-2 variants of concern including Delta. No additional sample collection, procedures, or visits are required for this subset. A randomized subset of 82 participants in Cohort 2 comprised of younger adults (18 to 55 years of age) will provide samples for cellular immune response and mucosal antibody assessments and will also be tested for additional variants of concern including Delta.

Disclosure Statement:

Original Phase II Cohort and Supplemental Cohort 2 Intervention Groups: 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

[a] The half dose of AS03 and the full dose of AS03 contain amounts of tocopherol of 5.93 mg and 11.86 mg, respectively

Intervention Group; and those preparing the study interventions will be unblinded to vaccine assignment group. This does not apply to the Supplemental Cohort 1 Booster Group and the Supplemental Cohorts Comparator Group which will be open-label.

Number of Participants:

Original Phase II Cohort: A total of 720 participants were planned to be enrolled. After stratification by age-group (18-59 years and ≥ 60 years), baseline SARS-CoV-2 rapid serodiagnostic test positivity (Positive/Negative [as determined at the time of enrollment]) and high-risk medical conditions (Yes/No), participants will be randomly assigned to the study groups.

For all study arms, half of the participants were to be 18-59 years of age and half of the participants were to be 60 years of age or older. Additionally, up to 20% of participants in each study group were allowed to be test-positive on the rapid serodiagnostic test at enrollment. A randomized subset of 120 rapid diagnostic test-negative participants stratified by age-group (20 participants/study group/age-group) was to provide samples for cellular immune response and mucosal antibody assessments.

Supplemental Phase III Cohorts: A total of approximately 3660 participants are planned to be enrolled and will be stratified as follows:

Supplemental Cohort 1: Adults vaccinated 4 to ≤ 10 months prior will be stratified by primary vaccine and by age to receive a single booster dose of CoV2 preS dTM-AS03 (D614):

- Primed with Pfizer/BioNTech:
  - 18-55 years of age: 215 participants
  - 56 years of age and older: 50 participants
- Primed with Moderna:
  - 18-55 years of age: 75 participants
  - 56 years of age and older: 25 participants
- Primed with Oxford University/AstraZeneca:
  - 18-55 years of age: 75 participants
  - 56 years of age and older: 25 participants
- Primed with J&J/Janssen:
  - 18-55 years of age: 75 participants
  - 56 years of age and older: 25 participants

Supplemental Cohort 2, Main Arms: Adults vaccinated 4 to ≤ 10 months prior will be stratified by primary vaccine and by age and randomized to receive 1 of the following as a single booster dose:

- Primed with Pfizer/BioNTech:
  - CoV2 preS dTM-AS03 (B.1.351):
    - 18-55 years of age: 515 participants
    - 56 years of age and older: 50 participants

  - CoV2 preS dTM-AS03 (D614 + B.1.351):
    - 18-55 years of age: 515 participants
    - 56 years of age and older: 50 participants
- Primed with CoV2 preS dTM-AS03 (actual numbers will depend on eligibility and consent for Cohort 2 participation of participants enrolled in the Original Phase II Cohort; numbers below are estimates and subject to change):
  - CoV2 preS dTM-AS03 (D614):
    - 18-55 years of age: 270 participants
    - 56 years of age and older: 75 participants
  - CoV2 preS dTM-AS03 (B.1.351):
    - 18-55 years of age: 30 participants
    - 56 years of age and older: 75 participants
- Primed with Moderna:
  - CoV2 preS dTM-AS03 (B.1.351):
    - 18-55 years of age: 75 participants
    - 56 years of age and older: 25 participants
  - CoV2 preS dTM-AS03 (D614 + B.1.351):
    - 18-55 years of age: 75 participants
    - 56 years of age and older: 25 participants
- Primed with Oxford University/AstraZeneca:
  - CoV2 preS dTM-AS03 (B.1.351):
    - 18-55 years of age: 75 participants
    - 56 years of age and older: 25 participants
  - CoV2 preS dTM-AS03 (D614 + B.1.351):
    - 18-55 years of age: 75 participants
    - 56 years of age and older: 25 participants
- Primed with J&J/Janssen:
  - CoV2 preS dTM-AS03 (B.1.351):
    - 18-55 years of age: 75 participants
    - 56 years of age and older: 25 participants
  - CoV2 preS dTM-AS03 (D614 + B.1.351):
    - 18-55 years of age: 75 participants
    - 56 years of age and older: 25 participants

Supplemental Cohort 2 Exploratory B.1.351 Arms: Adults vaccinated 4 to $\leq$ 10 months prior with the Pfizer/BioNTech mRNA vaccine will be stratified by age and randomized to receive a single booster dose of 1 of the following CoV2 preS dTM (B.1.351) formulations:

- 2.5 µg antigen with full-dose AS03 adjuvant:
  - 18-55 years of age: 75 participants
  - 56 years of age and older: 25 participants
- 2.5 µg antigen with half-dose AS03 adjuvant:

- 18-55 years of age: 75 participants
- 56 years of age and older: 25 participants

- 5 µg antigen with half-dose AS03 adjuvant:
  - 18-55 years of age: 75 participants
  - 56 years of age and older: 25 participants
- 5 µg antigen with no adjuvant:
  - 18-55 years of age: 75 participants
  - 56 years of age and older: 25 participants

Supplemental Cohorts Comparator Group: SARS-CoV-2-naïve, unvaccinated, adults will be enrolled into a parallel, non-randomized arm and receive CoV2 preS dTM-AS03 (D614) as a primary series vaccination of 2 injections given 21 days apart:

- 18-55 years of age only: 515 participants

Supplemental Cohorts Subsets and Assessment of Immunogenicity to Emerging Variants of Concern: A randomized subset of 70 participants in Cohort 1 will be tested for additional SARS-CoV-2 variants of concern including Delta. No additional sample collection, procedures, or visits are required for this subset. A randomized subset of 82 participants in Cohort 2 comprised of younger adults (18 to 55 years of age) will provide samples for cellular immune response and mucosal antibody assessments and will also be tested for additional variants of concern including Delta.

Intervention Groups and Duration for Original Phase II Cohort:

Planned primary series sample size and approximate size of subsets

		Study Intervention Groups		
		Group 1	**Group 2**	**Group 3**
		CoV2 preS dTM-AS03 (5 µg antigen)	**CoV2 preS dTM-AS03 (10 µg antigen)**	**CoV2 preS dTM-AS03 (15 µg antigen)**
Total Overall		240	240	240
SARS-CoV-2 serodiagnostic test at baseline	**Negative**	At least 192*	At least 192*	At least 192*
	Positive	Up to 48†	Up to 48†	Up to 48†
Age Groups	**Adults (18-59 years)**	120	120	120
	Older adults (≥ 60 years)	120	120	120
Cellular Immunity and Mucosal subset‡		40 (20/age group)	40 (20/age group)	40 (20/age group)

* 96 per age group

† up to 24 per age group

‡ Participants SARS-CoV-2 serodiagnostic test negative at baseline would be randomized to this subset.

All participants in the Original Prime Cohort primary series were to receive 2 vaccine injections given at 3 weeks apart: the first injection will be at D01 (Vaccination [VAC] 1) and the second injection will be at D22 (VAC2). Blood samples were planned to be collected from all participants

prior to each injection, 14 days, 2 months, 4 months, 6 months, 9 months, and 12 months after last injection. Blood samples collected from all participants will be used for serological assessments in the study. Whole blood, peripheral blood mononuclear cells (PBMCs), and saliva samples will be collected from a subset of participants to assess cellular immune responses and mucosal antibody responses. Participants were asked to inform Investigators if they seek vaccination of an authorized/approved vaccine.

All participants will be followed for the duration of the study to capture occurrences of COVID-19 through passive surveillance wherein participants will be instructed to contact the site if they experience symptoms/conditions of a COVID-19-like illness at any time during the study. In addition, active surveillance will be undertaken in all participants wherein all participants will be contacted once every 2 weeks starting after the D43 contact to enquire about development of COVID-19-like illness.

The duration of participation in the Original Phase II Cohort will be approximately 365 days post-injection 2 (ie, approximately 386 days total).

In the event that the vaccine formulation evaluated in this study is deemed safe and effective by regulatory authorities, this authorized/approved vaccine may be offered to eligible participants in this study who received a formulation considered less effective to that authorized by the regulatory authorities, if permitted by local regulations and in alignment with local recommendations.

If an approved/authorized vaccine is available in the country or region where the study is conducted, Investigators were to discuss this information with prospective study participants at the time of informed consent to encourage them to obtain the approved/authorized vaccine if applicable to them. Recruitment of eligible participants will proceed only if, despite encouragement, the candidate participant expressed no intention to seek an authorized or approved vaccine at least until completion of the key follow-up timepoint (D43) for informing progression to Phase III and dose selection.

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 immunogenicity and safety. Participants will continue to be followed for the duration of the study as per scheduled visits and procedures. Participants will be invited to a visit prior to receiving the vaccine and invited to provide a blood sample for immunological assessment. If the visit occurs more than 1 month after the D134 visit, a PBMC sample will also be collected if the participant is in the cellular immunity and mucosal subset instead of the D387 sample. Participants will not receive the second vaccination if they have received the authorized/approved vaccine between the first and second scheduled vaccination.

If a participant elects to transition from the Original Phase II Cohort to Supplemental Cohort 2, the participant should be scheduled to complete the next planned visit. Enrollment (V01) to the Supplement Cohort may be performed on another day, to be scheduled as soon as possible after the Original Phase II Cohort visit. All required procedures for the Original Cohort visit and the Supplemental Cohort 2 visit should be conducted for each visit, respectively.

Intervention Groups and Duration for Supplemental Phase III Cohorts:

Planned sample sizes for Supplemental Cohorts 1 and 2

		Cohort 1	Cohort 2 Main Arms			Comparator
		Booster	Booster	Booster	Booster	Primary Series
		CoV2 preS dTM-AS03 (D614)	CoV2 preS dTM-AS03 (B.1.351)	CoV2 preS dTM-AS03 (D614 + B.1.351)	CoV2 preS dTM-AS03 (D614)	CoV2 preS dTM-AS03 (D614)
Total Overall		**565**	**970**	**865**	**345**	**515**
SARS-CoV-2-naïve, Unvaccinated, Adults (18-55 years)		--	--	--	--	515
Pfizer/BioNTech	**Adults (18-55 years)**	215	515	515	--	--
	Older adults (≥ 56 years)	50	50	50	--	--
CoV2 preS dTM-AS03 (Original Phase II Cohort participants)	**Adults (18-55 years)**	--	30	--	270	--
	Older adults (≥ 56 years)	--	75	--	75	--
Moderna	**Adults (18-55 years)**	75	75	75	--	--
	Older adults (≥ 56 years)	25	25	25	--	--
Oxford University/ AstraZeneca	**Adults (18-55 years)**	75	75	75	--	--
	Older adults (≥ 56 years)	25	25	25	--	--
J&J/Janssen	**Adults (18-55 years)**	75	75	75	--	--
	Older adults (≥ 56 years)	25	25	25	--	--

Planned sample sizes for Supplemental Cohort 2 Exploratory B.1.351 Arms

		CoV2 preS dTM (B.1.351) Treatment Groups			
		2.5 µg with full-dose AS03	**5 µg with half-dose AS03**	**5 µg with no adjuvant**	**2.5 µg with half-dose AS03**
Total Overall		**100**	**100**	**100**	**100**
Age Groups	**Adults (18-55 years)**	75	75	75	75
	Older adults (≥ 56 years)	25	25	25	25

Supplemental Cohort 1 and Cohort 2 Booster Arms Only: all participants will receive a single booster dose (VAC) at D01. Blood samples will be collected from all participants prior to the booster injection, 14 days, 1 month, 3 months, 6 months, and 12 months after the injection.

Supplemental Cohorts Comparator Group: all participants will receive 2 vaccine injections given 3 weeks apart: the first injection will be at D01 (VAC1) and the second injection will be at D22 (VAC2). Blood samples will be collected from all participants prior to each injection, 14 days, 4 months, 6 months, 9 months, and 12 months after last injection.

Approximate sample size of Supplemental Cohort subsets and Variant Testing for CMI/Mucosal Subset for Cohorts 1 and 2

	Cohort 1*	**Cohort 2***	
	Variant Testing Only	**Participants in the Pfizer/BioNTech Group**	**Participants in the CoV2 preS dTM-AS03 Group (Original Phase II Cohort)**
Total Overall	**70**	**52**	**30**
CoV2 preS dTM-AS03 (D614)	44	--	27
CoV2 preS dTM-AS03 (B.1.351)	--	26	3
CoV2 preS dTM-AS03 (D614 + B.1.351)	--	26	--
Comparator	26	--	--

*All subset participants will be 18-55 years of age only

Supplemental Cohorts Subsets and Assessment of Immunogenicity to Emerging Variants of Concern: A randomized subset of 70 participants in Cohort 1, will be tested for additional SARS-CoV-2 variants of concern including Delta. No additional sample collection, procedures, or visits are required for this subset. A randomized subset of 82 participants in Cohort 2 comprised of younger adults (18 to 55 years of age) will provide samples for cellular immune response and mucosal antibody assessments and will also be tested for additional variants of concern including Delta.

For all cohorts: blood samples collected from all participants will be used for serological assessments in the study. Whole blood, PBMCs, and saliva samples will be collected from a subset of participants in Cohort 2 to assess cellular immune responses and mucosal antibody responses.

Reactogenicity will be assessed by collecting solicited AEs for 7 days after each vaccination, unsolicited AEs for 21 days after the last vaccination, and SAEs, MAAEs, and AESIs for the duration of the study.

All Supplemental Phase III Cohort participants will be followed for the duration of the study to capture occurrences of COVID-19 through passive surveillance wherein participants will be instructed to contact the site if they experience symptoms/conditions of a COVID-19-like illness at any time during the study. In addition, participants will be contacted once every 2 weeks starting at D43 (for the Original Phase II Cohort and Supplemental Phase III Cohorts Comparator Group) and D30 (for Supplemental Phase III Cohorts 1 and 2 Booster Groups) to inquire about the development of symptoms/conditions of COVID-19-like illness and to remind participants to contact study staff if they experience symptoms/conditions of COVID-19-like illness or if they have a positive COVID-19 test from any other source.

The duration of participation in the study for each participant will be:

- Supplemental Cohorts 1 and 2: approximately 365 days post-booster injection (ie, approximately 366 days total)
- Supplemental Cohorts Comparator Group approximately 365 days post-injection 2 (ie, approximately 386 days total)

Data Monitoring/Other Committee:

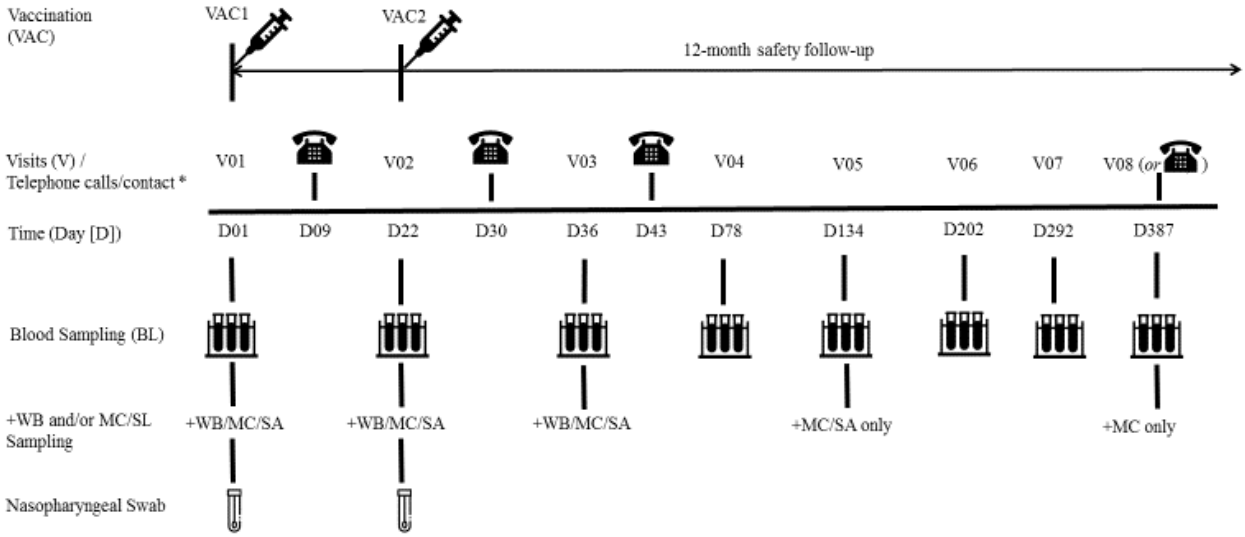
Not Applicable

1.2 Schemas

The graphical designs for the VAT00002 study are presented as follows:

- Figure 1.1: Original Phase II Cohort
- Figure 1.2: Booster arms for Supplemental Cohorts 1 and 2
- Figure 1.3: Supplemental Cohorts Comparator Group
- Figure 1.4: Design for COVID-19-like illness follow-up for the Original Series and all Supplemental Cohorts

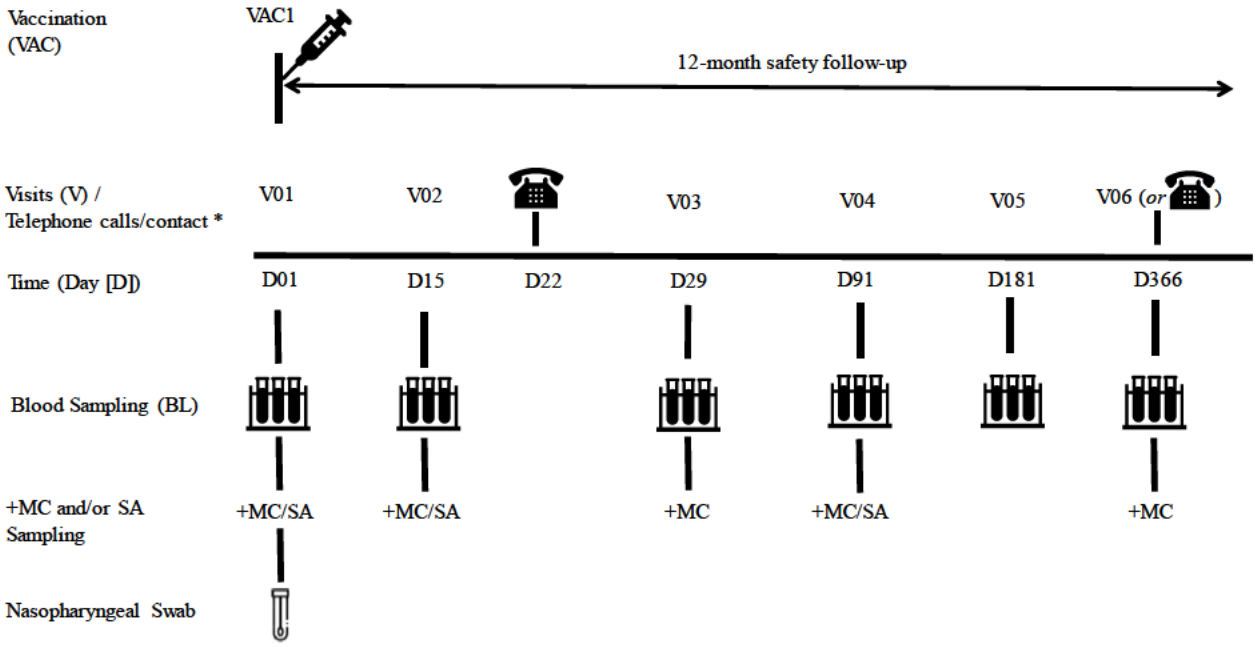
Figure 1.1: Graphical study design for Original Phase II Cohort



BL, blood sample; MC; mononuclear cell sample; SA, saliva sample; TC, telephone call; V, visit; VAC, vaccination; WB, whole blood sample; MC/SA are only for selected participants

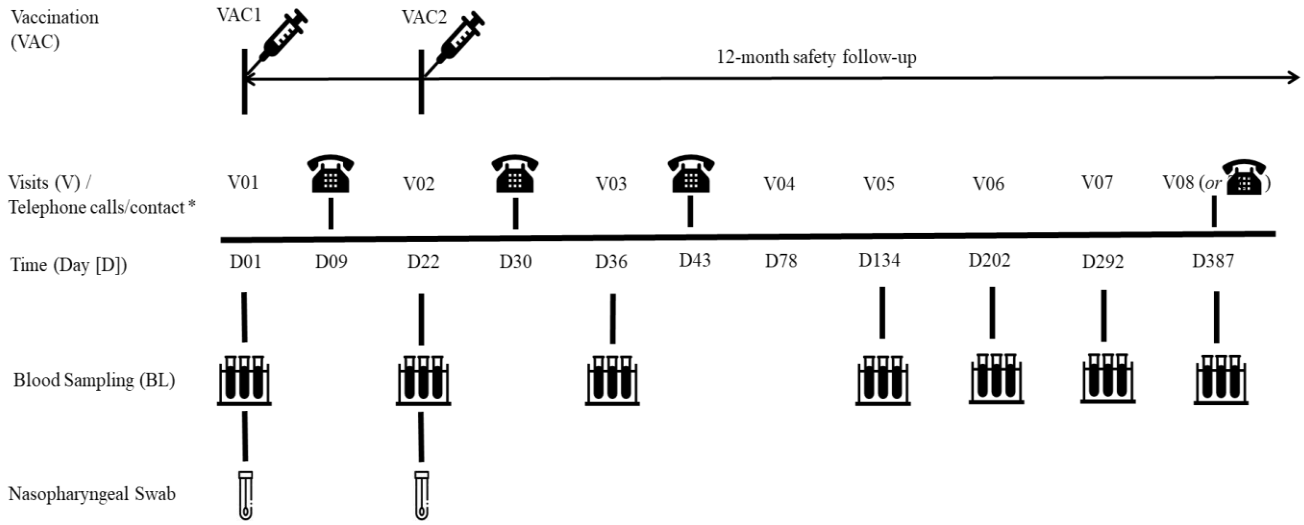
* During the D09, D30, and D43 telephone call, staff will review the DC pertaining to solicited AEs (D09 and D30 only), unsolicited AEs, SAEs, AESIs, MAAEs and COVID-19 like illness since the last visit and will remind participants to bring the DC for the next visit. Data on unsolicited AEs, SAEs, AESIs, MAAEs collected at the D43 telephone call will be collected in the CRF prior to the D78 visit. These telephone calls will NOT be collected in the CRF.
For the V08 contact or phone call, all participants will be scheduled to attend V08 for blood sampling and the 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: Graphical study design for Supplemental Cohorts 1 and 2 Booster Arms



BL, blood sample; MC; mononuclear cell sample; SA, saliva sample; TC, telephone call; V, visit; VAC, vaccination; * For the V06 contact or phone call, all participants will be scheduled to attend V06 for blood sampling and the 12-Month (post-VAC) 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.

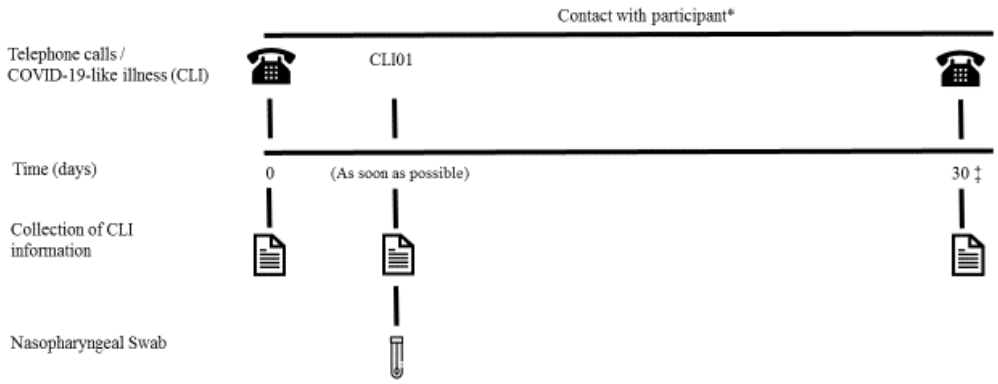
Figure 1.3: Graphical study design for Supplemental Cohorts Comparator Group



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

* During the D09, D30, and D43 telephone call, staff will review the DC pertaining to solicited AEs (D09 and D30 only), unsolicited AEs, SAEs, AESIs, MAAEs and COVID-19 like illness since the last visit and will remind participants to bring the DC for the next visit. Data on unsolicited AEs, SAEs, AESIs, MAAEs collected at the D43 telephone call will be collected in the CRF prior to the D78 visit. These telephone calls will NOT be collected in the CRF.
For the V08 contact or phone call, all participants will be scheduled to attend V08 for blood sampling and the 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 1.4: Follow-up of COVID-19-like illness for the Original Phase II Cohort and all Supplemental Phase III Cohorts



CLI, COVID-like illness (visit)

* The frequency of contact for medical monitoring is up to the discretion of the Investigator.

At the CLI01 visit, participants will be provided with a pulse oximeter and asked to record pulse oximetry readings twice a day from onset of illness until the results of the respiratory swab collected for NAAT testing at CLI01 are available. Continuation of pulse oximetry readings by the participant after availability of test results will be based on Investigator judgment.

‡ Follow-up telephone call approximately 30 days after onset of illness. If symptoms are ongoing 30 days after illness onset, a second telephone call 60 days after onset of illness will be scheduled.

1.3 Schedule of Activities (SoA)

Visit procedures are detailed in the Operating Guidelines.

Table 1.1 presents the overall study Schedule of Activities (SoA) for the Original Phase II Cohort.

Table 1.2 presents the overall study SoA for the booster arms of Supplemental Cohorts 1 and 2.

Table 1.3 presents the overall study SoA for the Supplemental Cohorts Comparator Group.

Table 1.4 presents the SoA for the follow-up of COVID-19-like illness for the Original Phase II Cohort and Supplemental Cohorts.

Table 1.1: Schedule of Activities for Original Phase II Cohort

Phase II Study, 8 Visits, 3 Telephone Calls, 2 Vaccinations, 8 Blood Sample Time points, Approximately 13 Months' Duration Per Participant

Visit (V) / Contact	***Collection of information in the CRF***	**V01**	**TC1‡‡**	**V02**	**TC2‡‡**	**V03**	**TC3‡‡**	**V04**	**V05**	**V06**	**V07‡‡‡‡**	**V08 Or safety follow-up ‡‡‡‡‡**
Study timelines (Day [D])		D01	D09	D22	D30	D36	D43	D78	D134	D202	D292	D387
Time interval (days)			V01 +8 days	V01 +21 days	V02 +8 days	V02+14 days	V02+21 days	V02 +56 days	V02 +112 days	V02 +180 days	V02 +270 days	V02+365 days
Time windows (days)		N/A	[+2days]	[+3 days]	[+2 days]	[+3 days]	[+2 days]	[+9 days]	[+14 days]	[+21 days]	[+21 days]	[+21 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 significant medical history including high risk medical conditions	X	X										

Visit (V) / Contact	***Collection of information in the CRF***	**V01**	**TC1‡‡**	**V02**	**TC2‡‡**	**V03**	**TC3‡‡**	**V04**	**V05**	**V06**	**V07‡‡‡‡**	**V08 Or safety follow-up ‡‡‡‡‡**
Study timelines (Day [D])		D01	D09	D22	D30	D36	D43	D78	D134	D202	D292	D387
Time interval (days)			V01 +8 days	V01 +21 days	V02 +8 days	V02+14 days	V02+21 days	V02 +56 days	V02 +112 days	V02 +180 days	V02 +270 days	V02+365 days
Time windows (days)		N/A	[+2days]	[+3 days]	[+2 days]	[+3 days]	[+2 days]	[+9 days]	[+14 days]	[+21 days]	[+21 days]	[+21 days]
Visit procedures:												
Collection of risk factors for SARS-CoV-2 exposure and COVID-19	X	X										
Physical examination*		X										
Pre-vaccination temperature		X		X								
Urine/serum pregnancy test (if applicable)†		X		X								
Contact IRT system for randomization, participant number, and unique dose number allocation	X	X										
Contact IRT system for unique dose number allocation	X			X								
Temporary and definitive contraindications	X			X								
Nasopharyngeal sample collection	X	X		X								

Visit (V) / Contact	***Collection of information in the CRF***	**V01**	**TC1‡‡**	**V02**	**TC2‡‡**	**V03**	**TC3‡‡**	**V04**	**V05**	**V06**	**V07‡‡‡‡**	**V08 Or safety follow-up ‡‡‡‡‡**
Study timelines (Day [D])		D01	D09	D22	D30	D36	D43	D78	D134	D202	D292	D387
Time interval (days)			V01 +8 days	V01 +21 days	V02 +8 days	V02+14 days	V02+21 days	V02 +56 days	V02 +112 days	V02 +180 days	V02 +270 days	V02+365 days
Time windows (days)		N/A	[+2days]	[+3 days]	[+2 days]	[+3 days]	[+2 days]	[+9 days]	[+14 days]	[+21 days]	[+21 days]	[+21 days]
Visit procedures:												
Blood sampling (BL): Serum samples for Ab assays (30 mL)**	X	BL0001‡		BL0002‡		BL0003		BL0004	BL0005	BL0006	BL0007	BL0008
PBMCs for Cellular immune responses (40 mL)§		MC0001‡		MC0002‡		MC0003			MC0004			MC0005††
TruCulture samples (4 mL)§		WB0001‡		WB0002‡		WB0003						
Saliva samples for mucosal immunity§		SA0001‡		SA0002‡		SA0003			SA0004			
Vaccination (VAC)	X	X		X								
Telephone call			X‡‡		X‡‡		X‡‡					X ††††
Immediate surveillance (30 minutes)	X	X		X								
DC provided		DC1 §§		DC2 ‡‡‡				DC3 §§§				
DC reviewed			DC1 ***		DC2 ***	DC2 ‡‡	DC2 ***		DC3 ***	DC3 ***	DC3 ***	
DC collected				DC1 †††				DC2 †††				DC3 †††

Visit (V) / Contact	***Collection of information in the CRF***	**V01**	**TC1‡‡**	**V02**	**TC2‡‡**	**V03**	**TC3‡‡**	**V04**	**V05**	**V06**	**V07‡‡‡‡**	**V08 Or safety follow-up ‡‡‡‡‡**
Study timelines (Day [D])		D01	D09	D22	D30	D36	D43	D78	D134	D202	D292	D387
Time interval (days)			V01 +8 days	V01 +21 days	V02 +8 days	V02+14 days	V02+21 days	V02 +56 days	V02 +112 days	V02 +180 days	V02 +270 days	V02+365 days
Time windows (days)		N/A	[+2days]	[+3 days]	[+2 days]	[+3 days]	[+2 days]	[+9 days]	[+14 days]	[+21 days]	[+21 days]	[+21 days]
Visit procedures:												
Collection of solicited injection site & systemic reactions	X	D01-D08 *(up to 7 days post-VAC1)*		D01-D08 *(up to 7 days post-VAC2)*								
Collection of unsolicited AEs	X	D01-D22 *(up to 21 days post-VAC1)*										
				D01-D22 *(up to 21 days post-VAC2)*								
Collection of concomitant medications	X Reportable concomitant medication	All reportable concomitant medications (including influenza and COVID-19 vaccination)						Influenza and COVID-19 vaccination, COVID-19 prophylaxis (eg, SARS-CoV-2 antivirals, monoclonal antibodies, plasma) only				
Active surveillance	X						Participants will be contacted once every 2 weeks starting at D43 to inquire about the development of symptoms/conditions of COVID-like illness and to remind participants to contact study staff if they experience symptoms/conditions of COVID-like illness or if they have a positive COVID-19 test from any other source.					
Passive surveillance	X	Participants will be instructed to contact the site if they experience symptoms/conditions 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.										
Collection of SAEs, MAAEs, and AESIs****	X	To be reported at any time during the study										

Visit (V) / Contact	***Collection of information in the CRF***	**V01**	**TC1‡‡**	**V02**	**TC2‡‡**	**V03**	**TC3‡‡**	**V04**	**V05**	**V06**	**V07‡‡‡‡**	**V08 Or safety follow-up ‡‡‡‡‡**
Study timelines (Day [D])		D01	D09	D22	D30	D36	D43	D78	D134	D202	D292	D387
Time interval (days)			V01 +8 days	V01 +21 days	V02 +8 days	V02+14 days	V02+21 days	V02 +56 days	V02 +112 days	V02 +180 days	V02 +270 days	V02+365 days
Time windows (days)		N/A	[+2days]	[+3 days]	[+2 days]	[+3 days]	[+2 days]	[+9 days]	[+14 days]	[+21 days]	[+21 days]	[+21 days]
Visit procedures:												
Collection of pregnancies	X	To be reported at any time during the study										
End of phase participation record							X			X		
End of active phase participation record††††	X									X†††††		X
12 Month Post-VAC2 Follow-up participation record (only for those discontinued early) ‡‡‡‡	X											X

Abbreviations: Ab, Antibody; AE, adverse event; AESI, adverse event of special interest; BL, blood sample (#); CRF, (electronic) Case Report Form; DC, Diary Card; IRT, Interactive Response Technology; MAAE, medically-attended adverse event; MC, mononuclear cell sample (#); SA, saliva sample (#); SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TC, telephone call; V, visit; VAC, Vaccination; WB, whole blood sample (#)

*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 post-menopausal for at least 1 year or surgically sterile). Urine or serum pregnancy test is to be performed before vaccination.

‡ BL/MC/WB/SA0001 and BL/MC/WB/SA0002 will be collected pre-vaccination.

§ These samples will be collected only from a subset of participants.

** If a participant seeks an authorized/approved vaccine, they will be invited to an unscheduled visit prior to receiving the vaccine and requested to provide a blood sample for serological assessment.

Visit (V) / Contact	***Collection of information in the CRF***	**V01**	**TC1‡‡**	**V02**	**TC2‡‡**	**V03**	**TC3‡‡**	**V04**	**V05**	**V06**	**V07‡‡‡‡**	**V08 Or safety follow-up ‡‡‡‡‡**
Study timelines (Day [D])		D01	D09	D22	D30	D36	D43	D78	D134	D202	D292	D387
Time interval (days)			V01 +8 days	V01 +21 days	V02 +8 days	V02+14 days	V02+21 days	V02 +56 days	V02 +112 days	V02 +180 days	V02 +270 days	V02+365 days
Time windows (days)		N/A	[+2days]	[+3 days]	[+2 days]	[+3 days]	[+2 days]	[+9 days]	[+14 days]	[+21 days]	[+21 days]	[+21 days]
Visit procedures:												

†† If a participant in the cellular immunity and mucosal subset seeks an authorized/approved vaccine, they will be invited to an unscheduled visit prior to receiving the vaccine and requested to provide a blood sample for serological assessment and PBMCs. If the visit occurs more than 1 month after the D134 visit, a PBMC sample will be collected instead of the PBMC collection at D387.

‡‡ During the telephone call, staff will review the DC pertaining to solicited AEs, unsolicited AEs, SAEs, MAAEs, AESIs and COVID-19 like illness since the last visit and will remind participants to bring the DC for the next visit. Data on unsolicited AEs, SAEs, AESIs, MAAEs collected at the D43 telephone call will be collected in the CRF prior to the D78 visit. These telephone calls will NOT be collected in the CRF.

§§ Participants will use this DC1 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, SAEs, MAAEs, and AESIs from D09 to V02. In addition, the participant will use the DC 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 at the next visit and will answer any questions.

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

‡‡‡ Participants will use this DC2 to record solicited reactions, unsolicited AEs, SAEs, MAAEs, and AESIs (from V02 to TC2) and will continue to collect unsolicited AEs, SAEs, MAAEs, and AESIs (from TC2 to V04). In addition, the participant will use the DC to report the information related to COVID-19-like illness.

§§§ Participants will use this DC3 to record SAEs, MAEs, AESIs, and information related to COVID-19-like-illness from V04 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.

‡‡‡‡ V07 and V08 will not be applicable for participants in the Original Phase II Cohort who enroll in Supplemental Cohort 2.

‡‡‡‡‡ 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. 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

Visit (V) / Contact	***Collection of information in the CRF***	**V01**	**TC1‡‡**	**V02**	**TC2‡‡**	**V03**	**TC3‡‡**	**V04**	**V05**	**V06**	**V07‡‡‡‡**	**V08 Or safety follow-up ‡‡‡‡‡**
Study timelines (Day [D])		D01	D09	D22	D30	D36	D43	D78	D134	D202	D292	D387
Time interval (days)			V01 +8 days	V01 +21 days	V02 +8 days	V02+14 days	V02+21 days	V02 +56 days	V02 +112 days	V02 +180 days	V02 +270 days	V02+365 days
Time windows (days)		N/A	[+2days]	[+3 days]	[+2 days]	[+3 days]	[+2 days]	[+9 days]	[+14 days]	[+21 days]	[+21 days]	[+21 days]
Visit procedures:												

(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.

†††††End of participation record to occur if participant moves from the Original Phase II Cohort to the Supplemental Phase III Cohorts.

Table 1.2: Schedule of Activities for Supplemental Cohorts 1 and 2 (Booster Arms Only)

Booster Arms Only*: Phase II/III Study, 6 Visits, 1 Phone call, 1 Vaccination, 6 Blood Sample Time points, Approximately 12 Months' Duration Per Participant

Visit (V) / Contact	***Collection of information in the CRF***	**V01**	**V02**	**TC1‡‡**	**V03**	**V04**	**V05**	**V06 Or Safety Follow-up ‡‡‡‡**
Study timelines (Day [D])		D01	D15	D22	D29	D91	D181	D366
Time interval (days)			V01 + 14 days	V01 + 21 days	V01+28 days	V01 +90 days	V01 +180 days	V01 +365 days
Time windows (days)		N/A	[+2 days]	[+2 days]	[+7 days]	[+7 days]	[+21 days]	[+21 days]
Visit procedures:								
Informed consent	X	X						
Inclusion/exclusion criteria	X	X						
Collection of demographic data	X	X						
Collection of previous COVID-19 vaccination	X	X						
Collection of significant medical history including high risk medical conditions	X	X						
Physical examination**		X						
Pre-vaccination temperature		X						
Urine/serum pregnancy test (if applicable)†		X						
Contact IRT system for randomization, participant number, and unique dose number allocation	X	X						
Nasopharyngeal sample collection	X	X						
Blood sampling (BL): Serum samples for Ab assays (30 mL)	X	BL0001	BL0002		BL0003	BL0004	BL0005	BL0006
PBMCs for Cellular immune responses (40 mL)§		MC0001	MC0002		MC0003	MC0004		MC0005
Saliva samples for mucosal immunity§		SA0001	SA0002			SA0003		

Visit (V) / Contact	***Collection of information in the CRF***	**V01**	**V02**	**TC1‡‡**	**V03**	**V04**	**V05**	**V06 Or Safety Follow-up ‡‡‡‡**
Study timelines (Day [D])		D01	D15	D22	D29	D91	D181	D366
Time interval (days)			V01 + 14 days	V01 + 21 days	V01+28 days	V01 +90 days	V01 +180 days	V01 +365 days
Time windows (days)		N/A	[+2 days]	[+2 days]	[+7 days]	[+7 days]	[+21 days]	[+21 days]
Visit procedures:								
Vaccination (VAC)	X	X						
Telephone call				X				X
Immediate surveillance (30 minutes)	X	X						
DC provided		DC1 §§			DC2 ‡‡‡	DC3 §§§		
DC reviewed			DC1 ***				DC3 ***	
DC collected					DC1 †††	DC2 †††		DC3 †††
Collection of solicited injection site & systemic reactions	X	D01-D08 *(up to 7 days post-VAC*						
Collection of unsolicited AEs	X	D01-D22 *(up to 21 days post-VAC)*						
Collection of concomitant medications	X Reportable concomitant medication	All reportable concomitant medications (including influenza and COVID-19 vaccination)		Influenza and COVID-19 vaccination, COVID-19 prophylaxis (eg, SARS-CoV-2 antivirals, monoclonal antibodies, plasma) only				
Active surveillance	X				Participants will be contacted once every 2 weeks starting at D30 to inquire about the development of symptoms/conditions of COVID-like illness and to remind participants to contact study staff if they experience symptoms/conditions of			
Passive surveillance	X	Participants will be instructed to contact the site if they experience symptoms/conditions 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.						
Collection of SAEs, 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			X				X
12 Month Post-VAC1 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, Diary Card; IRT, Interactive Response Technology; MAAE, medically-attended adverse event; MC, mononuclear cell sample (#); SA, saliva sample (#); SAE, serious adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; V, visit; VAC, Vaccination

*Supplemental Cohorts Comparator Group participants will receive a 2 injection primary series 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 post-menopausal for at least 1 year or surgically sterile). Urine or serum pregnancy test is to be performed before vaccination.

§ These samples will be collected only from a subset of participants in Cohort 2 who received the Pfizer/BioNTech vaccine priming series only.

§§ Participants will use this DC1 to record information about solicited reactions, unsolicited AEs, SAEs, MAAEs, and AESIs from D01 to D15 after vaccination and will continue to record information about unsolicited AEs, SAEs, MAAEs, and AESIs from D16 to V03. In addition, the participant will use the DC 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 at the next visit and will answer any questions.

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

‡‡‡ Participants will use this DC2 to record SAEs, MAAEs, and AESIs. In addition, the participant will use the DC to report the information related to COVID-19-like illness.

§§§ Participants will use this DC3 to record SAEs, MAEs, AESIs, and information related to COVID-19-like-illness from V04 to V06.

**** 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.

‡‡‡‡ All participants will be scheduled to attend V06 for blood sampling and 12-Month (post-VAC) Safety Follow-up. However, if any participants discontinue the study early, they are still to be followed for safety and are to be contacted with a Safety Follow-up call to identify the occurrence of any SAEs and AESIs that had not yet been reported. If discontinuation occurs at a scheduled visit, the participant will be provided a Memory Aid instead of a DC for SAE follow-up (including AESIs) until the Safety Follow-up call. If a participant discontinues between visits (with no Memory Aid provided yet), the participant will use the last DC received to collect information for the Safety Follow-up call. 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.

Table 1.3: Schedule of Activities for Supplemental Cohorts Comparator Group

Phase II/III Study, 8 Visits, 3 Telephone Calls, 2 Vaccinations, 8 Blood Sample Time points, Approximately 13 Months' Duration Per Participant

Visit (V) / Contact	***Collection of information in the CRF***	**V01**	**TC1‡‡**	**V02**	**TC2‡‡**	**V03**	**TC3‡‡**	**V04**	**V05**	**V06**	**V07**	**V08 or Safety Follow-up ‡‡‡‡**
Study timelines (Day [D])		D01	D09	D22	D30	D36	D43	D78	D134	D202	D292	D387
Time interval (days)			V01 +8 days	V01 +21 days	V02 +8 days	V02+14 days	V02+21 days	V02 +56 days	V02 +112 days	V02 +180 days	V02 +270 days	V02+365 days
Time windows (days)		N/A	[+2days]	[+3 days]	[+2 days]	[+3 days]	[+2 days]	[+9 days]	[+14 days]	[+21 days]	[+21 days]	[+21 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 significant medical history including high risk medical conditions	X	X										
Collection of risk factors for SARS-CoV-2 exposure and COVID-19	X	X										
Physical examination*		X										

Visit (V) / Contact	***Collection of information in the CRF***	**V01**	**TC1‡‡**	**V02**	**TC2‡‡**	**V03**	**TC3‡‡**	**V04**	**V05**	**V06**	**V07**	**V08 or Safety Follow-up ‡‡‡‡**
Study timelines (Day [D])		D01	D09	D22	D30	D36	D43	D78	D134	D202	D292	D387
Time interval (days)			V01 +8 days	V01 +21 days	V02 +8 days	V02+14 days	V02+21 days	V02 +56 days	V02 +112 days	V02 +180 days	V02 +270 days	V02+365 days
Time windows (days)		N/A	[+2days]	[+3 days]	[+2 days]	[+3 days]	[+2 days]	[+9 days]	[+14 days]	[+21 days]	[+21 days]	[+21 days]
Visit procedures:												
Pre-vaccination temperature		X		X								
Urine/serum pregnancy test (if applicable)†		X		X								
Contact IRT system for randomization, participant number, and unique dose number allocation	X	X										
Contact IRT system for unique dose number allocation	X			X								
Temporary and definitive contraindications	X			X								
Nasopharyngeal sample collection	X	X		X								
Blood sampling (BL): Serum samples for Ab assays (30 mL)**	X	BL0001‡		BL0002‡		BL0003			BL0004	BL0005	BL0006	BL0007
Vaccination (VAC)	X	X		X								
Telephone call			X‡‡		X‡‡		X‡‡					X ††††
Immediate surveillance (30 minutes)	X	X		X								

Visit (V) / Contact	***Collection of information in the CRF***	**V01**	**TC1‡‡**	**V02**	**TC2‡‡**	**V03**	**TC3‡‡**	**V04**	**V05**	**V06**	**V07**	**V08 or Safety Follow-up ‡‡‡‡**
Study timelines (Day [D])		D01	D09	D22	D30	D36	D43	D78	D134	D202	D292	D387
Time interval (days)			V01 +8 days	V01 +21 days	V02 +8 days	V02+14 days	V02+21 days	V02 +56 days	V02 +112 days	V02 +180 days	V02 +270 days	V02+365 days
Time windows (days)		N/A	[+2days]	[+3 days]	[+2 days]	[+3 days]	[+2 days]	[+9 days]	[+14 days]	[+21 days]	[+21 days]	[+21 days]
Visit procedures:												
DC provided		DC1 §		DC2 ‡‡‡				DC3 §§				
DC reviewed			DC1 ***		DC2 ***	DC2 ‡‡	DC2 ***		DC3 ***	DC3 ***	DC3 ***	
DC collected				DC1 †††				DC2 †††				DC3 †††
Collection of solicited injection site & systemic reactions	X	D01-D08 *(up to 7 days post-VAC1)*		D01-D08 *(up to 7 days post-VAC2)*								
Collection of unsolicited AEs	X	D01-D22 *(up to 21 days post-VAC1)*										
				D01-D22 *(up to 21 days post-VAC2)*								
Collection of concomitant medications	X Reportable concomitant medication	All reportable concomitant medications (including influenza and COVID-19 vaccination)						Influenza and COVID-19 vaccination, COVID-19 prophylaxis (eg, SARS-CoV-2 antivirals, monoclonal antibodies, plasma) only				
Active surveillance	X						Participants will be contacted once every 2 weeks starting at D43 to inquire about the development of symptoms/conditions of COVID-like illness and to remind participants to contact study staff if they experience symptoms/conditions of COVID-like illness or if they have a positive COVID-19 test from any other source.					
Passive surveillance	X	Participants will be instructed to contact the site if they experience symptoms/conditions 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.										
Collection of SAEs, MAAEs, and AESIs****	X	To be reported at any time during the study										

Visit (V) / Contact	***Collection of information in the CRF***	**V01**	**TC1‡‡**	**V02**	**TC2‡‡**	**V03**	**TC3‡‡**	**V04**	**V05**	**V06**	**V07**	**V08 or Safety Follow-up ‡‡‡‡**
Study timelines (Day [D])		D01	D09	D22	D30	D36	D43	D78	D134	D202	D292	D387
Time interval (days)			V01 +8 days	V01 +21 days	V02 +8 days	V02+14 days	V02+21 days	V02 +56 days	V02 +112 days	V02 +180 days	V02 +270 days	V02+365 days
Time windows (days)		N/A	[+2days]	[+3 days]	[+2 days]	[+3 days]	[+2 days]	[+9 days]	[+14 days]	[+21 days]	[+21 days]	[+21 days]
Visit procedures:												
Collection of pregnancies	X	To be reported at any time during the study										
End of phase participation record							X			X		
End of active phase participation record††††	X											X
12 Month Post-VAC2 Follow-up participation record (only for those discontinued early) ‡‡‡‡	X											X

Abbreviations: Ab, Antibody; AE, adverse event; AESI, adverse event of special interest; BL, blood sample (#); CRF, (electronic) Case Report Form; DC, Diary Card; IRT, Interactive Response Technology; MAAE, medically-attended adverse event; MC, mononuclear cell sample (#); SA, saliva sample (#); 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 post-menopausal 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.

** If a participant seeks an authorized/approved vaccine, they will be invited to an unscheduled visit prior to receiving the vaccine and requested to provide a blood sample for serological assessment.

‡‡ During the telephone call, staff will review the DC pertaining to solicited AEs, unsolicited AEs, SAEs, MAAEs, AESIs and COVID-19 like illness since the last visit and will remind participants to bring the DC for the next visit. These telephone calls will NOT be collected in the CRF.

§ Participants will use this DC1 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, SAEs, MAAEs, and AESIs from D09 to V02. In addition, the participant will use the DC 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 at the next visit and will answer any questions.

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

Visit (V) / Contact	***Collection of information in the CRF***	**V01**	**TC1‡‡**	**V02**	**TC2‡‡**	**V03**	**TC3‡‡**	**V04**	**V05**	**V06**	**V07**	**V08 or Safety Follow-up ‡‡‡‡**
Study timelines (Day [D])		D01	D09	D22	D30	D36	D43	D78	D134	D202	D292	D387
Time interval (days)			V01 +8 days	V01 +21 days	V02 +8 days	V02+14 days	V02+21 days	V02 +56 days	V02 +112 days	V02 +180 days	V02 +270 days	V02+365 days
Time windows (days)		N/A	[+2days]	[+3 days]	[+2 days]	[+3 days]	[+2 days]	[+9 days]	[+14 days]	[+21 days]	[+21 days]	[+21 days]
Visit procedures:												

‡‡‡ Participants will use this DC2 to record solicited reactions, unsolicited AEs, SAEs, MAAEs, and AESIs (from V02 to TC2) and will continue to collect unsolicited AEs, SAEs, MAAEs, and AESIs (from TC2 to V04). In addition, the participant will use the DC to report the information related to COVID-19-like illness.
§§ Participants will use this DC3 to record SAEs, MAEs, AESIs, and information related to COVID-19-like-illness from V04 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.
‡‡‡‡ 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. 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 (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.

Table 1.4: Schedule of Activities 2 (Follow-up of COVID-19-like Illness) for the Original Phase II Cohort and all Supplemental Phase III Cohorts

Contact type	Initial Telephone Call*	CLI01	Follow-up Telephone Call†
		As soon as possible after symptom onset	30 days after symptom onset
Verify information on COVID-19-like illness, remind participant of use of pulse oximeter** and schedule appointment for collection of respiratory sample as soon as possible after illness start date‡	X		
Remind participant to complete Memory Aid or Diary Card	X		
Collection of respiratory specimen		NPXXXX§	
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

* Initial illness identification phone call. During the illness episode, participants may be contacted by the site staff for medical monitoring. The frequency of contact for medical monitoring is at the discretion of the Investigator.

† Follow-up telephone call approximately 30 days after onset of illness. If symptoms are ongoing 30 days after illness onset, a second telephone call 60 days after onset of illness will be scheduled.

‡ 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. A nasopharyngeal swab for central laboratory testing will be collected. A sample for local laboratory testing (clinical care) may be collected in addition to the NP swab for central laboratory testing. The swab will not be collected during a CLI visit if the date of collection is more than 14 days after resolution of symptoms.

**At the CLI01 visit, participants will be provided a pulse oximeter, explained about its use, and asked to record pulse oximetry readings every day from the CLI01 visit until the results of the NP swab at CLI01 and any other swab collected for local NAAT testing at CLI01 are available. Participants will be instructed to contact sites if the reading were to be lower than a threshold value (eg, 93% or equivalent based on altitude). Participant-recorded pulse oximeter readings are for safety monitoring and will not be collected in the diary card or CRF. 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.

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 on 20 January 2020 of a Public Health Emergency of International Concern, followed by the declaration on 11 March 2020 of a pandemic (1). The virus has been detected in 222 countries/regions and led to significant morbidity, mortality, and economic impact (2).

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 (18). In the majority of cases, the manifestations are mild, or individuals may be asymptomatic (4). 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 for up to 2 months after illness onset despite viral clearance (5). Based on early data, adults over 50 years of age and individuals with chronic medical conditions are at a higher risk of severe outcomes and death (4) (6).

A number of vaccine candidates in clinical development including viral vector-based vaccines, messenger ribonucleic acid (mRNA), protein subunit, and inactivated vaccines encoding the Spike (S)-protein of SARS-CoV-2 induce neutralizing antibodies. These include:

- 2 COVID-19 mRNA vaccine candidates
  - BNT162b2: International Non-Proprietary Name (INN)- COVID-19 mRNA vaccine (nucleoside-modified) from Pfizer/BioNTech (hereafter called Pfizer/BioNTech)
  - mRNA-1273: INN- COVID-19 mRNA vaccine (nucleoside modified) from Moderna (hereafter called Moderna)
- 2 adenovirus-vectored vaccine candidates
  - ChAdOx1-nCOV-19: INN- COVID-19 vaccine (ChAdOx1-S [recombinant]) vaccine from Oxford University/AstraZeneca (hereafter called Oxford University/AstraZeneca)
  - Ad26.COV2-S: INN- COVID-19 vaccine (Ad26.COV2-S [recombinant]) from Johnson & Johnson/Janssen (hereafter called J&J/Janssen)

These vaccine candidates have demonstrated efficacy against COVID-19 illness and severe disease in their Phase III clinical studies (7) (8) (9). Emergency authorization or other forms of regulatory approval have been granted in multiple countries for vaccines against COVID-19.

Sanofi Pasteur'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 (19). 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 (20). 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 (21). 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 (10). The prefusion stabilized SARS-CoV-2 S construct to be evaluated in the current study is based on this research.

The S1 subunit and RBD of the prefusion SARS-CoV-2 S antigen used in this vaccine is similar in sequence to the S antigens encoded by the mRNA vaccine constructs that have been shown to induce neutralizing antibody responses and confer robust efficacy against COVID-19 (7) (8), suggesting that other vaccines capable of inducing similar levels of neutralizing antibodies may also provide protection.

The antigen will be manufactured using the same technology as is used to manufacture a recombinant quadrivalent influenza vaccine (rQIV), licensed in the US and EU and commercialized as Flublok® and Supemtek®, respectively for the prevention of influenza in adults 18 years of age and older (22). 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 (expreSF+). 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 studies 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 (23). 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 (24). 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 (25) (26). In addition to a Phase I/II study using the Sanofi Pasteur CoV2 preS dTM antigen with AS03-adjuvanted system (NCT04537208), AS03 has also been used in combination with other AS03-adjuvanted recombinant S proteins (Medicago [NCT04450004] (27) and Clover Biopharmaceuticals [NCT04405908]).

A potential (yet theoretical) safety concern with coronavirus vaccines is the ability to potentiate immunopathology in vaccinees upon exposure to wild-type virus (28), called vaccine associated enhanced disease (VAED) The theoretical molecular mechanism for this phenomenon, 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 (29) (30) (31). 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 (10) (21). The inclusion of adjuvanted formulation is anticipated to further enhance the magnitude of neutralizing antibody responses and induce balanced Th1/Th2 cell responses (32) (23). Taken together, these strategies mitigate by design the theoretical risks of immune enhancement of viral infection.

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 II 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 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 doses of 1.3 µg and 2.6 µg, respectively, of purified recombinant SARS-CoV-2 S-protein 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 have informed the design of this Phase II study (VAT00002) aiming at selecting a suitable antigen dose adjuvanted with AS03 in a 2-injection schedule for further progression to a Phase III study.

A Phase II/III study in the pediatric population is planned to be initiated following generation of evidence in adults of a favorable benefit-risk of the vaccine. A Phase III study to assess the safety and immunogenicity of the vaccine in pregnant women is also planned after availability of a nonclinical DART (Developmental and reproductive toxicity) study and interim safety and immunogenicity data from the Phase II study in adults.

2.1 Study Rationale

New, highly transmissible SARS-CoV-2 variants of concern have emerged and are spreading globally. The UK first identified a variant of concern called Alpha (B.1.1.7) which has been shown to be more transmissible and has since been detected in many other countries around the world (12) Other variants have emerged first identified in South Africa (Beta [B.1.351] variant), Brazil (Gamma [P.1]variant), and India (Delta [B.1.617] variant) 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 (33) (34) (35). However, data from the Ad26CoV2.S vaccine (Johnson & Johnson/Janssen [J&J/Janssen]) showed efficacy against symptomatic disease in South Africa suggesting that the prototype vaccines 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 most notable against the 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. 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 (17). 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 variants of concern.

This Phase II/III study will assess the safety and immunogenicity of a CoV2 preS dTM-AS03 vaccine in adults 18 years of age and older. The goal of this study is to select an antigen dose adjuvanted with AS03 for further progression to a Phase III study.

This study will also assess the safety and immunogenicity of the CoV2 preS dTM-AS03 vaccine, including monovalent and bivalent formulations, for use as a universal late booster.

The data collected during this study will also support future development in other populations.

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 (2). In many locations, the rapid emergence of COVID-19 has overwhelmed the capacity of health systems to provide care for COVID-19-affected patients, let alone unaffected patients. Interventions to reduce transmission through reduction of population contact (also called social distancing) has had profound economic consequences. Safe and effective vaccines with sufficient doses would be vital to address the significant medical and societal burden caused by the pandemic.

The CoV2 preS dTM-AS03 vaccines developed by Sanofi Pasteur 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).

2.2.1 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 suggest 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 NZW 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 immunized twice on D0 and D21 either with 2 antigen-doses (5 µg and 15 µg) 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 (11). In another NHP study with Rhesus macaques (CoV2-04_NHP), using a formulation with an effective S antigen dose of 4 µg or 12 µg with AS03 adjuvant to assess efficacy against SARS-CoV-2 viral challenge was performed. In addition, the ability of the vaccine to elicit cross-neutralizing Abs against Alpha (B.1.1.7), Beta (B.1.351), Gamma (B.1.1.28 or P.1), Delta (B.1.617.2), and Epsilon (B.1.429) SARS-CoV-2 virus variants was evaluated in NHP samples using the lentivirus-based pseudo-neutralization assay.

Two 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) supported the Original Phase II Cohort dose-ranging clinical trial assessing 5 µg, 10 µg, and 15 µg of CoV2 preS dTM vaccine antigen adjuvanted with AS03.

With regards to the emerging virus variants Alpha (B.1.1.7) and Epsilon (B.1.429), no reduction in neutralization Ab titers were observed in the NHP studies with the AS03-adjuvanted CoV2 preS dTM vaccine. However, a significant decrease was observed in the neutralizing Ab titers against the Beta (B.1.351) and Gamma (B.1.1.28 or P.1) variants, with a level of reduction consistent with that described for other vaccines (36). 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*), in which it was found that AS03-adjuvanted vaccine conferred protection against viral replication in the lungs and upper respiratory tract (CoV2-03_Hm).

Nonclinical variant booster studies

Nonclinical studies were performed to document the CoV2 preS dTM-AS03 (D614) and variant vaccine formulations (monovalent B.1.351 and bivalent D614 + B.1.351) when used as a booster 7 months after a primary vaccination with different vaccine platforms (mRNA-primed and subunit-primed). The role of AS03 in potentiating the immune response was also evaluated as it is unknown if the adjuvant will be necessary in a boosting scenario. In addition, the ability of the vaccine to elicit cross-neutralizing antibodies against Alpha (B.1.1.7), Beta (B.1.351), Gamma (B.1.1.28 or P.1), Delta (B.1.617.2), and Epsilon (B.1.429)SARS-CoV-2 virus variants was evaluated in NHP serum samples using the lentivirus-based pseudo-neutralization assay.

In order to address the emergence of variants of concern, vaccine encoding the Beta (B.1.351) variant was developed and the immunogenicity of a monovalent vaccine based on the B.1.351 Spike and a bivalent vaccine (D614 + B.1.351) was evaluated. A third immunization (booster) with monovalent (D614), monovalent (B.1.351) or bivalent (D614 + B.1.351) formulations, 7 months after a priming immunization with messenger ribonucleic acid (mRNA) or subunit vaccine, adjuvanted with AS03, was also evaluated (CoV2-07_NHP and CoV2-08_NHP). In order to address the risk of lower vaccine efficacy due to variants of concerns, vaccines containing the variant CoV2 preS dTM antigen (B.1.351) as a monovalent or bivalent (D614 + B.1.351) formulation were evaluated for immunogenicity and efficacy in a primary series given to naïve animals, and as a late booster given to NHPs previously vaccinated with subunit or mRNA COVID-19 vaccine candidates.

Booster immunization was evaluated in cynomolgus macaques previously immunized with COVID-19 mRNA-LNP candidates developed by Sanofi Pasteur (CoV2-07_NHP) and in Rhesus macaques previously immunized with CoV2 preS dTM-AS03 vaccine (CoV2-08_NHP) (37).

In the CoV2-07_NHP study, Mauritian cynomolgus macaques were immunized with mRNA vaccine candidates corresponding to various full-length spike constructs 7 months before the booster vaccination. The animals were randomized into 4 groups of 4 macaques based on their baseline characteristics, including their neutralizing responses measured 1 month before the booster vaccination. Macaques from group 1 were boosted with 5µg of non-adjuvanted CoV2 preS dTM (B.1.351), group 2 with 5µg of AS03-adjuvanted CoV2 preS dTM (D614), group 3 with 5µg AS03-adjuvanted CoV2 preS dTM (B.1.351) and group 4 with 5µg AS03-adjuvanted CoV2 preS dTM (D614 + B.1.351).

In the CoV2-08_NHP study, Indian Rhesus macaques were immunized with CoV2 preS dTM-AS03 (Phase I/II or intermediate Phase III manufacturing process) 7 months before the booster vaccination. Prior to the booster, animals were randomized into 5 groups of 4 to 5 macaques based on their baseline characteristics, including their neutralizing responses measured 1 month before the booster vaccination. The animals from group 1 were vaccinated with 5µg of non-adjuvanted CoV2 preS dTM (B.1.351), group 2 with 5µg of AS03-adjuvanted CoV2 preS dTM (D614), group 3 with 5µg AS03-adjuvanted CoV2 preS dTM (B.1.351), group 4 with 5µg AS03-adjuvanted CoV2 preS dTM (D614 + B.1.351) and group 5 with 10µg AS03-adjuvanted CoV2 preS dTM (D614 + B.1.351).

Blood samples were collected weekly after the booster vaccination up to D28 for S-binding IgG and neutralizing antibody titers on SARS-CoV-2 parental (D614) and variant strains (Alpha, Beta, Gamma, and Delta).

The nonclinical studies showed that the bivalent CoV2 preS dTM-AS03 (D614 + B.1.351) induced strong neutralizing antibody responses against the 4 variants of concern known to date: Alpha (B.1.1.7), Beta (B.1.351), Delta (B.1.617.2), and Gamma (B.1.1.28 or P.1) in naïve macaques. The benefit of a late 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. The booster vaccine induced very high neutralizing antibodies against the 4 variants of concern and robust neutralization of the distant SARS-CoV-1. Finally, 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 Beta (B.1.351) variant (CoV2-03_Hm).

2.2.2 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. The study objectives were to evaluate the safety and immunogenicity of the 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 of age 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 and were included in the Safety Analysis Set (SafAS) as shown in Table 2.1 below.

Table 2.1: VAT00001 safety analysis set by injection group

Participants 18-49 years of age					
Cohort	**Group**	**Dose-Level***	**Adjuvant**	**N**	
				Sentinel Safety† (N=30)	**Total (N=299)**
Cohort 1: 1 injection	**1**	LD	AF03	6	26
	2	LD	AS03	6	26
	3	HD	AF03	6	24
	4	HD	AS03	6	24
	5	Placebo	None	6	24
Cohort 2: 2 injections	**6**	LD	AF03	N/A	16
	7	LD	AS03	N/A	52
	8	HD	AF03	N/A	17
	9	HD	AS03	N/A	54
	10	HD	None	N/A	18
	11	Placebo	None	N/A	18
Participants 50 years of age and older					
Cohort	**Group**	**Dose-Level***	**Adjuvant**	**N (N=140)**	
Cohort 1: 1 injection	**1**	LD	AF03	10	
	2	LD	AS03	10	
	3	HD	AF03	11	
	4	HD	AS03	10	
	5	Placebo	None	10	
Cohort 2: 2 injections	**6**	LD	AF03	10	
	7	LD	AS03	28	
	8	HD	AF03	9	
	9	HD	AS03	31	
	10	HD	None	N/A‡	
	11	Placebo	None	11	

*Antigen Formulation naming for each dose level: CoV2 preS dTM antigen: LD: low dose target antigen dose 5 µg/effective dose 1.3 µg, HD: high dose with target antigen dose 15 µg/effective dose 2.6 µg

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

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

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 scheduled 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 most frequent injection site reaction in the pooled AS03 group after the second injection was pain (90.2%), and the most frequent solicited systemic reactions were malaise (75.0%), myalgia (75.8%), and headache (66.7%). The frequency of 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. Higher than expected frequency of Grade 3 solicited reactions were observed after the second injection in the adjuvanted groups. All Grade 3 injection site reactions were reported post-injection 2 and the most frequent Grade 3 injection site reaction was erythema, reported in 24% and swelling in 13% of participants in the high dose + AS03 arm. 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. The lower than expected immunogenicity in combination with the higher than expected reactogenicity observed in the Phase I/II study indicates that assessment of optimized antigen formulations (with higher

antigen dose and lower HCP content) is necessary to select a formulation to progress to Phase III evaluation.

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 (38). 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. 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 (39) (40), as well as studies showing that potent RBD-specific monoclonal antibodies can protect against SARS-CoV-2 challenge in macaques (41) (42).

Two COVID-19 mRNA vaccine candidates, BNT162b2 from Pfizer/BioNTech, and mRNA-1273 from Moderna, which induce neutralizing antibody responses show high levels of efficacy against COVID-19 illness and severe disease in their Phase III clinical studies (7) (8).

Thus, there is a growing body of evidence indicating that the induction of antibodies, particularly neutralizing antibodies to the S protein of SARS-CoV-2 may be associated with protection against COVID-19 (10) (21).

However, recent preliminary data have shown a decrease in vaccine efficacy in regions where the B.1.351 variant is prevalent. 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 B.1.351 predominates compared to efficacy in the UK (33) (34) (35). However, data from the Ad26.COV2.S vaccine (J&J/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 most notable against the South African B.1.351 variant which has a E484K mutation in the receptor-binding domain of the 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 B.1.351 convalescent sera compared to cross-neutralization of variants from D614 convalescent sera.

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 Ab 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.

A potential theoretical risk with coronavirus vaccines is the ability to potentiate immunopathology in vaccinees upon exposure to wild-type virus (28), 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.

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 (43). 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 (24). 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). 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 (44). 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 (24). Taken together, these studies and post-licensure data showed that AS03 enhanced antibody and T cell responses and that the corresponding AS03-containing vaccines had a clinically 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 (45) (46). Current data suggest that cases of narcolepsy seen immediately following the 2009/2010 pandemic were the result of an immune cascade, triggered by CD4 T cell cross-reactivity to HA proteins from the H1N1 virus itself and hypocretin. This conclusion is consistent with the position reached by the EMA in 2016 when it concluded that: "*Based on the evidence generated so far, a hypothesis that takes into account the potential role of antigen is more likely to explain the increased risk of narcolepsy observed with Pandemrix than hypotheses that are based on a direct role for the AS03 adjuvant"* (47) (48) (49) (50) (51) (52) (53) (54).

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 adverse events of special interest (AESIs) undergoing special safety monitoring for vaccines containing Adjuvant Systems. pIMDs are a subset of AEs that include

autoimmune diseases and other inflammatory and/or neurological disorders of interest which may or may not have an autoimmune etiology (see Table 10.4 for a full list).

The CoV2 preS dTM-AS03 primary series 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. The booster vaccines may prolong and broaden protection. 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.

The safety and immunogenicity of the candidate vaccine formulations have been established in a recent VAT00002 primary series interim analysis (key results for primary safety up to 21 days after injection 2 and primary and secondary immunogenicity up to 14 days after injection 2). In naïve adults, a high proportion of 2-fold and 4-fold or greater rise in neutralizing antibody titers were observed after 2 injections in both younger and older adults with similar proportions observed across the different antigen dose groups. The magnitude of neutralizing antibody responses was higher in 18 to 59 year old age groups compared to the $\geq$60 year old age group. An increase in titers with an increase in antigen dose was observed in the 18 to 59 year old age group. A single injection did not generate meaningful neutralizing titers above background consistent with previous results in the Phase I/II study.

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. Based on these results, a total dose of $\leq$ 5 µg of S protein antigen was selected to be evaluated as booster vaccine candidates in the Supplemental Cohorts in this study

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 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 (with AS03)		
Anaphylactic reactions	Class-effect for all vaccines (even non-adjuvanted).	Observation period after vaccination for early detection and treatment. Risk management includes exclusion criterion E04 (see Section 5.2). No anaphylactic reactions were observed in the Phase I/II and Phase II studies for the candidate vaccine.
Enhanced COVID-19	A theoretical concern with coronavirus vaccines is VAED. This is the potential (hypothetical) increased disease severity in vaccinees upon exposure to wild-type virus (28). 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 (29) (30) (31).	During the informed consent process, the participants enrolling in the study will be informed of this potential risk. COVID-19 episodes and severity of illness will be monitored with active and passive surveillances for the duration of the study. Data from Phase I/II active and passive case surveillance and data from active surveillance from Phase II shows no severe COVID-19 cases to date and no excess of severe COVID-19 cases in older participants. 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 (10) (21). The adjuvanted formulation is anticipated to further enhance the magnitude of neutralizing antibody responses and induce balanced Th1/Th2 cell responses

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
		(32) (23). Data from NHP studies and interim data from the Phase I/II study show induction of neutralizing Ab titers after 2 doses of antigen + AS03 adjuvant shows no evidence of Th2 bias and consistent INFg responses. Thus, these strategies (antigen design and adjuvant) mitigate by design the theoretical risks of immune enhancement of viral infection. Available data for mRNA COVID-19 vaccines (Moderna, Pfizer) and a COVID-19 vaccine based on viral vector (Janssen) do not indicate a risk of vaccine enhanced disease (7) (8) (55).
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 pIMDs were observed to date during the Phase I/II and Phase II studies for the candidate vaccine.
Refer to CoV2 preS dTM IB Section 5 and Section 6 for more information regarding potential risks.	Refer to the CoV2 preS dTM 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

The benefit of the candidate vaccine formulations at the individual level are largely unknown. Participants may not receive any benefits from participating in this study or receiving the study vaccine. However, 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.

2.3.3 Overall Benefit-Risk Conclusion

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

3 Objectives and Endpoints

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

Table 3.1: Objectives and endpoints

Primary Safety (applicable to Original Phase II Cohort as well as Supplemental Phase III Cohorts)	
To assess the safety profile of all participants in each age group and in each study Intervention Group.	• Presence of unsolicited systemic AEs reported in the 30 minutes after each vaccination • Presence of solicited (pre-listed in the participant's diary card [DC] and [electronic] Case Report Form [CRF]) injection site reactions and systemic reactions occurring up to 7 days after each vaccination • Presence of unsolicited AEs reported up to 21 days after the last vaccination • Presence of serious adverse events (SAEs) throughout the study • Presence of AESIs throughout the study • Presence of MAAEs throughout the study
Primary Immunogenicity-Original Phase II Cohort	
To assess the neutralizing antibody profile 14 days after the last vaccination (D36) in SARS-CoV-2-naïve adults in each study Intervention Group.	Neutralizing antibody titers will be measured in SARS-CoV-2-naïve participants for each study Intervention Group against the D614G variant. • Individual serum neutralizing titer at D01 and D36 • Individual serum neutralization titer fold-rise post-vaccination relative to D01 at D36 • 2-fold-rise and 4-fold-rise in serum neutralization titer [post/pre] (fold-rise ≥ 2 and ≥ 4) at D36 relative to D01 • Responders in SARS-CoV-2 naive, defined as participants who had baseline values below lower limit of quantification (LLOQ) with quantifiable neutralization titer above assay LLOQ at D36
Primary Immunogenicity-Supplemental Cohort 1	
Co-primary objectives: 1) To demonstrate in adults 18-55 years of age and previously vaccinated with the Pfizer/BioNTech vaccine that a booster dose of CoV2 preS dTM-AS03 (D614) vaccine induces an immune response that is non-inferior to the response induced by a two‑dose priming series with the CoV2 preS dTM-AS03 (D614) vaccine in naïve, previously unvaccinated individuals. 2) To demonstrate in adults 18-55 years of age and previously vaccinated with the Pfizer/BioNTech vaccine that a booster dose of CoV2 preS dTM-AS03 (D614) vaccine induces an immune response that is superior to that observed immediately before booster.	Neutralizing antibody titers will be measured for each study Intervention Group against the D614G strain. • Individual serum neutralizing titer at D01 and D15 (Intervention Group) • Individual serum neutralizing titer at D36 (Comparator Group)

Primary Immunogenicity-Supplemental Cohort 2	
Co-primary objectives: 3) To demonstrate in adults 18-55 years of age and previously vaccinated with the Pfizer/BioNTech vaccine that a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine induces an immune response that is non-inferior to the response induced by a two-dose priming series with the CoV2 preS dTM-AS03 (D614) vaccine in naïve, previously unvaccinated individuals. 4) To demonstrate in adults 18-55 years of age and previously vaccinated with the Pfizer/BioNTech vaccine that a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine induces an immune response that is superior to that observed immediately before booster.	• Individual serum neutralizing titer at D01 and D15 against the B.1.351 variant for the CoV2 preS dTM-AS03 (B.1.351) vaccine and the CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine Intervention Groups. • Individual serum neutralizing titer at D01 and D15 against the D614G strain for the CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine Intervention Group. • Individual serum neutralizing titer against the D614G strain at D36 (Comparator Group)
Secondary Immunogenicity-Original Phase II Cohort	
1) To assess the neutralizing antibody profile at D22, D78, D134, D202, D292, and D387 in SARS-CoV-2 naïve adults in each study Intervention Group. 2) To assess the neutralizing antibody profile at D01, D22, D36, D78, D134, D202, D292, and D387 in each study Intervention Group for SARS-CoV-2 non-naïve participants. 3) To assess the binding antibody profile at D01, D22, D36, D78, D134, D202, D292, and D387 in each study Intervention Group in SARS-CoV-2 naïve and non-naïve participants.	Endpoints for secondary immunogenicity objectives #1 and #2: Neutralizing antibody titers will be measured in participants for each study Intervention Group against the D614G variant. • 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 timepoint and participants with baseline values above LLOQ with a 4-fold increase in neutralizing antibody titers at each pre-defined post-vaccination timepoint Endpoints for secondary immunogenicity objective #3: Binding antibody concentrations will be measured in participants for each study Intervention Group against the D614G variant. • 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 (fold-rise 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 pre-defined post-

	vaccination timepoints and participants with baseline values above LLOQ with a 4-fold increase in binding antibody concentration at each pre-defined post-vaccination timepoint
Secondary Immunogenicity-Supplemental Cohort 1	
Conditional secondary objectives: conditional on meeting the primary objectives for Supplemental Cohort 1: 1) To demonstrate, in adults 18-55 years of age, previously vaccinated with the CoV2 preS dTM-AS03 (D614) vaccine, that a booster dose of CoV2 preS dTM-AS03 (D614) vaccine induces an immune response that is noninferior to the response induced by a two-dose priming series with CoV2 preS dTM-AS03 (D614) vaccine in naïve, previously unvaccinated, individuals. 2) To demonstrate, in adults 18-55 years of age, previously vaccinated with CoV2 preS dTM-AS03 (D614) vaccine, that a booster dose of CoV2 preS dTM-AS03 (D614) vaccine induces an immune response that is superior to that observed immediately before booster. Conditional secondary objectives: conditional on meeting the conditional secondary objectives (1) and (2) for Supplemental Cohort 1: 3) To demonstrate in adults 18-55 years of age and previously vaccinated with an mRNA COVID-19 vaccine, that a booster dose of CoV2 preS dTM-AS03 (D614) vaccine induces an immune response that is non-inferior to the response induced by a two-dose priming series with CoV2 preS dTM-AS03 (D614) vaccine in naïve, previously unvaccinated individuals. 4) To demonstrate in adults 18-55 years of age and previously vaccinated with an mRNA COVID-19 vaccine, that a booster dose of CoV2 preS dTM-AS03 (D614) vaccine induces an immune response that is superior to that observed immediately before booster. Conditional secondary objectives: conditional on meeting the conditional secondary objectives (3) and (4) for Supplemental Cohort 1: 5) To demonstrate, in adults 18-55 years of age previously vaccinated with an adenovirus-vectored COVID-19 vaccine, that a booster dose of CoV2 preS dTM-AS03 (D614) vaccine induces an immune response that is non-inferior to the response induced by a two-dose priming series with CoV2 preS dTM-AS03 (D614) vaccine in naïve, previously unvaccinated, individuals.	Endpoints for conditional secondary objectives #1 and #2: • Individual serum neutralizing titer against the D614G strain at D01 and D15 (group primed with CoV2 preS dTM-AS03 [D614] vaccine) • Individual serum neutralizing titer against the D614G strain at D36 (Comparator Group) Endpoints for conditional secondary objectives #3 and #4: • Individual serum neutralizing titer against the D614G strain at D01 and D15 (groups primed with mRNA COVID-19 vaccines) • Individual serum neutralizing titer against the D614G strain at D36 (Comparator Group) Endpoints for conditional secondary objectives #5 and #6: • Individual serum neutralizing titer against the D614G strain at D01 and D15 (group primed with adenovirus-vectored COVID-19 vaccine) • Individual serum neutralizing titer against the D614G strain at D36 (Comparator Group) Endpoints for secondary objectives #7 - #10: • Seroresponse rate, defined as a 4-fold or greater rise in serum neutralization titer [post/pre] against the D614G strain, at D15 relative to D01, in each study Intervention Group • Seroresponse rate, defined as a 4-fold or greater rise in serum neutralization titer [post/pre] against the D614G strain, at D36 relative to D01 (Comparator Group) Endpoints for secondary objectives #11 - #14: • Individual serum neutralizing titer at D01 and D15 against the D614G strain in each Intervention Group • Individual serum neutralization titer fold-rise post-vaccination relative to D01 at D15 against the D614G strain in each Intervention Group • ≥ 2-fold-rise and ≥ 4-fold-rise in serum neutralization titer [post/pre] (fold-rise ≥ 2 and ≥ 4) at D15 relative to D01 against the D614G strain in each study Intervention Group • Seroresponse rate, defined as a 4-fold or greater rise in serum neutralization titer [post/pre] at D15 relative to D01, against the D614G strain in each study Intervention Group Endpoints for secondary objective #15: • Individual serum neutralizing titer at D01 and D15 to the B.1.351 variant in each Intervention Group • Individual serum neutralizing titer at D01 and D36 to B.1.351 variant in the Comparator Group

6) To demonstrate, in adults 18-55 years of age previously vaccinated with adenovirus-vectored COVID-19 vaccines, that a booster dose of CoV2 preS dTM-AS03 (D614) vaccine induces an immune response that is superior to that observed immediately before booster. Conditional secondary objective: conditional on meeting the conditional secondary objectives (5) and (6) for Supplemental Cohort 1, the following objectives will be sequentially tested: 7) To demonstrate in adults 18-55 years of age and previously vaccinated with the Pfizer/BioNTech vaccine that a booster dose of CoV2 preS dTM-AS03 (D614) vaccine induces a seroresponse that is non-inferior to the seroresponse induced by a two‑dose priming series with the CoV2 preS dTM-AS03 (D614) vaccine in naïve, previously unvaccinated individuals. 8) To demonstrate, in adults 18-55 years of age previously vaccinated with the CoV2 preS dTM-AS03 (D614) vaccine, that a booster dose of CoV2 preS dTM-AS03 (D614) vaccine induces a seroresponse that is noninferior to the seroresponse induced by a two-dose priming series with CoV2 preS dTM-AS03 (D614) vaccine in naïve, previously unvaccinated, individuals. 9) To demonstrate in adults 18-55 years of age and previously vaccinated with an mRNA COVID-19 vaccine, that a booster dose of CoV2 preS dTM-AS03 (D614) vaccine induces a seroresponse that is non-inferior to the seroresponse induced by a two-dose priming series with CoV2 preS dTM-AS03 (D614) vaccine in naïve, previously unvaccinated individuals. 10) To demonstrate, in adults 18-55 years of age previously vaccinated with an adenovirus-vectored COVID-19 vaccine, that a booster dose of CoV2 preS dTM-AS03 (D614) vaccine induces a seroresponse that is noninferior to the seroresponse induced by a two-dose priming series with CoV2 preS dTM-AS03 (D614) vaccine in naïve, previously unvaccinated, individuals. Secondary objectives: 11) To describe, in adults 18-55 years of age previously vaccinated with the Moderna vaccine, the immune response to a booster dose of CoV2 preS dTM-AS03 (D614) vaccine. 12) To describe, in adults 18-55 years of age previously vaccinated with the	Endpoints for secondary objective #16: • Individual serum neutralizing titer at D01 and D15 to the B.1.351 variant in each Intervention Group • Individual serum neutralizing titer at D01 and D36 against the D614G strain in the Comparator Group Endpoints for secondary objective #17: • Individual serum neutralizing titer to the D614G strain and B.1.351 variant in each Intervention Group at each pre-defined timepoint • Individual serum neutralization titer fold-rise post-vaccination to the D614G strain and B.1.351 variant at each pre-defined timepoint relative to D01 in each Intervention Group • ≥ 2-fold-rise and ≥ 4-fold-rise in serum neutralization titer [post/pre] (fold-rise ≥ 2 and ≥ 4) to the D614G strain and B.1.351 variant at each pre-defined timepoint relative to D01 in each study Intervention Group Endpoints for secondary objective #18: • Individual serum neutralizing titer at D01 and D15 against the D614G strain in each Intervention Group • Individual serum neutralization titer fold-rise post-vaccination relative to D01 at D15 against the D614G strain in each Intervention Group • ≥ 2-fold-rise and ≥ 4-fold-rise in serum neutralization titer [post/pre] (fold-rise ≥ 2 and ≥ 4) at D15 relative to D01 against the D614G strain in each study Intervention Group • Seroresponse rate, defined as a 4-fold or greater rise in serum neutralization titer [post/pre] at D15 relative to D01, against the D614G strain in each study Intervention Group • Individual serum neutralizing titer at D01 and D15 profile to the B.1.351 variant in each Intervention Group • Individual serum neutralization titer fold-rise post-vaccination relative to D01 at D15 profile to the B.1.351 variant in each Intervention Group • ≥ 2-fold-rise and ≥ 4-fold-rise in serum neutralization titer [post/pre] (fold-rise ≥ 2 and ≥ 4) at D15 relative to D01 profile to the B.1.351 variant in each study Intervention Group • Seroresponse rate, defined as a 4-fold or greater rise in serum neutralization titer [post/pre] at D15 relative to D01, profile to the B.1.351 variant in each study Intervention Group Endpoints for secondary objective #19: • 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 (fold-rise in antibody concentration [post/pre] ≥ 2 and ≥ 4) at each pre-defined post-vaccination time point relative to D01

Oxford/AstraZeneca vaccine, the immune response to a booster dose of CoV2 preS dTM-AS03 (D614) vaccine. 13) To describe, in adults 18-55 years of age previously vaccinated with the J&J/Janssen vaccine, the immune response to a booster dose of CoV2 preS dTM-AS03 (D614) vaccine. 14) To describe, in adults 18-55 years of age previously vaccinated with any COVID-19 vaccine, the immune response to a booster dose of CoV2 preS dTM-AS03 (D614) vaccine. 15) To compare the neutralizing antibody profile to the B.1.351 variant at D01 and D15 in the booster groups and at D36 in the Comparator group. 16) To compare the neutralizing antibody profile to the B.1.351 variant at D01 and D15 in the booster groups and neutralizing antibody profile to the D614G strain at D36 in the Comparator Group. 17) To assess the neutralizing antibody profile to the D614G strain and to the B.1.351 variant at D29, D91, D181, and D366 overall, and by age group, by priming platform, and by priming vaccine. 18) To describe the neutralizing antibody profile to the B.1.351 variant and to the D614G strain at D01 and D15 in adults older than 55 years of age in the booster group, overall, by priming platform, and by priming vaccine. 19) To assess the binding antibody profile at D01, D15, D29, D91, D181, and D366 after booster immunization in adults previously vaccinated with COVID-19 vaccines, overall and by age group, by priming platform, and by priming vaccine.	• Responders, defined as participants who had baseline values below LLOQ with quantifiable antibody concentration above assay LLOQ at pre-defined post-vaccination timepoints and participants with baseline values above LLOQ with a 4-fold increase in binding antibody concentration at each pre-defined post-vaccination timepoint
Secondary Immunogenicity-Supplemental Cohort 2	
<u>Conditional co-secondary objectives: conditional on meeting the primary immunogenicity objectives for Supplemental Cohort 2</u>: 1) To demonstrate in adults 18-55 years of age and previously vaccinated with an mRNA COVID-19 vaccine, that a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine induces an immune response that is non-inferior to the response induced by a two-dose priming series with CoV2 preS dTM-AS03 (D614) vaccine in naïve, previously unvaccinated individuals. 2) To demonstrate in adults 18-55 years of age and previously vaccinated with an mRNA COVID-19 vaccine, that a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351)	<u>Endpoints for conditional secondary objectives #1 and #2:</u> • Individual serum neutralizing titer at D01 and D15 against the B.1.351 variant for the CoV2 preS dTM-AS03 (B.1.351) vaccine and the CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine Intervention Groups. • Individual serum neutralizing titer at D01 and D15 against the D614G strain for the CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine Intervention Group. • Individual serum neutralizing titer against the D614 strain at D36 (Comparator Group) <u>Endpoints for conditional secondary objectives #3:</u> • Individual serum neutralizing titer at D15 against the B.1.351 variant for the CoV2 preS dTM-AS03 (B.1.351) vaccine and the CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine Intervention Groups • Individual serum neutralizing titer at D36 against the B.1.351 variant for the Comparator Group

vaccine induces an immune response that is superior to that observed immediately before booster. Conditional secondary objective: conditional on meeting the primary immunogenicity objectives (1) and (2) and the co-secondary objectives for Supplemental Cohort 2: 3) To demonstrate in adults 18-55 years of age and previously vaccinated with the Pfizer/BioNTech vaccine, that a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine induces an immune response against the B.1.351 variant at D15 that is superior to that against the B.1.351 variant at D36 in the Comparator Group. Conditional secondary objectives: conditional on meeting the conditional secondary objective (3) for Supplemental Cohort 2, the following objectives will be sequentially tested: 4) To demonstrate in adults 18-55 years of age and previously vaccinated with the Pfizer/BioNTech vaccine that a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine induces a seroresponse that is non-inferior to the seroresponse induced by a two-dose priming series with the CoV2 preS dTM-AS03 (D614) vaccine in naïve, previously unvaccinated individuals. 5) To demonstrate in adults 18-55 years of age and previously vaccinated with an mRNA COVID-19 vaccine, that a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine induces a seroresponse that is non-inferior to the seroresponse induced by a two-dose priming series with CoV2 preS dTM-AS03 (D614) vaccine in naïve, previously unvaccinated individuals. Secondary objectives: 6) To describe, in adults 18-55 years of age and previously vaccinated with an adenovirus-vectored COVID-19 vaccine, the immune response to a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine compared to the response induced by a two dose priming series with CoV2 preS dTM-AS03 (D614) vaccine in naïve, previously unvaccinated individuals. 7) To describe, in adults 18-55 years of age and previously vaccinated with an adenovirus-	Endpoints for secondary objectives #4 - #5: • Seroresponse rate, defined as a 4-fold or greater rise in serum neutralization titer [post/pre] at D15 relative to D01, against the B.1.351 variant for the CoV2 preS dTM-AS03 (B.1.351) vaccine and the CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine Intervention Groups • Seroresponse rate, defined as a 4-fold or greater rise in serum neutralization titer [post/pre] at D15 relative to D01, against the D614G strain for the CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine Intervention Group • Seroresponse rate, defined as a 4-fold or greater rise in serum neutralization titer [post/pre] against the D614G strain at D36 relative to D01 (Comparator Group) Endpoints for secondary objectives #6 - #11: • Individual serum neutralizing titer at D01 and D15 against the D614G strain and to the B.1.351 variant in each Intervention Group • Individual serum neutralization titer fold-rise post-vaccination relative to D01 at D15 against the D614G strain and to the B.1.351 variant in each Intervention Group • ≥ 2-fold-rise and ≥ 4-fold-rise in serum neutralization titer [post/pre] (fold-rise ≥ 2 and ≥ 4) at D15 relative to D01 against the D614G strain and to the B.1.351 variant in each study Intervention Group • Seroresponse rate, defined as a 4-fold or greater rise in serum neutralization titer [post/pre] at D15 relative to D01, against the D614G strain and to the B.1.351 variant in each study Intervention Group Endpoints for secondary objective #12: • Individual serum neutralizing titer at D01 and D15 to the B.1.351 variant in each Intervention Group • Individual serum neutralizing titer at D01 and D36 to the B.1.351 variant in the Comparator Group Endpoints for secondary objective #13: • Individual serum neutralizing titer at D01 and D15 against the D614G strain in each Intervention Group • Individual serum neutralizing titer at D01 and D36 against the D614G strain in the Comparator Group Endpoints for secondary objective #14: • Individual serum neutralizing titer at D01 and D15 against the D614G strain in each Intervention Group • Individual serum neutralization titer fold-rise post-vaccination relative to D01 at D15 against the D614G strain in each Intervention Group • ≥ 2-fold-rise and ≥ 4-fold-rise in serum neutralization titer [post/pre] (fold-rise ≥ 2 and ≥ 4) at D15 relative to D01 against the D614G strain in each study Intervention Group • Seroresponse rate, defined as a 4-fold or greater rise in serum neutralization titer [post/pre] at D15 relative to

vectored COVID-19 vaccine, the immune response to a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine compared to that observed immediately before booster. 8) To describe, in adults 18-55 years of age previously vaccinated with the Moderna vaccine, the immune response to a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine. 9) To describe, in adults 18-55 years of age previously vaccinated with the Oxford/AstraZeneca vaccine, the immune response to a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine. 10) To describe, in adults 18-55 years of age previously vaccinated with the J&J/Janssen vaccine, the immune response to a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine. 11) To describe, in adults 18-55 years previously vaccinated with any COVID-19 vaccine, the immune response a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine. 12) To compare the neutralizing antibody profile to the B.1.351 variant at D15 in each study Intervention Group and D36 in the Comparator Group, overall, by priming platform, and by priming vaccine. 13) To compare the neutralizing antibody profile against the D614G strain at D15 following a booster dose of CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine and at D36 in the Comparator Group. 14) To describe, among adults previously primed with CoV2 preS dTM-AS03 (D614) vaccine, the immune response induced by a booster dose of CoV2 preS dTM-AS03 (D614) vaccine or CoV2 preS dTM-AS03 (B.1.351) vaccine or CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine, overall, by priming dose, and by age. 15) To assess the neutralizing antibody profile to the D614G strain at D29, D91, D181, and D366 in each study Intervention Group, overall, by age group, by priming platform, and by priming vaccine. 16) To assess the neutralizing antibody to the B.1.351 variant at D29, D91, D181, and D366 in each study Intervention Group, overall, by age group, by priming platform, and by priming vaccine.	D01, against the D614G strain in each study Intervention Group • Individual serum neutralizing titer at D01 and D15 profile to the B.1.351 variant in each Intervention Group • Individual serum neutralization titer fold-rise post-vaccination relative to D01 at D15 profile to the B.1.351 variant in each Intervention Group • ≥ 2-fold-rise and ≥ 4-fold-rise in serum neutralization titer [post/pre] (fold-rise ≥ 2 and ≥ 4) at D15 relative to D01 profile to the B.1.351 variant in each study Intervention Group • Seroresponse rate, defined as a 4-fold or greater rise in serum neutralization titer [pre/post] at D15 relative to D01, profile to the B.1.351 variant in each study Intervention Group <u>Endpoints for secondary objectives #15 and #16: neutralizing responses to be evaluated against the D614G strain and to the B.1.351 variant</u> • Individual serum neutralizing titers in each Intervention Group at each pre-defined timepoint • Individual serum neutralization titer fold-rise post-vaccination at each pre-defined timepoint relative to D01 in each Intervention Group • ≥ 2-fold-rise and ≥ 4-fold-rise in serum neutralization titer [post/pre] (fold-rise ≥ 2 and ≥ 4) at each pre-defined timepoint relative to D01 in each study Intervention Group <u>Endpoints for secondary objective #17:</u> • Individual serum neutralizing titer at D01 and D15 against the D614G strain in each Intervention Group • Individual serum neutralization titer fold-rise post-vaccination relative to D01 at D15 against the D614G strain in each Intervention Group • ≥ 2-fold-rise and ≥ 4-fold-rise in serum neutralization titer [post/pre] (fold-rise ≥ 2 and ≥ 4) at D15 relative to D01 against the D614G strain in each study Intervention Group • Seroresponse rate, defined as a 4-fold-or greater rise in serum neutralization titer [pre/post] at D15 relative to D01, against the D614G strain in each study Intervention Group • Individual serum neutralizing titer at D01 and D15 profile to the B.1.351 variant in each Intervention Group • Individual serum neutralization titer fold-rise post-vaccination relative to D01 at D15 profile to the B.1.351 variant in each Intervention Group • ≥ 2-fold-rise and ≥ 4-fold-rise in serum neutralization titer [post/pre] (fold-rise ≥ 2 and ≥ 4) at D15 relative to D01 profile to the B.1.351 variant in each study Intervention Group • Seroresponse rate, defined as a 4-fold-or greater rise in serum neutralization titer [pre/post] at D15 relative to

17) To describe, in adults over 55 years of age, the neutralizing antibody profile to the B.1.351 variant and to the D614G strain at D01 and D15 by Intervention Group, overall, by priming platform, and by priming vaccine. 18) To describe in adults previously vaccinated with the Pfizer/BioNTech vaccine the immune response (as assessed by pseudovirus neutralization assay geometric mean titers and geometric mean titer ratios) to a booster dose of CoV2 preS dTM-AS03 (B.1.351) vaccine exploratory formulations, overall and by age stratum. 19) To assess the binding antibody profile at D01, D15, D29, D91, D181, and D366 after booster immunization in adults previously vaccinated with COVID-19 vaccines, overall and by age group, by priming platform, and by priming vaccine.	D01, profile to the B.1.351 variant in each study Intervention Group <u>Endpoints for secondary objective #18:</u> • Individual serum neutralizing titer at D01 and D15 against the D614G strain in each Intervention Group • Individual serum neutralization titer fold-rise post-vaccination relative to D01 at D15 against the D614G strain in each Intervention Group • ≥ 2-fold-rise and ≥ 4-fold-rise in serum neutralization titer [post/pre] (fold-rise ≥ 2 and ≥ 4) at D15 relative to D01 against the D614G strain in each study Intervention Group • Seroresponse rate, defined as a 4-fold-or greater rise in serum neutralization titer [pre/post] at D15 relative to D01, against the D614G strain in each study Intervention Group • Individual serum neutralizing titer at D01 and D15 profile to the B.1.351 variant in each Intervention Group • Individual serum neutralization titer fold-rise post-vaccination relative to D01 at D15 profile to the B.1.351 variant in each Intervention Group • ≥ 2-fold-rise and ≥ 4-fold-rise in serum neutralization titer [post/pre] (fold-rise ≥ 2 and ≥ 4) at D15 relative to D01 profile to the B.1.351 variant in each study Intervention Group • Seroresponse rate, defined as a 4-fold or greater rise in serum neutralization titer [pre/post] at D15 relative to D01, profile to the B.1.351 variant in each study Intervention Group <u>Endpoints for secondary objective #19:</u> • 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 (fold-rise 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 pre-defined post-vaccination timepoints and participants with baseline values above LLOQ with a 4-fold increase in binding antibody concentration at each pre-defined post-vaccination timepoint

Secondary Safety-Original Phase II Cohort	
1) To describe the occurrences of laboratory-confirmed symptomatic COVID-19 in all participants in each study Intervention Group. 2) To describe the occurrences of serologically-confirmed SARS-CoV-2 infection in each study Intervention Group.	Endpoints for secondary safety objective #1: • Occurrences of laboratory-confirmed symptomatic COVID-19 (based on locally-confirmed or protocol-defined NAAT) • Occurrences of symptomatic COVID-19 episodes associated with hospitalization. • Occurrences of severe symptomatic COVID-19 • Death associated with symptomatic COVID-19 Endpoints for secondary safety objective #2: • Occurrences of serologically-confirmed SARS-CoV-2 infection
Secondary Safety-Supplemental Cohorts 1 and 2	
To describe the occurrences of laboratory-confirmed symptomatic COVID-19, overall and in each study Intervention Group	• Occurrences of laboratory-confirmed symptomatic COVID-19 (based on locally-confirmed or protocol-defined NAAT) • Occurrences of symptomatic COVID-19 episodes associated with hospitalization. • Occurrences of severe symptomatic COVID-19 • Death associated with symptomatic COVID-19
Exploratory Immunogenicity-Original Phase II Cohort	
1) To describe the ratio between neutralizing antibodies and binding antibodies. 2) To assess the T-cell cytokine profile at D01, D22 and D36 in a subset of participants. 3) To further assess the cellular immune response at D01, D22, D36, D134 and D387 in a subset of participants. 4) To assess the mucosal antibody response at D01, D22, D36, and D134 in a subset of participants. 5) To describe the neutralizing antibody response to emergent SARS-CoV-2 variant strains	Endpoint for exploratory immunogenicity objective #1: • Ratio between binding antibody (enzyme-linked immunosorbent assay [ELISA]) concentration and neutralizing antibody titer Endpoint for exploratory immunogenicity objective #2: • T-helper cell (Th)1 and Th2 cytokines measured in whole blood following stimulation with full-length S protein at D01, D22 and D36. Endpoint for exploratory immunogenicity objective #3: • Other cellular-mediated immunity (CMI) assessments may be performed by Intracellular Cytokine Staining or/and enzyme-linked immunospot (ELISpot) assays. Endpoints for mucosal antibody responses (objective #4) will be specified in a supplemental analysis plan. Endpoints for exploratory immunogenicity objective #5: • Neutralizing antibody responses to emergent variant strains will be measured in participants for each study Intervention Group: • 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 timepoint and participants with baseline values above

	LLOQ with a 4-fold increase in neutralizing antibody titers at each pre-defined post-vaccination timepoint
Exploratory Immunogenicity-Supplemental Cohorts	
Supplemental Cohorts 1 and 2: 1) To describe the neutralizing antibody response to emergent SARS-CoV-2 variant strains 2) To further describe humoral immune responses based on relevant emerging assays, if applicable Supplemental Cohort 2: 3) To assess the cellular immune response at D01, D15, D29, D91, and D366 in a subset of participants. 4) To assess the mucosal antibody response at D01, D15, and D91 in a subset of participants. 5) To describe the neutralizing antibody response to emergent SARS-CoV-2 variant strains 6) To further describe humoral immune responses based on relevant emerging assays, if applicable Supplemental Cohorts 1 and 2: 7) To describe the neutralizing antibody response, by presence or absence of baseline high-risk medical conditions	Endpoints for exploratory immunogenicity objective #1 and #5: Neutralizing antibody responses to emergent variant strains will be measured: • 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] 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 Endpoint for exploratory immunogenicity objective #2 and #6: • Biomarker measurement at baseline and/or post-vaccination visits Endpoint for exploratory immunogenicity objective #3: • Other CMI assessments may be performed by Intracellular Cytokine Staining or/and enzyme-linked immunospot (ELISpot) assays. Endpoint for mucosal antibody responses (objective #4) will be specified in a supplemental analysis plan Endpoints for exploratory immunogenicity objective #7: Neutralizing antibody responses to D614G and B.1.351 strains will be measured: • 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] 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

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
Phase	II/III
Control method (for Supplemental Phase III Cohorts only)	active comparator (comparator = CoV2 preS dTM-AS03 [D614] administered as a 2-injection primary series)
Study population	Adults 18 years of age and older
Level and method of blinding	**Original Phase II Cohort:** Modified double-blind (observer-blind) • 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 **Supplemental Phase III Cohorts:** • Supplemental Cohorts Comparator Group will be open-label. • Supplemental Cohort 1 Booster Group will be open-label. • Supplemental Cohort 2 will involve sequential randomization to main arms (CoV2 preS dTM-AS03 [D614], CoV2 preS dTM-AS03 [B.1.351], and CoV2 preS dTM-AS03 [D614 + B.1.351]) followed by randomization to exploratory CoV2 preS dTM-AS03 (B.1.351) arms after filling the former. Intervention and exploratory groups will be modified double-blind (observer-blinded) as described
Study intervention assignment method	Participants will be screened for eligibility criteria at the time of inclusion. **Original Phase II Cohort:** The randomization was stratified by age groups (18-59 years of age and 60 years of age and older), baseline SARS-CoV-2 rapid serodiagnostic test positivity (Positive/Negative), and high-risk medical conditions

	(Yes/No). Eligible participants were randomly assigned to one of 3 study groups in a 1:1:1 ratio, corresponding to one of 3 formulations of CoV2 preS dTM-AS03 vaccine (with different antigen doses). **Supplemental Phase III Cohorts:** • Supplemental Cohort 1: previously-vaccinated participants will be stratified based on the priming vaccine received 4 to ≤ 10 months prior and by age group (18-55 years of age and 56 years of age and older) and will receive a single booster dose of CoV2 preS dTM-AS03 (D614). • Supplemental Cohort 2, Main Arms: participants previously vaccinated with an mRNA or adenovirus-vectored COVID-19 vaccine will be stratified based on the vaccine received 4 to ≤ 10 months prior and by age group (18-55 years of age and 56 years of age and older) and randomly assigned to 1 of the following booster formulations in a 1:1 ratio: o CoV2 preS dTM-AS03 (B.1.351) o CoV2 preS dTM-AS03 (D614 + B.1.351) Participants previously vaccinated 4 to ≤ 10 months prior with the protein-based vaccine in the Original Phase II Cohort will be stratified by age group (18-55 years of age and 56 years of age and older) and randomly assigned to 1 of the following booster formulations in a 9:1 ratio (D614:B.1.351) for younger adults and a 1:1 ratio for older adults: o CoV2 preS dTM-AS03 (D614) o CoV2 preS dTM-AS03 (B.1.351) • Supplemental Cohort 2 Exploratory B.1.351 Arms: participants previously vaccinated with the Pfizer/BioNTech mRNA vaccine will be enrolled after completion of enrollment of the above booster arms in Cohort 2 and will be stratified by age group (18-55 years of age and 56 years of age and older) and randomly assigned to receive 1 of the following CoV2 preS dTM (B.1.351) formulations in a 1:1:1:1 ratio: o 2.5 µg antigen with AS03 adjuvant o 2.5 µg antigen with half-dose[a] AS03 adjuvant

[a] The half dose of AS03 and the full dose of AS03 contain amounts of tocopherol of 5.93 mg and 11.86 mg, respectively

	○ 5 µg antigen with half-dose AS03 adjuvant ○ 5 µg antigen with no adjuvant • Supplemental Cohorts Comparator Group: SARS-CoV-2-naïve, unvaccinated, adults who are 18-55 years of age will be given CoV2 preS dTM-AS03 (D614) as a primary series vaccination of 2 injections given 21 days apart. • Supplemental Cohort Subsets and Assessment of Immunogenicity to Emerging Variants of Concern: A randomized subset of 70 participants in Cohort 1 will be tested for additional SARS-CoV-2 variants of concern including Delta. No additional sample collection, procedures, or visits are required for this subset. A randomized subset of 82 participants in Cohort 2 comprised of younger adults (18 to 55 years of age) will provide samples for cellular immune response and mucosal antibody assessments and will also be tested for additional variants of concern including Delta.
Number of participants	**Original Phase II Cohort:** A total of 720 participants are planned to be enrolled. After stratification by age-group (18-59 years and ≥ 60 years), baseline SARS-CoV-2 rapid serodiagnostic test positivity (Positive/Negative [as determined at the time of enrollment]) and high-risk medical conditions (Yes/No), participants will be randomly assigned to the study groups. For all study arms, half of the participants will be 18-59 years of age and half of the participants will be 60 years or older. Additionally, up to 20% of participants in each group may be test-positive on the rapid serodiagnostic test at enrollment. A randomized subset of 112 (40 participants/group) participants will provide samples for cellular immune response and mucosal antibody assessments. See Table 4.2. **Supplemental Phase III Cohorts:** A total of 3660 participants are planned to be enrolled and will be stratified as follows: **Supplemental Cohort 1:** Adults vaccinated 4 to ≤ 10 months prior will be stratified by primary vaccine and by age to receive a single booster dose of CoV2 preS dTM-AS03 (D614): • Primed with Pfizer/BioNTech: ○ 18-55 years of age: 215 participants

	○ 56 years of age and older: 50 participants • Primed with Moderna: ○ 18-55 years of age: 75 participants ○ 56 years of age and older: 25 participants • Primed with Oxford University/AstraZeneca: ○ 18-55 years of age: 75 participants ○ 56 years of age and older: 25 participants • Primed with J&J/Janssen: ○ 18-55 years of age: 75 participants ○ 56 years of age and older: 25 participants **Supplemental Cohort 2, Main Arms:** Adults vaccinated 4 to ≤ 10 months prior will be stratified by primary vaccine and by age and randomized to receive 1 of the following as a single booster dose: • Primed with Pfizer/BioNTech: ○ CoV2 preS dTM-AS03 (B.1.351): ▪ 18-55 years of age: 515 participants ▪ 56 years of age and older: 50 participants ○ CoV2 preS dTM-AS03 (D614 + B.1.351): ▪ 18-55 years of age: 515 participants ▪ 56 years of age and older: 50 participants • Primed with CoV2 preS dTM-AS03 (actual numbers will depend on eligibility and consent for Cohort 2 participation of participants enrolled in the Original Phase II Cohort; numbers below are estimates and subject to change): ○ CoV2 preS dTM-AS03 (D614): ▪ 18-55 years of age: 270 participants ▪ 56 years of age and older: 75 participants ○ CoV2 preS dTM-AS03 (B.1.351): ▪ 18-55 years of age: 30 participants ▪ 56 years of age and older: 75 participants • Primed with Moderna: ○ CoV2 preS dTM-AS03 (B.1.351): ▪ 18-55 years of age: 75 participants ▪ 56 years of age and older: 25 participants ○ CoV2 preS dTM-AS03 (D614 + B.1.351): ▪ 18-55 years of age: 75 participants ▪ 56 years of age and older: 25 participants • Primed with Oxford University/AstraZeneca:

	○ CoV2 preS dTM-AS03 (B.1.351): ▪ 18-55 years of age: 75 participants ▪ 56 years of age and older: 25 participants ○ CoV2 preS dTM-AS03 (D614 + B.1.351): ▪ 18-55 years of age: 75 participants ▪ 56 years of age and older: 25 participants • Primed with J&J/Janssen: ○ CoV2 preS dTM-AS03 (B.1.351): ▪ 18-55 years of age: 75 participants ▪ 56 years of age and older: 25 participants ○ CoV2 preS dTM-AS03 (D614 + B.1.351): ▪ 18-55 years of age: 75 participants ▪ 56 years of age and older: 25 participants **Supplemental Cohort 2 Exploratory B.1.351 Arms:** Adults vaccinated 4 to ≤ 10 months prior with the Pfizer/BioNTech mRNA vaccine will be stratified by age and randomized to receive a single booster dose of 1 of the following CoV2 preS dTM (B.1.351) formulations: • 2.5 µg antigen with full-dose AS03 adjuvant: ○ 18-55 years of age: 75 participants ○ 56 years of age and older: 25 participants • 2.5 µg antigen with half-dose AS03 adjuvant: ○ 18-55 years of age: 75 participants ○ 56 years of age and older: 25 participants • 5 µg antigen with half-dose AS03 adjuvant: ○ 18-55 years of age: 75 participants ○ 56 years of age and older: 25 participants • 5 µg antigen with no adjuvant: ○ 18-55 years of age: 75 participants ○ 56 years of age and older: 25 participants **Supplemental Cohorts Comparator Group**: SARS-CoV-2-naïve, unvaccinated, adults will be enrolled into a parallel, non-randomized arm and receive CoV2 preS dTM-AS03 (D614) as a primary series vaccination of 2 injections given 21 days apart: • 18-55 years of age only: 515 participants **Supplemental Cohorts Subsets and Assessment of Immunogenicity to Emerging Variants of Concern**: A randomized subset of 70 participants in Cohort 1 will be tested for additional SARS-CoV-2 variants of concern

	including Delta. No additional sample collection, procedures, or visits are required for this subset. A randomized subset of 82 participants in Cohort 2 comprised of younger adults (18 to 55 years of age) will provide samples for cellular immune response and mucosal antibody assessments and will also be tested for additional variants of concern including Delta. See Table 4.5
Intervention groups	**Original Phase II Cohort:** Participants will be randomized to receive 2 injections 21 days apart of one of the 3 different doses of CoV2 preS dTM antigen with fixed dose of AS03 adjuvant. **Supplemental Phase III Cohorts:** • Supplemental Cohort 1: Previously-vaccinated participants will be stratified based on the priming vaccine received 4 to ≤ 10 months prior and by age group (18-55 years of age and 56 years of age and older) and will receive a single booster dose of CoV2 preS dTM-AS03 (D614). • Supplemental Cohort 2, Main Arms: Participants previously vaccinated with an authorized/approved mRNA or adenovirus-vectored COVID-19 vaccine will be stratified based on the vaccine received 4 to ≤ 10 months prior and by age group (18-55 years of age and 56 years of age and older) and randomly assigned to 1 of the following booster formulations in a 1:1 ratio: o CoV2 preS dTM-AS03 (B.1.351) o CoV2 preS dTM-AS03 (D614 + B.1.351) Participants previously vaccinated with CoV2 preS dTM-AS03 (D614) as a primary series in the Original Phase II Cohort will be stratified by age group (18-55 years of age and 56 years of age and older) and randomly assigned to 1 of the following booster formulations in a 9:1 ratio (D614:B.1.351) for younger adults and a 1:1 ratio for older adults: o CoV2 preS dTM-AS03 (D614) o CoV2 preS dTM-AS03 (B.1.351) • Supplemental Cohort 2 Exploratory B.1.351 Arms: Participants previously vaccinated with the Pfizer/BioNTech mRNA vaccine will be enrolled after completion of enrollment of the above booster arms in Cohort 2 and will be stratified by age group (18-55 years of age and 56 years of age and older) and

	randomly assigned to receive 1 of the following CoV2 preS dTM (B.1.351) formulations in a 1:1:1:1 ratio: ○ 2.5 µg antigen with AS03 adjuvant ○ 2.5 µg antigen with half-dose[a] AS03 adjuvant ○ 5 µg antigen with half-dose AS03 adjuvant ○ 5 µg antigen with no adjuvant • Supplemental Cohorts Comparator Group: SARS-CoV-2-naïve, unvaccinated, adults who are 18-55 years of age will be given CoV2 preS dTM-AS03 (D614) as a primary series vaccination of 2 injections given 21 days apart. • Supplemental Cohort Subsets and Assessment of Immunogenicity to Emerging Variants of Concern: A randomized subset of 70 participants in Cohort 1 will be tested for additional SARS-CoV-2 variants of concern including Delta. No additional sample collection, procedures, or visits are required for this subset. A randomized subset of 82 participants in Cohort 2 comprised of younger adults (18 to 55 years of age) will provide samples for cellular immune response and mucosal antibody assessments and will also be tested for additional variants of concern including Delta.
Total duration of study participation	**Original Phase II Cohort:** Approximately 365 days post-last injection (ie, approximately 386 days total) **Supplemental Cohorts 1 and 2:** Approximately 365 days post-booster injection (ie, approximately 366 days total) **Supplemental Cohorts Comparator Group:** Approximately 365 days post-injection 2 (ie, approximately 386 days total)
Countries	Primary Series: United States, Honduras Supplemental Cohorts: to be determined (TBD)
Use of an independent Data and Safety Monitoring Board, Dose Escalation Committee, or similar review group	No

Disclosure Statement:

Original Phase II Cohort and Supplemental Cohort 2 Intervention Groups: Participants, outcome assessors, Investigators, laboratory personnel, Sponsor study staff, and those administering the

[a] The half dose of AS03 and the full dose of AS03 contain amounts of tocopherol of 5.93 mg and 11.86 mg, respectively

study intervention if not involved in preparing the study intervention will be blinded to Intervention Group; and those preparing the study interventions will be unblinded to vaccine assignment group.

This does not apply to the Supplemental Cohorts Booster Groups and the Supplemental Cohorts Comparator Group which will be open-label.

4.1.1 Intervention Groups and Duration for the Original Phase II Cohort

Table 4.2: Planned Original Phase II Cohort sample size and approximate size of subsets

		Study Intervention Groups		
		Group 1	**Group 2**	**Group 3**
		CoV2 preS dTM-AS03 (5 µg antigen)	**CoV2 preS dTM-AS03 (10 µg antigen)**	**CoV2 preS dTM-AS03 (15 µg antigen)**
Total Overall		240	240	240
SARS-CoV-2 serodiagnostic test at baseline	**Negative**	At least 192*	At least 192*	At least 192*
	Positive	Up to 48†	Up to 48†	Up to 48†
Age Groups	**Adults (18-59 years)**	120	120	120
	Older adults (≥ 60 years)	120	120	120
Cellular Immunity and Mucosal subset‡		40 (20/age group)	40 (20/age group)	40 (20/age group)

* 96 per age group
† up to 24 per age group
‡ Participants SARS-CoV-2 serodiagnostic test negative at baseline would be randomized to this subset.

All participants in the Original Phase II Cohort were to receive 2 vaccine injections given 3 weeks apart: the first injection will be at D01 (VAC1) and the second injection will be at D22 (VAC2). Blood samples were planned be collected from all participants prior to each injection, 14 days, 2 months, 4 months, 6 months, 9 months, and 12 months after last injection. Blood samples collected from participants will be used for serological assessments in the study. Whole blood, PBMCs, and saliva samples were to be collected from a subset of participants to assess cellular immune responses and mucosal antibody responses.

Reactogenicity was assessed by collecting solicited AEs for 7 days after each vaccination, unsolicited AEs for 21 days after the last vaccination, and SAEs, MAAEs, and AESIs are being assessed for the duration of the study. All participants will be followed for the duration of the study to capture occurrences of COVID-19 through passive surveillance wherein participants will be instructed to contact the site if they experience symptoms/conditions of a COVID-19-like illness at any time during the study. In addition, active surveillance will be undertaken in all participants wherein all participants will be contacted once every 2 weeks starting at the D43 contact to enquire about development of COVID-19-like illness.

The duration of each Original Phase II Cohort participant's participation in the study will be approximately 365 days post-injection 2 (ie, approximately 386 days total).

In the event that the vaccine formulation evaluated in this study is deemed safe and effective by regulatory authorities, this authorized/approved vaccine may be offered to eligible participants in this study who received a formulation considered less effective to that authorized by the regulatory authorities, if permitted by local regulations and in alignment with local recommendations.

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 least until completion of the key follow-up timepoint (D43) for informing progression to Phase III and dose selection.

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 immunogenicity and safety. Participants will continue to be followed for the duration of the study as per scheduled visits and procedures. Participants will be invited to a visit prior to receiving the vaccine and invited to provide a blood sample for immunological assessment. If the visit occurs more than 1 month after the D134 visit, a PBMC sample will also be collected if the participant is in the cellular immunity and mucosal subset instead of the D387 sample. Participants will not receive the second vaccination if they have received the authorized/approved vaccine between the first and second scheduled vaccination.

Interim data from this study will be utilized to inform progression to Phase III and selection of antigen dose. This interim analysis will occur after availability of reactogenicity data up to 21 days post-injection 2 and neutralizing antibody responses at D01 and 14 days post-injection 2 in all participants.

4.1.2 Intervention Groups and Duration for Supplemental Phase III Cohorts

Table 4.3: Planned sample sizes for Supplemental Cohorts 1 and 2

		Cohort 1	Cohort 2 Main Arms			Comparator
		Booster	Booster	Booster	Booster	Primary Series
		CoV2 preS dTM-AS03 (D614)	CoV2 preS dTM-AS03 (B.1.351)	CoV2 preS dTM-AS03 (D614 + B.1.351)	CoV2 preS dTM-AS03 (D614)	CoV2 preS dTM-AS03 (D614)
Total Overall		**565**	**970**	**865**	**345**	**515**
SARS-CoV-2-naïve, Unvaccinated, Adults (18-55 years)		--	--	--	--	515
Pfizer/BioNTech	**Adults (18-55 years)**	215	515	515	--	--
	Older adults (≥ 56 years)	50	50	50	--	--
CoV2 preS dTM-AS03 (Original Phase II Cohort)	**Adults (18-55 years)**	--	30	--	270	--
	Older adults (≥ 56 years)	--	75	--	75	--
Moderna	**Adults (18-55 years)**	75	75	75	--	--
	Older adults (≥ 56 years)	25	25	25	--	--
Oxford University/ AstraZeneca	**Adults (18-55 years)**	75	75	75	--	--
	Older adults (≥ 56 years)	25	25	25	--	--
J&J/Janssen	**Adults (18-55 years)**	75	75	75	--	--
	Older adults (≥ 56 years)	25	25	25	--	--

Table 4.4: Planned sample sizes for Supplemental Cohort 2 Exploratory B.1.351 Arms

		CoV2 preS dTM (B.1.351) Treatment Groups			
		2.5 µg with full-dose AS03	**5 µg with half-dose AS03**	**5 µg with no adjuvant**	**2.5 µg with half-dose AS03**
Total Overall		**100**	**100**	**100**	**100**
Age Groups	**Adults (18-55 years)**	75	75	75	75
	Older adults (≥ 56 years)	25	25	25	25

Supplemental Cohort 1 and Cohort 2 Booster Arms Only: all participants will receive a single booster dose (VAC) at D01. Blood samples will be collected from all participants prior to the booster injection, 14 days, 1 month, 3 months, 6 months, and 12 months after the injection.

Supplemental Cohorts Comparator Group: all participants will receive 2 vaccine injections given 3 weeks apart: the first injection will be at D01 (VAC1) and the second injection will be at D22 (VAC2). Blood samples will be collected from all participants prior to each injection, 14 days, 4 months, 6 months, 9 months, and 12 months after last injection.

Table 4.5: Approximate sample size of Supplemental Cohort subsets for variant testing in CMI/Mucosal/Variant Subset for Cohorts 1 and 2

	Cohort 1*	**Cohort 2***	
	Variant Testing Only	**Participants in the Pfizer/BioNTech Group**	**Participants in the CoV2 preS dTM-AS03 Group (Original Phase II Cohort)**
Total Overall	**70**	**52**	**30**
CoV2 preS dTM-AS03 (D614)	44	--	27
CoV2 preS dTM-AS03 (B.1.351)	--	26	3
CoV2 preS dTM-AS03 (D614 + B.1.351)	--	26	--
Comparator	26	--	--

*All subset participants will be 18-55 years of age only

Supplemental Cohorts Subsets and Assessment of Immunogenicity to Emerging Variants of Concern: A randomized subset of 70 participants in Cohort 1 will be tested for additional SARS-CoV-2 variants of concern including Delta. No additional sample collection, procedures, or visits are required for this subset. A randomized subset of 82 participants in Cohort 2 comprised of younger adults (18 to 55 years of age) will provide samples for cellular immune response and mucosal antibody assessments and will also be tested for additional variants of concern including Delta.

For all cohorts: blood samples collected from all participants will be used for serological assessments in the study. Whole blood, PBMCs, and saliva samples will be collected from a subset of participants in each cohort to assess cellular immune responses and mucosal antibody responses.

Reactogenicity will be assessed by collecting solicited AEs for 7 days after each vaccination, unsolicited AEs for 21 days after the last vaccination, and SAEs, MAAEs, and AESIs for the duration of the study.

All Supplemental Cohort participants will be followed for the duration of the study to capture occurrences of COVID-19 through passive surveillance wherein participants will be instructed to contact the site if they experience symptoms/conditions of a COVID-19-like illness at any time during the study. In addition, active surveillance will be undertaken in all participants wherein all participants will be contacted once every 2 weeks starting after the last injection to enquire about development of COVID-19-like illness.

The duration of participation in the study for each participant will be:

- Supplemental Cohorts 1 and 2: approximately 365 days post-booster injection (ie, approximately 366 days total)
- Supplemental Cohorts Comparator Group: approximately 365 days post-injection 2 (ie, approximately 386 days total)

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 5-15 µg in the study). While clinical and post-marketing experience with proteins manufactured with the baculovirus manufacturing system is specific for influenza proteins, it is relevant to point out that these include different proteins (H1, H3, B Yamagata, B Victoria HAs), with each one changed over time to support the recommended compositions of seasonal influenza vaccines. This provides reassurance about the safety of the protein manufacturing platform, at protein doses higher than planned in this study, and for a variety of different protein constructs.

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 (56). Notably, more than 20 000 older adults received AS03-adjuvanted influenza vaccine in a large, multi-country efficacy study (44). 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 (24). 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 safe and well tolerated and led to robust immune responses.

Nonclinical studies in multiple animal models with the CoV2 preS dTM vaccine with AS03 adjuvant have demonstrated induction of immune responses and protection against viral challenge. The 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. 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).

Rationale for study design

The VAT00001 study evaluated different formulations of the recombinant protein vaccine (antigen concentration and adjuvant) and administration schedules (1 injection versus 2 injections 21 days apart). During characterization studies performed on the final filled clinical materials administered in VAT00001 it was identified that the key polyclonal antibody reagent used for the detection of SARS-CoV-2 S protein also detects some HCPs rendering it inappropriate for use in the purity and HCP release assays. As a result, the purity and HCP values reported for the Phase I/II clinical study materials were inaccurate and the concentration of SARS-CoV-2 S protein within the formulated vaccine product is significantly lower than expected. Following re-calculation of the SARS-CoV-2 S protein, within a 0.5mL vaccine dose, it has been defined that the effective doses administered in VAT00001 are 1.3 µg and 2.6 µg of functional SARS-CoV-2 S protein instead of 5 µg and 15 µg, respectively. 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).

The neutralizing antibody responses observed in the VAT00001 study were lower than expected particularly in the older adults. A dose-response was observed with the high-dose group with AS03 inducing higher levels of neutralizing antibodies than the low-dose group with AS03. 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 of age and older, 62.5% in 60 years of age and older). The magnitude of neutralizing antibody responses was also lower in adults aged 50 years of age and older compared to the younger age group suggesting a need for further dose-optimization with doses higher than the effective high dose of 2.6 µg used in this study. Higher than expected reactogenicity was observed in the study. Specifically, for the high-dose + AS03 arm, the frequency of Grade 3 (severe)

reactions were highest for malaise (17%), followed by myalgia (11%) and headache (7%). Overall, 41% of study participants receiving the high-dose + AS03 formulation in a 2-dose schedule reported Grade 3 reactions. Although these reactions were not deemed serious and were transient and of short duration, a formulation associated with lower reactogenicity is desirable. The current hypothesis proposed to explain the observed high reactogenicity is that it may be related to the HCP content in the administered product when given with an adjuvant in a 2-dose schedule. If this hypothesis is correct, lower content of HCPs in the VAT00002 study product should result in lower reactogenicity.

The lower than expected immunogenicity in combination with the higher than expected reactogenicity observed in the Phase I/II study indicate that that assessment of optimized antigen formulations (with higher antigen dose and lower HCP content) is necessary to select a formulation to progress to Phase III evaluation.

The Original Cohort enrolled in VAT00002 corresponds to Phase II, randomized, modified double-blind, multi-center, dose-finding study to be conducted in adults 18 years of age and older to evaluate the safety, reactogenicity, and immunogenicity of 2 injections of CoV2 preS dTM-AS03 vaccine administered by IM route. In this study, 3 different antigen doses (effective doses of 5 µg, 10 µg, and 15 µg of CoV2 preS dTM monovalent D614 antigen) of the candidate vaccine are being evaluated utilizing a 2-injection schedule, as supported by data from the VAT00001 study, with doses administered 21 days apart. Interim safety, reactogenicity, and immunogenicity data from this Phase II Cohort was used to decide on progression to Phase III and for selecting a dose formulation to progress to Phase III.

As part of an amendment to the original study, Supplemental Phase III Cohorts have been incorporated into the study. 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 late booster.

Justification for the age range and study population

Original Phase II Cohort: The study is being conducted in adults 18 years of age and older with stratification by 2 age groups: 18-59 years of age and 60 years of age and older. Approximately 360 adults 18-59 years of age and 360 adults 60 years of age or older were to be enrolled. The study is designed to ensure that close to 50% of the study population will be 60 years of age and older and stratification of this age-group ensures the benefits of randomization within this age-stratum. 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. Moreover, interim data from the VAT00001 study showed lower levels of response in older adults indicating the need to identify the optimal antigen dose for this older age group. No upper age-range is specified in this study, and participants with medical conditions associated with higher risk of COVID-19 disease (detailed in Section 5.3) were not excluded from this study cohort. Moreover, to ensure evaluation of vaccine performance in high-risk groups, this study cohort allowed enrollment of participants with high-risk medical conditions. This is supported by data generated in NHPs (Section 2.2) indicating evidence of protection against viral replication in the upper and lower respiratory tract and against lung inflammation and pathology with no evidence of vaccine

enhanced disease at effective doses similar to the doses targeted in this study (effective doses of 4 µg and 12 µg of protein were evaluated in such study). The study also indicated robust humoral immune responses and a balanced Th1/Th2 cellular response. Participants with well-controlled human immunodeficiency virus infection were not excluded from this study cohort.

Supplemental Phase III Cohorts: For evaluation of booster and variant responses, in accordance with the FDA's updated Emergency Use Authorization (EUA) guidance for vaccine developers addressing virus variants (57) and the European Medicines Agency's (EMA) reflection paper on the regulatory requirements for vaccines intended to provide protection against variant strain(s) of SARS-CoV-2 (58), the booster and variant priming cohorts will be powered to demonstrate non-inferiority of the vaccine candidates in one age group, adults 18-55 years old, with inclusion of a proportion of older adults (≥ 56 years old) aimed at enabling extrapolation of results.

Justification for modified double-blind (observer-blind) and open-label groups

Original Phase II Cohort: This Cohort corresponds to a modified double blind (observer-blind) study. Designated site staff involved in preparing the vaccine was unblinded because the vaccine formulation was prepared by mixing the recombinant protein and adjuvant at the study site out of sight of the participant. Study staff involved in administering the vaccine may be unblinded 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 remain blinded in order to decrease the risk of potential bias in safety and immunogenicity assessments. Laboratories performing the assays evaluating immunogenicity and efficacy endpoints remain blinded to study intervention.

Supplemental Phase III Cohorts:

- Supplemental Cohort 1 Booster Group will be open-label. This group will be initiated as soon as possible to generate data on the role of a booster with the CoV2 preS dTM-AS03 (D614) vaccine. Given the importance of generating data as early as possible to address both waning of immune responses and the emergence of variants of concern, the Sponsor considers justified to enroll this group in an open-label fashion given that the availability of variant-containing candidates will only occur later.
- Supplemental Cohort 2 Intervention Groups will be blinded to treatment assignment; all participants will receive active vaccine, but the formulation administered will remain blind (observer-blind for the same reasons explained above).

  Supplemental Cohorts Comparator Group: since this group of naïve, unvaccinated individuals overtly differs from the previously vaccinated individuals to be enrolled into the booster arms, it will be an open-label arm recruited in geographic locations having similar population characteristics as the populations recruited in the booster arms.

4.3 Justification for Dose and Dosing Schedule

Original Phase II Cohort

The dose of the recombinant protein and dosing schedule chosen for this study cohort were based on results from nonclinical studies in animal models, manufacturing capacity limitations, and results from the Phase I/II safety and immunogenicity study. 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 (CoV2-04_NHP) 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 informed the desirable dose range to assess in this Phase II study cohort:

- 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 (59).
- 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 (60).
- A stabilized prefusion form of the SARS-CoV-2 S 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 studies (27).
- 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 (61).

Taken together, the available evidence supported the dose levels that are being evaluated in this study cohort (range between 5 µg and 15 µg of S-protein, administered with AS03 in a 2-injection schedule, 21 days apart).

Supplemental Phase III Cohorts

The antigen dose levels utilized in the Supplemental Phase III Cohorts are based on the interim data obtained from the Original Phase II Cohort in this study.

The reactogenicity and safety profile was similar across antigen dose groups and therefore the choice of antigen dose for the priming cohorts (naïve individuals), is consistent with the dose selected for the VAT00008 Phase III efficacy study and is largely informed by 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 of age and older). A pattern of higher neutralizing antibody titers with higher antigen doses was observed in the younger adults age group, a pattern that was not evident in the older age group.

The ratio of neutralizing antibody responses in vaccinees compared to human convalescent sera has 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% (62) (63). This relationship is modeled for neutralizing antibody responses and efficacy against the homologous variants, with the expectation that the predicted vaccine efficacy against heterologous variants will be lower for a similar ratio of vaccine-induced antibody response to human convalescent sera (HCS).

In the Original Phase II Cohort in this protocol the geometric mean titers (GMTs) observed in naïve individuals at D36 in the overall study population were comparable to GMTs observed in a panel of human convalescent sera (GMT 2140; 95% confidence interval [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 naïve adults, the ratio ranged from 0.7 - 0.75 across the 3 dosages. 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 the Beta (B.1.351) and Gamma (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.

These considerations were the basis for selecting a 10 µg dose for the monovalent D614 vaccine to be evaluated in Stage 1 of the Phase III efficacy study. This selection mitigates the risk of having lower titers against variants.

For Stage 2 of the Phase III efficacy study with the CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine, a 5 µg (D614 component) + 5 µg (B.1.351 component) antigen dose (total amount of S antigen of 10 µg) 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.

This rationale underpins selection of a total S antigen dose of 10 µg to be evaluated in all study arms of the Supplemental Phase III Cohorts of the present study in which previously unvaccinated, SARS-CoV-2 naïve individuals will receive a 2-dose primary vaccination series: 10 µg for CoV2 preS dTM-AS03 (B.1.351) vaccine, and 5 µg (D614 Component) + 5 µg (B.1.351 Component) for the CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine, and 10 µg for the CoV2 preS dTM-AS03 (D614) (Comparator) for the Supplemental Cohorts Comparator Group. Importantly, the comparator CoV2 preS dTM-AS03 (D614) antigen dosage is the same as that which will be evaluated in Stage 1 of VAT00008, serving as a bridge back to the formulation and dose for which efficacy will be established.

Antigen dosage selection for the booster groups is informed by data generated in non-naïve individuals in the Original Phase II Cohort of this protocol. As noted in Section 2.3 above across all 3 dose levels, the neutralizing antibody GMTs achieved 21 days following a single dose of the monovalent (D614) CoV2 preS dTM vaccine in non-naïve participants was greater than the peak response at D36 following two doses in naïve participants. These findings informed selection of a single injection of 5 µg of S antigen dose adjuvanted with AS03 in the context of booster immunization. A total S antigen dose of 5 µg will therefore be utilized for each of the booster arms in the Supplemental Phase III Cohorts in this present study: 5 µg for CoV2 preS dTM-AS03 (D614) vaccine in Supplemental Cohorts 1 and 2, 5 µg for CoV2 preS dTM-AS03 (B.1.351) vaccine in Supplemental Cohort 2, and 2.5 µg (D614 Component) + 2.5 µg (B.1.351 Component) for the CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine in Cohort 2. In addition, exploratory groups will evaluate a lower dose of 2.5 µg of monovalent (B.1.351) to investigate potential alternative doses for use in boosting that could be dose-sparing.

At present, there is limited evidence as to the durability of efficacy beyond the 2 to 6 months following the completion of the primary series of vaccines that have received emergency use authorization or conditional approval. While the evidence to define a correlate of risk or correlate of protection is not yet fully matured, modelling shows a strong correlation between efficacy and peak neutralizing antibody titers (62) (63). Furthermore, extensions of such modelling allow for prediction of the effects of waning immunity on efficacy. For mRNA-1273, one authorized COVID-19 vaccine for which post-vaccination functional antibody titers up to a half-year have been published, neutralizing antibody levels against the prototype strain decline by 4- to 7-fold at

6 months from the peak titers achieved post-vaccination (64). Modelling predicts the loss-of-efficacy impact would be magnified against variants with larger reductions in neutralizing activity compared to the prototype strain, thus implying the need for an earlier booster dose. Given these uncertainties, this study will evaluate the administration of booster doses among individuals who received a primary series with an authorized COVID-19 vaccine starting 4 to 10 months previously.

In lieu of clinical booster vaccination data, responses after the first dose of the monovalent CoV2 preS dTM-AS03 (D614) vaccine in participants with evidence of prior SARS-CoV-2 infection (non-naïve participants) serve as a reasonable proxy from which to draw inferences on the utility of a seroresponse co-primary endpoint and success criterion. Below are findings from VAT00002 participants aged 18-59 who received CoV2 preS dTM-AS03 (D614) at a dose of 5 or 10 µg, the primary age group in which the planned booster and variant studies will be performed and the antigen dosages that will be used for the booster and comparator priming arms, respectively. Non-naïve participants had by definition appreciable pre-existing pseudovirus neutralizing antibody titers against S-antigen (D614G)-expressing pseudovirions (Table 4.6). Among 18-59 year-olds that received 5 and 10 µg of CoV2 preS dTM (D614), seroconversion rates post-dose 1 (D22) amongst the non-naïve participants were -10% to -18% lower (≥ 2-fold seroconversion) and -18% to -20% (≥ 2-fold seroconversion) lower than the corresponding seroconversion rates post-dose 2 in naïve participants. This is not unexpected, given that in the context of pre-existing responses a proportion of booster recipients will not reach a given level of seroresponse, while naïve individuals that have no pre-existing responses are anticipated to mount seroresponses at very high frequencies (close to 100%). At the same time, in the corresponding age and dose groups, clinically meaningful boosting of pseudovirus neutralizing antibody titers were observed after the first vaccine injection in the non-naïve participants, which were 3.3-5.8 fold higher than the corresponding responses in non-naïve participants after two vaccine doses.

We believe that demonstrating a significant benefit from the booster dose in terms of improvement of pre-booster antibody levels (by demonstrating superiority of post-booster titers to pre-booster titers), complemented by the co-demonstration that such antibody levels are at least non-inferior to the comparator group (unvaccinated and SARS-CoV-2 naïve) that receives the same lot and schedule of CoV2 preS dTM-AS03 (D614) being used in the Phase III efficacy study will allow concluding that there is a clear benefit from the booster dose and that such benefit is expected to be reasonably associated with at least the restoration of vaccine protection to levels observed in the Phase III efficacy study.

Table 4.6: GMTs and GMT ratios in non-naïve participants after 1 dose (D22) and naïve participants after 2 doses (D36) with the D614G pseudovirus neutralization assay (Monogram) in the 18-59 year old age group of VAT00002 (Populations, PPAS Naïve-D01+D22, PPAS Non-naïve-D01+D22)

		Group 1 (5 µg + AS03)			Group 2 (10 µg + AS03)		
Population	**Time point/ratio**	**M**	**GMT/GMTR**	**(95% CI)**	**M**	**GMT/GMTR**	**(95% CI)**
Naïve[†]	D01	51	20	(NC, NC)	55	20	(NC, NC)
	D36	53	2938	(2155, 4007)	58	3961	(2795, 5612)

		Group 1 (5 µg + AS03)			Group 2 (10 µg + AS03)		
Population	**Time point/ratio**	**M**	**GMT/GMTR**	**(95% CI)**	**M**	**GMT/GMTR**	**(95% CI)**
Non-naïve‡	D01	10	316	(90.8, 1096)	11	486	(112, 2101)
	D22	10	16962	(2754, 104000)	12	13039	(3175, 53540)
	D22 (non-naïve) / D36 (naïve)		5.77			3.29	

Note: NC=not calculable.
† Naïve denotes 18-59-year-old age group in the PPAS Naïve-D01+D22 population
‡ Non-naïve denotes 18-59-year-old age group in the PPAS Non-naïve-D01+D22 population

Table 4.7: Comparison of ≥ 2-fold and ≥ 4-fold seroconversion rates with the D614G pseudovirus neutralization assay (Monogram) in non-naïve participants after 1 dose (D22) compared to naïve participants after 2 doses (D36) in the 18-59 year old age group of VAT00002 (Populations, PPAS Naïve-D01+D22, PPAS Non-naïve-D01+D22)

			Group 1 (5 µg + AS03)			Group 2 (10 µg + AS03)		
Population	**Time point**	**Fold rise**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Naïve†	D36	≥ 2	51/51	100	(93.0, 100)	54/55	98.2	(90.3, 100)
Non-naïve‡	D22	≥ 2	9/10	90	(55.5, 99.7)	8/10	80	(44.4, 97.5)
Difference (Non-naïve D22 - naïve D36)				-10	(-40.4, 0.8)		-18.2	(-49.2, -1.9)
Naïve†	D36	≥ 4	51/51	100	(93, 100)	54/55	98.2	(90.3, 100)
Non-naïve‡	D22	≥ 4	8/10	80	(44.4, 97.5)	8/10	80	(44.5, 97.5)
Difference (Non-naïve D22 - naïve D36)				-20	(-51.0, -4.0)		-18.2	(-49.2, -1.9)

† Naïve denotes 18-59-year-old age group in the PPAS Naïve-D01+D22 population
‡ Non-naïve denotes 18-59-year-old age group in the PPAS Non-naïve-D01+D22 population

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, 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 least until completion of the key follow-up timepoint (D43) for informing progression to Phase III and dose selection.

5.1 Inclusion Criteria

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

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

I02: 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 vaccination until at least 12 weeks after the last vaccination (ie, second dose of primary series or booster injection).
- A participant of childbearing potential must have a negative highly sensitive pregnancy test (urine or serum as required by local regulation) within 4 hours before any dose of study intervention, see Section 8.4.5 (pregnancy testing).

I03: Informed consent form has been signed and dated

I04: Able to attend all scheduled visits and to comply with all study procedures

I05: Covered by health insurance, only if required by local, regional, or national regulations

I06: SARS-CoV-2 rapid serodiagnostic test performed at the time of enrollment to detect presence of SARS-CoV-2 antibodies (Original Phase II Cohort)

[a] Participants in the Comparator Group for Supplemental Cohorts 1 and 2 must be 18 to 55 years of age.

I07: For persons living with human immunodeficiency virus (HIV), stable HIV infection determined by participant currently on ARVs with CD4 count > 200/mm^3

I08: Does not intend to receive an authorized/approved COVID-19 vaccine from first vaccination to 3 weeks after the second vaccination (D43) despite encouragement by the Investigator to receive the authorized vaccine available to them at the time of enrollment[a]

I09: Supplemental cohorts: for participants originally enrolled in the Phase II Cohort of the study, informed consent has to be signed and dated for transitioning to Supplemental Cohort 2

I10: Supplemental Cohorts, Booster Arms: received a complete primary vaccination series[b] with an authorized/conditionally approved mRNA COVID-19 vaccine (mRNA-1273 [Moderna] or BNT162b2 [Pfizer/BioNTech]) or adenovirus-vectored COVID-19 vaccine (ChAdOx1 nCoV-19 [Oxford University/AstraZeneca] or Ad26.CoV2.S [J&J/Janssen]), with the last dose administered a minimum of 4 months prior to inclusion but not longer than 10 months prior to inclusion

5.2 Exclusion Criteria

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

E01: 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

E02: 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.

E03: Applicable to Original Phase II Cohort, Supplemental Cohort 1, Cohort 2 Comparator Group: Prior administration of a coronavirus vaccine (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2], SARS-CoV, Middle East Respiratory Syndrome [MERS-CoV])[c]

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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 least until completion of the key follow-up timepoint (D43), 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 immunogenicity 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] To be confirmed either by official written or electronic record

[c] Not applicable to booster arms in Supplemental Cohorts 1 and 2

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E04: 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[a]

E05: Dementia or any other cognitive condition at a stage that could interfere with following the study procedures based on Investigator's judgment

E06: Self-reported thrombocytopenia, contraindicating intramuscular (IM) vaccination based on Investigator's judgment

E07: Bleeding disorder, or receipt of anticoagulants in the past 21 days preceding inclusion, contraindicating IM vaccination based on Investigator's judgment

E08: Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily

E09: 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

E10: Receipt of solid-organ or bone marrow transplants in the past 180 days

E11: Receipt of anti-cancer chemotherapy in the last 90 days

E12: Receipt of immunoglobulins[b], blood, or blood-derived products in the past 3 months

E13: 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

E14: 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

E15: Exclusion criterion for the Supplemental Cohort 1 and Cohort 2 Comparator Group: positive rapid diagnostic test for SARS-CoV-2 antibodies at time of enrollment

E16: Exclusion criterion for Supplemental Cohort 2 CoV2 preS dTM-AS03 (D614) primed individuals (ie, primed as participant in the Original Phase II Cohort of the present study): Receipt of authorized/conditionally approved COVID-19 vaccine after enrollment in Original Phase II Cohort

E17: Exclusion criterion for all Booster Groups: Documented virologically-confirmed SARS-CoV-2 infection (by NAAT) after first dose of primary immunization

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.

[a] The components of SARS-CoV-2 Recombinant Protein vaccine are listed in Section 6.1 and in the CoV2 preS dTM Investigator's Brochure and the AS03 adjuvant Investigator's Brochure

[b] Including investigational monoclonal antibodies

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

5.4 Representation of Study Subpopulations

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

For the Original Phase II Cohort, participants who are rapid serodiagnostic test positive at baseline will be capped to a maximum of approximately 20% of the study population to ensure sufficient number of SARS-CoV-2 naïve participants in the study.

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 Intervention

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

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

6.1.1 Original Phase II Cohort Study Interventions

The study interventions for the Original Phase II Cohort are described in Table 6.1 below.

Table 6.1: Identity of Original Phase II Cohort study interventions

CoV2 preS dTM-AS03 (recombinant, adjuvanted)			
Intervention Names	**COVID-19 vaccine (recombinant, adjuvanted) or CoV2 preS dTM-AS03 (5 µg antigen)**	**COVID-19 vaccine (recombinant, adjuvanted) or CoV2 preS dTM-AS03 (10 µg antigen)**	**COVID-19 vaccine (recombinant, adjuvanted) or CoV2 preS dTM-AS03 (15 µg antigen)**
Study Group	**Group 1**	**Group 2**	**Group 3**
Use	Experimental		
Type	Vaccine		
Dose Formulation	Solution and emulsion for injection, mix pre-injection according to dose preparation protocol. Final mixed solution and emulsion is in a single dose 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.		
Unit Dose Strengths	Each 0.5 mL dose of Study Intervention will contain the following:		
	preS-delta TM monovalent: prefusion S delta TM COVID-19 antigen, low-dose (5 µg)	preS-delta TM monovalent: prefusion S delta TM COVID-19 antigen, medium-dose (10 µg)	preS-delta TM monovalent: prefusion S delta TM COVID-19 antigen, high-dose (15 µg)

	AS03 adjuvant is composed of squalene (10.69 milligrams), DL-α-tocopherol (11.86 milligrams) and polysorbate 80 (4.86 milligrams).
Excipients/Diluent	Excipients: *Solution vial:* • 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	2 injections / 21 days apart
Route of Administration	IM injection
Site of Administration	Deltoid muscle in the upper arm
Sourcing	CoV2 preS dTM: Provided by the Sponsor AS03: Provided by GSK
Packaging and Labeling	Each study intervention will be provided in an individual box (antigen and adjuvant will be kitted together in a 2-vial box). Each study intervention (vial) will bear one fixed label and each box will bear one fixed label containing the dose number. All will be labeled in accordance with local Health Authority requirements.
Batch Number	TBD
Storage Conditions	2 to 8ºC (35°F to 46°F) and protected from light

6.1.2 Supplemental Phase III Cohorts Study Interventions

Study interventions for the Supplemental Cohorts are as follows:

- Table 6.2: Monovalent (D614)
- Table 6.3: Monovalent (B.1.351)
- Table 6.4: Bivalent (D614 + B.1.351)

Table 6.2: Identity of Monovalent (D614) study interventions

Intervention Names	**Monovalent (D614) CoV2 preS dTM (5 µg antigen) + AS03 (full-dose adjuvant)**	**Monovalent (D614) CoV2 preS dTM (10 µg antigen) + AS03 (full-dose adjuvant)**
Cohort	Supplemental Cohorts 1 and 2	Supplemental Cohort 1
Cohort Group/Arm	Booster Arms	Comparator Group and Primary Series
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, (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).	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 • 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	0.5 mL per dose
Number of Doses / Dosing Interval	1 injection only (booster)	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 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	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

Table 6.3: Identity of Monovalent (B.1.351) study interventions

Intervention Names	**Monovalent (B.1.351) CoV2 preS dTM (5 µg antigen) + AS03 (full-dose adjuvant)**	**Monovalent (B.1.351) CoV2 preS dTM (5 µg antigen) + AS03 (half-dose adjuvant)**	**Monovalent (B.1.351) CoV2 preS dTM (2.5 µg antigen) + AS03 (half-dose adjuvant)**	**Monovalent (B.1.351) CoV2 preS dTM (2.5 µg antigen) + AS03 (full-dose adjuvant)**	**Monovalent (B.1.351) CoV2 preS dTM (5 µg antigen) (no adjuvant)**
Cohort	Cohort 2	Cohort 2	Cohort 2	Cohort 2	Cohort 2
Cohort Group / Arm	Booster Group / Main Arm	Booster Group / Exploratory Arm	Booster Group / Exploratory Arm	Booster Group / Exploratory Arm	Booster Group / Exploratory Arm
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	Each 0.25 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 (half-dose) is an oil-in-water	Each 0.25 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, (2.5 µg) • AS03 adjuvant (half-dose) is an oil-in-water	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, (2.5 µg) • AS03 adjuvant (full-dose) is an oil-in-water	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) • No adjuvant

	emulsion containing squalene (10.69 milligrams), DL-α-tocopherol (11.86 milligrams) and polysorbate 80 (4.86 milligrams).	emulsion containing squalene (5.35 milligrams), DL-α-tocopherol (5.93 milligrams) and polysorbate 80 (2.43 milligrams).	emulsion containing squalene (5.35 milligrams), DL-α-tocopherol (5.93 milligrams) and polysorbate 80 (2.43 milligrams).	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	0.25 mL per dose	0.25 mL per dose	0.5 mL per dose	0.5 mL per dose
Number of Doses / Dosing Interval	1 injection (booster)	1 injection (booster)	1 injection (booster)	1 injection (booster)	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	TBD	TBD	TBD	TBD
Storage Conditions	2ºC to 8ºC (35°F to 46°F) and protected from light				

Table 6.4: Identity of Bivalent (D614 + B.1.351) study intervention

Intervention Name	**Bivalent (D614 + B.1.351) CoV2 preS dTM (2.5 µg D614 antigen + 2.5 µg B.1.351 antigen) + AS03 (full-dose adjuvant)**
Cohort	Supplemental Cohort 2
Cohort Group / Arm	Booster Group / mRNA and Adenovirus-vector COVID-19 Vaccine Main Arm
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, (2.5 µg) • preS-delta TM B.1.351: prefusion S delta TM B.1.351 COVID-19 antigen, (2.5 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 Antigens):* • 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 only (booster)
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 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 interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3) The multidose vial of CoV2 preS dTM antigen, either monovalent or bivalent antigen, will be mixed with the multi-dose vial of AS03 adjuvant prior to administration (when applicable). Vaccine formulations will be prepared in the CoV2 preS dTM antigen vials by adding an equal volume of 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

6.3.1 Randomization and Allocation Procedures

Original Phase II Cohort:

On the day of enrollment, participants were tested for presence of SARS-CoV-2 antibodies using a rapid serodiagnostic test. All participants who meet the inclusion/exclusion criteria and sign the informed consent form (ICF) were randomly assigned to one of the study groups.

The randomization was stratified by age groups (18-59 years of age and 60 years of age and older), baseline SARS-CoV-2 rapid serodiagnostic test positivity (positive/negative), and high-risk medical conditions (Yes/No). Up to 20% of participants were allowed to be positive by the rapid serodiagnostic test in each group.

Eligible participants were randomly assigned to one of the 3 study groups in this cohort in a 1:1:1 ratio, corresponding to one of the 3 formulations of CoV2 preS dTM-AS03 vaccine (with different antigen doses).

A subset of 120 participants (40 participants in each of the 3 dosing group [20 per age group]) with negative results of baseline SARS-CoV-2 rapid serodiagnostic test were randomly assigned to collect CMI and mucosal samples.

Site staff was to connect to the Interactive Response Technology (IRT) system, enter the identification and security information, and confirm a minimal amount of data in response to IRT prompts. The IRT was to 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 (see Section 5.4). The IRT was then to provide the group assignment. The full detailed procedures for group allocation are described in the Operating Guidelines. If the participant was not eligible to participate in the study, then the information was to be only be recorded on the participant recruitment log.

Supplemental Phase III Cohorts

Supplemental Cohort 1, Booster Groups:

The Booster Groups in this Cohort will be open-label and not randomly assigned as all participants in these groups will receive 1 injection of the CoV2 preS dTM-AS03 (D614) booster vaccine candidate. Participants meeting eligibility criteria will be allocated to different groups according to 2 stratification variables: age group and priming vaccine. The age criterion will be based on 2 age strata: 18-55 years of age and 56 years of age and older. The priming vaccine criterion will include 4 strata: Pfizer/BioNTech, Moderna, Oxford University/AstraZeneca, and J&J/Janssen. A subset of 10% of participants aged 18-55 years old (~22 participants) in the Pfizer/BioNTech-primed CoV2 preS dTM-AS03 (D614) booster vaccine group and a subset of 10% of participants aged 18-55 years old (~8 participants) each in the other primed (Moderna, Oxford University/AstraZeneca, J&J/Janssen) CoV2 preS dTM-AS03 (D614) booster vaccine groups will be randomly assigned to variant testing subsets. The number of eligible participants allocated to strata defined by age and priming vaccine will be as described in Section 4.1.

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, priming vaccine, high-risk medical conditions, ethnicity/race (the last 2 for monitoring purposes and high-risk medical conditions for potential capping). The IRT will then confirm the group assignment within this cohort. The full detailed procedures for group allocation are described in the Operating Guidelines.

Supplemental Cohort 2, Booster Groups:

The Booster Groups in this cohort will be randomly assigned based on stratification variables. Participants meeting eligibility criteria will be stratified according to the following variables: age group (2 strata: 18-55 years of age and 56 years of age and older), priming vaccine (5 strata: Pfizer/BioNTech, Moderna, Oxford University/Astra Zeneca, J&J/Janssen, and CoV2 preS dTM-AS03), exploratory vs. non-exploratory ("main") arms, and high-risk medical condition (Yes/No).

Eligible participants who have received the Pfizer/BioNTech vaccine will be first assigned to the non-exploratory groups (ie, main arms, N = 1130), and will be randomized in a 1:1 ratio to receive a single injection of either the CoV2 preS dTM-AS03 (B.1.351) booster vaccine or the CoV2 preS dTM-AS03 (D614 + B.1.351) booster vaccine. Randomization will occur by age strata (1030 [515 per group] belonging to the 18-55 years of age group, and 100 [50 per group] belonging to the 56 years of age and older group). A subset of 5% of participants aged 18-55 years old (~26 participants in each of these 2 Booster Groups) will be randomly assigned to collect CMI

and mucosal samples plus variant testing. Once enrollment for the main arms has been completed for the Pfizer/BioNTech-primed individuals, eligible individuals who have received this vaccine will be randomized in a 1:1:1:1 ratio into one of the four Monovalent B.1.351 exploratory groups (total N = 400) as described in Section 4.1 No CMI and mucosal samples will be collected in these exploratory groups.

Eligible participants who have received the Moderna (N = 200), Oxford University/Astra Zeneca (N = 200), or J&J/Janssen (N = 200) vaccines will be randomized in a 1:1 ratio to receive a single injection of either the CoV2 preS dTM-AS03 (B.1.351) booster vaccine or the CoV2 preS dTM-AS03 (D614 + B.1.351) booster vaccine. Randomization will occur by age strata (with ¾ of participants belonging to the 18-55 years of age group). No CMI and mucosal samples will be collected in these groups.

Eligible participants transitioning from the VAT00002 Original Phase II Cohort who have received the CoV2 preS dTM-AS03 (D614) candidate vaccine (targeted N = 450; actual number to be determined by number of VAT00002 participants meeting eligibility criteria for transition) will be randomized to receive a single injection of either the CoV2 preS dTM-AS03 (D614) or the CoV2 preS dTM-AS03 (B.1.351) booster vaccine. Randomization will occur by age strata (assumption that about 2/3 of participants will be 18-55 years of age (ie, 300 adults 18-55 years old, allocation ratio of 9:1 between CoV2 preS dTM-AS03 [D614] group and the CoV2 preS dTM-AS03 [B.1.351] group); the actual number and age distribution will be determined by characteristics of those who meet eligibility criteria for transition). A subset of 10% of participants aged 18-55 (~30 participants in the 2 Booster Groups combined) will be randomly assigned to collect CMI and mucosal samples plus variant testing.

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, priming vaccine, high-risk medical conditions, and ethnicity/race (the last 2 for monitoring purposes and high-risk medical conditions for potential capping). The IRT will then provide the group assignment (intervention arm and CMI/mucosal subset [if applicable]). The full detailed procedures for group allocation are described in the Operating Guidelines.

Supplemental Cohorts Comparator Group:

This Group will be open-label and not randomly assigned as all eligible participants will have common baseline characteristics (previously unvaccinated) and all will receive two injections of the CoV2 preS dTM-AS03 (D614) candidate vaccine 21 days apart. Eligible participants must be 18-55 years of age and have a negative baseline SARS-CoV-2 rapid serodiagnostic test to be enrolled into this group. A subset of 5% of participants aged 18-55 (~26 participants) will be randomly assigned to variant testing subsets.

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, documentation of negative baseline SARS-CoV-2 rapid serodiagnostic test, high-risk medical conditions, and ethnicity/race (the last 2 for monitoring purposes and high-risk medical conditions for potential capping). The IRT will then confirm the assignment to this group. The full detailed procedures for group allocation are described in the Operating Guidelines.

Applicable to All Cohorts:

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 leading number of the last 5-digit participant identifier will be designed as the indication of the cellular immunity and mucosal subset. Participants from the Original Phase II Cohort who will be transitioning to Supplemental Cohort 2 will be assigned a new participant identification number.

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

6.3.2 Blinding and Code-breaking Procedures

With the exception of the Booster Arms in Supplemental Cohort 1 and the Comparator Arm common to Supplemental Cohorts 1 and 2, the study will be performed in a modified double-blind (observer-blind) fashion:

- Investigators and study staff who conduct the safety assessment and monitoring 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 the vaccine and are not involved with the safety evaluation will know which vaccine is administered
- Testing laboratories will be blinded

At the time of the interim analysis (see Section 9.5) of the Original Phase II Cohort, unblinding at the group-level occurred to inform Sponsor decision on dose-selection and progression to Phase III. Individual level code will be maintained by the Independent unblinded statistical group till the end of the study. In addition to that, Global Clinical Immunology (GCI) and other laboratories undertaking assays for the study will be kept blinded until all test results are released.

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

The blind can be broken by the Investigator or a delegate through the IRT system, as explained in the code-breaking procedures described in the Operating Guidelines. Once the emergency has been addressed by the site, the Investigator or a delegate must notify the Sanofi Pasteur 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 Pasteur 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 study intervention or group assignment) will not be communicated to either the Investigator or the immediate team working on the study, except for the GPV representative.

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

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 Modifications

Not applicable

6.6 Access to Authorized/Approved vaccine during 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 who have not yet received an authorized/approved vaccine at the time of informed consent and who will be encouraged to obtain the approved/authorized vaccine if applicable to them. Recruitment of eligible participants into one of the study cohorts evaluating priming vaccines (Original Phase II Cohort and the Supplemental Cohorts Comparator Group) will proceed only if, despite encouragement, the candidate participant expresses no intention to seek an authorized or approved vaccine at least until completion of the key follow-up timepoint (D43 for the study cohorts evaluating priming vaccines) for informing either progression to Phase III and dose selection (for Original Phase II Cohort participants) or suitability of variant-containing vaccines for authorization/approval (for the Supplemental Cohorts Comparator Group)

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

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

participant's data up to the point of receipt of authorized/approved vaccine will be included in the primary analysis for immunogenicity and safety. Participants will continue to be followed for the duration of the study as per scheduled visits and procedures. Participants in the cohorts evaluating priming vaccines will not receive the second vaccination if they have received the authorized/approved vaccine between the first and second scheduled vaccination.

6.7 Continued Access to Study Intervention After the End of the Study

In the event that the vaccine formulation evaluated in this study is deemed safe and effective by regulatory authorities, this authorized/approved vaccine may be offered to eligible participants in this study who received a formulation considered less effective to that authorized by the regulatory authorities, if permitted by local regulations and in alignment with local recommendations.

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

At the time of enrollment, all ongoing medications and other therapies (eg, some vaccines, immunoglobulins and monoclonal antibodies) should be recorded in the source document.

Documentation in the CRF of ongoing concomitant medication(s) will be limited to specific categories of medication(s) of interest beginning on the day of first vaccination.

Reportable medications/vaccinations will be collected in the CRF from the day of each study vaccination to the end of the solicited and unsolicited follow-up period after each 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 prophylaxis (eg, SARS-CoV-2 antivirals, monoclonal or polyclonal antibodies or plasma) will be collected throughout the study in all participants.

Reportable medications include medications that impact or may impact the consistency of the safety information collected after any vaccination and/or the immune response to vaccination.

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.

Dosage and administration route, homeopathic medication, inhaled steroids, as well as topical treatments, 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 and will not be considered as concomitant medications. Medications will not 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

Should a participant[a] experience one of the conditions listed below, the Investigator will postpone further vaccination (if applicable, ie, for groups evaluating priming vaccine candidates) until the condition is resolved.

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

Participants will permanently discontinue (definitive discontinuation) study intervention (if applicable, ie, for groups evaluating priming vaccine candidates) 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 1 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.

[a] Applies to the Primary Series only

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 immunogenicity and safety. Participants will be invited to a visit prior to receiving the vaccine and invited to provide a blood sample for immunological assessment. If the visit occurs more than 1 month after the D134 visit for the groups evaluating priming vaccine candidates (Original Phase II Cohort Arms and the Comparator Arm for the Supplemental Cohorts) or more than 1 month after D91 visit for groups evaluating booster vaccine candidates (Booster Arms in Supplemental Cohorts 1 and 2), a PBMC sample will also be collected if the participant is in the cellular immunity and mucosal subset instead of the D366 sample. 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.

7.2 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.

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.

For participants from Original Phase II Cohort who terminate the study at D202 if they are included in the Supplemental Phase III Cohort 2.

All participants will be scheduled to attend V08 (or V07 for booster vaccine study participants) for blood sampling and 12-Month Safety Follow-up. However, if any participants discontinue the study early, they are still to be followed for safety and are to be contacted with a Safety Follow-up call to identify the occurrence of any SAEs and AESIs that had not yet been reported. If

discontinuation occurs at a scheduled visit, the participant will be provided a Memory Aid instead of a DC for SAE follow-up (including AESIs) until the Safety Follow-up call. If a participant discontinues between visits (with no Memory Aid provided yet), the participant will use the last DC received to collect information for the Safety Follow-up call. 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.

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, text messages, or e-mails, 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 discussed in Appendix 10.1.

8 Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoAs. 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 SoAs, 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, including any extra assessments that may be required, is not planned to exceed 240 mL (see Table 8.1, Table 8.2, and Table 8.3). Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

In addition, for the primary series, 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. If the visit occurs more than 1 month after the D134 visit, a PBMC sample will also be collected if the participant is in the cellular immunity and mucosal subset instead of the D387 sample (D366 for groups receiving booster vaccine).

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

Table 8.1: Original Phase II Cohort: samples collected per visit

	D01	D22	D36	D78	D134	D202	D292	D387
Vaccination	X	X						
	BL0001	BL0002	BL0003	BL0004	BL0005	BL0006	BL0007	BL0008
SARS CoV2 Microneutralization assay (SP)	X	X	X	X	X	X	X	X
Anti-S IgG ELISA	X	X	X	X	X	X	X	X
SARS-CoV-2 Pseudovirus Neutralization Assays	X	X	X	X	X	X	X	X
ECLIA Multiplex Assay			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 on respiratory sample during a COVID-19-like illness	Illness visit (see Section 8.3.3)							
Rapid SARS-CoV-2 serodiagnostic Test	X							
Whole Blood TruCulture assay	X	X	X					
Flow Cytometry and Intracellular Cytokine Staining	X	X	X		X			X*
B-cell memory Fluorospot	X				X			X*
Saliva samples	X	X	X		X			

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*If a participant seeks an authorized/approved vaccine, they will be invited to a visit prior to receiving the vaccine. If the visit occurs more than 1 month after the D134 visit, a PBMC sample will also be collected if the participant is in the cellular immunity and mucosal subset instead of the D387 sample.

Table 8.2: Participants in Supplemental Groups receiving a single booster dose: Cohort 1, Cohort 2 Main Arm, Cohort 2 Exploratory B.1.351 Arm: samples collected per visit

	D01	D15	D29	D91	D181	D366
Vaccination	X					
	BL0001	BL0002	BL0003	BL0004	BL0005	BL0006
Anti-S IgG ELISA	X	X	X	X	X	X
SARS-CoV-2 Pseudovirus Neutralization Assays	X	X	X	X	X	X
SARS-CoV-2 Pseudovirus Neutralization Assays Variants of Concern	X	X	X		X	X
ECLIA Multiplex Assay	X		X			
Anti-S Immunoassay	X					
SARS-CoV-2 NAAT on nasopharyngeal sample	X					
SARS-CoV-2 NAAT on respiratory sample during a COVID-19-like illness	Illness visit (see Section 8.3.3)					
Flow Cytometry and Intracellular Cytokine Staining	X		X	X		X
B-cell memory Fluorospot	X			X		X
Saliva samples	X	X		X		

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**PBMC collected only in Cohort 2

Table 8.3: Participants in Supplemental Cohorts Comparator Group receiving 2-dose schedule: samples collected per visit

	D01	D22	D36	D134	D202	D292	D387
Vaccination	X	X					
	BL0001	BL0002	BL0003	BL0004	BL0005	BL0006	BL0007
Anti-S IgG ELISA	X	X	X	X	X	X	X
SARS-CoV-2 Pseudovirus Neutralization Assays	X	X	X	X	X	X	X
SARS-CoV-2 Pseudovirus Neutralization Assays Variants of Concern	X		X		X		X
Anti-S Immunoassay	X						
SARS-CoV-2 NAAT on nasopharyngeal sample	X	X					
SARS-CoV-2 NAAT on respiratory sample during a COVID-19-like illness	Illness visit (see Section 8.3.3)						
Rapid SARS-CoV-2 serodiagnostic Test	X						
B-cell memory Fluorospot**	X			X			X*
Saliva samples	X	X	X	X			

SP, Sanofi Pasteur

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. The type of demographic information is determined by laws in each country. 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 (for the Supplemental Cohorts Comparator Group only). 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.

8.1.2 Physical Examinations 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 8.3.5 and Section 8.3.6.

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 Clinical Safety Laboratory Assessments

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

8.1.5 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 (not applicable to Supplemental Cohort 1 or 2). 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 (for the Original Phase II Cohort), or for restricting enrollment to those individuals without evidence of prior exposure based on the test (for the Supplemental Cohorts Comparator Group, 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 for the Original Phase II Cohort, or the combination of information from the S ELECSYS and NAAT at baseline for comparator for Supplemental Cohorts 1 and 2) see Section 9.3.

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.

8.1.5.1 Healgen COVID-19 IgG/IgM Rapid Test

The Healgen COVID-19 IgG/IgM Rapid Test Cassette was performed at the clinical site by trained personnel for the Original Phase II Cohort only.

The Rapid Diagnostic Test will be used according to the product insert provided by the manufacturer. The COVID-19 IgG/IgM Rapid Test Cassette is a lateral flow immunochromatographic assay intended for the qualitative detection and differentiation of IgM and IgG antibodies to SARS-CoV-2 in human venous whole blood, plasma from anticoagulated blood (Lithium (Li+) heparin, dipotassium ethylenediaminetetraacetic acid (K2EDTA), and sodium citrate), or serum. The test uses anti-human IgM antibody, anti-human IgG antibody, and

rabbit IgG (control) immobilized on a nitrocellulose strip. The burgundy colored conjugate pad contains colloidal gold conjugated to recombinant COVID-19 antigens (SARS-CoV-2 Spike S1 antigen) conjugated with colloid gold (COVID-19 conjugates). 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 forming antigen-antibody complexes. This complex migrates through the 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 burgundy colored band which confirms a reactive test result. The absence of a colored band in the test region indicates a non-reactive test result. A colored line must change from blue to red in the control line region to be valid, indicating that the proper volume of specimen has been added and membrane wicking has occurred.

The results of this test were to be used for determining the randomization strata and to cap the enrollment of SARS-CoV-2 seropositive participants in the Original Phase II Cohort, but not for the determination of whether participants are SARS-CoV-2 naïve or non-naïve. This test was to inform capping of seropositive participants to a maximum of 20% of enrolled individuals in the Original Phase II Cohort.

8.1.5.2 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 for the Supplemental Cohorts Comparator Group.

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 SARS-CoV-2 non-naïve individuals for inclusion into the Supplemental Cohort 1 Comparator Group.

While this serodiagnostic test will be utilized to provide real-time information about eligibility for enrollment (ie, eligibility requires a negative result in the above mentioned groups in which the

test will be applied), classification of naïve and non-naïve status will be based on other assays (specifically, the combination of information from the S ELECSYS, and NAAT at baseline).

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.

8.1.5.3 ELECSYS Anti-SARS-CoV-2 Anti-N ECLIA

This test was to be used on D01 and D22 samples to determine naïve and non-naïve status in participants in the Original Phase II Cohort. Details were provided in the Operating Guidelines and the PPD laboratory manual. Based on data from the Original Phase II Cohort, the performance of this test is very similar to that of the ELECSYS Anti-SARS-CoV-2 Anti-S ECLIA described below, but the sensitivity of the ELECSYS Anti-SARS-CoV-2 Anti-S ECLIA is marginally higher. Therefore, it is considered that the ELECSYS Anti-SARS-CoV-2 Anti-N ECLIA is not adding meaningful value beyond the ELECSYS Anti-SARS-CoV-2 Anti-S ECLIA for determination of naïve vs. non-naïve status in the priming groups included in the Supplemental Cohorts.

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.

8.1.5.4 ELECSYS Anti-SARS-CoV2 Anti-S ECLIA

This test will be used on D01 samples in all participants belonging to any groups evaluating priming vaccines (Original Phase II Cohort and the Supplemental Cohorts Comparator Group) to determine naïve and non-naïve status. Details will be provided in the Operating Guidelines and the PPD laboratory manual. This testing will be performed in all Cohorts.

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.

8.1.6 NAAT Assessment Prior to Vaccination

All participants will have a single bilateral nasopharyngeal swab collected at the enrollment visit. Participants belonging to groups evaluating primary vaccination (Original Phase II Cohort and the Supplemental Cohorts Comparator Group) will also have a single bilateral nasopharyngeal swab collected at the second vaccination visit. This will be used for confirmation of SARS-CoV-2 infection as part of the assessment to determine whether the individual is SARS-CoV-2 naïve or non-naïve (see Section 9.3) in previously unvaccinated individuals (ie, priming vaccine groups), and to identify acute or recent infection in those previously vaccinated with a COVID-19 vaccine (ie, boosting vaccine groups). This testing will be performed in all cohorts.

8.2 Immunogenicity Assessments

8.2.1 Primary Immunogenicity Assays

8.2.1.1 SARS-CoV-2 Pseudovirus Neutralization Assay

This testing will be performed on all participants at all timepoints.

The PhenoSense (PS) CoV nAb 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 PS SARS-CoV-2 neutralizing antibody assay is performed by generating HIV-1 pseudovirions that express the SARS-CoV-2 S 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 nAb. Data are displayed by plotting the percent inhibition of luciferase activity vs. $\log_{10}$ reciprocal of the serum/plasma dilution and nAb titers are reported as the reciprocal of the serum dilution conferring 50% inhibition (ID_{50}) of pseudovirus infection.

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

To ensure that the measured neutralizing antibody 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).

This assay will be used to measure neutralizing antibody responses to the prototype strain (D614G variant) at all timepoints in all participants (all Cohorts). The neutralizing antibody response to the emerging variant B.1.351 will also be performed at D36 in the Original Phase II Cohort and all timepoints in Supplemental Cohort 2.

8.2.2 Secondary Immunogenicity Assays

8.2.2.1 SARS-CoV-2 Neutralizing Antibody Assessment (SP)

SARS-CoV-2 neutralizing antibodies will be measured using a live virus neutralization assay in all participants included in the Original Phase II Cohort at all timepoints. This testing will be performed in the Original Phase II Cohort.

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

8.2.2.2 Detection of binding antibody levels by ECLIA

SARS-CoV-2 binding antibodies will be measured using an electrochemiluminescence immunoassay (ECLIA) in participants included in the Original Phase II Cohort at D36 and on D01 and D29 samples in all participants belonging to any groups evaluating priming vaccines (Cohort 1, Cohort 2 Main Arm, Cohort 2 Exploratory B.1.351 Arm).

The 4-plex SARS-CoV-2 assay (detecting serum IgG binding to SARS-CoV-2 antigens S Protein [S-2P], Receptor Binding Domain [RBD], and Nucleocapsid [N], with a Bovine Serum Albumin [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 S-2P, RBD protein, N protein, and a 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.

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

SARS-CoV-2 Anti-S protein IgG antibodies will be measured using an ELISA at all timepoints and in all participants (all Cohorts).

Microtiter plates will be coated with SARS-CoV-2 S 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.

8.2.3 Exploratory Immunogenicity Assays

8.2.3.1 TruCulture Whole-Blood Cytokine Profiling

Th1/Th2 cytokines will be measured in whole blood following stimulation with full-length S protein. This will be done in the subset of participants belonging to the cellular immunity and mucosal subset of the Original Phase II Cohort at D01, D22, and D36. This testing will be performed in the Original Phase II Cohort only.

8.2.3.2 Cellular Immune Assays

These assays will be done in the subset of participants belonging to the cellular immunity and mucosal subset in whom PBMCs will be collected. These subsets will be selected for the Original Phase II Cohort and for Supplemental Cohort 2 as described in Table 8.2 and Table 8.3. B cell memory responses using a multiplexed B cell FluroSpot assay evaluating IgG and IgA specific B cells to S protein will be measured at D01, D134, and D387 in the Original Phase II Cohort and D01, D91, and D366 in the Booster Cohort in vaccinees and D01, D134 and D387 in the Booster Cohort in naïves.

Multiparametric flow cytometry will be used to identify antigen-specific CD4+ and CD8+ T-cells following stimulation with S protein or S-antigen peptide pools is planned in the subset of participants belonging to the cellular immunity and mucosal subset at D01, D22, D36, D134, and D387 in the Primary series, D01, D15, D29, D91 and D366 in the Booster Cohort in vaccinees and D01, D22, D363, D134 and D387 in the Booster Cohort in naïves. Preparation of blood samples and shipping instructions for cellular immunology assays are outlined in the Operating Manual.

Timepoints for these assessments are specified in Table 8.1, Table 8.2, and Table 8.3.

Preparation of blood samples and shipping instructions for cellular immunology assays are outlined in the Operating Manual.

8.2.3.3 Mucosal Antibody assays

The OraSure SARS-CoV-2 Antibody ELISA is intended to be used for detection of total antibodies to SARS-CoV-2 in human oral fluid specimens collected with the OraSure Oral Antibody Collection Device. This will be done in the subset of participants belonging to the cellular immunity and mucosal subset at timepoints as follows: at D01, D22, D36 and D134 in the Primary Series and in the Booster Cohort in naïves and at D01, D15 and D91 in the Booster Cohort in vaccinees. Details on collection and processing of sample are outlined in the Operating Manual. This testing will be performed in all Cohorts

8.2.3.4 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. This testing will be performed in all Cohorts.

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, Delta (B.1.617) variant, and other variant strains (eg, Alpha [B.1.17], Gamma [P1]).

8.3 Safety Assessments

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

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

8.3.1 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 / 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-19-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):

- Pharyngitis
- 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 / Memory Aid terms

CRF term	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

Laboratory-confirmed SARS-CoV-2 infection

Laboratory-confirmed SARS-CoV-2 infection is defined as a positive result for SARS-CoV-2 by NAAT (done by the central laboratory [Section 8.3.3] or locally) on at least one respiratory sample.

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 ECLIA.

SARS-CoV-2 infection

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

Symptomatic COVID-19

Symptomatic COVID-19 is defined as laboratory-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.

Hospitalized COVID-19

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

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

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 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.

8.3.2 Schedule of Activities for COVID-19-like Illness

Surveillance for COVID-19

Active and passive surveillance will take place as shown below. 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.

Passive Surveillance:

All participants will be instructed to contact the site if they experience symptoms/conditions 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.

Active Surveillance:

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

Participants will be contacted once every 2 weeks starting at D43 (for the Original Phase II Cohort and Supplemental Cohorts Comparator Group) and D30 (for Supplemental Cohorts 1 and 2 Booster Groups) to inquire about the development of symptoms/conditions of COVID-19-like illness and to remind participants to contact study staff if they experience symptoms/conditions of COVID-19-like illness or if they have a positive COVID-19 test from any other source. Inquiry about the development of symptoms/conditions of COVID-19-like illness will also take place at scheduled study visits and phone calls occurring at D43 (the Original Phase II Cohort and the Supplemental Cohorts Comparator Group) or D29 (for Supplemental Cohorts 1 and 2 Booster Groups) or earlier timepoints.

Schedule of Visits

During the surveillance for symptoms/conditions of COVID-19-like illness, participants will notify Investigators about the onset of COVID-19-like symptoms/conditions or if they had a positive COVID-19 test from any other source. Sites will contact participants to verify the symptoms/conditions 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 for diagnosis of laboratory-confirmed SARS-CoV-2 infection. Participants will be reminded to collect the start date, end date, maximum intensity, health care utilization and medication in their diary card during the course of the illness. Participants will also be reminded to use the pulse oximeter provided to them at the CLI01 visit to take a pulse oximeter reading every day from the CLI01 visit until the results of the NP swab at CLI1 and any other swab collected for local NAAT testing at the CLI01 visit are available. Participants will be informed that if the readings are repeatedly (on at least 2 readings separated by 5 minutes) below the

pre-defined 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. Participants will also be informed of the danger signs and symptoms/conditions of COVID-19 at the time of the visit.

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 central laboratory NAAT or a local laboratory NAAT to ascertain whether the symptoms correspond to a SARS-CoV-2 infection. While either option is provided to facilitate testing, the central laboratory NAAT testing is preferred as it would enable further evaluation of viral sequence for positive samples. Any study participant reporting any of the other COVID-19-like illness definitory symptoms/conditions during the 7-day period after each vaccination should be evaluated for COVID-19 with COVID-19-like illness visit and procedure 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 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 bilateral nasopharyngeal swab for central laboratory testing or a respiratory specimen as needed for local clinical laboratory testing 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 will be reviewed by an appropriate site staff member. 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 pre-defined 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.

A respiratory specimen during a COVID-19-like illness will not be collected if the date of collection is more than 14 days after resolution of symptoms.

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.

The frequency of subsequent contact for medical monitoring is at the discretion of the Investigator.

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

All participants will be required to record their symptoms, maximum severity of symptoms and start and stop date for each symptom for the duration of the illness.

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 or healthcare facility visit (emergency room, urgent care, medical office) during the course of illness, detailed information on the course of the illness including duration of symptoms, vital signs including peripheral oxygen saturation, 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.

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 central laboratory 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 positive, Investigators will inform participants of local guidelines and requirements for

COVID-19 cases, provide local health care details, inform participants of the need to continue twice daily SpO2 measurement.

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

8.3.3 Nucleic Acid Amplification Test (NAAT) for Detection of Laboratory-Confirmed SARS-CoV-2 infection

The Abbott RealTime SARS-CoV-2 assay will be used for the detection of laboratory-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 (for the Original Phase II Cohort and the Supplemental Cohorts Comparator Group)
- Nasopharyngeal swab collected at COVID-19-like illness visit

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 2 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.

8.3.4 ELECSYS Anti-SARS-CoV-2 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 participants belonging to the Original Phase II Cohort. In addition, this test will be used on D01 and D22 samples for the Original Phase II Cohort in all participants to aid in determination of naïve and non-naïve status (see Section 8.1.5.3). Details will be provided in the Operating Guidelines and the PPD laboratory manual.

8.3.5 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.

8.3.6 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-19-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.

8.4 Adverse Events (AEs), 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.

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

For the Original Phase II Cohort, enrollment and further vaccination was to be paused 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 SAE assessed as related to the vaccine by the Investigator and the Sponsor are reported in the study
- ≥ 20% participants experiencing Grade 3 systemic reaction (without concurrent infectious disease)
- ≥ 20% participants experiencing Grade 3 solicited injection site pain
- ≥ 20% participants experiencing Grade 3 unsolicited non serious reactions (reactions not explained by any other possible etiology)
- > 5% of the study population is hospitalized due to SARS-CoV-2 infection

- > 10 ICU admissions due to SARS-CoV-2 infection
- Any other adverse event that, in the opinion of the Investigator, would expose participants to unreasonable risk of illness or injury

If any of these conditions are met, enrollment and further vaccination was to be paused to investigate any potential signal or concern. The Sponsor determines continuation or adaptation in study design. Case unblinding may be performed if necessary.

For the Supplemental Phase III Cohorts, similar criteria will apply for further vaccination to be paused 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 SAE assessed as related to the vaccine by the Investigator and the Sponsor are reported in the study
- > 5% of the study population is hospitalized due to SARS-CoV-2 infection
- > 10 ICU admissions due to SARS-CoV-2 infection
- Any other adverse event that, in the opinion of the Investigator, would expose participants to unreasonable risk of illness or injury

For the Supplemental Phase III Cohorts, reactogenicity criteria will serve as alert threshold rather than pause criteria:

- ≥ 20% participants experiencing Grade 3 systemic reaction (without concurrent infectious disease)
- ≥ 20% participants experiencing Grade 3 solicited injection site pain
- ≥ 20% participants experiencing Grade 3 unsolicited non serious reactions (reactions not explained by any other possible etiology)

Given the information gained based on interim data from the Original Phase II Cohort for reactogenicity events (Grade 3 reactogenicity events being of short duration, non-serious and mostly self-limited), it is considered appropriate to monitor the above criteria as alert thresholds rather than direct pause triggers. These reactogenicity criteria will be evaluated for individual groups (for open-label Arms, ie, Cohort 1 Booster Arm and the Comparator Group for Supplemental Cohorts 1 and 2) or as aggregate data (for observer-blind Groups, ie, Supplemental Cohort 2 and 3 Groups), as applicable. Upon review of the details of the nature of these reactogenicity events, the Sponsor will decide whether or not enrollment and/or further vaccination is to be paused or if enrollment and/or further vaccinations can continue.

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]).

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

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 potential safety signal.

Safety will be evaluated through:

- Assessment of the reactogenicity profile of each study intervention for participants in each age group through 21 days after each vaccination in SARS-CoV-2 naïve and non-naïve subgroups:
  - Presence of solicited (prelisted in the participant's DC and CRF) injection site reactions and systemic reactions occurring up to 7 days after each vaccination
  - Presence of unsolicited AEs reported up to 21 days after the last vaccination
- 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 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 SARS-CoV-2 infection and/or symptomatic COVID-19
- Assessment of frequency of disease in episodes of laboratory-confirmed COVID-19 illness:
  - Occurrences of hospitalized COVID-19
  - Occurrences of severe COVID-19
  - Death associated with COVID-19

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 the day of vaccination (D01) until 7 days after each vaccination (D01 + 7 days).

Solicited systemic reactions will be collected from the day of vaccination (D01) until 7 days after each vaccination (D01 + 7 days).

The solicited injection site reactions and systemic reactions that are pre-listed in the DCs 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 the day of vaccination (D01) until 21 days after the last vaccination (D01 + 21 days).

SAEs will be collected and assessed throughout the study, from inclusion until 12 months after the last vaccination up to D366 (Supplemental Cohorts 1 and 2 Booster Arms) or D387 (Original

Phase II Cohort and Supplemental Cohorts Comparator Group). 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.

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, 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 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 a designee will interview the participants to collect the information recorded in the DC 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 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 at Visit 7 (Supplemental Cohorts 1 and 2 Booster Arms) or Visit 8 (Original Phase II Cohort and Supplemental Cohorts Comparator Group) (or over the telephone if the visit cannot be performed in-person) using a questionnaire to capture SAEs and AESIs, if applicable.

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

8.4.3 Follow-up of AEs and SAEs

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 to be related to the study intervention administered or that led to study or vaccination discontinuation, 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, IRB / IEC, and Investigators.
- Investigator safety reports must be prepared for SUSAR according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for SUSARs 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 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 no later than 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), any serious event experienced by the pregnant women or by the newborn are considered SAEs and will be reported as such.
- The participant will be followed till the outcome of the pregnancy and the pregnancy outcome reported. 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. 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.
- 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 no later than 1 month of learning of the pregnancy. Pregnancy status will be collected, follow-up of the participant will continue as part of the study, but the participant will not be followed-up until the pregnancy outcome and the offspring will not be followed.
- 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 immunogenicity assessment, if applicable).

8.4.6 Adverse Events of Special Interest

AESIs will include (see Appendix 10.5):

- Anaphylactic reactions, Generalized convulsion, Thrombocytopenia
- Myocarditis*
- Pericarditis*
- Thrombosis with thrombocytopenia syndrome*
- New onset and worsening of pIMDs (Table 10.4)

*Due to safety signals detected after the use of other COVID-19 vaccine platforms from other manufacturers, Myocarditis, Pericarditis, and Thrombosis with thrombocytopenia syndrome are also considered AESIs.

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

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 Pharmacodynamics

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

8.7 Genetics

Genetics are not evaluated in this study.

8.8 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) may be evaluated in this study in exploratory analyses.

8.9 Immunogenicity Assessments

See Section 8.2.

8.10 Medical Resource Utilization and Health Economics

Medical Resource Utilization will be collected as part of COVID-19-like illness in this study (see Section 8.3.2) 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 participant for the purpose 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 are 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.

8.11 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 Pasteur 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 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 Pasteur 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-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

9.1 Statistical Hypotheses

9.1.1 Original Phase II Cohort

No hypothesis testing will be performed in this Original Phase II Cohort study.

9.1.2 Evaluation of Booster Candidates in Supplemental Cohorts 1 and 2

For Supplemental Cohorts 1 and 2 in younger adults (18-55 years of age), 3 booster candidates in total: CoV2 preS dTM-AS03 (D614) in Supplemental Cohort 1 and CoV2 preS dTM-AS03 (B.1.351) and CoV2 preS dTM-AS03 (D614 + B.1.351) in Supplemental Cohort 2, share the same Comparator Group of SARS-CoV-2-naïve adults, unvaccinated, 18-55 years of age, who will receive the CoV2 preS dTM-AS03 (D614) vaccine as a primary series of 2 injections given 21 days apart, for hypothesis testing. To control for multiple testing, the Bonferroni adjustment will be applied to maintain overall type I error at 0.025 one-sided (0.025/3 for each comparison of booster candidate).

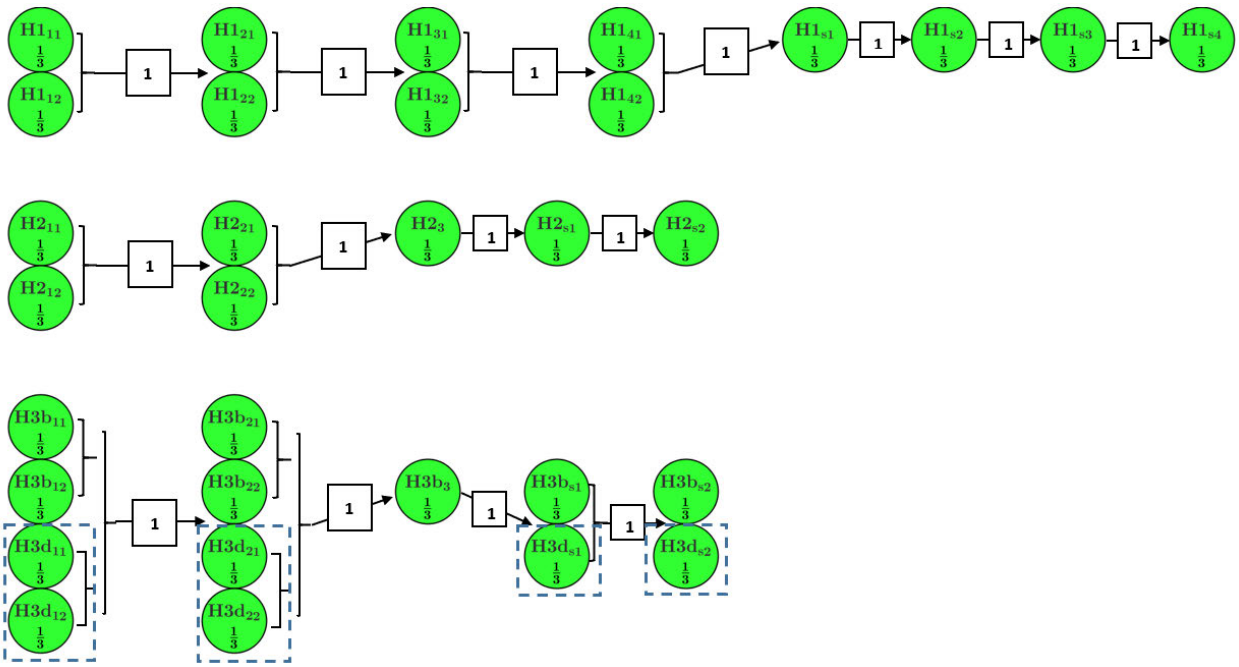
For the CoV2 preS dTM-AS03 (D614) booster candidate, there are 2 co-primary endpoints to be hypotheses tested with one-sided alpha 0.025/3 in participants primed with the Pfizer/BioNTech vaccine. If the primary objectives are met, then 2 conditional secondary endpoints will be hypotheses tested with one-sided alpha 0.025/3 applying the sequential testing strategy in participants primed with the protein-based vaccine in the Original Phase II Cohort. If the primary objectives in the Pfizer/BioNTech vaccine primed and conditional secondary objectives in the protein-based vaccine primed are both met, then 2 conditional secondary endpoints will be hypotheses tested with one-sided alpha 0.025/3 applying the sequential testing strategy in participants primed with an mRNA vaccine. If the primary objectives in the Pfizer/BioNTech vaccine primed, conditional secondary objectives in the protein-based vaccine primed, and conditional secondary objectives in the mRNA vaccine primed are all met, then 2 conditional secondary endpoints will be hypotheses tested with one-sided alpha 0.025/3 applying the sequential testing strategy in participants primed with an adenovirus vector vaccine. If the primary objectives in the Pfizer/BioNTech vaccine primed and conditional secondary objectives in the protein-based vaccine primed, the mRNA vaccine primed, and adenovirus vector vaccine primed are all met, then 1 conditional secondary endpoint on seroresponse will be hypotheses tested at one-sided alpha 0.025/3 in each Pfizer/BioNTech primed, protein-based primed, mRNA primed, and adenovirus vector primed sequentially by applying the sequential testing strategy.

For the CoV2 preS dTM-AS03 (B.1.351) booster candidate, there are 2 co-primary endpoints to be hypotheses tested at 0.025/3 one-sided level in participants primed with the Pfizer/BioNTech vaccine. If the primary objectives are met, then 2 conditional secondary endpoints will be hypotheses tested at 0.025/3 one-side level in participants primed with an mRNA vaccine applying the sequential testing strategy. If primary objectives and conditional secondary objectives are both met, then 1 conditional secondary endpoint (GMT) will be hypothesis tested with one-sided alpha 0.025/3 in participants primed with the Pfizer/BioNTech vaccine applying the sequential testing strategy. If the primary objectives, conditional secondary objectives, and conditional secondary objective on GMT are all met, then 1 conditional secondary endpoint on

seroresponse will be hypothesis tested at one-sided alpha 0.025/3 in each Pfizer/BioNTech primed and mRNA primed sequentially by applying the sequential testing strategy.

For the bivalent booster candidate, there are 4 co-primary endpoints on both D614G and B.1.351 variants (if the SARS-CoV-2 D614G variant remains in circulation globally based on reports from authorities [eg, WHO]) or 2 co-primary endpoints on the B.1.351 variant to be hypotheses tested at 0.025/3 one-sided level in participants primed with the Pfizer/BioNTech vaccine. If the primary objectives are met, then 4 conditional secondary endpoints on both D614G and B.1.351 variants (if the SARS-CoV-2 D614G variant remains in circulation globally based on reports from authorities [eg, WHO]) or 2 conditional secondary endpoints on the B.1.351 variant will be hypotheses tested at 0.025/3 one-sided level in participants primed with an mRNA vaccine applying the sequential testing strategy. If primary objectives and conditional secondary objectives are both met, then 1 conditional secondary endpoint on GMT will be hypothesis tested with one-sided alpha 0.025/3 in participants primed with the Pfizer/BioNTech vaccine applying the sequential testing strategy. If the primary objectives, conditional secondary objectives, and conditional secondary objective on GMT are all met, then 2 conditional secondary endpoints on seroresponse for both D614G and B.1.351 variants (if the SARS-CoV-2 D614G variant remains in circulation globally based on reports from authorities [eg, WHO]) or 1 conditional secondary endpoint on seroresponse for B.1.351 variant will be hypotheses tested at one-sided alpha 0.025/3 in each Pfizer/BioNTech primed and mRNA primed sequentially by applying the sequential testing strategy.

Figure 9.1: Multiplicity adjustment strategy using Bonferroni and sequential testing method in Supplemental Cohort 1 and Supplemental Cohort 2



Note:

i. H1, H2 and H3 corresponding to the hypothesis testing of CoV2 preS dTM-AS03 (D614) in Supplemental Cohort 1, CoV2 preS dTM-AS03 (B.1.351) in Supplemental Cohort 2 and CoV2 preS dTM-AS03 (D614 + B.1.351) in Supplemental Cohort 2.
ii. H3 of CoV2 preS dTM-AS03 (D614 + B.1.351) in Supplemental Cohort 2 will include hypothesis testing of D614G (H3d, dotted circled ones in Figure 9.1) (if the SARS-CoV-2 D614G variant remains in circulation globally based on reports from authorities [eg, WHO]) and B.1.351 (H3b).
iii. $H(=1,2,3b, \text{ or } 3d)_1$ corresponding to the hypothesis testing of co-primary endpoints. $H(=1,2,3b, \text{ or } 3d)_{(=2,3,4)}$ corresponding to the hypothesis testing of conditional secondary endpoint(s).
iv. $H(=2 \text{ or } 3b)_3$ corresponding to the hypothesis testing of conditional secondary endpoints for superiority claim on B.1.351.
v. $H(=1,2,3b, \text{ or } 3d)_{(=s1,s2,s3,s4)}$ corresponding to the hypothesis testing of conditional secondary endpoint(s) for non-inferiority claim on seroresponse.
vi. $H(=1,2,3b, \text{ or } 3d)_{(=1,2,3,4)1}$ corresponding to the hypothesis testing of non-inferiority. $H(=1,2,3b, \text{ or } 3d)_{(=1,2,3,4)2}$ corresponding to the hypothesis testing of superiority.

The hypothesis testing strategy of each booster candidate is as follows:

- Supplemental Cohort 1 – CoV2 preS dTM-AS03 (D614)
  - Overall type 1 error at 0.0.25/3 one-sided level will be maintained
    a) 2 co-primary endpoints will be hypothesis tested in participants primed with the Pfizer/BioNTech vaccine at one-sided 0.025/3 alpha level
    b) A sequential testing strategy will be applied for the 2 conditional co-secondary endpoints in participants primed with the protein-based vaccine in the Original Phase II Cohort if the 2 co-primary endpoints in participants primed with the Pfizer/BioNTech vaccine at one-sided 0.025/3 alpha level is achieved
    c) A sequential testing strategy will be applied for the 2 conditional co-secondary endpoints in pooled participants primed with an mRNA vaccine if the 2 co-primary endpoints in participants primed with the Pfizer/BioNTech vaccine and 2 conditional co-secondary endpoints in participants primed with the protein-based vaccine in the Original Phase II Cohort at one-sided 0.025/3 alpha level are both achieved
    d) A sequential testing strategy will be applied for the 2 conditional co-secondary endpoints in pooled participants primed with an adenovirus vector vaccine if the 2 co-primary endpoints in participants primed with the Pfizer/BioNTech vaccine, 2 conditional co-secondary endpoints in participants primed with the protein-based vaccine and 2 conditional co-secondary endpoints in pooled participants primed with an mRNA vaccine at one-sided 0.025/3 alpha level are all achieved
    e) A sequential testing strategy will be applied for the 1 conditional secondary endpoint on seroresponse in participants primed with the Pfizer/BioNTech vaccine, in participants primed with the protein-based vaccine, in pooled

participants primed with an mRNA vaccine, and in pooled participants primed with an adenovirus vector vaccine at one-sided 0.025/3 alpha level will be tested sequentially if the 2 coprimary endpoints in participants primed with the Pfizer/BioNTech vaccine, 2 conditional co-secondary endpoints in participants primed with the protein-based vaccine, 2 conditional co-secondary endpoints in pooled participants primed with an mRNA vaccine, 2 conditional co-secondary endpoints in pooled participants primed with an adenovirus vector vaccine at one-sided 0.025/3 alpha level are all achieved

- Supplemental Cohort 2 – CoV2 preS dTM-AS03 (B.1.351)
  - Overall type I error at 0.025/3 one-sided level will be maintained
    a) 2 co-primary endpoints will be hypothesis tested in participants primed with the Pfizer/BioNTech vaccine at one-sided 0.025/3 alpha level
    b) A sequential testing strategy will be applied for the 2 conditional co-secondary endpoints in pooled participants primed with an mRNA vaccine if the 2 co-primary endpoints in participants primed with the Pfizer/BioNTech vaccine at one-sided 0.025/3 alpha level is achieved
    c) A sequential testing strategy will be applied for the 1 conditional secondary endpoint of superiority testing on B.1.351 in participants primed with the Pfizer/BioNTech vaccine if the 2 co-primary endpoints in participants primed with the Pfizer/BioNTech vaccine and 2 co-secondary endpoints in pooled participants primed with an mRNA vaccine at one-sided 0.025/3 alpha level are both achieved
    d) A sequential testing strategy will be applied for the 1 conditional secondary endpoint on seroresponse in participants primed with the Pfizer/BioNTech vaccine at one-sided 0.025/3 alpha level if the 2 co-primary endpoints in participants primed with the Pfizer/BioNTech vaccine, 2 conditional co-secondary endpoints in pooled participants primed with an mRNA vaccine, and 1 conditional secondary endpoint on GMT at one-sided 0.025/3 alpha level are all achieved
    e) A sequential testing strategy will be applied for the 1 conditional secondary endpoint on seroresponse in pooled participants primed with an mRNA vaccine at one-sided 0.025/3 alpha level if the 2 coprimary endpoints in participants primed with the Pfizer/BioNTech vaccine, 2 conditional co-secondary endpoints in pooled participants primed with an mRNA vaccine, 1 conditional secondary endpoint on GMT, and 1 conditional secondary endpoint on seroresponse in participants primed with the Pfizer/BioNTech vaccine at one-sided 0.025/3 alpha level are all achieved

- Supplemental Cohort 2 – CoV2 preS dTM-AS03 (D614 + B.1.351)
  - Overall type I error at 0.025/3 one-sided level will be maintained
  - The objectives will be evaluated on the pseudovirus neutralizing titers to the B.1.351 variant and the pseudovirus neutralizing titers to the D614G variant (if the SARS-CoV-2 D614G variant remains in circulation globally based on reports from

authorities [eg, WHO]). The objective would be considered to be achieved if both variants or only B.1.351 variant are met based on the D614G variant circulation situation for whether testing on D614G variant is needed or not

a) Two co-primary endpoints for pseudovirus neutralizing titers against B.1.351 and 2 co-primary endpoints for pseudovirus neutralizing titers against D614G (if the SARS-CoV-2 D614G variant remains in circulation globally based on reports from authorities [eg, WHO]) will be hypothesis tested in participants primed with the Pfizer/BioNTech vaccine at one-sided 0.025/3 alpha level
b) A sequential testing strategy will be applied for the 2 conditional co-secondary endpoints for pseudovirus neutralizing titers against B.1.351 and 2 conditional co-secondary endpoints for pseudovirus neutralizing titers against D614G (if the SARS-CoV-2 D614G variant remains in circulation globally based on reports from authorities ([eg, WHO]) in pooled participants primed with an mRNA vaccine if the 4 co-primary endpoints both on the B.1.351 variant and the D614G variant (if the SARS-CoV-2 D614G variant remains in circulation globally based on reports from authorities [eg, WHO]) or 2 co-primary endpoints on the B.1.351 variant in participants primed with the Pfizer/BioNTech vaccine at one-sided 0.025/3 alpha level are achieved
c) A sequential testing strategy will be applied for the conditional secondary endpoint of superiority testing on B.1.351 in participants primed with the Pfizer/BioNTech vaccine if the primary objectives in participants primed with the Pfizer/BioNTech vaccine and conditional secondary objectives in pooled participants primed with an mRNA vaccine at one-sided 0.025/3 alpha level are both achieved
d) A sequential testing strategy will be applied for the 2 conditional secondary endpoints on seroresponse for both B.1.351 and D614G variants if the SARS-CoV-2 D614G variant remains in circulation globally based on reports from authorities (eg, WHO) or 1 conditional secondary endpoint on seroresponse only for B.1.351 variant in participants primed with the Pfizer/BioNTech vaccine at one-sided 0.025/3 alpha level if the primary objectives in participants primed with the Pfizer/BioNTech vaccine, conditional secondary objectives in pooled participants primed with an mRNA vaccine, and conditional secondary objective on GMT in participants primed with the Pfizer/BioNTech vaccine at one-sided 0.025/3 alpha level are all achieved
e) A sequential testing strategy will be applied for the 2 conditional secondary endpoints on seroresponse for both B.1.351 and D614G variants if the SARS-CoV-2 D614G variant remains in circulation globally based on reports from authorities (eg, WHO) or 1 conditional secondary endpoint on seroresponse only for the B.1.351 variant in pooled participants primed with an mRNA vaccine at one-sided 0.025/3 alpha level if the primary objectives in participants primed with the Pfizer/BioNTech vaccine, conditional secondary objectives in pooled participants primed with an mRNA vaccine, conditional secondary objective on

GMT in participants primed with the Pfizer/BioNTech vaccine, and conditional secondary objective on seroresponse in participants primed with the Pfizer/BioNTech vaccine at one-sided 0.025/3 alpha level are all achieved.

9.1.2.1 A Pooled Primary Series Cohort as Supplemental Cohort 2 Comparator Group

As the number of authorized and/or approved COVID-19 vaccines increases, promptly enrolling the planned 515 naïve participants into the Comparator Group shared by Supplemental Cohorts 1 and 2 may become unattainable. In order to maintain sufficient target power for Supplemental Cohort 2 hypothesis testing, in case of a substantial shortfall in numbers of naïve Comparator Group participants, a pooled primary series cohort with a sample size of at least 464 (a 10% dropout rate from 515) evaluable participants may be planned to serve as the Comparator Group for Supplemental Cohort 2.

Participants in this pooled primary series cohort will be added from 2 potential sources, in the following order:

1. All SARS-CoV-2-naïve participants contemporaneously enrolled in Supplemental Cohort 1
2. Eligible participants from studies involving the same CoV2 preS dTM-AS03 vaccine
   a) Eligible participants in the VAT00002 Original Phase II Cohort
   b) Eligible participants in other studies of this same investigational SARS-CoV-2 vaccine program

Evaluable participants will be pooled in sequence from the above sources. Eligible participants will be selected and pooled base on the comparability of population and assessments per clinical justification outlined in the SAP.

An exploratory sensitivity analysis will be performed on the hypothesis testing for Supplemental Cohort 2 to test the robustness of the primary analyses by using the pooling primary series as the Comparator Group.

9.1.2.2 Supplemental Cohort 1

Hypothesis testing will be conducted for the 2 co-primary immunogenicity endpoints in participants, 18-55 years old, primed with the Pfizer/BioNTech vaccine, 2 conditional co-secondary immunogenicity endpoints in participants, 18-55 years old, primed with the protein-based vaccine, 2 conditional co-secondary immunogenicity endpoints in participants, 18-55 years old, primed with an mRNA vaccine, 2 conditional co-secondary immunogenicity endpoints in participants, 18-55 years old, primed with an adenovirus vector vaccine, 1 conditional secondary immunogenicity endpoint on seroresponse in participants, 18-55 years old, primed with the Pfizer/BioNTech vaccine, the protein-based vaccine, an mRNA vaccine, and an adenovirus vector vaccine sequentially.

Primary objective 1: non-inferiority to the comparator for participants primed with the Pfizer/BioNTech vaccine:

For participants, 18-55 years old, primed with the Pfizer/BioNTech vaccine, 14 days after the booster dose (ie, D15) with CoV2 preS dTM-AS03 (D614) and 14 days after the second dose (ie,

D36) of the Comparator Group, the GMT against D614G of the Booster Group CoV2 preS dTM-AS03 (D614), is non-inferior to the GMT against D614G of the Comparator Group.

Null hypothesis (H_0) : $GMT_{(booster)} / GMT_{(comparator)} \leq (1/1.5)$

Alternative hypothesis (H_1) : $GMT_{(booster)} / GMT_{(comparator)} > (1/1.5)$

The non-inferiority in terms of GMT will be demonstrated if the lower limit of the two-sided 98.3% CI of the ratio of the GMT is great than (1/1.5).

Primary objective 2: superiority to the pre-booster for participants primed with the Pfizer/BioNTech vaccine:

For participants, 18-55 years old, primed with the Pfizer/BioNTech vaccine, 14 days after the booster dose (ie, D15) with CoV2 preS dTM-AS03 (D614), the serum neutralization titer against D614G is superior to the serum neutralization titer against D614G prior to the booster dose at D01.

Null hypothesis (H_0) : $Ratio_{(post\text{-}booster/pre\text{-}booster)} \leq 2$

Alternative hypothesis (H_1) : $Ratio_{(post\text{-}booster/pre\text{-}booster)} > 2$

The superiority will be demonstrated if the lower limit of the two-sided 98.3% CI of the ratio of serum neutralization titer is great than 2.

The primary immunogenicity objective will be demonstrated only if both non-inferiority and superiority testing described above are demonstrated.

If the primary immunogenicity objective in participants primed with the Pfizer/BioNTech vaccine is reached, 2 conditional secondary immunogenicity endpoints will be tested for participants primed with the protein-based vaccine.

Conditional secondary objective 1.1: non-inferiority to the comparator for participants primed with the protein-based vaccine:

For participants, 18-55 years old, primed with the protein-based vaccine in the Original Phase II Cohort, 14 days after the booster dose (ie, D15) in the CoV2 preS dTM-AS03 (D614) Group and after the second dose of the primary vaccination Comparator Group (ie, D36), GMT against D614G of the Booster Group, CoV2 preS dTM-AS03 (D614), is non-inferior to the GMT against D614G of the primary vaccination Comparator Group in younger adults.

Null hypothesis (H_0) : $GMT_{(booster)} / GMT_{(comparator)} \leq (1/1.5)$

Alternative hypothesis (H_1) : $GMT_{(booster)} / GMT_{(comparator)} > (1/1.5)$

The non-inferiority in terms of GMT will be demonstrated if the lower limit of the two-sided 98.3% CI of the ratio of the GMT is great than (1/1.5).

Conditional secondary objective 1.2: superiority to the pre-booster for participants primed with the protein-based vaccine:

For participants, 18-55 years old, primed with the protein-based vaccine in the Original Phase II Cohort, 14 days after the booster dose (ie, D15) with CoV2 preS dTM-AS03 (D614), the serum neutralization titer against D614G is superior to the serum neutralization titer against D614G prior booster dose at D01 in younger adults.

Null hypothesis (H_0) : Ratio $_{(post\text{-}booster/pre\text{-}booster)} \leq 2$

Alternative hypothesis (H_1) : Ratio $_{(post\text{-}booster/pre\text{-}booster)} > 2$

The superiority will be demonstrated if the lower limit of the two-sided 98.3% CI of the ratio of serum neutralization titer is great than 2.

The conditional secondary objective will be reached if both non-inferiority and superiority testing described above are demonstrated.

If the primary immunogenicity objective in participants primed with the Pfizer/BioNTech vaccine and secondary immunogenicity objective in participants primed with the protein-based vaccine are both reached, 2 conditional secondary immunogenicity endpoints will be tested for participants primed with an mRNA vaccine.

Conditional secondary objective 2.1: non-inferiority to the comparator for participants primed with an mRNA vaccine:

For participants, 18-55 years old, primed with an mRNA vaccine, 14 days after the booster dose (ie, D15) in the CoV2 preS dTM-AS03 (D614) Group and after the second dose of the primary vaccination Comparator Group (ie, D36), GMT against D614G of the Booster Group, CoV2 preS dTM-AS03 (D614), is non-inferior to the GMT against D614G of the primary vaccination Comparator Group in younger adults.

Null hypothesis (H_0) : $GMT_{(booster)} / GMT_{(comparator)} \leq (1/1.5)$

Alternative hypothesis (H_1) : $GMT_{(booster)} / GMT_{(comparator)} > (1/1.5)$

The non-inferiority in terms of GMT will be demonstrated if the lower limit of the two-sided 98.3% CI of the ratio of the GMT is great than (1/1.5).

Conditional secondary objective 2.2: superiority to the pre-booster for participants primed with an mRNA vaccine:

For participants, 18-55 years old, primed with an mRNA vaccine, 14 days after the booster dose (ie, D15) with CoV2 preS dTM-AS03 (D614), the serum neutralization titer against D614G is superior to the serum neutralization titer against D614G prior booster dose at D01 in younger adults.

Null hypothesis (H_0) : Ratio $_{(post\text{-}booster/pre\text{-}booster)} \leq 2$

Alternative hypothesis (H_1) : Ratio $_{(post\text{-}booster/pre\text{-}booster)} > 2$

The superiority will be demonstrated if the lower limit of the two-sided 98.3% CI of the ratio of serum neutralization titer is great than 2.

The conditional secondary objective will be reached if both non-inferiority and superiority testing described above are demonstrated.

If the primary immunogenicity objective in participants primed with the Pfizer/BioNTech vaccine, secondary immunogenicity objective in participants primed with the protein-based vaccine, and secondary immunogenicity objective in participants primed with an mRNA are all reached, 2 conditional secondary immunogenicity endpoints will be tested for participants primed with an adenovirus vector vaccine.

Conditional secondary objective 3.1: non-inferiority to the comparator for participants primed with an adenovirus vector vaccine:

For participants, 18-55 years old, primed with an adenovirus vector vaccine, 14 days after the booster dose (ie, D15) with CoV2 preS dTM-AS03 (D614) and 14 days after the second dose (ie, D36) of the Comparator Group, the GMT against D614G of the Booster Group, CoV2 preS dTM-AS03 (D614), is non-inferior to the GMT against D614G of the Comparator Group.

Null hypothesis (H_0) : $GMT_{(booster)} / GMT_{(comparator)} \leq (1/1.5)$

Alternative hypothesis (H_1) : $GMT_{(booster)} / GMT_{(comparator)} > (1/1.5)$

The non-inferiority in terms of GMT will be demonstrated if the lower limit of the two-sided 98.3% CI of the ratio of the GMT is great than (1/1.5).

Conditional secondary objective 3.2: superiority to the pre-booster for participants primed with an adenovirus vector vaccine:

For participants, 18-55 years old, primed with an adenovirus vector vaccine, 14 days after the booster dose (ie, D15) with CoV2 preS dTM-AS03 (D614), the serum neutralization titer against D614G is superior to the serum neutralization titer against D614G prior to the booster dose at D01.

Null hypothesis (H_0): Ratio $_{(post\text{-}booster/pre\text{-}booster)} \leq 2$

Alternative hypothesis (H_1): Ratio $_{(post\text{-}booster/pre\text{-}booster)} > 2$

The superiority will be demonstrated if the lower limit of the two-sided 98.3% CI of the ratio of serum neutralization titer is greater than 2.

The conditional primary immunogenicity objective will be demonstrated only if both non-inferiority and superiority testing described above are demonstrated.

If the primary immunogenicity objective in participants primed with the Pfizer/BioNTech vaccine, conditional secondary immunogenicity objective in participants primed with the protein-based vaccine, conditional secondary immunogenicity objective in participants primed with an mRNA vaccine, and conditional secondary immunogenicity objective in participants primed with an adenovirus vector vaccine are all achieved, 1 conditional secondary immunogenicity endpoint on seroresponse for participants primed with the Pfizer/BioNTech vaccine, the protein-based vaccine, an mRNA vaccine, and an adenovirus vector vaccine will be tested sequentially.

Conditional secondary objective 4: non-inferiority in terms of seroresponse rate for participants primed with the Pfizer/BioNTech, protein-based, mRNA, or adenovirus vector vaccines:

For participants, 18-55 years old, primed with the Pfizer/BioNTech vaccine, the protein-based vaccine, an mRNA vaccine, or an adenovirus vector vaccine, 14 days after the booster dose (ie, D15) with CoV2 preS dTM-AS03 (D614) and 14 days after the second dose (ie, D36) of the Comparator Group, the seroresponse rate against D614G of the Booster Group CoV2 preS dTM-AS03 (D614), is non-inferior to the seroresponse rate against D614G of the Comparator Group.

Null hypothesis (H0) : $p_{(booster)} - p_{(comparator)} \leq -10\%$

Alternative hypothesis (H1) : $p_{(booster)} - p_{(comparator)} > -10\%$

The Pfizer/BioNTech vaccine primed, protein-based vaccine primed, mRNA vaccine primed, and adenovirus vector vaccine primed will be tested sequentially. The non-inferiority will be demonstrated if the lower limit of the two-sided 98.3% CI of the difference between the 2 proportions is great than -10%.

9.1.2.3 Supplemental Cohort 2

For CoV2 preS dTM-AS03 (B.1.351) (non-exploratory arm only), hypothesis testing will be conducted for the 2 co-primary immunogenicity endpoints in participants, 18-55 years of age, primed with the Pfizer/BioNTech vaccine, 2 conditional co-secondary immunogenicity endpoints in participants, 18-55 years of age, primed with an mRNA vaccine, 1 conditional secondary endpoint on GMT in participants, 18-55 years of age, primed with the Pfizer/BioNTech vaccine, 1 conditional secondary endpoint on seroresponse in participants, 18-55 years of age, primed with the Pfizer/BioNTech vaccine and an mRNA vaccine sequentially.

For CoV2 preS dTM-AS03 (D614 + B.1.351), hypothesis testing will be conducted for the 4 co-primary immunogenicity endpoints (if the SARS-CoV-2 D614G variant remains in circulation globally based on reports from authorities [eg, WHO]) or 2 co-primary immunogenicity endpoints on the B.1.351 variant in participants, 18-55 years of age, primed with the Pfizer/BioNTech vaccine, 4 conditional co-secondary immunogenicity endpoints on both B.1.351 and D614G variants (if the SARS-CoV-2 D614G variant remains in circulation globally based on reports from authorities [eg, WHO]), or 2 conditional co-secondary immunogenicity endpoints on the B.1.351 variant in participants, 18-55 years of age, primed with an mRNA vaccine, 1 conditional secondary endpoint on GMT in participants, 18-55 years of age, primed with the Pfizer/BioNTech vaccine, 2 conditional endpoints on seroresponse for both B.1.351 and D614G variants (if the SARS-CoV-2 D614G variant remains in circulation globally based on reports from authorities [eg, WHO]) or 1 conditional endpoint on seroresponse for only the B.1.351 variant in participants, 18-55 years of age, primed with the Pfizer/BioNTech vaccine and an mRNA vaccine sequentially.

Primary objective 1: non-inferiority to the comparator for participants primed with the Pfizer/BioNTech vaccine:

For participants, 18-55 years of age, primed with the Pfizer/BioNTech vaccine, 14 days after the booster dose (ie, D15) of CoV2 preS dTM-AS03 (B.1.351) (non-exploratory arm only) or CoV2 preS dTM-AS03 (D614 + B.1.351) and after the second dose of the primary vaccination Comparator Group (ie, D36), the GMT against B.1.351 of CoV2 preS dTM-AS03 (B.1.351) or GMT against D614G (if the SARS-CoV-2 D614G variant remains in circulation globally based on reports from authorities [eg, WHO]) and B.1.351 of CoV2 preS dTM-AS03 (D614 + B.1.351) is non-inferior to the GMT against D614G of the Comparator Group.

Null hypothesis (H0) : $GMT_{(booster)} / GMT_{(comparator)} \leq (1/1.5)$

Alternative hypothesis (H1) : $GMT_{(booster)} / GMT_{(comparator)} > (1/1.5)$

Each of the 2 Booster Groups, CoV2 preS dTM-AS03 (B.1.351) or CoV2 preS dTM-AS03 (D614 + B.1.351), will be tested separately. The non-inferiority in terms of GMT will be demonstrated for either or both Booster Group(s) if the lower limit of the two-sided 98.3% CI of the ratio of the GMT is greater than (1/1.5).

Primary objective 2: superiority to pre-booster for participants primed with the Pfizer/BioNTech vaccine:

For participants, 18-55 years of age, primed with the Pfizer/BioNTech vaccine, 14 days after the booster dose (ie, D15) of CoV2 preS dTM-AS03 (B.1.351) (non-exploratory arm only) or CoV2 preS dTM-AS03 (D614 + B.1.351) the serum neutralization titer against B.1.351 of CoV2 preS dTM-AS03 (B.1.351) or serum neutralization titer against D614G (if the SARS-CoV-2 D614G variant remains in circulation globally based on reports from authorities [eg, WHO]) and B.1.351 of CoV2 preS dTM-AS03 (D614 + B.1.351) is superior to the serum neutralization titer prior to the booster dose at D01.

Null hypothesis (H_0) : Ratio $_{(post\text{-}booster/pre\text{-}booster)} \leq 2$

Alternative hypothesis (H_1) : Ratio $_{(post\text{-}booster/pre\text{-}booster)} > 2$

Each of the 2 Booster Groups, CoV2 preS dTM-AS03 (B.1.351) or CoV2 preS dTM-AS03 (D614 + B.1.351), will be tested separately. The superiority will be demonstrated for either or both Booster Group(s) if the lower limit of the two-sided 98.3% CI of the ratio of serum neutralization titer is greater than 2.

The primary objectives for either or both of the Booster Group(s), CoV2 preS dTM-AS03 (B.1.351) or CoV2 preS dTM-AS03 (D614 + B.1.351), will be reached if both non-inferiority and superiority testing are demonstrated.

If the primary immunogenicity objective in participants primed with the Pfizer/BioNTech vaccine is reached, 2 conditional secondary immunogenicity endpoints will be tested for participants primed with an mRNA vaccine for CoV2 preS dTM-AS03 (B.1.351), 4 conditional secondary immunogenicity endpoints on both the B.1.351 and D614G variants if the SARS-CoV-2 D614G variant remains in circulation globally based on reports from authorities [eg, WHO], or 2 conditional secondary immunogenicity endpoints on the B.1.351 variant will be tested for CoV2 preS dTM-AS03 (D614 + B.1.351).

Conditional secondary objective 1.1: non-inferiority to the comparator in participants primed with an mRNA vaccine:

For participants, 18-55 years of age, primed with an mRNA vaccine, 14 days after the booster dose (ie, D15) of CoV2 preS dTM-AS03 (B.1.351) or CoV2 preS dTM-AS03 (D614 + B.1.351) and after the second dose of the Comparator Group (ie, D36), the GMT against B.1.351 of CoV2 preS dTM-AS03 (B.1.351) or GMT against D614G (if the SARS-CoV-2 D614G variant remains in circulation globally based on reports from authorities [eg, WHO]) and B.1.351 of CoV2 preS dTM-AS03 (D614 + B.1.351) is non-inferior to the GMT against D614G of primary vaccination Comparator Group.

Null hypothesis (H0) : $GMT_{(booster)} / GMT_{(comparator)} \leq (1/1.5)$

Alternative hypothesis (H1) : $GMT_{(booster)} / GMT_{(comparator)} > (1/1.5)$

Each of the 2 Booster Groups, CoV2 preS dTM-AS03 (B.1.351) or CoV2 preS dTM-AS03 (D614 + B.1.351), will be tested separately. The non-inferiority in terms of GMT will be demonstrated for either or both of the Booster Group(s) if the lower limit of the two-sided 98.3% CI of the ratio of the GMT is greater than (1/1.5).

Conditional secondary objective 1.2: superiority to pre-booster in participants primed with an mRNA vaccine:

For participants, 18-55 years of age, primed with an mRNA vaccine, 14 days after the booster dose (ie, D15) of CoV2 preS dTM-AS03 (B.1.351) or CoV2 preS dTM-AS03 (D614 + B.1.351) the serum neutralization titer against B.1.351 of CoV2 preS dTM-AS03 (B.1.351) or serum neutralization titer against D614G (if the SARS-CoV-2 D614G variant remains in circulation globally based on reports from authorities [eg, WHO]) and B.1.351 of CoV2 preS dTM-AS03 (D614 + B.1.351) is superior to the paired serum neutralization titer prior to booster dose at D01.

Null hypothesis (H_0) : Ratio $_{(\text{post-booster/pre-booster})} \leq 2$

Alternative hypothesis (H_1) : Ratio $_{(\text{post-booster/pre-booster})} > 2$

Each of the 2 Booster Groups, CoV2 preS dTM-AS03 (B.1.351) or CoV2 preS dTM-AS03 (D614 + B.1.351), will be tested separately. The superiority will be demonstrated for either or both of the Booster Groups(s) if the lower limit of the two-sided 98.3% CI of the ratio of serum neutralization titer is great than 2.

For each of the Booster Groups, the conditional secondary objective will be reached if both non-inferiority and superiority testing described above are demonstrated. For CoV2 preS dTM-AS03 (D614 + B.1.351), the approach is used across strains (B.1.351 and D614) (if the SARS-CoV-2 D614G variant remains in circulation globally based on reports from authorities [eg, WHO]) or only on the B.1.351 variant.

If the primary immunogenicity objective in participants primed with the Pfizer/BioNTech vaccine and conditional secondary immunogenicity objectives for participants primed with an mRNA vaccine are both achieved, then 1 conditional secondary endpoint on GMT for CoV2 preS dTM-AS03 (B.1.351) or CoV2 preS dTM-AS03 (D614 + B.1.351), will be tested separately.

Conditional secondary objective 2: superiority to the comparator in terms of GMT against B.1.351:

For participants, 18-55 years of age, primed with the Pfizer/BioNTech vaccine, 14 days after the booster dose (ie, D15) of CoV2 preS dTM-AS03 (B.1.351) (non-exploratory arm only) or CoV2 preS dTM-AS03 (D614 + B.1.351), GMT against B.1.351 of CoV2 preS dTM-AS03 (B.1.351) or/and CoV2 preS dTM-AS03 (D614 + B.1.351) is superior to the GMT against B.1.351 of the primary vaccination Comparator Group.

Null hypothesis (H0) : $GMT_{(\text{variant})} / GMT_{(\text{comparator})} \leq 1.5$

Alternative hypothesis (H1) : $GMT_{(\text{variant})} / GMT_{(\text{comparator})} > 1.5$

Each of the 2 variant-containing vaccine groups, CoV2 preS dTM-AS03 (B.1.351) or CoV2 preS dTM-AS03 (D614 + B.1.351), will be tested separately. The superiority will be demonstrated if the lower limit of the two-sided 98.3% CI of the ratio of the GMT is greater than 1.5 for each or both variant-containing vaccine group(s).

If the primary immunogenicity objective in participants primed with the Pfizer/BioNTech vaccine, conditional secondary immunogenicity objective in participants primed with an mRNA vaccine, and conditional secondary immunogenicity objective on GMT in participants primed with the Pfizer/BioNTech vaccine are all achieved. Conditional secondary immunogenicity objective on

seroresponse for participants primed with the Pfizer/BioNTech vaccine and an mRNA vaccine will be tested sequentially.

Conditional secondary objective 3: non-inferiority in terms of seroresponse rate for participants primed with the Pfizer/BioNTech or mRNA vaccines:

For participants, 18-55 years old, primed with the Pfizer/BioNTech vaccine or an mRNA vaccine , 14 days after the booster dose (ie, D15) with CoV2 preS dTM-AS03 (B.1.351) or CoV2 preS dTM-AS03 (D614 + B.1.351) and 14 days after the second dose (ie, D36) of the Comparator Group, the seroresponse rate against D614G (if the SARS-CoV-2 D614G variant remains in circulation globally based on reports from authorities [eg, WHO]) and B.1.351 of the Booster Group CoV2 preS dTM-AS03 (D614), is non-inferior to the seroresponse rate against D614G of the Comparator Group.

Null hypothesis (H0) : $p_{(booster)} - p_{(comparator)} \leq -10\%$

Alternative hypothesis (H1) : $p_{(booster)} - p_{(comparator)} > -10\%$

Each of the 2 Booster Groups, CoV2 preS dTM-AS03 (B.1.351) or CoV2 preS dTM-AS03 (D614 + B.1.351), will be tested separately. The Pfizer/BioNTech vaccine primed and mRNA vaccine primed will be tested sequentially. The non-inferiority will be demonstrated for either or both of the Booster Groups(s) if the lower limit of the two-sided 98.3% CI of the difference between the 2 proportions is great than -10%.

9.2 Sample Size Determination

9.2.1 Original Phase II Cohort of VAT00002

A total of 720 participants are planned to be enrolled. The 3 adjuvanted vaccine groups have a planned sample size of 240 participants in each group. While formal hypothesis testing will not be performed, the targeted sample size is intended to generate sufficient evidence to enable comparison of immune responses generated in this study to those generated by efficacious vaccines (either in the literature or through testing of historical samples from clinical studies with an efficacious vaccine) to inform decisions about progression to and formulation selection for further investigation at Phase III. A sample size of 130 evaluable naïve participants per group enables detecting a minimum observed GMT ratio of 0.73 assuming GMT ratio of 1 and standard deviation of 0.67 (estimated for the Pseudovirus assay) with 95% probability. To generate data in SARS-CoV-2 non-naïve participants, up to 20% of participants may be rapid serodiagnostic test positive at baseline.

An attrition rate of roughly 15% is assumed in the study to account for the potential deployment and availability of authorized/approved vaccines to study participants.

9.2.2 Supplemental Phase III Cohorts 1 and 2

A Bonferroni adjustment is used to control the overall type I error rate at 0.025 one-sided in Supplemental Cohorts 1 and 2, so each comparison of the Booster Group with the Comparator Group will be performed at one-sided significance level of 0.00833 (0.025/3). No alpha-splitting within hypothesis testing of co-primary endpoints. Assumed attrition rate of Primary Vaccination Group is 10% and Booster Group is 3% (it is anticipated that attrition to 14 days post booster will

be limited and smaller than the attrition to D36 in the Comparator Group). Other assumptions for sample size calculation are as follows:

- The PsVN Std Dev is around 0.65 for primary vaccination at D36 and around 1.0 for booster vaccination at D22 on log_{10} scale base on immunogenicity data obtained from Monogram for the corresponding assay
    - Note : The assumption of the standard deviation of the assay is based on the final interim data of D614G on the PPAS Naïve-D01+D22 at D36 and FAS NonNaïveD01 at D22 from VAT0002 Original Phase II Cohort in participants 18-55 years of age.
- For the primary and secondary objectives in terms of GMT non-inferiority against the comparator (using the D614G titers elicited by the comparator as the benchmark), the ratio of group GMT margin is 1/1.5, the assumed true ratio of group GMT for D614 containing vaccines (comparing D614G titers in both booster vaccine and priming comparator) is 1.5 (this is informed by preliminary interim data from VAT00002 Original Phase II Cohort, indicating titers generally higher in the non-naïve individuals after a single dose, compared to the titers in naïve individuals after 2 doses); and the assumed true ratio of group GMT for the B1.351 variant-containing vaccines (comparing B.1.351 titers in variant-containing vaccines versus D614G titers in the comparator D614 vaccine) is 1 (this is assumed in the absence of data).
- For the primary and secondary objectives in terms of superiority on ratio of serum neutralization titer (post-booster compared to pre-booster), the margin of ratio is 2, and the assumed true ratio is 5 (this is a conservative assumption informed by interim data from VAT00002 Original Phase II Cohort for non-naïve individuals indicating ratio of individual serum neutralization titer for D614G post single immunizations compared to baseline in the range of 14-16). Std Dev 1.0 difference on log10 scale is assumed for the post/pre antibody response.
- For the conditional secondary objective in Supplemental Cohort 2 on superiority of B.1.351 strain (Booster Group versus Comparator Group), the margin of ratio is 1.5, and the assumed true ratio is 3 (this is assumed in the absence of data).
- For the conditional secondary objective on seroresponse (Booster Group at D15 versus Comparator Group at D36), the margin of proportion difference is -10%, the assumed true seroresponse rate for the Booster Group is around 96.5% (this is assumed in the absence of data) and for the Comparator Group is 99%.

For non-inferiority testing of the difference between 2 means (ratio of group GMT on log_{10} scale), the sample size estimation used a one-sided, two-sample t-test. For superiority by a margin tests for paired means, a one-sided t-test was used.

For the vaccine groups undergoing hypothesis testing, a total of 215 participants, 18-55 years of age, are planned to be enrolled in Supplemental Cohort 1 CoV2 preS dTM-AS03 (D614) vaccine groups.

A total of 515 participants, 18-55 years old, primed with the Pfizer/BioNTech vaccine are planned to be enrolled in each of the 2 Supplemental Cohort 2 vaccine groups, CoV2 preS dTM-AS03 (B.1.351) or CoV2 preS dTM-AS03 (D614 + B.1.351).

A total of 75 participants 18-55 years of age and 25 participants ≥ 56 years of age who have received each of the priming vaccines other than those primed with Pfizer/BioNTech, Moderna, Oxford University/AstraZeneca, and J&J/Janssen, are planned to be enrolled to receive the CoV2 preS dTM-AS03 (D614) booster in Supplemental Cohort 1, and the monovalent (B.1.351) booster and CoV2 preS dTM-AS03 (D614 + B.1.351) booster in Cohort 2.

A total of 515 participants, 18-55 years of age, who are SARS-CoV-2 naïve (no evidence of previous infection or vaccination) receiving 2 doses of the CoV2 preS dTM-AS03 (D614) parental vaccine will be enrolled as the Comparator Group for both Supplemental Cohorts 1 and 2. Additionally, for enabling extrapolation, approximately 50 participants ≥ 56 years of age are planned to be enrolled in each Supplemental Cohort 1 and Cohort 2 groups primed with the Pfizer/BioNTech vaccine (in the non-exploratory arms).

Approximately 300 participants, 18-55 years of age, primed with the CoV2 PreS dTM-AS03 vaccine and 150 participants, ≥ 56 years of age, primed with the CoV2 PreS dTM-AS03 vaccine are assumed to transition from the Original Phase II Cohort into the 2 Supplemental Cohort 2 vaccine groups, CoV2 preS dTM-AS03 (B.1.351) and CoV2 preS dTM-AS03 (D614); however, the actual number of Original Phase II Cohort participants meeting eligibility criteria for transition cannot be accurately determined, and as such the actual number of CoV2 PreS dTM-AS03 booster participants in Supplemental Cohort 2 may be smaller or larger than assumed. For detailed power estimations for Supplemental Cohorts 1 and 2 refer to Table 9.1.

Table 9.1: Power estimations for Supplemental Cohorts 1 and 2 (18-55 years old)

<table>
<tr><th>Cohort/ Objective(s)</th><th>Arm</th><th>Parameters for Non-inferiority</th><th>Parameters for Superiority</th><th>Study Power</th></tr>
<tr><td colspan="5">Cohort 1 CoV2 preS dTM-AS03 (D614) Booster Group</td></tr>
<tr><td>Primary Objectives (Type I error: 0.00833)</td><td>Pfizer primed CoV2 preS dTM-AS03 (D614) Booster Group (N=215)</td><td rowspan="5">• Assumed true ratio of group GMT: 1.5
• Margin: 1/1.5
• Std Dev (booster): 1.0
• Std Dev (comparator): 0.65</td><td rowspan="5">• Assumed true ratio: 5
• Margin: 2
• Std Dev (booster): 1.0</td><td>• Non-inferiority: 98.7%
• Superiority: > 99.9%
• Overall: 98.7%</td></tr>
<tr><td>Conditional Secondary Objectives (Type I error: 0.00833)</td><td>Protein-based primed CoV2 preS dTM-AS03 (D614) Booster Group (N~=270)</td><td>• Non-inferiority: 99.7%
• Superiority: > 99.9%
• Overall: 99.6%</td></tr>
<tr><td>Conditional Secondary Objectives (Type I error: 0.00833)</td><td>mRNA primed CoV2 preS dTM-AS03 (D614) Booster Group (N=290)</td><td>• Non-inferiority: 99.8%
• Superiority: > 99.9%
• Overall: 99.8%</td></tr>
<tr><td>Conditional Secondary Objectives (Type I error: 0.00833)</td><td>Adenovirus vector primed CoV2 preS dTM-AS03 (D614) Booster Group (N=150)</td><td>• Non-inferiority: 94%
• Superiority: 99.1%
• Overall: 93.2%</td></tr>
<tr><td>Conditional Secondary Objective</td><td>Pfizer primed CoV2 preS dTM-AS03</td><td colspan="2">Non-inferiority on seroresponse</td><td>95.3%</td></tr>
</table>

(Type I error: 0.00833)	(D614) Booster Group (N=215)	• Assumed true Comparator Group seroresponse rate: 99% • Assumed actual difference between Booster and Comparator Groups: -2.5% • Margin: -10%		
Conditional Secondary Objectives (Type I error: 0.00833)	Protein-based primed CoV2 preS dTM-AS03 (D614) Booster Group (N=270)			98.9%
Conditional Secondary Objective (Type I error: 0.00833)	mRNA primed CoV2 preS dTM-AS03 (D614) Booster Group (N=290)			99.4%
Conditional Secondary Objective (Type I error: 0.00833)	Adenovirus vector primed CoV2 preS dTM-AS03 (D614) Booster Group (N=150)			78.2%
Cohort 2 CoV2 preS dTM-AS03 (B.1.351) Booster Group				
Primary Objectives (Type I error: 0.00833)	Pfizer primed CoV2 preS dTM-AS03 (B.1.351) Booster Group (N=515)	• Assumed true ratio of group GMT: 1 • Margin: 1/1.5 • Std Dev (booster): 1.0 • Std Dev (comparator): 0.65	• Assumed true ratio: 5 • Margin: 2 • Std Dev (booster): 1.0	• Non-inferiority: 80.5% • Superiority: > 99.9% • Overall: 80.5%
Conditional Secondary Objectives (Type I error: 0.00833)	mRNA primed CoV2 preS dTM-AS03 (B.1.351) Booster Group (N=590)			• Non-inferiority: 84.5% • Superiority: > 99.9% • Overall: 84.5%
Conditional Secondary Objective on B.1.351 variant (Type I error: 0.00833)	Pfizer primed CoV2 preS dTM-AS03 (B.1.351) booster group (N=515)	Superiority on ratio of group GMT (GMT against B.1.351 vs comparator GMT against B.1.351) • Assumed true ratio of group GMT: 3 • Margin: 1.5 • Std Dev (booster): 1.0 • Std Dev (comparator): 0.65		> 99.9%
Conditional Secondary Objective on seroresponse (Type I error: 0.00833)	Pfizer primed CoV2 preS dTM-AS03 (B.1.351) booster group (N=515)	Non-inferiority on seroresponse • Assume true comparator group seroresponse rate: 99% • Assumed actual difference between booster and comparator group: -2.5% • Margin: -10%		> 99.9%
Conditional Secondary Objective on seroresponse (Type I error: 0.00833)	mRNA primed CoV2 preS dTM-AS03 (B.1.351) booster group (N=590)			> 99.9%
Cohort 2 CoV2 preS dTM-AS03 (D614 + B.1.351) Booster Group				
Primary Objectives (Type I error: 0.00833)	Pfizer primed CoV2 preS dTM-AS03 (D614 + B.1.351) Booster Group (N=515)	B.1.351 variant: • Assumed true ratio of group GMT: 1 • Margin: 1/1.5 • Std Dev (booster): 1.0	• Assumed true ratio: 5 • Margin: 2 • Std Dev (booster): 1.0	• Non-inferiority (B.1.351 variant): 80.5% • Non-inferiority (D614G variant): > 99.9%

		• Std Dev (comparator): 0.65 D614 variant: • Assumed true ratio of group GMT: 1.5 • Margin: 1/1.5 • Std Dev (booster): 1.0 • Std Dev (comparator): 0.65		• Superiority: > 99.9% • Overall (across two strains): 80.5%
Conditional Secondary Objectives (Type I error: 0.00833)	mRNA primed CoV2 preS dTM-AS03 (D614 + B.1.351) Booster Group (N=590)			• Non-inferiority (B.1.351 variant): 84.5% • Non-inferiority (D614 variant): > 99.9% • Superiority: > 99.9% • Overall (across two strains): 84.5%
Conditional Secondary Objective on B.1.351 variant (Type I error: 0.00833)	Pfizer primed CoV2 preS dTM-AS03 (D614 + B.1.351) Booster Group (N=515)	Superiority on ratio of group GMT (GMT against B.1.351 vs comparator GMT against B.1.351) • Assumed true ratio of group GMT: 3 • Margin: 1.5 • Std Dev (booster): 1.0 • Std Dev (comparator): 0.65		> 99.9%
Conditional Secondary Objective on seroresponse (Type I error: 0.00833)	Pfizer primed CoV2 preS dTM-AS03 (D614 + B.1.351) Booster Group (N=515)	Non-inferiority on seroresponse • Assumed true Comparator Group seroresponse rate: 99% • Assumed actual difference between Booster and Comparator groups: -2.5% • Margin: -10%		> 99.9%
Conditional Secondary Objective on seroresponse (Type I error: 0.00833)	mRNA primed CoV2 preS dTM-AS03 (D614 + B.1.351) Booster Group (N=590)			> 99.9%

Note: Std Dev of 0.65 for the comparator at D36, 1.0 for the boosters at D22 were on $\log_{10}$ scale and 1.0 for the post/pre booster at D15 relative to D01 was on $\log_{10}$ scale.

A total of 75 participants 18-55 years of age and 25 participants ≥ 56 years of age who have been primed with the Pfizer/BioNTech vaccine are planned to be enrolled to receive the different monovalent (B.1.351) booster formulations in Supplemental Cohort 2. The sample sizes are not based on hypothesis to be tested but rather to provide information on potential future adjustments of the booster vaccines.

9.3 Analysis Sets

The following subgroup definitions of SARS-CoV-2 Naïve and Non-Naïve at D01 or both D01 and D22 timepoints are applied for all randomized participants in the Original Phase II Cohort:

Prior SARS-CoV-2 infection status (Original Phase II Cohort)	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 sample AND • Negative NAAT for SARS-CoV-2 on respiratory sample 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 sample OR • Positive NAAT for SARS-CoV-2 on respiratory sample collected on D01 or D22

The following subgroup definitions of SARS-CoV-2 Naïve and Non-Naïve at D01 timepoint are applied for all randomized participants in all Supplemental Cohorts:

Prior SARS-CoV-2 infection status (Supplemental Cohorts)	Description
SARS-CoV-2 Naïve at baseline (Naïve-D01)	• Negative by the anti-S immunoassay (Roche Elecsys) 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 NAAT for SARS-CoV-2 on respiratory sample collected on D01

The following subgroup definitions of SARS-CoV-2 Naïve and Non-Naïve at both D01 and D22 timepoints are applied for all randomized participants in the Supplemental Cohorts Comparator Group:

Prior SARS-CoV-2 infection status (Supplemental Cohorts)	Description
SARS-CoV-2 Naïve at second injection (Naïve-D01+D22)	• Negative by the anti-S immunoassay (Roche Elecsys) on D01 serum sample AND • Negative NAAT for SARS-CoV-2 on respiratory sample 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 NAAT for SARS-CoV-2 on respiratory sample collected on D01 or D22

The following populations are defined for analysis:

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), inclusion/exclusion criteria and prior vaccination platform for booster vaccination groups. 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 have been allocated by IRT.
Safety Analysis Set (SafAS)	Participants randomized and who have received at least 1 dose of the study vaccines. All participants will have their safety data analyzed after each dose according to the vaccine they truly received, and after any dose according to the vaccine received at the first dose. Safety data recorded for participants not administered a study intervention will be excluded from the analysis (and listed separately).
Full analysis set (FAS)	All randomized participants who receive at least 1 study injection. Participants will be analyzed according to the intervention to which they were randomized.
Per-protocol analysis set (PPAS)	Subset of the FAS. Participants presenting with at least 1 of the following criteria 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 • Participants did not receive both injections for 2 doses primary vaccination groups or 1 dose booster injection for booster vaccination groups • Participant received a vaccine 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 protocol defined vaccine in the proper time window • Participants who did not provide all post-dose blood samples within the proper time window or no post-dose blood sample was drawn • Participant received the second injection (in the primary vaccination groups) despite meeting any of the definitive contraindication criteria • Participant receives an authorized/approved COVID-19 vaccine prior to D36 for primary vaccination groups or D15 for booster vaccination groups The definition may be complemented with additional criteria for exclusion after the review of protocol deviations reported on site.

Cellular Immunity and Mucosal analysis set (CMIAS)	Subset of the FAS and randomly assigned to the Cellular Immunity and mucosal subset (Original Phase II Cohort, Supplemental Cohort 2 primed with the Pfizer/BioNTech vaccine in the non-exploratory groups and Supplemental Cohort 2 CoV2 preS dTM-AS03 (D614) primary series from the Original Phase II Cohort). Participants presenting with at least one of the following criteria will be excluded from the CMIAS: • Participant did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria • Participants did not receive both injections in the primary vaccination groups or one injection in the booster vaccination groups • Participant received a vaccine 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 in the proper time window • Participants received the second injection (in the primary vaccination groups) despite meeting any of the definitive contraindication criteria. • Participant receives an authorized/approved COVID-19 vaccine prior to D36 for primary vaccination groups or D15 for booster vaccination groups The definition may be complemented with additional criteria for exclusion after the review of protocol deviations reported on site.
Variant Testing analysis set (VTAS)	Subset of the FAS and randomly assigned to the Variant Testing subset: Supplemental Cohort 1, Supplemental Cohorts 1 and 2 Comparator Group, Supplemental Cohort 2 primed with the Pfizer/BioNTech vaccine in the non-exploratory groups and Supplemental Cohort 2 CoV2 preS dTM-AS03 (D614) primary series from the Original Phase II Cohort. Participants presenting with at least 1 of the following criteria will be excluded from the VTAS: • Participant did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria • Participants did not receive both injections in the primary vaccination groups or one injection in the booster vaccination groups • Participant received a vaccine 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 in the proper time window • Participants received the second injection (in the primary vaccination groups) despite meeting any of the definitive contraindication criteria. • Participant receives an authorized/approved COVID-19 vaccine prior to D36 for primary vaccination groups or D15 for booster vaccination groups

	The definition may be complemented with additional criteria for exclusion after the review of protocol deviations reported on site.

9.4 Statistical Analyses

The initial statistical analysis plan (SAP) was finalized prior to the database lock for the interim analysis informing progression to Phase III for the Original Phase II Cohort; an amended SAP will be finalized prior to the database lock for any interim analysis applicable to the Supplemental Phase III Cohorts. Additional SAP amendments may be performed after execution of the interim analysis and before any additional analysis that occurs between any such interim analyses and the final analysis. The SAP 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.

The endpoints for safety and immunogenicity are as shown in Table 3.1.

9.4.1 General Considerations

For the Original Phase II Cohort, analyses of safety and immunogenicity objectives will be descriptive. For the Supplemental Phase III Cohorts, hypothesis testing will be conducted for the primary immunogenicity objectives and conditional secondary objectives as described above. Analyses of other secondary objectives and exploratory objectives will be descriptive. Exploratory objectives will be included in either the SAP or supplemental SAP.

9.4.2 Statistical Considerations

9.4.2.1 Original Phase II Cohort

9.4.2.1.1 Primary - Safety

The main parameter will be described for all safety endpoints. The percentage of participants (using as denominator the number of participants) will be provided for analysis of solicited AEs, unsolicited AEs (including immediate systemic AEs within 30 minutes), SAEs, AESIs and MAAEs. The corresponding 95% CIs for the percentages will be calculated based on the Clopper-Pearson method. Subgroup analyses will be performed for age group, baseline SARS-CoV-2 Naïve status (Naïve at D01 and Non-Naïve at D01) (as defined in Section 9.3), and high-risk medical conditions group for the main safety analyses.

The SafAS population will be used for safety analyses for the following endpoints:

- Presence, and relationship of unsolicited (immediate) systemic AEs reported in the 30 minutes after each vaccination.
- 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 and 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 unsolicited AEs reported up to 21 days after the last 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, nature (MedDRA SOC and PT), relationship to vaccination of MAAEs throughout the study.

9.4.2.1.2 Primary - Immunogenicity

The percentage of responders and participants having a 2-fold rise (2FR), 4-fold rise (4FR) will be provided against each endpoint with the corresponding 95% CIs using the Clopper-Pearson method. Differences of percentages of responders and participants with 2FR, 4FR will be provided with 95% CI calculated by the Newcombe-Wilson score method without continuity correction for the main immunogenicity analyses (65). GMTs in each injection group and GMT ratios between injection groups will be summarized along with their 95% CIs using the normal approximation of log-transformed titers. GMTs will be presented in original scale that are re-converted from log-transformed titers. GMTRs is defined as geometric mean of individual titers ratios (post-vaccination/pre-vaccination for each injection). GMTR will be summarized with 95% CI (normal approximation) for D36 compared to D01. Reverse Cumulative Distribution Curves (RCDC) will be generated for baseline (D01) and post-vaccination immunogenicity. Additional parameters may be displayed as appropriate.

The PPAS Naïve-D01+D22 will be utilized for primary immunogenicity endpoints. Subgroup analyses will be performed by age-group (18-59 years old and ≥ 60 years old), and high-risk medical conditions groups. The primary immunogenicity endpoints will also be evaluated on FAS Naïve-D01 and FAS Naïve-D01+D22. Details of the analysis and any additional analysis will be described in the SAP if applicable.

9.4.2.1.3 Secondary – Safety

The occurrences of serologically-confirmed SARS-CoV-2 infection will be described by percentages of participants with infection during the analysis period with 95% CI by Clopper-Pearson methods. The occurrences of each endpoint related to laboratory-confirmed symptomatic COVID-19 will be described by percentages with 95% CI (by Clopper-Pearson methods). SafAS population will be utilized for analysis.

Participants with an active SARS-CoV-2 infection at baseline (as determined by positive NAAT at D01) will be listed separately, if applicable.

If the total number of observed COVID-19 clinical illness cases at the analysis time point is less than 5 in all groups, no summary analysis will be performed, and a listing of observed cases will be provided. Additional analyses will be described in the SAP.

9.4.2.1.4 Secondary - Immunogenicity

The same analysis methods stated in Section 9.4.2.1.2 will be applied for both neutralizing antibody titers and binding antibody titers in all listed timepoints. Geometric mean value of concentrations (GMCs), GMC ratios and geometric mean concentration ratios (GMCRs) will be used for notations against binding antibody concentrations instead of GMT, GMT ratios and GMTR against neutralizing antibody titers. Analysis of 2FR, 4FR and proportion of responders in naïve and non-naive will be estimated as described above.

The PPAS Naïve-D01+D22 and PPAS Non-Naïve-D01/D22 populations will be utilized for secondary immunogenicity endpoints. Analysis will also be performed in FAS Naïve D01+D22, FAS Naïve-D01, and FAS Non-Naïve-D01. Details of the analysis and any additional analysis will be described in the SAP if applicable.

9.4.2.1.5 Exploratory – Immunogenicity

Details of the exploratory analysis will be described in the SAP or supplemental SAP.

9.4.2.2 Supplemental Phase III Cohorts

9.4.2.2.1 Primary - Immunogenicity

Due to the nature of immunogenicity titer, logarithm transformation of the individual data (titers or concentrations) ($\log_{10}$(data)) will be calculated and assumed to be normally distributed. The statistical inference will be based on the use of the two-sided 98.3% CI (Supplemental Cohorts 1 and 2) for non-inferiority of difference in means of post-vaccination log10 transformed concentrations between the 2 groups with normal approximation.

The calculation of the CI for the GMT ratio between Booster Arms and the Comparator Group for Supplemental Cohorts 1 and 2 will use Welch's t-interval.

For the geometric mean of individual titer ratios post-boost versus pre-boost for superiority testing, the two-sided 98.3% CI (Supplemental Cohorts 1 and 2) of post-booster versus pre-booster will be calculated using $\log_{10}$-transformed titers assume normal distribution by applying paired t-interval.

The PPAS will be utilized for primary immunogenicity objectives. The primary immunogenicity endpoints will also be evaluated in the FAS (Table 9.2).

Subgroup analyses, where applicable, will be performed by age group (18-55 years old and ≥ 56 years old) for Intervention Groups, by priming vaccine (Supplemental Cohorts 1 and 2), and by priming platform (Supplemental Cohorts 1 and 2), in addition to the Overall Group.

Table 9.2: Analysis set used in analyses

Cohort	Intervention Group(s)	Comparator Group
Supplemental Cohort 1	PPAS, FAS	PPAS Naïve at D01+D22, FAS Naïve at D01, FAS Naïve at D01+D22

Supplemental Cohort 2	PPAS, FAS	PPAS Naïve at D01+D22, FAS Naïve at D01, FAS Naïve at D01+D22

9.4.2.2.2 Primary - Safety

The main parameter will be described for all safety endpoints. The percentage of participants (using as denominator the number of participants) will be provided for analysis of solicited AEs, unsolicited AEs (including immediate systemic AEs within 30 minutes), SAEs, AESIs and MAAEs. The corresponding 95% CIs for the percentages will be calculated based on the Clopper-Pearson method. In the priming vaccine groups (comparator for Cohorts 1 and 2), subgroup analyses will be performed by age group (18-55 years old and ≥ 56 years old), high-risk medical conditions group, and baseline SARS-CoV-2 naïve status for the main safety analyses. In the Booster Groups (in Cohorts 1 and 2), subgroup analyses will be performed by age group (18-55 years old and ≥ 56 years old), high-risk medical conditions group, priming vaccine platform, and individual priming vaccine. Safety endpoints will be analyzed for each of the CoV2 preS dTM primary series dosages administered in the Original Phase II Cohort (ie, 5-10-15 µg). The SafAS population will be used for safety analyses for the following endpoints:

- Presence and relationship of unsolicited (immediate) systemic AEs reported in the 30 minutes after each vaccination.
- 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 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 unsolicited AEs reported up to 21 days after the last 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, nature (MedDRA SOC and PT), relationship to vaccination of MAAEs throughout the study.

9.4.2.2.3 Secondary - Immunogenicity

The percentage of responders and participants having 2FR, 4FR will be provided against each endpoint with the corresponding 95% CIs using the Clopper-Pearson method. FR is defined as fold-rise from post-vaccination relative to pre-vaccination. Differences of percentages of responders and participants with 2FR and 4FR will be provided with 95% CI calculated by the Newcombe-Wilson score method without continuity correction. GMTs or GMCs in each injection group and GMT ratios between injection groups will be summarized along with their 95% CIs using the normal approximation of log-transformed titers. GMTs will be presented in original

scale that are re-converted from log-transformed titers. GMTRs are defined as the ratio of individual geometric mean titer for each injection group. GMTR will be summarized with 95% CI (normal approximation). Additional parameters may be displayed as appropriate.

The same method will be applied for calculating the two-sided CI as in Section 9.4.2.2.1.

The PPAS will be utilized for secondary immunogenicity objectives. Subgroup analyses will be performed but not limited to age group (18-55 years old and ≥ 56 years old) for Intervention Groups. The secondary immunogenicity endpoints will also be evaluated on the FAS.

9.4.2.2.4 Secondary – Safety

The occurrences of each endpoint related to laboratory-confirmed symptomatic COVID-19 will be described by percentages with 95% CI (by Clopper-Pearson methods). The SafAS population will be utilized for analysis.

Participants with active SARS-CoV-2 infection at baseline (as determined by positive NAAT at D01) will be listed separately, if applicable. If the total number of observed COVID-19 clinical illness cases at the analysis time point is less than 5 in all groups, no summary analysis will be performed, and a listing of observed cases will be provided. Additional analyses will be described in the SAP.

9.4.2.2.5 Exploratory – Immunogenicity

The PPAS will be applied for exploratory immunogenicity analyses. These analyses may also be performed in the FAS. Details of exploratory analyses will be described in the SAP or supplemental SAP.

9.5 Interim Analyses

For the Original Phase II Cohort, the interim analyses were to be performed on data collected for primary immunogenicity objectives and on data collected for primary safety objectives up to 21 days post-injection 2. A partial database lock was conducted for the interim analysis. The statistical analyses of this interim analysis were used for dose selection and to support progression to Phase III. The study blind was broken at the group level to the Sponsor at that time.

A second interim analysis for the Original Phase II Cohort will be performed when safety and immunogenicity data collected up to D202 are available. The SAP will describe the planned interim analyses in greater detail.

For Supplemental Cohort 1, an interim analysis will be carried out once the following conditions apply:

- Primary immunogenicity data is available up to D15 and primary safety data is available up to D22 for the Booster Group in Supplemental Cohort 1
- Primary immunogenicity data is available up to D36 and primary safety data is available up to D43 in the Comparator Group for Supplemental Cohorts 1 and 2
- Partial database lock is performed

For Supplemental Cohort 2, an interim analysis may be carried out once the following conditions apply:

- Primary immunogenicity data is available up to D15 and primary safety data is available up to D22 for the Booster Groups in Supplemental Cohort 2
- Primary immunogenicity data is available up to D36 and primary safety data is available up to D43 in the Comparator Group for Supplemental Cohorts 1 and 2
- Partial database lock is performed

For Supplemental Cohorts 1 and 2, additional interim analyses may be performed at later timepoints.

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, protocol amendments, 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), 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 and answer all questions regarding 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 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 least until completion of the key follow-up timepoint (D43) for informing progression to Phase III and dose selection. 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 ICF during their participation in the study.
- A copy of the ICF must be provided to the participant.

The ICF will contain a specific section that addresses the use of remaining mandatory samples for optional exploratory research, unless prohibited by local laws or IRBs/IECs. The Investigator or designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

Recruitment Procedures

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

10.1.4 Data Protection

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 (35) 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 local data protection law. The level of disclosure must also be explained to the participant as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- 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 Dissemination of Clinical Study Data

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

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

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

10.1.6 Data Quality Assurance

- Participant data as specified in the protocol 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 a 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.

10.1.7 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, DCs, medical and hospital records, screening logs, informed consent 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.

10.1.8 Study and Site Start and Closure

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

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

The Sponsor 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.

10.1.9 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	pre-injections 1 and 2 at D01 and V02 (D22*), respectively	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

* For SARS-CoV-2-naïve participants only

** 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 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.

Note: any AEs at and around the NIMP injection / administration site regardless of its nature and onset is to be reported as unsolicited systemic AE since it does not occur at and around the IMP injection/administration site.

Medically-Attended AE (MAAE)

An MAAE is a new onset or a worsening of a condition that prompts the participant or participant's parent/guardian 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.

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.

Potential Immune-Mediated Disease (pIMDs): pIMDs constitute a group of AEs that need to be recorded and reported as pIMDs and 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 • 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 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 authorised 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[a] as either ***not related*** or ***related***, based on the following definitions:

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

- Not related – The AE is clearly / most probably caused by other etiologies such as an 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 postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed 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 Pasteur contact, as needed. The toll-free contact information for the Call Center is provided in the Operating Guidelines.

This process does not replace the need to report an SAE. The Investigator is still required to follow the protocol-defined process for reporting SAEs to the GPV Department.

In case of emergency code-breaking, the Investigator is required to follow the code-breaking procedures described in Section 6.3.2.

10.3.5 Assessment of Intensity

The Investigator will make an assessment of intensity for each AE reported during the study. An intensity grade will be assigned to each AE. The intensity grading scales used in this study are adapted from the "FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007".

10.3.5.1 Tables for Clinical Abnormalities

10.3.5.1.1 Solicited AR Intensity Grading Scale

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

CRF term (MedDRA lowest level term [LLT])	Injection site pain	Injection site erythema	Injection site swelling
Diary card term	Pain	Redness	Swelling
Definition	Pain either present spontaneously or when the injection site is touched or injected limb is mobilized	Presence of a redness including the approximate point of needle entry	Swelling at or near the injection site Swelling or edema is caused by a fluid infiltration in tissue or cavity and, depending on the space available for the fluid to disperse, swelling may be either soft (typically) or firm (less typical) to touch and thus can be best described by looking at the size of the swelling
Intensity scale*	**CRF:** Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living. Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant. Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. **Diary Card:** Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity	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	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:** Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity	Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. **Diary card:** Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity

DC, Diary Card; 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: No interference with activity.
- 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 activity.
- 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 daily activity.

10.3.5.1.3 COVID-19 Symptoms Intensity and 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 1 – sense of smell/sense of taste is less than usual
- Grade 2 – no sense of smell/sense of taste

10.4 Appendix: Collection of Pregnancy Information

DEFINITIONS:

Females of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).
If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

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.

COLLECTION OF PREGNANCY INFORMATION

- The Investigator will collect pregnancy information on all female participants who becomes pregnant while participating in this study.
- The initial information together with the contraceptive method if any will be recorded on the appropriate form and promptly submitted to the Sponsor and no later than 1 month of learning of a participant's pregnancy.

Female Participants who become pregnant

- If the female participant becomes pregnant during the contraception/abstinence period where the participant is requested to be under contraception with effective method of contraception or abstinence (from at least 4 weeks prior to the first vaccination until at least 12 weeks after the last vaccination, the participant will be followed to determine the outcome of the pregnancy), the Investigator will collect follow-up information on the participant up to delivery and the offspring and the information will be promptly forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date but will be in accordance with local regulations. The offspring will be followed for up to 12 months. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- If the pregnancy occurs after the contraception/abstinence period, 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 no later than 1 month of learning of the pregnancy. Pregnancy status will be collected, follow-up of the participant will continue as part of the study, but the participant will not be followed-up until the pregnancy outcome and the offspring will not be followed.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at < 22 weeks gestational age), or intrauterine demise or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.4.4. 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.
- In case of pregnancy during the primary series and if at least 1 dose of the study vaccine(s) has been administered, the participant will not be discontinued from the study, but no further vaccination will be administered until after she is no longer pregnant (if applicable). However, the participant will be followed for safety assessment (and may be followed for immunogenicity assessment, if applicable).

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

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: o Acute macular neuroretinopathy (also known	- Autoimmune / Immune-mediated pancreatitis - Celiac disease	- Autoimmune cholangitis - Autoimmune hepatitis - Primary biliary cirrhosis - Primary sclerosing cholangitis

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	
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 o Juvenile spondyloarthritis o Keratoderma blenorrhagica o Psoriatic 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: o Variants such as Miller Fisher syndrome and the acute motor	- 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 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)	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 - Pyoderma gangrenosum - Reactive granulomatous dermatitis, including :	- 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) o Microscopic polyangiitis o Necrotizing vasculitis o Polyarteritis nodosa	- 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 enhancement of infection”, “disease enhancement”, “immune enhancement”, and

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 Single organ cutaneous vasculitis, including leukocytoclastic vasculitis, hypersensitivity vasculitis and acute hemorrhagic edema of infancy (AHEI) o Wegener's granulomatosis	"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: Risk-based Approach

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

10.7 Appendix: Abbreviations

AC	Adjudication Committee
AE	adverse event
AESI	adverse event of special interest
AR	adverse reactions
ccIAS	Case-cohort immunogenicity analysis set
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CMI	cellular-mediated immunity
CMIAS	Cellular-Mediated Immunity analysis set
CoV2 preS dTM	SARS-CoV2 prefusion Spike delta TM
COVPN	COVID-19 Prevention Trials Network
CRF	(electronic) case report form
CSR	clinical study report
DC	diary card
DMC	Data Monitoring Committee
DSMB	Data and Safety Monitoring Board
ECMO	Extracorporeal membrane oxygenation
ELISA	enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immunospot
EMA	European Medicines Agency
EU	European Union
EUA	Emergency Use Authorization
FAS	Full analysis set
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
GMC	geometric mean concentration
GMT	geometric mean titer
GMTR	geometric mean titer ratio
GPV	Global Pharmacovigilance
HA	hemagglutinin
HCP	Host-Cell Protein

HR	heart rate
HRT	Hormonal replacement therapy
IB	Investigator's Brochure
IC	internal control
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committees
IM	intramuscular
IMP	Investigational Medicinal Product
INN	International non-proprietary name
IRB	Institutional Review Boards
IRT	Interactive Response Technology
LB	lower bound
LLOQ	lower limit of quantification
MAAE	medically-attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
mFAS-PD2	Modified full analysis set post-dose 2
mRNA	messenger ribonucleic acid
NAAT	Nucleic Acid Amplification Test
NHP	non-human primate
NIH	National Institutes of Health
NIMP	Non- Investigational Medicinal Product
OG	Oversight Group
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
pIMD	potential immune-mediated disease
PPAS	Per-protocol analysis set
PS	PhenoSense
PT	preferred term
PV	pharmacovigilance
rIAS	Random immunogenicity analysis set
rapIAS	Rapid immunogenicity analysis set
RMO	Responsible Medical Officer

RNA	ribonucleic acid
RP2	Respiratory Panel 2
RR	respiratory rate
S	Spike
SA	saliva sample
SAE	serious adverse event
SafAS	Safety Analysis Set
SAP	Statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SoA	Schedule of Activities
SP	Sanofi Pasteur
SUSAR	suspected unexpected serious adverse reaction
TBD	to be determined
Th	T-helper
US	United States
USG	United States Government
VAED	vaccine associated enhanced disease

10.8 Appendix: Protocol Amendment/Update History

The Protocol Amendment rationale for the current change in versions (from Version 9.0 to Version 10.0) is located directly before the Table of Contents.

Protocol Version 2.0, dated 15 January 2021

The major protocol revisions and rationale for revisions from Version 1.0 to Version 2.0 are as shown below:

Revision	Rationale
The study design changed to a Phase II dose-finding study evaluating safety and immunogenicity of 3 different doses of recombinant protein antigen with a fixed dose of AS03 adjuvant to generate data to decide on progression to Phase III and dose-selection.	The safety and immunogenicity of the CoV2 preS dTM-AS03 adjuvanted vaccine was evaluated in the Phase I/II study in healthy adults 18 years of age and older. The objective of the Phase I/II study was to inform progression to a Phase III study, dose selection, formulation choice, and injection schedule selection. A low-dose and a high-dose antigen formulation corresponding to an effective dose of 1.3 µg and 2.6 µg of CoV2 preS dTM antigen were evaluated in the study in combination with a fixed dose of either AS03 or AF03 adjuvants. Interim data from the study indicated that a 2-injection schedule of the adjuvanted vaccine was necessary to induce neutralizing antibody responses and that the AS03 adjuvanted vaccine attained higher immune responses than the AF03 adjuvanted vaccine. Interim data from the study showed lower than expected immunogenicity, particularly in older adults, in combination with higher than expected reactogenicity indicating that assessment of optimized antigen formulations (with higher antigen dose and lower host-cell protein content) is necessary to select a formulation to progress to Phase III evaluation. Therefore, the study design is revised as a Phase II study to determine progression to Phase III and selection of an optimized formulation for the Phase III.

Protocol Version 3.0, dated 04 February 2021

The major protocol revisions and rationale for revisions from Version 2.0 to Version 3.0 are as shown below:

Revision	Rationale
Data Safety Monitoring Board / Oversight Group / Protocol Safety Review Team text removed throughout	As the funding structure for this study has changed, the common DSMB under the US government funded COVID-19 programs and the OG have been removed for the Phase II administrative structure.
Table 6.1 (Identity of Study Interventions): Dose Formulation Row: Added: CoV2 preS dTM vaccine is a sterile, clear, colorless solution (with possible presence of endogenous particles) of SARS-CoV-2 prefusion S proteins for IM injection. Endogenous particles, if present, would be seen as light in color flocculates that are slow sinking and suspended in solution.	New product appearance information received since previous protocol update.
Any mention of "OWS" for Operation Warp Speed has been changed to "USG" for US Government	Due to change in funding and administrative structure after shift from Phase III and II/III to Phase II as well as the new name provided to the US Government funded COVID-19 effort.
Besides deletion of DSMB/PSRT text, revised text to state that the Sponsor may recommend a pause and determines continuation/adaptation of study design.	Revisions due to decision made for administrative structure and safety monitoring after the study changed to Phase II.
Section 9.3: Per-protocol analysis set bullet below revised: "Participant receives an authorized/approved COVID-19 vaccine prior to ~~D43~~ D36"	Correction, as D36 is the key BL collection date.
Section 9.4.2.1 / Section 9.4.2.3 : Biostats assessments revisions	It is planned to maintain the standard format for safety reporting using proportion of participants rather than person-time as this is Phase II study.

Protocol Version 4.0, dated 08 April 2021

The major protocol revisions and rationale for revisions from Version 3.0 to Version 4.0 are as shown below:

Revision	Rationale
Major revision	
Section 8.2.1.2 (old) / Section 8.2.2.1 (new): The SARS-CoV-2 Neutralizing Antibody assay has been moved to a secondary immunogenicity assay. The only assay identified for the primary immunogenicity assay is the SARS-CoV-2 Pseudovirus Neutralization assay.	Safety, reactogenicity, and immunogenicity data from this Phase II study will be used to determine progression to a Phase III and inform dose selection. To clarify that neutralizing antibody responses to the D614 strain measured by the pseudovirus neutralization assay will be the primary immunogenicity data to support this decision making, one assay is designated as the primary immunogenicity assay.
Section 8.3.2 Added the following text: 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 should be generally triggered if the new symptom or	Revised text to clarify the onset of COVID-like-illness and define schedule of events if ongoing.

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).	
Section 8.4: Added the following halting rule: "Any other adverse event that, in the opinion of the Investigator, would expose participants to unreasonable risk of illness or injury."	Halting rule added per CBER non-hold comment.
Minor revisions	
Primary and Secondary Immunogenicity Endpoints Added the following text for clarification Neutralizing antibody titers will be measured in SARS-CoV-2-naïve participants for each study Intervention Group against the D614G variant.	Added "D614G" to clarify in the primary and secondary immmunogenicty endpoints that the neutralizing antibody responses will be measured against the parental D614G strain.
Synopsis: Overall Design / Table 4.1 Countries: Changed "TBD" to "and Honduras"	Added actual country study population which includes United States and Honduras.
Table 1.1: Schedule of Activities: Added "End of phase participation record" row, with "X" in columns at D43 and D202	End of phase D43 / End of Phase D202 added in the Schedule of Activities to be consistent with the planned interim locks.
Table 2.2: Potential risks Anaphylactic reactions" row / "Risk management" column: "Observation period after vaccination for early detection and treatment. Risk management includes also exclusion criterion E06 ~~E04~~ (see…"	Administrative revision to correct the exclusion criterion number referenced.
"Enhanced COVID-19" row / "Risk management" column: Added text and reference citation for Janssen: "Available data for mRNA COVID-19 vaccines (Moderna, Pfizer) and a COVID-19 vaccine based on viral vector (Janssen) do not indicate a risk of vaccine enhanced disease"	Janssen vaccine has received authorization since the previous protocol version (protocol version 3.0). Mention of Janssen product and literature reference added.
Table 6.1: Identity of study interventions - Revised text for product appearance	Text added/revised for clarity at the site level. Storage conditions clarified, in line with important information in the Investigator's Brochure.

- Added protected from light for storage conditions	
Table 8.1: Samples collected per visit B-cell memory Flurospot row: deleted timepoints at D22 and D36	Administrative revision to correct error. Timepoints now align with text in Section 8.2.3.2.
Section 8.2.1.1 SARS-CoV-2 Pseudovirus Neutralization Assay revised for new PhenoSense Assay text and to add text on assay timepoints and emergent variants.	Updated test procedure due to change in laboratory for USG assay.
Section 8.2.2.1 (old) / Section 8.2.3.4 (new): SARS-CoV-2 Virus Neutralization Assays (USG) section moved from secondary immunogenicity assay subsection (8.2.2.1) to exploratory immunogenicity assay subsection (8.2.3.4).	Updated test scope due to change in assay strategy.
Section 8.2.2.2 Deleted "USG" from the title. Added text as below: SARS-CoV-2 binding antibodies will be measured using an electrochemiluminescence immunoassay (ECLIA) in all participants at all timepoints.	Clarification that this assay will be performed in all participants at all timepoints. Updated that this assay will be undertaken at a laboratory that is not a USG laboratory. This assay transferred from the US Government designated laboratory.
Section 8.2.3.4 (old): Section deleted and text added as part of Section 8.2.1.1 text.	Deleted as separate section and added to Section 8.2.1.1 to be more precise on the testing plan. Due to global spread of variants of concern, updated test scope to reflect increased importance of generating data in SARS-CoV-2 variants.
Section 8.2.3.5: New "SARS-CoV-2 Pseudovirus Neutralization Assay" section added.	Assays at Nexelis added as an exploratory endpoint as a backup to cover the eventuality of the Monogram PSV assay not being available
Section 8.4: Halting Rules Bullet #1 (Death/SAE): split into 2 separate bullets: one for Death and one for SAEs Added the following halting rule: "Any other adverse event that, in the opinion of the Investigator, would expose participants to unreasonable risk of illness or injury."	- First halting bullet split to distinguish for both situations. - Halting rule added per CBER non-hold comment.
Section 8.4.5:	Text revised for clarity.

Pregnancy Text updated for reporting of pregnancy period starting before period of contraception or abstinence and also as after period of contraception or abstinence.	
Section 9.2: Sample size determination text revised as below: "A sample size of ~~160~~ 130 evaluable naïve participants per group enables detecting a minimum observed GMT ratio of ~~0.71~~ 0.73 assuming GMT ratio of 1 and standard deviation of 0.67 (estimated for the Pseudovirus assay) with 95% probability."	Revised to clarify how the calculation is done with the number of evaluable participants emphasized and to provide a more accurate number from the calculation.
Section 9.3 Text on the analysis for population revised for clarification The following subgroup definitions of SARS-CoV-2 Naïve and Non-Naïve at D01 or both D01 and D22 timepoints ~~participants~~ are applied for all randomized participants.	Revised to clarify that the for each analysis set, the following subgroups of naive and non-naive as defined by the table will be used in the analysis.
Section 10.3.5.1.3 COVID-19 symptoms (except for loss of taste and loss of smell) will be classified according to the following intensity scale~~, except for loss of taste, loss of smell, shortness of breath, where presence at rest or on exercise will be used for defining severity~~:	Changes made to reflect that the usual Grading Scale (Grade 1/2/3) will be applied for "shortness of breath".
Section 10.3.5.1.3 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	This line will not be completed by Investigators as participants will not notify them that they have the usual sense of smell/sense of taste.

Protocol Version 5.0, dated 10 June 2021

The main reason for updating the protocol from Version 4.0 to Version 5.0 was to add Supplemental Phase III Cohorts for Booster Study 1.

Revision	Rationale
The study design changed to add a Supplemental Phase III Cohorts (Booster Study 1)	Booster Study 1 consists of Supplemental Phase III Cohorts and will test different formulations for specific variants and to develop a universal booster vaccine
Phase change	From Phase II to Phase II/III
Study name changed to add Supplemental Phase III Cohorts	The original Phase II in this protocol is now called "Original Phase II Cohort" The added study is called "Supplemental Phase III Cohorts"
Titles changed to add Supplemental Phase III Cohorts	Full title: "Immunogenicity and Safety of SARS-CoV-2 Recombinant Protein Vaccines with AS03 Adjuvant in Adults 18 Years of Age and Older as a Primary Series and Immunogenicity and Safety of a Booster Dose of SARS-CoV-2 Adjuvanted Recombinant Protein Vaccines (two Monovalent and one Bivalent)" Brief title: "Study of Recombinant Protein Vaccines with Adjuvant as a Primary Series and as a Booster Dose against COVID-19 in Adults 18 Years of Age and Older"
New formulations added for the Supplemental Phase III Cohorts	These formulations have been added to the Phase III study: 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, monovalent B.1.351 (CoV2 preS dTM-AS03 [B.1.351]): monovalent vaccine with the S protein sequence from the B.1.351 variant SARS-CoV2 prefusion Spike delta TM, monovalent B.1.351 (Monovalent [B.1.351]): monovalent vaccine with the S protein sequence from the B.1.351 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
Study Design changed to add the Supplemental Phase III Cohorts	• **Supplemental Cohort 1**: adults 18 years of age and older who were vaccinated 4 to ≤ 10 months prior with an authorized/approved mRNA or adenovirus-vectored COVID-19 vaccine will be given Monovalent (D614) CoV2

	preS dTM-AS03 (CoV2 preS dTM-AS03 [D614]) as a single booster injection. • **Supplemental Cohort 2, Main Arms:** adults 18 years of age and older who were vaccinated 4 to ≤ 10 months prior with an authorized/approved mRNA or adenovirus-vectored COVID-19 vaccine, or who received the protein-based vaccine in the Original Phase II Cohort will be randomized to receive a single booster injection of one of the following: o Monovalent (B.1.351) CoV2 preS dTM-AS03 (CoV2 preS dTM-AS03 [B.1.351]) o Bivalent (D614 + B.1.351) CoV2 preS dTM-AS03 (CoV2 preS dTM-AS03 [D614 + B.1.351]) o CoV2 preS dTM-AS03 (D614) Note: Original Phase II Cohort participants will be randomized across all 3 vaccines, while participants who received authorized/approved mRNA or adenovirus-vectored COVID-19 vaccines will be randomized across the B.1.351-containing vaccines only. • **Supplemental Cohort 2 Exploratory B.1.351 Arms:** in these arms, different antigen doses of CoV2 preS dTM, monovalent B.1.351 (Monovalent [B.1.351]) with and without adjuvants will be evaluated. Adults 18 years of age and older who received the Pfizer/BioNTech mRNA vaccine 4 to < 10 months prior will be randomized to receive a single booster injection of one of the following Monovalent (B.1.351) formulations: o 2.5 µg antigen with AS03 adjuvant o 2.5 µg antigen with half-dose AS03 adjuvant o 5 µg antigen with half-dose AS03 adjuvant o 5 µg antigen with no adjuvant • **Supplemental Cohorts 1 and 2 Comparator Group:** SARS-CoV-2 naïve, unvaccinated, adults who are 18-55 years of age will be given CoV2 preS dTM-AS03 (D614) as a primary series vaccination of 2 injections given 21 days apart. • **Supplemental Variant Prime Cohort 3:** SARS-CoV-2naïve, unvaccinated, adults who are 18 years of age and older will be randomized to receive one of the following as a primary series vaccination of 2 injections given 21 days apart: o CoV2 preS dTM-AS03 (B.1.351) o CoV2 preS dTM-AS03 (D614 + B.1.351) o Monovalent (D614)AS03 (Comparator Group) • **Supplemental Cohorts Subsets and Assessment of Immunogenicity to Emerging Variants of Concern:** A randomized subset of 70 participants in Cohort 1 will be

	tested for additional SARS-CoV-2 variants of concern. No additional sample collection, procedures, or visits are required for this subset. A randomized subset of 112 participants in Cohort 2 and 87 participants in Cohort 3 comprised of younger adults (18 to 55 years of age) will provide samples for cellular immune response and mucosal antibody assessments and will also be tested for additional variants of concern
Objectives and Endpoints added for the Supplemental Phase III Cohorts	All objectives and endpoints have been added as pertains to the Supplemental Phase III Cohorts (Booster Study 1) added to this protocol
Schemas added for the Supplemental Phase III Cohorts	Schemas added for the Supplemental Phase III Cohorts: • Figure 1.2 Booster arms for Supplemental Cohorts 1 and 2 • Figure 1.3: Supplemental Variant Prime Cohort 3 and Comparator Groups • Figure 1.4: Design for COVID-19-like illness follow-up for the Original Series and all Supplemental Cohorts
Schedule of Activities added for the Supplemental Phase III Cohorts	Schedule of Activities tables added for the Supplemental Phase III Cohorts: • Table 1.2 presents the overall study SoA for the booster arms of Supplemental Cohorts 1 and 2. • Table 1.3 presents the overall study SoA for Supplemental Variant Prime Cohort 3 and both Comparator Group arms. • Table 1.4 presents the SoA for the follow-up of COVID-19like illness for the Original Phase II Cohort and Supplemental Cohorts.
Section 2 Introduction: Section 2.1 Rationale / Section 2.2 Background / Section 2.3 Benefit/Risk Assessment Section 4 Study Design: Section 4.2 Scientific Rationale for Study Design / Section 4.3 Justification for Dose and Dosing Schedules	Text added: information on SARS-CoV-2 variants, Phase II interim analysis results, justification for dosing in the Supplemental Phase III Cohorts, updated literature information regarding evolving understanding of SARS-CoV-2 informing the Phase III trial design
Section 4 Study Design: Section 4.1.2 Intervention Groups and Duration for Supplemental Cohorts	Subsections added for Intervention Groups and Duration for Supplemental Phase III Cohorts: Cohorts 1, 2 and 3 arms, participant numbers, duration of study involvement

Section 5 Study Population: Section 5.1 Inclusion Criteria / Section 5.2 Exclusion Criteria	Inclusion criteria, exclusion criteria updated to add list items for Supplemental Phase III Cohorts
Section 6 Study Intervention (through entire section) Subsection 6.1.2 Supplemental Phase III Cohorts Study Interventions	Text added throughout to add the information for the Supplemental Phase III Cohort study interventions Subsection 6.1.2 added to include tables of all study formulations for the Supplemental Phase III Cohorts
Section 7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal / Section 8 Study Assessments and Procedures	Text added throughout each section specific to the additional Supplemental Phase III Cohorts
Section 9 Statistical Considerations (through entire section) Subsection 9.1.2 / Subsection 9.1.3 / Subsection 9.2.2 / Subsection 9.2.3 /	Text added throughout to add the statistics information for the Supplemental Phase III Cohorts Subsections added to include statistical considerations specific to the Supplemental Phase III Cohorts
Section 9.5 Interim Analyses	Text added for interim analyses specific to the Supplemental Phase III Cohorts
Section 10 Supporting Documentation and Operational Considerations Section 11 References	Text added throughout each section specific to the additional Supplemental Phase III Cohorts References updated for additional references

Protocol Version 7.0, dated 31 August 2021

Protocol updated from Version 5.0 to Version 6.0 to add conditional co-primary objectives for Supplemental Cohort 1 and relevant nonclinical non-human primate (NHP) study results. Version 6.0 was not submitted to Health Authorities. The protocol was updated from Version 6.0 to Version 7.0 with minor changes to inclusion and exclusion criteria.

Revision	Rationale
Throughout: Shortened names of vaccine candidates changed: • CoV2 preS dTM-AS03 (D614) • CoV2 preS dTM-AS03 (B.1.351) • CoV2 preS dTM-AS03 (D614 + B.1.351)	Changed to align with study intervention naming conventions across all documents in the program.
Throughout: Greek letter names for the virus variants have been added, ie Alpha (B.1.1.7), Beta (B.1.351), Delta (B.1.617)	In early June 2021, the World Health Organization issued new naming conventions for each SARS-CoV-2 virus variant. Variants will now be named by Greek alphabet letters; protocol updated to reflect this change.
Synopsis: Rationale / Section 2.2 / Section 4.2: Added text "the virus has been detected in 192 countries/regions and led to significant morbidity, mortality, and economic impact"	Text added to replace pandemic scope text in previous versions.
Synopsis: Rationale / Section 2.2: Nonclinical studies text added for monovalent and bivalent vaccine data.	Additional data added at time of this protocol update, in line with text in the Investigator's Brochure update.
Objectives and Endpoints table in Synopsis Rationale and Section 3: Objectives added for Supplemental Cohort 1: "Conditional Co-Primary Objectives: Conditional on meeting the primary objectives for Supplemental Cohort 1:" #1: "To demonstrate, in adults 18-55 years of age previously vaccinated with an adenovirus-vectored COVID-19 vaccine, that a booster dose of CoV2 preS dTM-AS03 (D614) vaccine induces an immune response that is non-inferior to the response induced by a two-dose priming series with CoV2 preS dTM-AS03 (D614) vaccine in naïve, previously unvaccinated, individuals." #2: "To demonstrate, in adults 18-55 years of age previously vaccinated with adenovirus-vectored COVID-19 vaccines, that a booster dose of CoV2 preS dTM-AS03 (D614) induces an immune response that is superior to that observed immediately before booster."	Additional objectives for Supplemental Cohort 1 added to further assess the immune response of a booster dose of CoV2 preS dTM-AS03 (D614) vaccine in participants previously vaccinated with adenovirus-vectored COVID-19 vaccines.

Objectives and Endpoints table in Synopsis Rationale and Section 3: Objective and corresponding endpoint text added for Supplemental Cohort 2: "Conditional Secondary Objective: Conditional on meeting the Primary Immunogenicity Objectives and the Co-Secondary Objectives for Supplemental Cohort 2:" #1: "To demonstrate in adults 18-55 years of age and previously vaccinated with the Pfizer/BioNTech mRNA COVID-19 vaccine, that a booster dose of CoV2 preS dTM-AS03 (B.1.351) or CoV2 preS dTM-AS03 (D614 + B.1.351) induces an immune response against the B.1.351 variant at D15 that is superior to that against the B.1.351 variant at D36 in the Comparator Group." #15: "To describe, in adults over 55 years of age, the neutralizing antibody profile to the B.1.351 variant and to the D614G strain at D01 and D15 by Intervention Group, overall, by priming platform, and by priming vaccine."	Additional objectives for Supplemental Cohort 2 added to further assess the immune response of a booster dose of CoV2 preS dTM-AS03 (B.1.351) or CoV2 preS dTM-AS03 (D614 + B.1.351) against the B.1.351 variant.
Throughout document, at all mentions of Supplemental Cohort subsets, modified participant numbers for Cohort 3 subset to 87 participants (previously 88).	Changed to clarify number of participants in the subset.
Figure 1.4 / Table 1.4 / Section 8.3.2 Pulse oximeter text updated to explain participants will receive it at the CLI01 visit rather than enrollment	Changed to clarify when participants will receive their pulse oximeter.
Table 6.1 / Table 6.2 / Table 6.3 / Table 6.4 Dose formulation text updated	Text updated for clarity.
Section 6.2: List item #3 text added "…either monovalent or bivalent antigen…"	Text added to clarify both monovalent and bivalent antigens are included.
Section 5.1 Inclusion Criteria: Text modified : "I02: Is of childbearing potential and agrees to use an effective contraceptive method or abstinence from at least 4 weeks prior to the first vaccination until at least 12 weeks after the ~~second~~ last vaccination (ie, second dose of primary series or booster injection)."	Text modified to be applicable to both primary series and booster vaccination.
Section 5.2 Exclusion Criteria: Text modified: "E12: Receipt of immunoglobulins[a], blood, or blood-derived products in the past 3 months"	Footnote added for clarity regarding investigational monoclonal antibodies.

Footnote added: “Including investigational monoclonal antibodies.”	
Table 8.1 / Section 8.2.3.4 Removed text for SARS-CoV-2 Virus Neutralization Assays	Text removed as assay will not be done.
Section 9 Statistics text added/modified throughout the section corresponding to the updates in the Objectives and Endpoints table.	

Protocol Version 8.0, dated 12 October 2021

The major protocol revisions and rationale for revisions from Version 7.0 to Version 8.0 are as shown below:

Revision	Rationale
Throughout: For protein-primed dosing groups only: • Participants who were primed with the protein-based vaccine candidate in the Original Phase II Cohort will receive one of the 2 monovalent booster formulations and will not receive a booster dose of the bivalent vaccine candidate CoV2 preS dTM-AS03 (D614 + B.1.351). • Added hypothesis testing of monovalent D614 booster responses. • Added descriptive analyses for monovalent Beta variant responses. • Changed to 9:1 enrollment allocation in younger adults (D614:Beta), and 1:1 for older adults.	To more fully characterize the response of CoV2 preS dTM-AS03-primed individuals to a homologous booster, and thereby address the requirement for pre-specified testing of homologous booster responses, the protocol has been modified to generate data to support a homologous prime boost vaccination with our recombinant vaccine platform. Eligible CoV2 preS dTM-AS03-primed individuals from the Original Phase II Cohort will be randomly assigned in Supplemental Cohort 2 to receive a booster dose of one of the two monovalent booster formulations (CoV2 preS dTM-AS03 [D614]) OR CoV2 preS dTM-AS03 [B.1.351]). The bivalent booster formulation will not be evaluated. Randomization will be weighted in the 18 to 55 year-old age stratum to ensure adequate power to perform hypothesis testing for the D614 (parental) strain booster formulation. The booster response overall following any priming dose will be assessed. The hypothesis will be specified as for the other powered arms in Cohort 2. Responses to the B.1.351 variant booster formulation will be descriptively analyzed.
Throughout: Seroresponse to be included as conditional secondary endpoint for powered comparisons	Owing to uncertainties of the interpretation of titre values and of a 4-fold rise in the setting of pre-existing antibody responses, hypothesis testing to evaluate 4-fold seroresponse will be performed as a secondary endpoint.
Throughout: AESIs: include myocarditis and pericarditis	To address CBER request
Throughout: Specify that Delta variant is to be evaluated	To address CBER request
Section 9.1 Statistical Hypotheses New subsection added: Section 9.1.2.1 A Pooled Primary Series Cohort as Supplemental Cohorts 1 and 2 Comparator Group	Section added to address the possibility of a pooled primary series cohort with a sample size of at least 515 evaluable SARS-CoV-2 naïve participants could be planned to serve as the Comparator Group for Supplemental Cohorts 1 and 2.

Protocol Version 9.0, dated 12 November 2021

The major protocol revisions and rationale for revisions from Version 8.0 to Version 9.0 are as shown below:

Revision	Rationale
Throughout: Removed bivalent vaccine candidate arm from Variant Prime Cohort 3	1) Operational feasibility of recruiting SARS-CoV-2 naive, unvaccinated participants has become significantly more challenging 2) Initiation of other studies to support evaluation of the bivalent vaccine
Throughout: • Participant numbers change in remaining 2 main monovalent arms as follows: ○ Monovalent (B.1.351), 18-55 years of age: 239 participants (was 294) ○ Monovalent (D614), 18-55 years of age: 239 participants (was 294) • Participant numbers change in monovalent arms for variant testing CMI/Mucosal subset groups as follows: ○ Monovalent (B.1.351), 18-55 years of age: 24 participants (was 29) ○ Monovalent (D614), 18-55 years of age: 24 participants (was 29) • Total participant numbers change in remaining 2 monovalent arms (main + subset) as follows: ○ Monovalent (B.1.351), 18-55 years of age: 289 participants (was 344) ○ Monovalent (D614), 18-55 years of age: 289 participants (was 344)	Recalculation of required sample size due to removal of bivalent vaccine arm from Variant Prime Cohort 3.
Throughout: Total participant numbers changed to 4238 (was 4692)	Total changed due to no bivalent arm in Variant Prime Cohort 3 and participant numbers change in remaining monovalent arms.
Section 6.1.2, Table 6.4, removed bivalent vaccine candidate formulation	Bivalent formulation no longer tested in Variant Prime Cohort 3.
Section 8.3.1 Definitions; under COVID-19-like illness, in the definition for "Fever" temperature measurement, symbol changed as follows: <u>Previous text:</u> • Fever (measured temperature > 100.4ºF OR 38.0ºC) <u>Revised text:</u> • Fever (measured temperature ≥ 100.4ºF OR ≥ 38.0ºC)	Revised to "≥" to align with measurement used in the Case Report Forms and intensity grading scales
Sections 9.1.3 and 9.2.3 Variant Prime Cohort 3 statistical analysis updated	Statistical analysis sections for Variant Prime Cohort 3 updated to remove bivalent vaccine candidate arm.

11 References

1. World Health Organization. Virtual press conference on COVID-19 – 11 March 2020 [homepage on the Internet]. [cited 2020 Mar 28]. Available from: https://www.who.int/docs/default-source/coronaviruse/transcripts/who-audio-emergencies-coronavirus-press-conference-full-and-final-11mar2020.pdf?sfvrsn=cb432bb3_2.

2. Johns Hopkins School of Engineering. Coronavirus COVID-19 Global Cases by the Centers for Systems Science and Engineering (CSSE) at Johns Hopkins School of Engineering. [homepage on the Internet].[Last updated 2021 November 18 5:00 pm] [Cited 2021 November 18]. Available from: http://www.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6.

3. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020.

4. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020.

5. Carfi A, Bernabei R, Landi F, Gemelli Against C-P-ACSG. Persistent Symptoms in Patients After Acute COVID-19. JAMA. 2020.

6. Docherty A HE, Green C, et al. Features of 16,749 hospitalised UK patients with COVID-19 using the ISARIC WHO Clinical Characterisation Protocol. medRxiv 2020.

7. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020.

8. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med. 2020.

9. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet (London, England). 2021;397(10269):99-111.

10. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020;367(6483):1260-3.

11. Francica JR, Flynn BJ, Foulds KE, Noe AT, Werner AP, Moore IN, et al. Vaccination with SARS-CoV-2 Spike Protein and AS03 Adjuvant Induces Rapid Anamnestic Antibodies in the Lung and Protects Against Virus Challenge in Nonhuman Primates. bioRxiv : the preprint server for biology. 2021.

12. Davies NG, Abbott S, Barnard RC, Jarvis CI, Kucharski AJ, Munday JD, et al. Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. Science. 2021.

13. Shinde V, Bhikha S, Hoosain Z, Archary M, Bhorat Q, Fairlie L, et al. Efficacy of NVX-CoV2373 Covid-19 Vaccine against the B.1.351 Variant. N Engl J Med. 2021;384(20):1899-909.

14. Novavax COVID-19 Vaccine Demonstrates 89.3% Efficacy in UK Phase 3 Trial [press release]. 2021.

15. Madhi SA, Baillie V, Cutland CL, Voysey M, Koen AL, Fairlie L, et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant. N Engl J Med. 2021;384(20):1885-98.

16. Sadoff J, Gray G, Vandebosch A, Cardenas V, Shukarev G, Grinsztejn B, et al. Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19. N Engl J Med. 2021.

17. US Department of Health and Human Services. Emergency Use Authorization for Vaccines to Prevent COVID-19. Guidance for Industry. 2021 February 22. [cited 2021 March 20]. Available from: https://www.fda.gov/media/142749/download.

18. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;382(18):1708-20.

19. Li F. Structure, Function, and Evolution of Coronavirus Spike Proteins. Annu Rev Virol. 2016;3(1):237-61.

20. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-3.

21. Pallesen J, Wang N, Corbett KS, Wrapp D, Kirchdoerfer RN, Turner HL, et al. Immunogenicity and structures of a rationally designed prefusion MERS-CoV spike antigen. Proc Natl Acad Sci U S A. 2017;114(35):E7348-E57.

22. Cox MM, Hashimoto Y. A fast track influenza virus vaccine produced in insect cells. J Invertebr Pathol. 2011;107 Suppl:S31-41.

23. Garcon N, Vaughn DW, Didierlaurent AM. Development and evaluation of AS03, an Adjuvant System containing alpha-tocopherol and squalene in an oil-in-water emulsion. Expert Rev Vaccines. 2012;11(3):349-66.

24. Cohet C, van der Most R, Bauchau V, Bekkat-Berkani R, Doherty TM, Schuind A, et al. Safety of AS03-adjuvanted influenza vaccines: A review of the evidence. Vaccine. 2019;37(23):3006-21.

25. Cox RJ, Madhun AS, Hauge S, Sjursen H, Major D, Kuhne M, et al. A phase I clinical trial of a PER.C6 cell grown influenza H7 virus vaccine. Vaccine. 2009;27(13):1889-97.

26. Couch RB, Patel SM, Wade-Bowers CL, Nino D. A randomized clinical trial of an inactivated avian influenza A (H7N7) vaccine. PLoS One. 2012;7(12):e49704.

27. Ward BJ, Gobeil P, Séguin A, Atkins J, Boulay I, Charbonneau P-Y, et al. Phase 1 trial of a Candidate Recombinant Virus-Like Particle Vaccine for Covid-19 Disease Produced in Plants. 2020:2020.11.04.20226282.

28. Smatti MK, Al Thani AA, Yassine HM. Viral-Induced Enhanced Disease Illness. Front Microbiol. 2018;9:2991.

29. Tseng CT, Sbrana E, Iwata-Yoshikawa N, Newman PC, Garron T, Atmar RL, et al. Immunization with SARS coronavirus vaccines leads to pulmonary immunopathology on challenge with the SARS virus. PLoS One. 2012;7(4):e35421.

30. Yasui F, Kai C, Kitabatake M, Inoue S, Yoneda M, Yokochi S, et al. Prior immunization with severe acute respiratory syndrome (SARS)-associated coronavirus (SARS-CoV)

nucleocapsid protein causes severe pneumonia in mice infected with SARS-CoV. J Immunol. 2008;181(9):6337-48.

31. Czub M, Weingartl H, Czub S, He R, Cao J. Evaluation of modified vaccinia virus Ankara based recombinant SARS vaccine in ferrets. Vaccine. 2005;23(17-18):2273-9.

32. Del Giudice G, Rappuoli R, Didierlaurent AM. Correlates of adjuvanticity: A review on adjuvants in licensed vaccines. Semin Immunol. 2018;39:14-21.

33. Madhi SA, Baillie V, Cutland CL, Voysey M, Koen AL, Fairlie L, et al. Safety and efficacy of the ChAdOx1 nCoV-19 (AZD1222) Covid-19 vaccine against the B.1.351 variant in South Africa. 2021:2021.02.10.21251247.

34. Emary KRW, Golubchik T, Aley PK, Ariani CV, Angus BJ, Bibi S. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 VOC 202012/01 (B.1.1.7). Lancet preprint. 2021. [posted 2020 FEB 04] [cited 2021 MAR 11] Available from: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3779160.

35. Shinde V, Bhikha S, Hoosain Z, Archary M, Bhorat Q, Fairlie L, et al. Preliminary Efficacy of the NVX-CoV2373 Covid-19 Vaccine Against the B.1.351 Variant. 2021:2021.02.25.21252477.

36. Wang P, Nair MS, Liu L, Iketani S, Luo Y, Guo Y, et al. Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7. Nature. 2021;593(7857):130-5.

37. Pavot V, Berry C, Kishko M, Anosova NG, Huang D, Tibbitts T, et al. SARS-CoV-2 preS dTM vaccine booster candidates increase functional antibody responses and cross-neutralization against SARS-CoV-2 variants of concern in non-human primates. 2021:2021.09.20.461023.

38. McMahan K, Yu J, Mercado NB, Loos C, Tostanoski LH, Chandrashekar A, et al. Correlates of protection against SARS-CoV-2 in rhesus macaques. Nature. 2020.

39. Yu J, Tostanoski LH, Peter L, Mercado NB, McMahan K, Mahrokhian SH, et al. DNA vaccine protection against SARS-CoV-2 in rhesus macaques. Science. 2020;369(6505):806-11.

40. Mercado NB, Zahn R, Wegmann F, Loos C, Chandrashekar A, Yu J, et al. Single-shot Ad26 vaccine protects against SARS-CoV-2 in rhesus macaques. Nature. 2020;586(7830):583-8.

41. Zost SJ, Gilchuk P, Case JB, Binshtein E, Chen RE, Nkolola JP, et al. Potently neutralizing and protective human antibodies against SARS-CoV-2. Nature. 2020;584(7821):443-9.

42. Shi R, Shan C, Duan X, Chen Z, Liu P, Song J, et al. A human neutralizing antibody targets the receptor-binding site of SARS-CoV-2. Nature. 2020;584(7819):120-4.

43. Peeters M, Regner S, Vaman T, Devaster JM, Rombo L. Safety and immunogenicity of an AS03-adjuvanted A(H1N1)pmd09 vaccine administered simultaneously or sequentially with a seasonal trivalent vaccine in adults 61 years or older: data from two multicentre randomised trials. Vaccine. 2012;30(45):6483-91.

44. McElhaney JE, Beran J, Devaster JM, Esen M, Launay O, Leroux-Roels G, et al. AS03-adjuvanted versus non-adjuvanted inactivated trivalent influenza vaccine against seasonal

influenza in elderly people: a phase 3 randomised trial. The Lancet Infectious diseases. 2013;13(6):485-96.

45. Montplaisir J, Petit D, Quinn MJ, Ouakki M, Deceuninck G, Desautels A, et al. Risk of narcolepsy associated with inactivated adjuvanted (AS03) A/H1N1 (2009) pandemic influenza vaccine in Quebec. PLoS One. 2014;9(9):e108489.

46. Cohet C MJ, Petit D, Quinn M-J, Ouakki M, Deceuninck G, et al. Applying the test-negative design to vaccine safety studies: risk of narcolepsy associated with A/H1N1 (2009) pandemic influenza vaccination in Quebec [abstract 713]. . Pharmacoepidemiology Drug Safety. 2015;24:406-7.

47. Agency EM. Assessment report. Pandemrix. EMA/CHMP/566359/2015. 2016.

48. Sarkanen TO, Alakuijala APE, Dauvilliers YA, Partinen MM. Incidence of narcolepsy after H1N1 influenza and vaccinations: Systematic review and meta-analysis. Sleep Med Rev. 2018;38:177-86.

49. Luo G, Lin L, Jacob L, Bonvalet M, Ambati A, Plazzi G, et al. Absence of anti-hypocretin receptor 2 autoantibodies in post pandemrix narcolepsy cases. PLoS One. 2017;12(12):e0187305.

50. Giannoccaro MP, Waters P, Pizza F, Liguori R, Plazzi G, Vincent A. Antibodies Against Hypocretin Receptor 2 Are Rare in Narcolepsy. Sleep. 2017;40(2).

51. Vassalli A, Li S, Tafti M. Comment on "Antibodies to influenza nucleoprotein cross-react with human hypocretin receptor 2". Sci Transl Med. 2015;7(314):314le2.

52. Luo G. Autoimmunity to hypocretin and molecular mimicry to flu in type 1 narcolepsy. PNAS. 2018;115 (52):E12323 - 32.

53. Latorre D, Kallweit U, Armentani E, Foglierini M, Mele F, Cassotta A, et al. T cells in patients with narcolepsy target self-antigens of hypocretin neurons. Nature. 2018;562(7725):63-8.

54. Jiang W, Birtley JR, Hung SC, Wang W, Chiou SH, Macaubas C, et al. In vivo clonal expansion and phenotypes of hypocretin-specific CD4(+) T cells in narcolepsy patients and controls. Nat Commun. 2019;10(1):5247.

55. Vaccines and Related Biological Products Advisory Committee February 26, 2021 Meeting Announcement. 2021 February 26. [cited 2021 March 22]. Available from: https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-february-26-2021-meeting-announcement .

56. Burny W, Callegaro A, Bechtold V, Clement F, Delhaye S, Fissette L, et al. Different Adjuvants Induce Common Innate Pathways That Are Associated with Enhanced Adaptive Responses against a Model Antigen in Humans. Front Immunol. 2017;8:943.

57. Coronavirus (COVID-19) Update: FDA Issues Policies to Guide Medical Product Developers Addressing Virus Variants: FDA; 2021 [Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-policies-guide-medical-product-developers-addressing-virus.

58. Reflection paper on the regulatory requirements forvaccines intended to provide protection against variant strain(s) of SARS-CoV-2: European Medicines Agency; 2021 [Available from:

https://www.ema.europa.eu/documents/scientific-guideline/reflection-paper-regulatory-requirements-vaccines-intended-provide-protection-against-variant_en.pdf.

59. Jackson LA, Campbell JD, Frey SE, Edwards KM, Keitel WA, Kotloff KL, et al. Effect of Varying Doses of a Monovalent H7N9 Influenza Vaccine With and Without AS03 and MF59 Adjuvants on Immune Response: A Randomized Clinical Trial. JAMA. 2015;314(3):237-46.

60. Keech C, Albert G, Cho I, Robertson A, Reed P, Neal S, et al. Phase 1-2 Trial of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine. N Engl J Med. 2020;383(24):2320-32.

61. Richmond P, Hatchuel L, Dong M, Ma B, Hu B, Smolenov I, et al. A first-in-human evaluation of the safety and immunogenicity of SCB-2019, an adjuvanted, recombinant SARS-CoV-2 trimeric S-protein subunit vaccine for COVID-19 in healthy adults; a phase 1, randomised, double-blind, placebo-controlled trial. 2020:2020.12.03.20243709.

62. Khoury DS, Cromer D, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. Nat Med. 2021 May 17. doi: 10.1038/s41591-021-01377-8.

63. Earle KA, Ambrosino DM, Fiore-Gartland A, Goldblatt D, Gilbert PB, Siber GR, et al. Evidence for antibody as a protective correlate for COVID-19 vaccines. 2021:2021.03.17.20200246.

64. Doria-Rose N, Suthar MS, Makowski M, O'Connell S, McDermott AB, Flach B, et al. Antibody Persistence through 6 Months after the Second Dose of mRNA-1273 Vaccine for Covid-19. N Engl J Med. 2021;384(23):2259-61.

65. Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. Stat Med. 1998;17(8):873-90.

12 Sponsor Signature Page

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