Statistical Analysis Plan (SAP) Core Body

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

NCT Number: NCT04762680

Study Phase: Phase III

SAP Core Body Version: 5.0

SAP Core Body Date: 22 Mar 2022

Protocol Version Number: 10.0

Amendment Number: Amendment 6

The SAP Core Body should be used in conjunction of the study protocol and the SAP TLF and meant for statistical analysis plan of VAT00002 Supplemental Phase III Cohorts.

Version History

Previous Version(s)	Date	Comments
1.0	13 July 2021	Protocol amendment version 5.0 to add Supplemental Phase III Cohorts for Booster Study 1, SAP generation for Booster Study 1
2.0	27 Oct 2021	Updated per Protocol Amendment 4.0: • Add option of pooled primary series cohort as comparator group for Cohort 2 • Remove Bivalent vaccine candidate from protein-primed dosing group • Add conditional secondary objective of seroresponse endpoint in hypothesis testing order for Cohort 1 and Cohort 2
3.0	8 Dec 2021	Study design updated to remove the bivalent vaccine candidate arm from Variant Prime Cohort 3
4.0	27 Jan 2022	Study design updated to remove Variant Prime Cohort 3

Previous Version(s)	Date	Comments
5.0	22 Mar 2022	1. Add imputation for partial prior COVID-19 vaccination date 2. Enlarge the variant testing scope of Cohort 1 and Cohort 2 (Protein Primed Group) 3. Modify the definition of VTAS 4. Modify the analysis set for Comparator Group on Variant Testing to have Naive serostatus considered 5. Add study duration / safety follow-up calculation method for interim analysis

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1 Overall Design

The design of the study is summarized in Table 1.1.

Table 1.1: Overall design

Type of design	Parallel, multi-center
Phase	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	• 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 [B.1.351], CoV2 preS dTM-AS03 [D614], 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 groups and assignment method	Participants will be screened for eligibility criteria at the time of inclusion. • 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 (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 was originally planned to be tested for additional SARS-CoV-2 variants of concern including Delta. However, to address CBER requests, the Sponsor decided to expand the scope of testing and to perform the immunogenicity assessment for Delta in the whole Booster Cohort 1 and Cohort 2 (Protein Primed Group) instead of only in a subset of participants. 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	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: o 18-55 years of age: 215 participants o 56 years of age and older: 50 participants • Primed with Moderna: o 18-55 years of age: 75 participants o 56 years of age and older: 25 participants • Primed with Oxford University/AstraZeneca: o 18-55 years of age: 75 participants o 56 years of age and older: 25 participants

[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

	• Primed with J&J/Janssen: o 18-55 years of age: 75 participants o 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: o CoV2 preS dTM (D614 + B.1.351): ▪ 18-55 years of age: 515 participants ▪ 56 years of age and older: 50 participants o CoV2 preS dTM (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): o CoV2 preS dTM-AS03 (B.1.351): ▪ 18-55 years of age: 30 participants ▪ 56 years of age and older: 75 participants o CoV2 preS dTM-AS03 (D614): ▪ 18-55 years of age: 270 participants ▪ 56 years of age and older: 75 participants • Primed with Moderna: o CoV2 preS dTM-AS03 (D614 + B.1.351): ▪ 18-55 years of age: 75 participants ▪ 56 years of age and older: 25 participants o CoV2 preS dTM-AS03 (B.1.351): ▪ 18-55 years of age: 75 participants ▪ 56 years of age and older: 25 participants • Primed with Oxford University/AstraZeneca: o CoV2 preS dTM-AS03 (D614 + B.1.351): ▪ 18-55 years of age: 75 participants ▪ 56 years of age and older: 25 participants o CoV2 preS dTM-AS03 (B.1.351): ▪ 18-55 years of age: 75 participants ▪ 56 years of age and older: 25 participants • Primed with J&J/Janssen: o CoV2 preS dTM-AS03 (D614 + B.1.351): ▪ 18-55 years of age: 75 participants ▪ 56 years of age and older: 25 participants

	○ CoV2 preS dTM-AS03 (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 was originally planned to be tested for additional SARS-CoV-2 variants of concern including Delta. However, to address CBER requests, the Sponsor decided to expand the scope of testing and to perform the immunogenicity assessment for Delta in the whole Booster Cohort 1 and Booster Cohort 2 (Protein Primed Group) instead of only in a subset of participants. 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 1.4
Total duration of study participation	**Supplemental Cohorts 1 and 2:** Approximately 365 days post-booster injection (ie, approximately 366 days total) **Supplemental Cohorts Comparator Groups:** Approximately 365 days post-injection 2 (ie, approximately 386 days total)

Countries	Supplemental Cohorts: to be determined (TBD)
Use of an independent Data and Safety Monitoring Board, Dose Escalation Committee, or similar review group	No

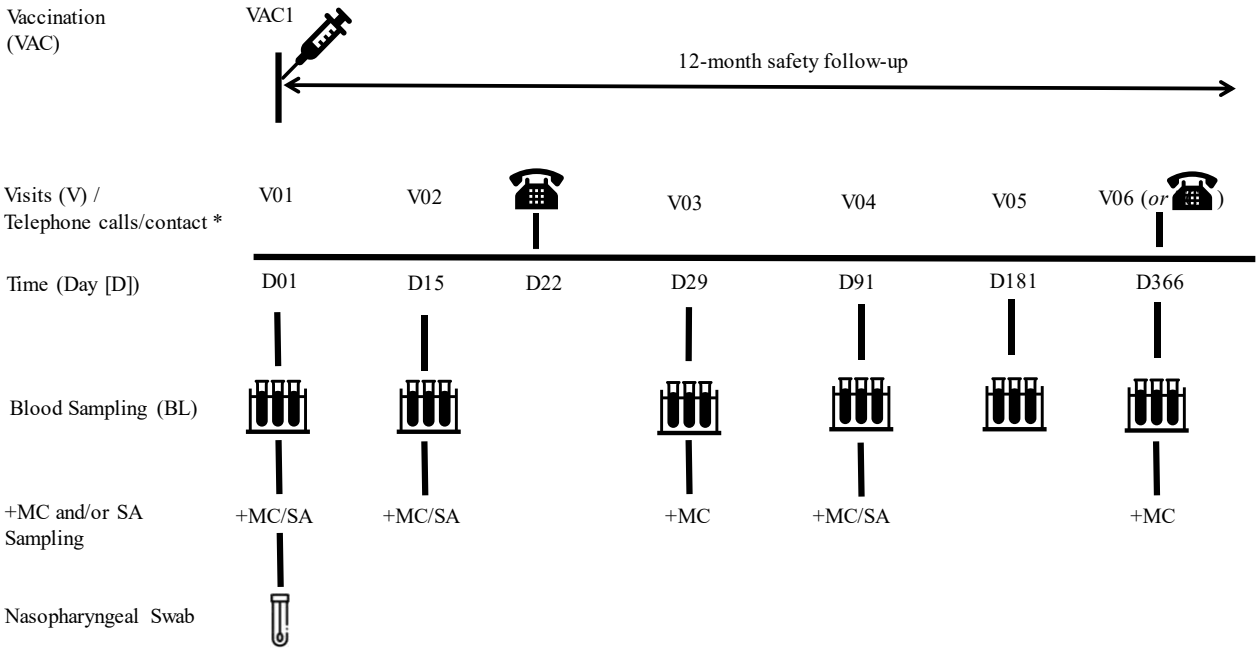
Disclosure Statement:

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 intervention group; and those preparing the study interventions will be unblinded to vaccine assignment group.

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

Intervention Groups and Duration

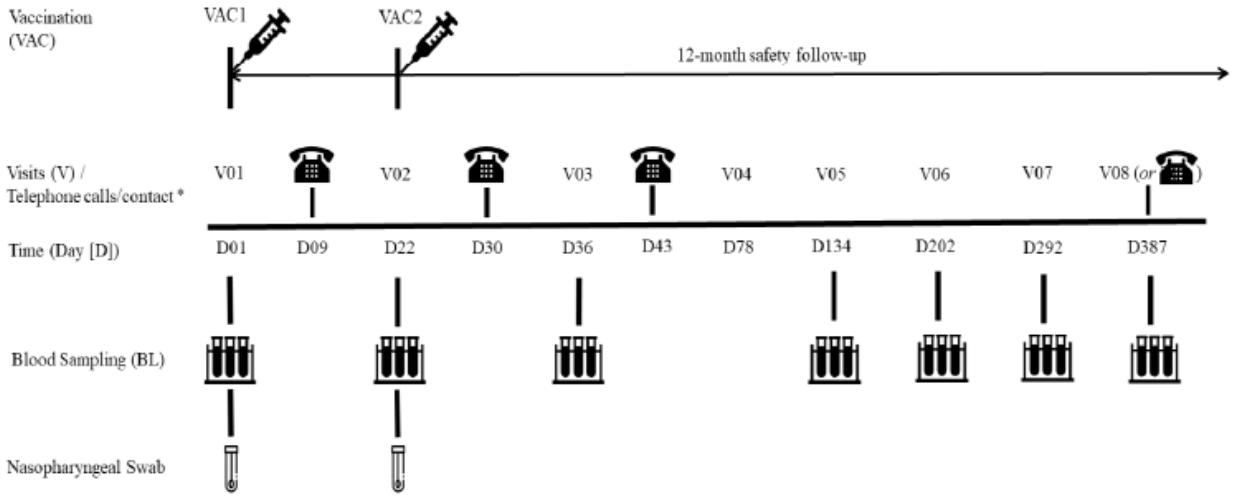
Figure 1.1: Graphical study design for Supplemental Cohorts 1 and 2 Booster Arms



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 1.2: Graphical study design for Supplemental Cohorts Comparator Groups

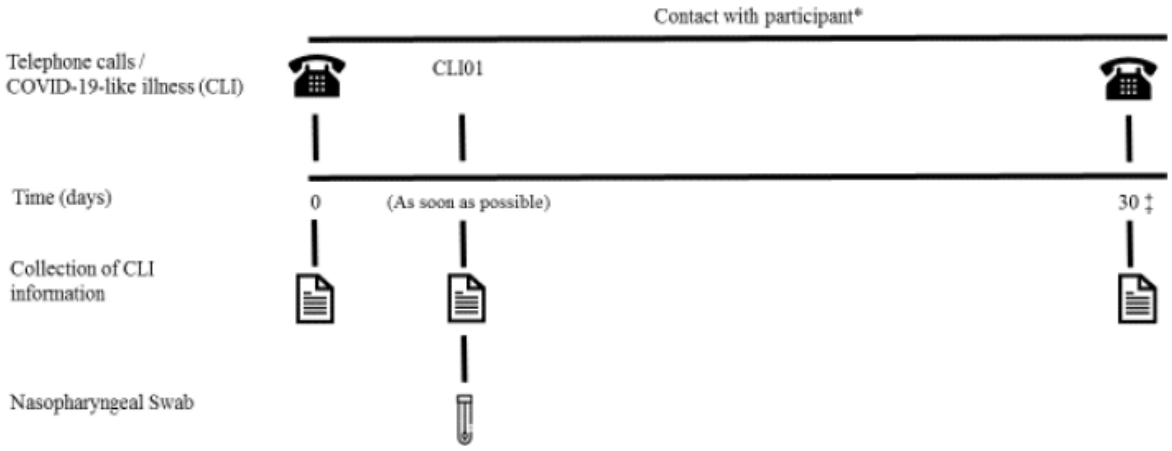


BL, blood sample; TC, telephone call; V, visit; VAC, vaccination

* 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 1.3: Follow-up of COVID-19-like illness for 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.

Table 1.2: 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	--	--
CoV 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 1.3: Planned sample sizes for Supplemental Cohort 2 Exploratory B.1.351 Arms

		CoV2 preS dTM-AS03 (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 1.4: Approximate sample size of Supplemental Cohort subsets for Variant Testing in 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 (B.1.351)-AS03	--	26	3
CoV2 preS dTM-AS03 (D614 + B.1.351)-AS03	--	26	--
CoV2 preS dTM-AS03 (D614)-AS03	44	--	27
Comparator	26	--	--

*All subset participants will be 18-55 years of age only
† The scope of testing expanded for Delta in the whole Booster Cohort 1 and Booster Cohort 2 (Protein Primed Group) instead of only in a subset of participants.

Supplemental Cohorts Subsets and Assessment of Immunogenicity to Emerging Variants of Concern: A randomized subset of 70 participants in Cohort 1 was originally planned to be tested for additional SARS-CoV-2 variants of concern including Delta. However, to address CBER requests, the Sponsor decided to expand the scope of testing and to perform the immunogenicity assessment for Delta in the whole Booster Cohort 1 and Booster Cohort 2 (Protein Primed Group) instead of only in a subset of participants. 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 total of 3660 participants are planned to be enrolled in the Supplemental Phase III Cohorts.

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 Groups: approximately 365 days post-injection 2 (ie, approximately 386 days total)

2 Objectives and Endpoints

Table 2.1: Objectives and endpoints

Primary Safety	
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-Supplemental Cohort 1	
Co-primary objectives: 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 (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 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.	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 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 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 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 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) and the CoV2 preS dTM-AS03 (D614 + B.1.351) Intervention Groups. • Individual serum neutralizing titer at D01 and D15 against the D614G strain for the CoV2 preS dTM-AS03 (D614 + B.1.351) Intervention Group. • Individual serum neutralizing titer against the D614G strain at D36 (Comparator Group)

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 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 CoV2 preS dTM-AS03 (D614) vaccine, that a booster dose of CoV2 preS dTM-AS03 (D614) 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) induces an immune response that is superior to that observed immediately before booster.	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 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 postvaccination relative to D01 at D15 against the D614G strain in each Intervention Group • $\geqslant$ 2-fold-rise and $\geqslant$ 4-fold-rise in serum neutralization titer [post/pre] (fold-rise $\geqslant$ 2 and $\geqslant$ 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

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 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 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 non-inferior 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 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: 11) To describe, in adults 18-55 years of age previously vaccinated with the Moderna COVID-19 mRNA vaccine, the immune response to a booster dose of CoV2 preS dTM-AS03 (D614). 12) To describe, in adults 18-55 years of age previously vaccinated with the Oxford/Astra-Zeneca COVID-19 vaccine, the immune response to a booster dose of CoV2 preS dTM-AS03 (D614). 13) To describe, in adults 18-55 years of age previously vaccinated with the Janssen COVID-19 vaccine, the immune response to a booster dose of CoV2 preS dTM-AS03 (D614). 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).	• 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 • 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 postvaccination to the D614G strain and B.1.351 variant at each pre-defined timepoint relative to D01 in each Intervention Group • $\geqslant$ 2-fold-rise and $\geqslant$ 4-fold-rise in serum neutralization titer [post/pre] (fold-rise $\geqslant$ 2 and $\geqslant$ 4) to the D614G strain and B.1.351 variant at each predefined 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 postvaccination relative to D01 at D15 against the D614G strain in each Intervention Group • $\geqslant$ 2-fold-rise and $\geqslant$ 4-fold-rise in serum neutralization titer [post/pre] (fold-rise $\geqslant$ 2 and $\geqslant$ 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 postvaccination relative to D01 at D15 profile to the B.1.351 variant in each Intervention Group • $\geqslant$ 2-fold-rise and $\geqslant$ 4-fold-rise in serum neutralization titer [post/pre] (fold-rise $\geqslant$ 2 and $\geqslant$ 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

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.	<u>Endpoints for secondary objective #19:</u> • Individual antibody concentration at each predefined 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] $\geqslant$ 2 and $\geqslant$ 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 predefined post-vaccination timepoints and participants with baseline values above LLOQ with a 4-fold increase in binding antibody concentration at each pre-defined postvaccination 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) 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) or CoV2 preS dTM-AS03 (D614 + B.1.351) induces an immune response that is superior to that observed immediately before booster. <u>Conditional secondary objective: conditional on meeting the primary immunogenicity objectives (1) and (2) and the co-secondary objectives for Supplemental Cohort 2:</u> 3) 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.	<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) and the CoV2 preS dTM-AS03 (D614 + B.1.351) Intervention groups. • Individual serum neutralizing titer at D01 and D15 against the D614G strain for the CoV2 preS dTM-AS03 (D614 + B.1.351) 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) and the CoV2 preS dTM-AS03 (D614 + B.1.351) 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 D01, against the B.1.351 variant for the CoV2 preS dTM-AS03 (B.1.351) and the CoV2 preS dTM-AS03 (D614 + B.1.351) 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) Intervention 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 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) 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) 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) 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) or CoV2 preS dTM-AS03 (D614 + B.1.351) compared to that observed immediately before booster. 8) To describe, in adults 18-55 years of age previously vaccinated with the Moderna COVID-19 mRNA vaccine, the immune response to a booster dose of CoV2 preS dTM-AS03 (B.1.351) or CoV2 preS dTM-AS03 (D614 + B.1.351). 9) To describe, in adults 18-55 years of age previously vaccinated with the Oxford/Astra-Zeneca COVID-19 vaccine, the immune response to a booster dose of CoV2 preS dTM-AS03 (B.1.351) or CoV2 preS dTM-AS03 (D614 + B.1.351). 10) To describe, in adults 18-55 years of age previously vaccinated with the Janssen COVID-19 vaccine, the immune response to a booster dose of CoV2 preS dTM-AS03 (B.1.351) or CoV2 preS dTM-AS03 (D614 + B.1.351).	• 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 postvaccination 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 postvaccination 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

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) or CoV2 preS dTM-AS03 (D614 + B.1.351). 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) 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) or CoV2 preS dTM-AS03 (B.1.351) 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 D15 by Intervention Group, overall, by priming platform, and by priming vaccine. 18) To describe in adults previously vaccinated with the Pfizer/BioNTech COVID-19 mRNA 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) 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.	• Individual serum neutralization titer fold-rise postvaccination 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 postvaccination 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 predefined 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 postvaccination 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 postvaccination 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 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 postvaccination 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 postvaccination 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 Endpoints for secondary objective #19: • Individual antibody concentration at each predefined 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 predefined post-vaccination time point • Responders, defined as participants who had baseline values below LLOQ with quantifiable antibody concentration above assay LLOQ at predefined 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	
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	
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 predefined 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. Endpoints 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 predefined 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 predefined 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

3 Statistical Considerations

3.1 Statistical Hypotheses

Sequential hypotheses testing with Bonferroni-based multiplicity control over the overall Type I error rate at 5% for 2-sided tests and 2.5% for 1-sided tests for the co-primary endpoints and then the co-secondary/secondary endpoints will be performed in order as defined in each supplemental cohort. The margins of 1-sided non-inferiority tests on the neutralizing antibody titers to the COVID-19 variant of interest in the study intervention group are a 1.5-fold rise in geometric mean titers (GMTs) and -10% for seroresponse rates, compared to that in the comparator group. The margin of 1-sided superiority tests on the post-booster neutralizing antibody titers to the COVID-19 variant of interest in the study intervention group is a 2-fold rise in GMT compared to pre-booster.

3.1.1 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).

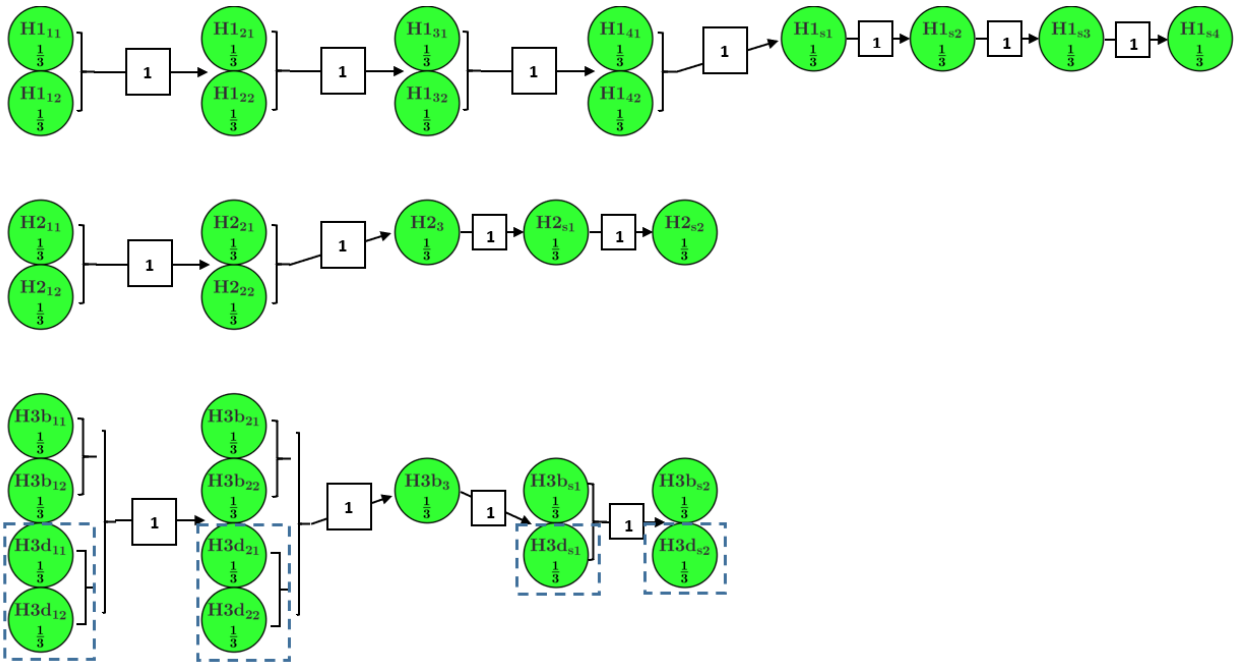
For the CoV2 preS dTM-AS03 (D614) booster candidate, there are 2 co-primary endpoints to be hypotheses tested with one-sided alpha 0.025/3 in participants primed with the Pfizer/BioNTech vaccine. If the primary objectives are met, then 2 conditional secondary endpoints will be hypotheses tested with one-sided alpha 0.025/3 applying the sequential testing strategy in participants primed with the CoV2 preS dTM-AS03 (D614) vaccine in the Original Phase II Cohort. If the primary objectives in the Pfizer/BioNTech vaccine primed and conditional secondary objectives in the CoV2 preS dTM-AS03 (D614) 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 CoV2 preS dTM-AS03 (D614) 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 CoV2 preS dTM-AS03 (D614) 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, CoV2 preS dTM-AS03 (D614) 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-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 (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 3.1: 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 CoV2 preS dTM-AS03 (D614) 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 CoV2 preS dTM-AS03 (D614) 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 CoV2 preS dTM-AS03 (D614) 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 CoV2 preS dTM-AS03 (D614)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 CoV2 preS dTM-AS03 (D614) 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) 2 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.

3.1.1.1 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 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 Phase III Cohort 1
2. Eligible participants from studies involving the same investigational CoV2 preS dTM-AS03 vaccine which include:
   a) VAT00002 Original Phase II Cohort participants, enrolled at US sites, who received the 10 μg antigen dose of the CoV2 preS dTM-AS03 vaccine and are included in the PPAS Naive-D01+D22 population
   b) VAT00008 participants enrolled at US sites who received the CoV2 preS dTM-AS03 (D614) and are included in the IAS Naïve-D01+D22 population

Evaluable participants will be pooled in sequence from the above sources. Three scenarios for pooling data will be applied, as applicable:

Scenario A: If the number of evaluable Supplemental Phase III Cohorts Comparator Group participants is ⩾ 260, which corresponds to a power of at least 70% for Cohort 2 primary objectives, Scenario A will be applied. This scenario is only applicable to VAT00002 Supplemental Phase III Cohort participants and there is no pooled primary series.

The evaluable participants in the Supplemental Cohorts Comparator Group will provide sufficient sample size, or despite a shortfall the Sponsor determines that the Supplemental Comparator Group would not be augmented with additional data sources. In this scenario, only the contemporaneously enrolled Supplemental Cohorts Comparator Group will be included in hypothesis testing, with no additional population sources.

Since no pooled Comparator Group is needed, exploratory sensitivity analysis for the pooled population will not be performed. The main analysis on the full population will be performed as planned.

Scenario B: If the number of evaluable Supplemental Cohorts Comparator Group participants is between 200-260, which corresponds to power of around 60%-70% for Supplemental Cohort 2 primary objectives, Scenario B will be applied. This scenario is applicable to the pooled primary series of VAT00002 Supplemental Phase III participants combined with the VAT00002 Original Phase II participants.

All eligible participants who were originally enrolled in VAT00002 Original Phase II Cohort and are evaluable for immunogenicity analysis will be combined with all evaluable participants recruited in the Supplemental Cohorts Comparator Group for the hypothesis testing for Supplemental Cohort 2.

First, population comparability on key factors at baseline between the sources will be assessed. Main analysis will be conducted using the pooled Comparator Group and an exploratory sensitivity analysis using the immunogenicity data from the contemporaneously-enrolled Supplemental Cohorts Comparator Group will be performed.

Scenario C: If the number of evaluable Supplemental Cohorts Comparator Group participants is < 200, which corresponds to power of < 60% for Cohort 2 primary objectives, Scenario C will be applied. This scenario is applicable to the pooled primary series of VAT00002 Supplemental

Phase III Cohort participants combined with VAT00002 Original Phase II Cohort participants and VAT00008 Phase III non-placebo participants.

Given the differences in the timing of key study measurements (the blood sampling timepoint after second injection: VAT00008 D43 vs VAT00002 D36), the possibility of pooling of data from 18-55 years individuals enrolled in the VAT00008 trial at sites in the US included in the IAS Naïve-D01+D22 is very low. Such pooling will require support through evaluation of population comparability at baseline. Should this need exist, the same pooling approach and analysis methods will be performed as described in Scenario B.

Eligible participants will be selected and pooled based on the comparability of population and assessments per clinical justification.

The population comparability will be descriptively compared for:

- Geographic region
- Age distribution
- Demographics
- High-risk medical conditions
- Primary series dosing schedule

If the pooling primary series is utilized in primary analyses (Scenario B and Scenario C), an exploratory sensitivity analysis will be performed on the hypothesis testing for Supplemental Cohort 2 by only using the contemporaneously-enrolled Supplemental Cohorts Comparator Group.

3.1.1.2 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 CoV2 preS dTM-AS03 (D614) 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 CoV2 preS dTM-AS03 (D614) 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) : $GMT_{(booster)} / GMT_{(comparator)} \leqslant (1/1.5)$

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% confidence interval (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 $_{(post\text{-}booster/pre\text{-}booster)} \leqslant 2$

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 CoV2 preS dTM-AS03 (D614) vaccine.

Conditional secondary objective 1.1: non-inferiority to the comparator for participants primed with the CoV2 preS dTM-AS03 (D614) vaccine:

For participants, 18-55 years old, primed with the CoV2 preS dTM-AS03 (D614) 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) : $GMT_{(booster)} / GMT_{(comparator)} \leqslant (1/1.5)$

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 CoV2 preS dTM-AS03 (D614) vaccine:

For participants, 18-55 years old, primed with the CoV2 preS dTM-AS03 (D614) 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 $_{(post\text{-}booster/pre\text{-}booster)} \leqslant 2$

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 CoV2 preS dTM-AS03 (D614) 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) : $GMT_{(booster)} / GMT_{(comparator)} \leqslant (1/1.5)$

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) : $Ratio_{(post\text{-}booster/pre\text{-}booster)} \leqslant 2$

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 CoV2 preS dTM-AS03 (D614) 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) : $GMT_{(booster)} / GMT_{(comparator)} \leqslant (1/1.5)$

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 $_{(post\text{-}booster/pre\text{-}booster)} \leqslant 2$

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 CoV2 preS dTM-AS03 (D614)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 CoV2 preS dTM-AS03 (D614)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, CoV2 preS dTM-AS03 (D614), mRNA, or adenovirus vector vaccines:

For participants, 18-55 years old, primed with the Pfizer/BioNTech vaccine, the CoV2 preS dTM-AS03 (D614) 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, CoV2 preS dTM-AS03 (D614) 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%.

3.1.1.3 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 $_{(post\text{-}booster/pre\text{-}booster)} \leqslant 2$

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 $_{(post\text{-}booster/pre\text{-}booster)} \leqslant 2$

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 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) : $GMT_{(variant)} / GMT_{(comparator)} \leq 1.5$

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

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%.

Sensitivity analysis with a pooled primary series cohort as Cohort 2 Comparator Group:

- ***Evaluate population comparability of enrolled comparator group for Cohort 2 vs a pooled primary series cohort***

  Those factors will be descriptively analyzed to compare the population to be pooled together:

  - Inclusion and Exclusion Criteria
  - Timepoints
  - Geographic
  - Age distribution
  - Demographic
  - Baseline characteristics (for example, high-risk medical condition)
  - Vaccine dose level

- ***Sensitivity analysis to test the robust of primary analyses by using pooling primary series as comparator group***

  The same methods will be used for each hypothesis testing of corresponding powered objective(s) by using enrolled comparator group and eligible participants from other studies separately.

3.2 Sample Size Determination

3.2.1 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 3.1.

Table 3.1: Power estimations for Supplemental Cohorts 1 and 2 (18-55 years old)

Cohort/ Objective(s)	Arm	Parameters for Non-inferiority	Parameters for Superiority	Study Power
Cohort 1 CoV2 preS dTM-AS03 (D614) Booster Group				
Primary Objectives (Type I error: 0.00833)	Pfizer primed CoV2 preS dTM-AS03 (D614) Booster Group (N=215)	• Assumed true ratio of group GMT: 1.5 • 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: 98.7% • Superiority: > 99.9% • Overall: 98.7%
Conditional Secondary Objectives (Type I error: 0.00833)	CoV2 preS dTM-AS03 (D614)primed CoV2 preS dTM-AS03 (D614) Booster Group (N=270)			• Non-inferiority: 99.7% • Superiority: > 99.9% • Overall: 99.6%
Conditional Secondary Objectives (Type I error: 0.00833)	mRNA primed CoV2 preS dTM-AS03 (D614) Booster Group (N=290)			• Non-inferiority: 99.8% • Superiority: > 99.9% • Overall: 99.8%
Conditional Secondary Objectives (Type I error: 0.00833)	Adenovirus vector primed CoV2 preS dTM-AS03 (D614) Booster Group (N=150)			• Non-inferiority: 94% • Superiority: 99.1% • Overall: 93.2%
Conditional Secondary Objective (Type I error: 0.00833)	Pfizer primed CoV2 preS dTM-AS03 (D614) Booster Group (N=215)	Non-inferiority on seroresponse • Assumed true Comparator Group seroresponse rate: 99% • Assumed actual difference between Booster and Comparator Groups: -2.5% • Margin: -10%		95.3%
Conditional Secondary Objectives	CoV2 preS dTM-AS03 (D614)primed CoV2 preS dTM-AS03 (D614)			98.9%

(Type I error: 0.00833)	Booster Group (N=270)			
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 • 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	• 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% • 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.

3.3 Populations for Analyses

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	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 Supplemental Cohorts comparator groups:

Prior SARS-CoV-2 infection status	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 one 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 one 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 one 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 sample 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 Pfizer/BioNTech vaccine in the non-exploratory groups, 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 Comparator Group, Supplemental Cohort 2 primed with Pfizer/BioNTech vaccine in the non-exploratory groups, 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 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 who did not provide all post-dose blood samples within the proper time window or no post-dose blood sample was drawn

	• 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.

3.3.1 Analysis sets Used in Analyses

The analysis set used in analyses is listed in Table 3.2.

Table 3.2: Analysis set used in analyses

Cohort	Type of Analyses		Intervention group(s)	Comparator group
Supplemental Cohort 1, Supplemental Cohort 2	Primary immunogenicity	Main	PPAS	PPAS Naïve at D01+D22
		Sensitivity	FAS	FAS Naïve at D01 FAS Naïve at D01+D22
	Secondary immunogenicity	Main	PPAS	PPAS Naïve at D01+D22
		Sensitivity	FAS	FAS Naïve at D01 FAS Naïve at D01+D22
	Exploratory immunogenicity regarding objective #11		PPAS	PPAS Naïve at D01+D22
	Exploratory immunogenicity in CMI subset for Cohort 2		CMIAS	CMIAS
	Exploratory immunogenicity in Variant Testing subset		VTAS Variant Testing Subset	VTAS Naïve at D01+D22 Variant Testing Subset Naïve at D01+D22
Supplemental Cohorts	Primary, Secondary safety		SafAS	SafAS

3.3.2 Derivation of Primed vaccine group

For Supplemental Cohort 1 and Cohort 2 booster arms:

- Actual prior COVID-19 vaccination history reported in eCRF will be used to derive the prior primed COVID-19 vaccine group for each participant.
- In case there will be mixed prior primed COVID-19 vaccine regimen, below derivation rule will be applied for each population analysis set:

Analysis set	Individual primed COVID-19 vaccine classification	Pooled platform classification	Consideration
PPAS	Not included in PPAS	Not included in PPAS	Violate IE, exclude from PPAS
FAS	Derived as first dose of primed COVID-19 vaccine	Derived as pooled primed platform	If primed COVID-19 vaccines belong to the same platform
CMIAS	Not included in CMIAS	Not included in CMIAS	Violate IE, exclude from CMIAS
VTAS	Not included in VTAS	Not included in VTAS	Violate IE, exclude from VTAS
SafAS	Derived as first dose of primed COVID-19 vaccine	Derived as pooled primed platform	If primed COVID-19 vaccines belong to the same platform

3.4 Statistical Analyses

The SAP will be finalized prior to the database lock for any interim analysis applicable to the Supplemental Cohorts 1 and 2. Additional SAP amendments may be performed after execution of interim analysis and before the database lock for any additional analysis occurring in between any such interim analyses and the final analysis.

3.4.1 General Considerations

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

For descriptive purposes, the following statistics will be presented:

Table 3.3: Descriptive statistics produced

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

The CI for the single proportion will be calculated using the exact binomial method (Clopper-Pearson method, quoted by Newcombe (1), ie, using the inverse of the beta integral with SAS®).

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

3.4.2 Primary Endpoints - 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.

Confidence interval for the GMT ratio between booster arms and comparator group for Supplemental Cohorts 1 and 2 – Welch's t-interval

The details about the calculations of the CI for the GMT ratio between 2 groups are as follows:

Logarithmic transformation of the individual titers will be calculated first. Assuming that individual $\log_{10}$ (titer) is normally distributed, the 98.3% CI (Supplemental Cohorts 1 and 2) for

the difference in $\log_{10}$ (GMT) between group i and group j will be in the form:

$$\bar{X}_i - \bar{X}_j \pm t(\alpha/2,r) \cdot \sqrt{S2/n_i + 1/n_j}\ \bar{X}_i - \bar{X}_j \pm t(\alpha/2,r) \cdot \sqrt{S_{X_i}^2/n_i + S_{X_j}^2/n_j}$$

where $\bar{X}_i = \log_{10}$(GMT) is the sample mean of $\log_{10}$(titer) of Group *i*, n_i and S_i^2 are the sample size and sample variance of Group i, $\bar{X}_j = \log_{10}$(GMT) is the sample mean of $\log_{10}$(titer) of Group *j*, n_j and S_j^2 are the sample size and sample variance of Group j,

where the r degrees of freedom are approximated by:

$$r = \frac{(\frac{S_{X_i}^2}{n_i} + \frac{S_{X_j}^2}{n_j})^2}{\frac{(S_{X_i}^2/n_i)^2}{n_i - 1} + \frac{(S_{X_j}^2/n_j)^2}{n_j - 1}}$$

take the integer portion of r, that is, use [r], $t(1-\alpha/2, [r])$ is the $100(1-\alpha/2)$ percentile of the *t*-distribution with degrees of freedom [r].

The margin used for non-inferiority hypothesis testing are 1/1.5=0.667 for GMTs. The non-inferiority in terms of GMTs will be demonstrated, if the lower limit of the 2-sided 98.3% CI (Supplemental Cohorts 1 and 2) for the difference of $\log_{10}$ (GMT) of tested vaccine candidate arm and $\log_{10}$ (GMT) of the control arm > $\log_{10}$ (1/1.5).

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.

Confidence interval for the paired GMTR

The Geometric mean of titer ratio is defined as:

$$GMTR = (\prod_{i=1}^{n} ratio_i)^{\frac{1}{n}} = 10^{\frac{\sum_{i=1}^{n} log_{10}(ratio_i)}{n}} = 10^{\frac{\sum_{i=1}^{n} log_{10}\left(\frac{post_i}{pre_i}\right)}{n}}$$

The normal approximation will be used to calculate the 2-sided 98.3% CIs for the individual group GMTRs as follows:

$$10^{(\bar{x} \pm t_{n-1,\alpha/2}\sqrt{v(\bar{x})})}$$

where $10^{(\bar{x})}$ is the GMTR, $\bar{x} = \frac{1}{N}\sum \log_{10}(x)$, $\log_{10}(x)$ is the log base 10 of the titer ratio (post/pre), *N* is the number of subjects with non-missing value for pre and post-vaccination,

$\sqrt{V(\bar{x})}$ is the estimated standard deviation of $\bar{x}$, and $t_{n-1,\,\alpha/2}$ is the 100(1-α/2) percentile of the central *t*–distribution with *n-1* degrees of freedom.

The margin used for superiority hypothesis testing are 2 for individual group GMTRs. The superiority in terms of GMTRs will be demonstrated if the lower limit of the 2-sided 98.3% CI (Supplemental Cohorts 1 and 2) for the mean of $\log_{10}$ (GMTRs) > $\log_{10}$ (2).

GMTs in each injection group and GMT ratios between injection groups will be descriptively 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. The 95% CI of GMT ratios between booster arms and comparator group will base on the Welch's t-interval for Supplemental Cohort 1 and 2 will base on the Student t-distribution.

Analyses will be performed for both FAS and PPAS, but the conclusion will be made mainly from results based on PPAS and supported by results based on FAS.

Subgroup analyses, where applicable, will be performed by age-group (18-55 years and ⩾ 56 years) 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.

3.4.3 Primary Endpoints - 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 and ⩾ 56 years), high-risk medical conditions group, and baseline SARS-CoV-2 Naïve status for main safety analyses. In the booster vaccine groups (in Cohorts 1 and 2), subgroup analyses will be performed by age group (18-55 years and ⩾ 56 years), 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 dosage administered in the original Phase II cohort (ie, 5-10-15 μg) for Cohort 2.

Safety endpoints that occurred after authorized/approved COVID-19 vaccine injection will be listed separately.

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, seriousness, intensity, nature (MedDRA SOC and PT), time of onset, duration, relationship to vaccination of all protocol-specified AESIs from the time of the first study vaccination throughout the study.
- Presence, seriousness, intensity, nature (MedDRA SOC and PT), time of onset, duration, relationship to vaccination of MAAEs throughout the study.

Confidence interval for the single proportion of AEs

The exact 2-sided 95% CI for the single proportion will be constructed using Clopper-Pearson's method, quoted by Newcombe where:

Lower bound: $1 - Beta(1-\alpha/2, n-r+1, r)$ and

Upper bound: $Beta(1-\alpha/2, r+1, n-r)$

where α=0.05, and *r* is the observed number of events/responders in *n* observations.

3.4.4 Secondary Endpoints - Immunogenicity

For Supplemental Cohorts 1 and 2 conditional secondary objectives on non-inferiority claim of post-booster versus post-primary vaccination, the statistical inference will be based on the use of the two-sided 98.3% CI of difference in geometric means of post-vaccination log10 transformed titer values between the 2 groups with normal approximation.

The margin used for non-inferiority hypothesis testing are 1/1.5=0.667 for GMTs. The non-inferiority in terms of GMTs will be demonstrated if the lower limit of the 2-sided 98.3% CI (Supplemental Cohorts 1 and 2) for the difference of $\log_{10}$ (GMT) of tested vaccine candidate arm and $\log_{10}$ (GMT) of the control arm > $\log_{10}$ (1/1.5).

For Supplemental Cohorts 1 and 2 conditional secondary objectives on superiority claim of post-booster versus pre-booster, the two-sided 98.3% CI of post-booster versus pre-booster will be calculated using $\log_{10}$-transformed titers assuming a normal distribution.

The margin used for superiority hypothesis testing on post-booster versus pre-booster responses in Supplemental Cohorts 1 and 2 on individual group GMTRs is 2. The superiority in terms of GMTRs will be demonstrated if the lower limit of the 2-sided 98.3% CI (Supplemental Cohorts 1 and 2) of $\log_{10}$ (GMTRs) > $\log_{10}$ (2).

For Supplemental Cohort 2 conditional secondary objective on superiority claim of B.1.351 for post-booster versus post-primary vaccination, the two-sided 98.3% CI of post-booster versus post-primary will be based on the use of the two-sided 98.3% CI of difference in geometric means of post-vaccination log10 transformed titer values between the 2 groups with normal approximation.

The margin used for superiority hypothesis testing on post-booster versus post-primary responses to B.1.351 in Supplemental Cohort 2 on individual group GMTRs is 1.5. The superiority in terms

of GMTRs will be demonstrated, if the lower limit of the 2-sided 98.3% CI (Supplemental Cohorts 1 and 2) of $\log_{10}$ (GMTRs) > $\log_{10}$ (1.5).

For Supplemental Cohorts 1 and 2 conditional secondary objectives on non-inferiority claim of seroresponse, the two-sided 98.3% CI difference in proportions between groups will be computed using the Wilson score method without continuity correction.

The margin used for non-inferiority hypothesis testing is -10% for seroresponse rate. The non-inferiority in terms of seroresponse rates will be demonstrated if the lower limit of the 2-sided 98.3% CI for the difference of seroresponse rates > -0.1.

Confidence interval for the difference in proportions between two groups

For the non-inferiority hypotheses in terms of seroresponse rate, the two-sided 95% CI difference in proportions between groups will be computed using the Wilson score method without continuity correction (2) as follows:

Let $\hat{\theta} = \pi_A - \pi_B$, then if $L = \hat{\theta} - \delta$ and $U = \hat{\theta} + \varepsilon$ are respectively the lower and the upper limits of the CI, where:

$$\delta = Z_{\alpha/2}\sqrt{\left\{\frac{l_1(1-l_1)}{n_1} + \frac{u_2(1-u_2)}{n_2}\right\}}$$

$$\varepsilon = Z_{\alpha/2}\sqrt{\left\{\frac{l_2(1-l_2)}{n_2} + \frac{u_1(1-u_1)}{n_1}\right\}}$$

l_1 and u_1 are calculated from the CI of the single proportion in Group A given by:

$$\frac{(2n_1p_1 + Z^2_{\alpha/2} \pm Z_{\alpha/2}\sqrt{(Z^2_{\alpha/2} + 4n_1p_1(1-p_1))})}{2(n_1 + Z^2_{\alpha/2})}$$

l_2 and u_2 are calculated from the CI of the single proportion in Group B given by:

$$\frac{(2n_2p_2 + Z^2_{\alpha/2} \pm Z_{\alpha/2}\sqrt{(Z^2_{\alpha/2} + 4n_2p_2(1-p_2))})}{2(n_2 + Z^2_{\alpha/2})}$$

where $Z_{\alpha/2}$ is the upper (1-α/2)th percentile of the standard normal distribution.

The margin used for non-inferiority hypothesis testing is -10% for seroresponse rate. The non-inferiority in terms of seroresponse rates will be demonstrated if the lower limit of the 2-sided 95% CI for the difference of seroresponse rates > -0.1.

The percentage of responders and participants having 2-fold rise (2FR), 4-fold rise (4FR) will be provided against each endpoint with the corresponding 95% CIs using the Clopper-Pearson method. FR defined as fold-rise from post-vaccination relative to pre-vaccination, the pre-vaccination could be the D01 at Phase III study or D01 at Phase II study for CoV2 preS dTM-

AS03 primed participants. Differences of percentages of responders and participants with 2FR, 4FR will be provided with 95% CI calculated by Newcombe-Wilson score method without continuity correction.

Confidence interval for the single proportion

The exact 2-sided 95% CI for the single proportion will be constructed using Clopper-Pearson's method, quoted by Newcombe where:

Lower bound: $1 - Beta(1-\alpha/2, n-r+1, r)$ and

Upper bound: $Beta(1-\alpha/2, r+1, n-r)$

where *r* is the observed number of events/responders in *n* observations.

GMTs or GMCs in each injection group and GMT or GMC ratios between injection groups will be descriptively summarized along with their 95% CIs using the normal approximation of log-transformed titers. GMTs or GMCs will be presented in original scale that are re-converted from log-transformed titers. The 95% CI of GMT or GMC ratios between booster arms and comparator group will base on the Welch's t-interval for Supplemental Cohort 1 and 2.

The 95% CI of GMT ratios after booster dose at D15 between booster arms based on the Student t-distribution and 95% CI of difference on seroresponse rate at D15 relative to D01 between booster arms based on the Newcombe-Wilson score method without continuity correction will be provided for homogeneity/comparability evaluation on booster effect across different primary series vaccines, by age group and overall.

GMTRs or GMCRs is defined as ratio of individual geometric mean titer or concentration for each injection group (post-vaccination/pre-vaccination for each injection). GMTR or GMCR will be summarized with 95% CI (Normal approximation). Additional parameters may be displayed as appropriate.

Confidence interval for the individual group GMT or GMC and GMTR or GMCR

The normal approximation will be used to calculate the 2-sided 95% CIs for the individual group GMT or GMC and GMTRs or GMCRs as follows:

$$10^{(\bar{x} \pm t_{n-1,\alpha/2}\sqrt{v(\bar{x})})}$$

where $10^{(\bar{x})}$ is the GMT or GMC, $\bar{x} = \frac{1}{N}\sum \log_{10}(x)$, $\log_{10}(x)$ is the log base 10 of the observed titer or concentration, *N* is the total observation in each injection group, $\sqrt{V(\bar{x})}$ is the estimated standard deviation of $\bar{x}$, and $t_{n-1,\alpha/2}$ is the 100(1-α/2) percentile of the central *t*–distribution with *n-1* degrees of freedom.

3.4.5 Secondary Endpoints - Safety

The occurrences of laboratory-confirmed symptomatic COVID-19 and 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.

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 collected during the analysis period is less than 5 in all groups, no summary analysis will be performed, and a listing of observed cases will be provided.

For Supplemental Cohorts Comparator group, laboratory-confirmed symptomatic COVID-19 and serologically-confirmed SARS-CoV-2 infection that occurred after authorized/approved COVID-19 vaccine injection will be listed separately.

For Supplemental Cohort 1 and Cohort 2 booster arms, laboratory-confirmed symptomatic COVID-19 and serologically-confirmed SARS-CoV-2 infection that occurred after authorized/approved COVID-19 vaccine injection during the study period will be listed separately.

3.4.6 Exploratory Endpoints

Cellular immune response/Mucosal antibody response

Data of each B-cell response and T-cell response will be summarized in GMT with 95% CI using the same method stated in Section 3.4.4. CMIAS population will be applied.

Neutralizing antibody response to emergent SARS-CoV-2 variant strains

Exploratory immunogenicity analysis will be performed by SARS-CoV-2 Pseudovirus Neutralization Assays at Nexelis testing variants (eg, B.1.1.7, P.1, B.1.617, etc.). The same analysis methods stated in Section 3.4.4 will be applied. GMT, GMTR, proportion of participants having 2FR, 4FR and proportion of responders based on neutralizing antibodies will be analyzed for each SARS-CoV-2 variant strain on each time point respectively.

Details of assay information and corresponding analysis performed are listed in Appendix A.

The neutralizing antibody response to SARS-CoV-2 variant strains (D614G, B.1.351, B.1.1.7, P.1, B.1.617, etc) will be evaluated by country as exploratory purpose.

3.4.7 Handling of Missing Data and Outliers

3.4.7.1 Safety

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

3.4.7.1.1 Immediate

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

3.4.7.1.2 Causal Relationship

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

- For unsolicited systemic AE, missing relationship will be considered as related to study vaccine at the time of analysis.
- The missing relationship to study procedures for SAEs will not be imputed.

3.4.7.1.3 Intensity

For solicited reactions, missing intensities will be handled as described in Section 4.2.1.1.1. For unsolicited non-serious AEs, missing intensities will remain missing and will not be imputed.

3.4.7.1.4 Start Date and End Date

Missing or partially missing start dates or end dates for unsolicited AEs (including SAEs) will remain missing and not be imputed. If the start date is missing or partially missing, the time of onset will be considered to be missing. Nevertheless, unsolicited AEs with missing time of onset will be included in analyses according to the last vaccination (computed according to the Section 4.2.1.2.3). If either the start date or end date is missing or partially missing, the duration will be considered missing.

Missing or partially missing end dates for ongoing solicited AEs will remain missing and not be imputed.

3.4.7.1.5 Action Taken

Missing actions taken will remain missing and not be imputed.

3.4.7.2 Date of COVD-19 Vaccination History Administration

Missing or partially missing date (day) of last prior non-study COVID-19 vaccine administration for Supplemental Cohort Booster Groups will be imputed as below to calculate the duration prior to on-study booster injection:

- Partially missing on day will be imputed as “01” day;
- Complete missing date or date missing on month will not be imputed and will be treated as missing.

3.4.7.3 Immunogenicity

No imputation of missing values and no search for outlier will be performed. LLOQ and ULOQ management will be performed as described in Section 4.2.3.1.

3.5 Interim Analyses

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 Cohort 2, a prespecified independent statistical group who will be unblinded at subject level to generate interim outputs including tables, listings, and figures. The treatment code will be masked from the interim outputs. A group of study members will review the interim outputs unblinded at group level, to perform decision-making. Furthermore, the study team will remain blinded on data collected after date cut-off of the interim analysis.

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

4 Complementary Information on Assessment Methods

Study assessments and procedures are detailed in Section 8 of the protocol. This section focuses on complementary/additional information not detailed in the protocol.

4.1 Complementary Information for Endpoints Assessment Methods

Not applicable

4.2 Complementary Information on Derived Endpoints: Calculation Methods

4.2.1 Safety

Main analysis, sensitivity analysis and complementary analysis will be undertaken based on safety analysis set. Main safety analysis will be performed as the key safety results, sensitivity and complementary analysis will be performed as supportive results. The rationale for conducting the sensitivity and complementary analysis is because of the high likelihood for participants in the study to receive a non-study authorized/approved COVID-19 vaccine for Supplemental Cohorts Comparator group, and for Supplemental Cohort 1 and Cohort 2 booster arms, in case the participants receive a non-study authorized/approval COVID-19 vaccine after booster dose. These study participants will be allowed to continue study participation if they choose to do so; while continuation in the study will include all study procedures including safety follow-up and therefore safety data will be collected after receipt of a non-study authorized/approved COVID-19 vaccine which will interfere with interpretation of the safety data following study vaccination.

Main analysis will be applied for all safety endpoints. It includes all adverse events or reactions with time of onset before the date of receiving a non-study authorized/approved COVID-19 vaccine (if applicable) during study period. For some selected endpoints, main analysis will only include safety data collected before the date of receiving a non-study authorized/approved COVID-19 vaccine (censored by the date) corresponding to those adverse events or reactions included. For the other endpoints, safety analysis will include all data collected in the entire collection period corresponding to those adverse events or reactions. Details of conducting main analysis for those endpoints including censored data are further clarified in the following subsections.

Sensitivity analysis will be conducted for some selected endpoints. It includes all adverse events or reactions with time of onset before receiving a non-study authorized/approved COVID-19 vaccine during the study period and includes safety data collected over the entire collection period corresponding to those adverse events or reactions. Details of conducting sensitivity analysis for those specific endpoints are further clarified in the following subsections.

Complementary analysis will be applied for some specific endpoints. It includes the adverse events or reactions with time of onset on or after receipt of a non-study authorized/approved COVID-19 vaccine (if applicable) during the study period and including all the corresponding safety data collected in the collection period. Details of conducting complementary analysis for those endpoints applicable will be clarified in the following subsections.

In general, sensitivity analysis will be conducted if there are at least 15 subjects with different values of the endpoint compared to the corresponding main analysis. Complementary analysis will be conducted if there are more than 15 subjects included in the corresponding analysis.

4.2.1.1 Solicited Reactions

Solicited reactions are collected within 7 days after each vaccination.

4.2.1.1.1 Daily Intensity

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

For measurable injection site reactions:

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

For Fever:

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

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

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

4.2.1.1.2 Maximum Intensity

Maximum intensity is derived from the daily intensities computed as described in Section 4.2.1.1.1 and is calculated as the maximum of the daily intensities over the period considered.

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

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

Main analysis, sensitivity analysis and complementary analysis will be applied by maximum intensity. The endpoint is derived from the general method mentioned above for sensitivity analysis and complementary analysis. Suppose participants receiving a non-study authorized/approved COVID-19 vaccine on Day X within the solicited collection period:

- The maximum intensity for main analysis will be derived on daily intensities from D01 to Day X-1.
- The maximum intensity for sensitivity analysis and complementary analysis will be derived from daily intensities collected over the entire solicited collection period.

4.2.1.1.3 Presence

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

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

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

4.2.1.1.4 Time of Onset

Time of onset is derived from the daily intensities computed as described in Section 4.2.1.1.1. It corresponds to the first day with intensity of Grade 1, Grade 2, or Grade 3.

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

Time of onset period will be categorized into and displayed as 1-4 days, 5-8 days for each injection.

Main analysis and complementary analysis will be conducted for solicited reactions by time of onset.

4.2.1.1.5 Number of Days of Occurrence During the Solicited Period

Number of days of occurrence over the period considered is derived from the daily intensities computed as described in Section 4.2.1.1.1. It corresponds to the number of days with daily

intensities of Grade 1, Grade 2, or Grade 3. Number of days of occurrence on the solicited period with a specified intensity may also be derived.

Main analysis, sensitivity analysis and complementary analysis will be applied by number of days of occurrence. The endpoint is derived from the general method mentioned above for sensitivity analysis and complementary analysis. Suppose participants receiving a non-study authorized/approved COVID-19 vaccine on Day X within the solicited collection period:

- The number of days of occurrence for main analysis will be derived on daily intensities from D01 to Day X-1.
- The number of days of occurrence for sensitivity analysis and complementary analysis will be derived from daily intensities collected over the entire solicited collection period.

Number of Days of Occurrence during the solicited period will be categorized into and displayed as 1-3 days, 4-7 days, and 8 days.

4.2.1.1.6 Overall Number of Days of Occurrence

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

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

If the stop date is missing or incomplete (contains missing data [MD]), the overall number of days of occurrence will be considered as Missing.

Main analysis and sensitivity analysis will be applied by overall number of days of occurrence. Complementary analysis may be applied for this endpoint. The endpoint is derived from the general method mentioned above for sensitivity analysis and complementary analysis. Suppose participants receiving a non-study authorized/approved COVID-19 vaccine on Day X within the solicited collection period:

- If the daily intensities are all “None” or “Missing” from day X within the solicited period and the ongoing status is “Not ongoing”, the overall number of days of occurrence will be the same with number of days of occurrence for main analysis.
- In all other situations, the overall number of days of occurrence will be analyzed as missing for main analysis.

Overall Number of Days of Occurrence will be categorized into and displayed as 2-3 days, 4-7 days, 8 days or more, Missing.

4.2.1.1.7 Ongoing

Ongoing is derived from the last daily intensity of the solicited period computed as described in Section 4.2.1.1.1 and the maximum intensity in the ongoing period. The Investigator’s ongoing flag is not used because the measurement would determine the ongoing status of the reaction.

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

Ongoing status will be derived for main analysis, sensitivity analysis and complementary analysis. Ongoing status is derived from the general method mentioned above for sensitivity analysis and complementary analysis. Ongoing status for main analysis is derived as follows:

- If ongoing status for sensitivity analysis is ongoing or missing, the ongoing status will be missing
- If ongoing status for sensitivity analysis is not ongoing, the ongoing status will be analyzed as not ongoing

4.2.1.2 Unsolicited AEs

Unsolicited AEs include unsolicited non-serious AEs, immediate unsolicited AEs, SAEs, AESIs and MAAEs. Analysis for unsolicited AEs only include those AEs collected within 21 days after each injection. SAEs, AESIs and MAAEs collected out of this range will only be presented in the analysis of SAEs/AESIs and MAAEs.

4.2.1.2.1 Presence

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

Grade 0 events will not be included in safety analysis but will be included in separate listings.

4.2.1.2.2 Intensity

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

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

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

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

The maximum intensity corresponds to the highest intensity for a unique term.
Main analysis, sensitivity analysis and complementary analysis will be applied by maximum intensity. The maximum intensity for sensitivity analysis and complementary analysis is derived

by the general method mentioned above. Suppose a participant receiving an authorized/approved COVID-19 vaccine on Day X, the maximum intensity for main analysis is as follows:

- If an unsolicited AE for the participant with both time of onset and stop date before Day X, then the maximum intensity for that AE will be analyzed as collected in CRF.

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

4.2.1.2.3 Last Vaccination

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

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

NOTE: This vaccination refers to the last study vaccination and not to a non-study authorized/approved COVID-19 vaccination.

4.2.1.2.4 Time of Onset

Time of onset is derived from the start date of the unsolicited AE provided in the clinical database and the date of last vaccination as described in Section 4.2.1.2.3:

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

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

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

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

Time of onset will be categorized into and displayed as 1-4 days, 5-8 days, 9-15 days, 16 days or later, and Missing.

Note: To further clarify the analysis:

- Any unsolicited AEs collected throughout the study (SAEs, MAAEs, AESIs) with time of onset > 22 days after each injection will not be presented in tables of unsolicited AEs within 21 days but only in tables of SAEs, MAAEs, AESIs.

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

Main analysis and complementary analysis will be applied by time of onset.

4.2.1.2.5 Duration

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

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

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

Main analysis, sensitivity analysis and complementary analysis will be applied by duration. The duration for sensitivity analysis and complementary analysis is derived by the general method mentioned above. Suppose a participant receiving an authorized/approved COVID-19 vaccine on Day X, the duration for main analysis is derived as follows:

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

Duration will be categorized into and displayed as 1-3 days, 4-7 days, 8 days or more, and Missing.

4.2.1.2.6 Medically-Attended Adverse Event

An event will be considered as an MAAE if "Yes' is checked for "Is the event an MAAE?" in the CRF. MAAEs will be analyzed throughout the study using the following periods:

For Supplemental Cohort 1 and Cohort 2 booster arms:

- From D01 to 21 days post dose 1
- During the 6 months follow up period
- During the entire study (ie, all MAAEs occurred during the study)

For Supplemental Cohorts Comparator Group:

- D01 to dose 2 (including the day of dose 2, use 21 days after D01 if dose 2 is not received)
- Within 21 days post dose 2
- From D01 to 21 days post dose 2

- During the 6 months follow up period
- During the entire study (ie, all MAAEs occurred during the study)

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

Main analysis and complementary analysis will be applied for MAAEs.

4.2.1.2.7 Serious Adverse Events

An event will be considered as a serious event if "Yes" is checked for "Serious" in the CRF.

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

For Supplemental Cohort 1 and Cohort 2 booster arms:

- From D01 to 21 days post dose 1
- During the 6 months follow up period
- During the entire study (ie, all SAEs occurred during the study)

For Supplemental Cohorts Comparator Group:

- D01 to dose 2 (including the day of dose 2, use 21 days after D01 if dose 2 is not received)
- Within 21 days post dose 2
- From D01 to 21 days post dose 2
- During the 6 months follow up period
- During the entire study (ie, all SAEs occurred during the study)

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

Main analysis and complementary analysis will be applied for SAEs.

4.2.1.2.8 Adverse Events of Special Interest

An event will be considered as an AESI if "Yes' is checked for "Is the event an AESI?" in the CRF. AESIs will be analyzed throughout the study using the following periods:

For Supplemental Cohort 1 and Cohort 2 booster arms:

- From D01 to 21 days post dose 1
- During the 6 months follow up period
- During the entire study (ie, all AESIs occurred during the study)

For Supplemental Cohorts Comparator group:

- D01 to dose 2 (including the day of dose 2, use 21 days after D01 if dose 2 is not received)
- Within 21 days post dose 2

- From D01 to 21 days post dose 2
- During the 6 months follow up period
- During the entire study (ie, all AESIs occurred during the study)

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

Main analysis and complementary analysis will be applied for AESIs.

4.2.2 Other Safety Endpoints

For the safety endpoint related to SARS-CoV-2 infections (endpoints from Section 4.2.2.1 to Section 4.2.2.7), main analysis will be applied including only those cases with start date before a participant received a non-study authorized/approved COVID-19 vaccine if applicable. Other cases with start date reported in participants after the receipt of an authorized/approved COVID-19 vaccine will be listed separately.

4.2.2.1 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 protocol section 8.3.3] or locally [Local Test for COVID-19 page in CRF]) on at least one respiratory sample collected throughout the study.

4.2.2.2 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 electrochemiluminescence immunoassay (ECLIA) collected throughout the study.

4.2.2.3 Symptomatic COVID-19

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

The start date of the illness episode is the first date of the first symptom onset corresponding to a single CLI. The stop date 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 CLI.

Exacerbation/worsening of symptoms can also be indicative of a new CLI. In the event of an illness with a positive NAAT for SARS-CoV-2, exacerbation/worsening of CLI symptoms or occurrence of new symptoms during the ongoing illness will be considered part of the ongoing COVID-19 illness episode.

In the event of exacerbation/worsening of CLI symptoms or occurrences of new symptoms during an ongoing illness which is not associated with a positive NAAT for SARS-CoV-2 (missing or

negative test), investigator judgement will determine if the new symptom(s) or/and the worsening of the symptom(s) suggest the possibility of a new illness that merits triggering a new illness form creation and new collection of respiratory samples and other illness related study procedures. In such 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).

In these instances of overlapping CLIs, the start date of the new CLI will be the date of exacerbation / worsening as collected in the CRF. The stop date of the 1st CLI will be the same as the stop date of the new CLI (following the rule stated above).

All information will be based on symptoms/features collected in the CRF corresponding to the same episode.

The derivation criteria for symptomatic COVID-19 is as follows:

- A CLI is identified in the CRF, the corresponding nasopharyngeal swab sample is collected during the CLI episode and the nasopharyngeal sample shows a positive result in the protocol-defined NAAT.
- A CLI is identified in the CRF, the CLI time of onset date is within the 7 days from the last vaccination dates (eg. D01 is visit 1, 7 days gives the range of D01 to D08) and the corresponding swab sample collected from the last visit or during the CLI shows a positive result from the protocol-defined NAAT.
- A CLI is identified, a positive COVID-19 local NAAT test result is recorded in CRF and the sample collection date for local test is within the range of [start date – 2 days, stop date] of a CLI for the participant.

4.2.2.4 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.

4.2.2.5 Hospitalized COVID-19

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

The start date of hospitalization is the date when the participant is admitted to a hospital as collected in CRF. The stop date of hospitalization is the participant's discharge date from the hospital as collected in CRF.

4.2.2.6 Severe COVID-19

Severe COVID-19 is defined as symptomatic 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, respiratory rate ≥ 30 breaths per minute at rest, heart rate ≥ 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

This endpoint is analyzed as data collected in CRF. The start date and stop date is the same than that of the corresponding symptomatic COVID-19.

4.2.2.7 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. This endpoint will be analyzed as data collected in CRF.

4.2.2.8 Pregnancy

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

4.2.2.9 Action Taken

Solicited injection site/systemic reactions after any vaccine injection(s) will be summarized, by action taken. Main analysis will be applied for this endpoint. Complementary analysis may be applied.

4.2.2.10 Seriousness

This information will be summarized as collected. No derivation or imputation will be done. Main analysis will be applied for this endpoint. Complementary analysis may be applied.

4.2.2.11 Outcome

This information will be summarized as collected. No derivation or imputation will be done. Main analysis will be applied for this endpoint. Complementary analysis may be applied.

4.2.2.12 Causal Relationship

This information will be summarized as collected. Missing causality (relationship) will be handled as described in Section 3.4.7.1.2. Main analysis will be applied for this endpoint. Complementary analysis may be applied.

4.2.2.13 Adverse Events Leading to Study Discontinuation

A flag will be available in the clinical database for all AEs in order to identify AEs leading to discontinuation. This information will be analyzed as collected.

In general, the items that are counted are:

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

Main analysis and complementary analysis will be applied for this endpoint.

4.2.3 Immunogenicity

4.2.3.1 Computed Values for Analysis

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

- If a value is < LLOQ, then use the computed value LLOQ/2.
- If a value is between LLOQ and ULOQ, then use the value reported.
- If a value is > ULOQ, then use ULOQ.
- Immunogenicity values at baseline (D01) with values < LLOQ are considered as negative whereas values ≥ LLOQ are considered as positive.

For SARS-CoV-2 pseudovirus neutralization assay at Monogram, LLOQ is < 40 and ULOQ is ≥ 787339.

For SARS-CoV-2 spike protein antibody serum IgG ELISA (Nexelis), LLOQ is 18.9.

4.2.3.2 Fold-rise

The derived endpoint fold-rise is driven by both baseline and post-vaccination computed values as described in Section 4.2.3.1 and is computed as individual titer ratio:

- Post-vaccination value divided by baseline value.

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

4.2.3.3 Responders

The responder's endpoint is determined by both baseline and post-baseline computed values with quantifiable titer values. Participants are identified as responders based on any one of the criteria:

- Baseline computed values < LLOQ and post-baseline values ≥ LLOQ at each pre-defined time point
- Baseline computed values ≥ LLOQ and < ULOQ with a 4-fold increase in post-baseline titers at each pre-defined timepoint
- Baseline value ≥ ULOQ is not within the scope of the responder' s definition (not applicable) and will be out of the analysis

Note: If baseline or post-baseline is missing, then responder endpoint for the corresponding timepoint(s) is missing.

4.2.3.4 Cellular Immune Response

Measurements of B cell responses and T cell responses will be tested independently, and data will be analyzed as reported by GCI.

4.2.3.5 Mucosal Immune response

Mucosal Ig values are derived by testing samples in duplicate in an indirect ELISA and comparing the Optical Density to a Cutoff Calibrator included with the kit. The cutoff value (Cutoff OD) is the mean value of the optical densities of the Cutoff Calibrator. Specimen results are calculated using the S / CO ratio: Specimen ratio = Specimen OD / Cutoff OD.

A specimen ratio less than or equal to 0.8 is negative for the presence of anti-SARS-CoV-2 antibodies, between 0.8 and 1.0 is equivocal for the presence of anti-SARS-CoV-2 antibodies, and greater than 1.0 is considered to be positive for the presence of anti-SARS-CoV-2 antibodies.

As samples are tested in duplicate, if one or more results are positive the final interpretation of the specimen is positive; if the repeat results are equivocal or negative the final interpretation is equivocal, and if both results are negative the final interpretation of the specimen is negative.

4.2.4 Derived Other Variables

4.2.4.1 Age for Demographics

The age of a participant in the study will be the calendar age in years at the time of inclusion and will be analyzed as collected in CRF.

Age group

The calendar age will be used for demographics summary and age-group definition. The age group of a participant in the study will be based on the calendar age as follows:

- "18 to 55 years": from the day of the 18th birthday to the day before the 56th birthday
- "≥ 56 years": from the day of the 56th birthday onwards, with no upper age limit

4.2.4.2 High-Risk Medical Conditions

The high-risk medical conditions at baseline are analyzed as collected in the CRF pages of high-risk medical conditions, smoking and BMI calculation.

Definition of High-Risk Medical Conditions

Comorbidities associated with increased risk of severe COVID-19 are defined as: High-risk 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 kg/m^2 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.

High-Risk Medical Conditions Group

- Yes: at least one high-risk medical conditions as defined above. Participants who are current smokers with either tobacco use or electronic cigarette use will be considered as in high-risk medical conditions group.
- No: no high-risk medical conditions as defined above. Participants who never smoked or are former smokers (either tobacco use or electronic cigarette use) will be considered as not in high-risk medical conditions group.

4.2.4.3 Duration of a Subject in the Trial

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

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

For ongoing subject in the interim analysis, the duration of a subject participation in the study is computed as follows:

- Minimum (Database lock/Database extraction date, Termination date, Death date) – V01 date + 1.

4.2.4.4 Duration of the Study

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

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

For interim analysis, the duration of the study is computed in days as follows:

- Maximum (Database lock/Database extraction date, Termination date, Death date) – minimum (date of V01) + 1.

4.2.4.5 Prior On-study Booster Injection

The duration in month of the prior on-study booster injection for Supplemental Cohort Booster Groups participants is computed as follows:

- (date of booster injection – date of last prior COVID-19 injection) / 30.44

4.2.4.6 Safety Follow-up Duration

The safety follow-up duration is computed as follows:

- Received other COVID-19 vaccination: first date of other COVID-19 vaccination - V01 date
- Not received other COVID-19 vaccination: Maximum (Database lock/Database extraction date, Termination date, Death date) – V01 date

4.3 Complementary Assessment of External Samples/Data

External blood samples/data from different sources will be analyzed as complemental analysis to further assess the immunogenicity profile of study vaccine.

The external blood samples/data from different sources will be analyzed separately by sample repository and combined as one per the primary series vaccine.

The sample selected from external sources are from adults, >= 18 years of age. As the samples are de-identified, other demographic and baseline characteristics are not available. The time point of blood samples are based on time interval of pre-vaccination and post-vaccination matched with the VAT00002 study time intervals as closely as possible. The external data is considered as belong to naïve participants before COVID-19 vaccination, however, no exact match to the study definition could be applied, for example, the participants are presumed to be naïve to SARS-CoV-2 base on antibody levels.

The Monogram assay will be used to evaluate immune responses in the blood samples.

GMTs in each and combined sample repository, and GMT ratios between external data group and booster arm will be descriptively 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. The 95% CI of GMT ratios between groups will based on the Welch's t-interval for primary series vaccination group and booster arm, the 95% CI of GMT ratios between primary series vaccination groups will based on the Student t-distribution.

GMTR or GMCR will be summarized with 95% CI (Normal approximation).

Estimated seroresponse will be calculated by post dose versus pre dose with antibody titer. Additional parameters may be displayed as appropriate.

5 Changes in the Conduct of the Trial or Planned Analyses

- **A pooled primary series cohort as Supplemental Cohorts 2 Comparator Group**

  A Pooled Primary Series Cohort as Supplemental Cohorts 2 Comparator Group was added in Protocol Amendment 4, version 8. The purpose is to maintain sufficient power for Cohort 2 hypothesis testing in primary analysis in case of a substantial shortfall in numbers of Comparator Group evaluable participants as the number of authorized and/or approved COVID-19 vaccines increases and RDT at baseline sensitivity to identify the Naïve participants is low. The pooling of evaluable participants from other trials of the same vaccine program is defined in SAP and the exploratory sensitivity analysis is added.

- **Complementary assessment of external samples/data**

  To further study immunogenicity profile of study vaccine, external samples/data will be analyzed along with study data. The assessment of external samples/data is considered as complementary analysis and corresponding part is added in SAP Section 4.3.

- **Study design updated to remove Variant Prime Cohort 3**

  The operational feasibility of recruiting SARS-CoV-2 naive, unvaccinated participants has become significantly more challenging, data are not required for regulatory purposes.

- **Enlarge the variant testing scope of Cohort 1 and Cohort 2 (Protein Primed Group)**

  A randomized subset of 70 participants in Cohort 1 was originally planned to be tested for additional SARS-CoV-2 variants of concern including Delta. However, to address CBER requests, the Sponsor decided to expand the scope of testing and to perform the immunogenicity assessment for Delta in the whole Cohort 1 and Cohort 2 (Protein Primed Group) instead of only in a subset of participants. Thus, the VTAS will not be applicable to Cohort 1 variant testing results. The PPAS and FAS will be utilized for analyzing the variant testing results.

- **Modify variant testing subset analysis set definition**

  The Variant Testing Subset Analysis Set (VTAS) will have the blood sample time window adherence considered in order to know the per-protocol participants immunogenicity response. The Variant Testing Subset without consider the exclusion criteria will be utilized to see the immunogenicity results furthermore.

- **Add study duration and safety follow-up duration calculation method for ongoing participants in interim analysis**

  The database lock or data extraction date will be utilized for calculation on study duration and safety follow-up duration in ongoing participants under interim analysis scope.

- **Modify the analysis set utilized for Comparator Group on variant testing results**

  The Naïve at D01+D22 Comparator Group participants will be used for Variant Testing results analyses. Consider the serostatus would be a factor to impact the immunogenicity response.

- **Add imputation rule for partial prior COVID-19 vaccination date**

  In order to calculate the duration of prior COVID-19 vaccination to booster injection, the partial COVID-19 vaccination date (day is missing) will be imputed using the "01" day.

6 Supporting Documentation

6.1 Appendix 1 List of Abbreviations

AE	Adverse Events
AESI	Adverse events of special interest
AR	Adverse reactions
CRF	Case report form
DMC	Data Monitoring Committee
FAS	Full analysis set
FR	Fold rise
GCI	Global Clinical Immunology
GM	Geometric mean
GMT	Geometric mean titer
GMC	Geometric mean concentration
LLOQ	Lower level of quantitation
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not applicable
PPAS	Per-protocol analysis set
RCDC	Reverse cumulative distribution curve
SAE	Serious adverse events
SafAS	Safety analysis set
SAP	Statistical analysis plan
SOC	(Primary) System organ class
PT	Preferred term
TLF	Tables, listings and figures
ULOQ	Upper level of quantitation

7 References

1. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med. 1998;17(8):857-72.

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

8 Appendix A

Table 8.1: Table of Assay Information*

Protocol Section	Protocol Assay Name	Response Type	Testing Variants		Testing Timepoints		LLOQ/ULOQ	Short Name	Full Description	Used in Statistical Analysis
			Cohort 1, Cohort 2	Cohorts Comparator Group	Cohort 1, Cohort 2	Cohorts Comparator Group				
Immunogenicity Assays										
8.2.1.1	SARS-CoV-2 Pseudovirus Neutralization Assay	Continuous on Neutralizing antibodies (serum dilution conferring 50% inhibition (ID50))	D614G, B.1.351	D614G, B.1.351	All visits	All visits	LLOQ is 40 and ULOQ is 787339	Monogram neutralization antibodies	SARS-CoV-2 Pseudovirus Neutralization Assay at Monogram for variant strains	Primary immunogenicity, Secondary immunogenicity
8.2.2.3	SARS-CoV-2 Spike Protein Antibody Serum IgG ELISA	Continuous on Binding antibodies	D614	D614	All visits	All visits	LLOQ is 18.9	binding antibodies by ELISA	SARS-CoV-2 Spike Protein Antibody Serum IgG ELISA at Nexelis for matched vaccine strain (D614 parental)	Secondary immunogenicity

Protocol Section	Protocol Assay Name	Response Type	Testing Variants		Testing Timepoints		LLOQ/ULOQ	Short Name	Full Description	Used in Statistical Analysis
			Cohort 1, Cohort 2	Cohorts Comparator Group	Cohort 1, Cohort 2	Cohorts Comparator Group				
8.2.3.2	Cellular Immune Assays	Continuous on B cell memory responses (IgG, IgA) and	D614G	D614G	D01, D134, and D387	D01, D91, and D366	NA	B cell response	Cellular Immune Assays for B cell memory responses (IgG, IgA) at SP (REI)	Exploratory immunogenicity (Cellular immune response)
8.2.3.2	Cellular Immune Assays	Continuous on T-cells CD4+ / CD8+	D614G	D614G	D01, D29, D91, and D366	D01, D22, D36, D134 and D387	NA	T cell response	Cellular Immune Assays for CD4+ / CD8+ T-cells at FH	Exploratory immunogenicity (Cellular immune response)
8.2.3.3	Mucosal Antibody assays	Continuous on total antibodies to SARS-Continuous on CoV-2 in human oral fluid specimens	D614	D614	D01, D15 and D91	D01, D22, D36 and D134	NA	Saliva antibodies	Mucosal Antibody assays for total antibodies to SARS-CoV-2 in human oral fluid specimens at SP (GCI lab)	Exploratory immunogenicity (Mucosal antibody response)

Protocol Section	Protocol Assay Name	Response Type	Testing Variants		Testing Timepoints		LLOQ/ULOQ	Short Name	Full Description	Used in Statistical Analysis
			Cohort 1, Cohort 2	Cohorts Comparator Group	Cohort 1, Cohort 2	Cohorts Comparator Group				
8.2.3.5	SARS-CoV-2 Pseudovirus Neutralization Assay (Nexelis)	Continuous on Neutralizing SARS-CoV-2 pseudovirus antibodies	D614G, B.1.1.7, P.1, B.1.617, etc.	D614G, B.1.1.7, P.1, B.1.617, etc.	D01, D15, D29, D181 and D366	D01, D36, D202 and D387	To be determined	Nexelis neutralization antibodies	SARS-CoV-2 Pseudovirus Neutralization Assay at Nexelis for variant strains	Secondary immunogenicity, Exploratory immunogenicity (variant strains analysis)
Diagnostic Assays										
8.1.5.3	ELECSYS Anti-SARS-CoV2 Anti-S ECLIA	Categorical on SARS-CoV-2 infection status (positive/negative/NR)	NA	NA	D01	D01	NA	NA	NA	Prior SARs-CoV-2 Naïve/Non-Naïve status
8.1.6	NAAT Assessment Prior to Vaccination	Categorical OR continuous on SARS-CoV-2 infection status (positive/negative/NR)	NA	D01	D01, D22 and all CLI01	D01, D22 and all CLI01	NA	NA	NA	Prior SARs-CoV-2 Naïve/Non-Naïve status, COVID related endpoints

*** Assay information are based on the current best knowledge and potential to be updated when more information become available.**