A Parallel-group, Phase III, Multi-stage, Modified Double-blind, Multi-armed Study to Assess the Efficacy, Safety, and Immunogenicity of two SARS-CoV-2 Adjuvanted Recombinant Protein Vaccines (monovalent and bivalent) for Prevention Against COVID-19 in Adults 18 Years of Age and Older as a primary series and open-label extension to assess immunogenicity, safety, efficacy of a monovalent booster dose of SARS-CoV2 Adjuvanted Recombinant Protein Vaccine

Phase III, randomized, multi-stage, modified double-blind, placebo-controlled, multi-center study as a primary series and open-label extension of the booster dose in 18 years of age and older.

Statistical Analysis Plan (SAP) - Core Body Part

Trial Code:	VAT00008 (Protocol Version 8.0)
Development Phase:	Phase III
Sponsor:	Sanofi Pasteur Inc. Discovery Drive, Swiftwater, PA 18370-0187, USA
Investigational Product:	CoV2 preS dTM-AS03 (D614) CoV2 preS dTM-AS03 (D614 + B.1.351)
Form / Route:	IM injection

Indication For This Study:	Active immunization for the prevention of SARS-CoV-2 infection or disease
Version and Date of the SAP core body part:	Version 5.0, July 2024

The following two tables (one for Stage 1 and Stage 2, and another for Crossover/Booster) provide the reduced scope of objectives/endpoints from Protocol Version 8.0.

Objectives and Endpoints: Initial double-blind primary series design (These apply to Stage 1 and Stage 2 of the initial, double-blind, primary series study design, unless otherwise specified)		
Objectives	**Endpoints**	**Changes**
Other Secondary Efficacy Objectives		
3) To assess, in participants who are SARS-CoV-2 naïve, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for the prevention of symptomatic COVID-19 occurring ≥ 14 days after the first injection.	Endpoint for secondary efficacy objective #3: • Occurrences of symptomatic COVID-19	Dropped.
11) To assess, in participants who are SARS-CoV-2 naïve, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for the prevention of symptomatic COVID-19 occurring ≥ 7 days after the second injection.	Endpoint for secondary efficacy objective #11: • Occurrences of symptomatic COVID-19	Dropped.
Secondary Immunogenicity		
The following objectives will be assessed in participants regardless of prior SARS-CoV-2 infection and in SARS-CoV-2 non-naïve and naïve participants. 6) To describe the association of neutralizing antibody responses and the risk of symptomatic COVID-19. 7) To describe the association of neutralizing antibody responses and the risk of SARS-CoV-2 infection. 8) To describe the association of neutralizing antibody responses and the risk of other COVID-19 disease endpoints. 9) To evaluate the immunological correlates of risk and correlates of protection against symptomatic COVID-19, SARS-CoV-2 infection, and other COVID-19 disease endpoints.	Endpoints for secondary immunogenicity objectives #6 - 9: Neutralizing antibody titers will be measured in participants for each study group against the D614G and B.1.351 variants. • Individual serum neutralizing titer at each pre-defined time point • Individual serum neutralization titer fold-rise post-vaccination relative to D01 at each pre-defined time point • 2-fold rise and 4-fold-rise in serum neutralization titer [post/pre] (fold rise ≥ 2 and ≥ 4) at each pre-	Secondary immunogenicity objectives #6 and #8 will not be covered by this SAP but will be covered by either a separate SAP or a post-hoc analysis. Dropped secondary immunogenicity objectives #7 and #9.

Objectives and Endpoints: Initial double-blind primary series design (These apply to Stage 1 and Stage 2 of the initial, double-blind, primary series study design, unless otherwise specified)		
Objectives	**Endpoints**	**Changes**
	defined post-vaccination timepoint • Responders, defined as participants who had baseline values below LLOQ with quantifiable neutralization titer above assay LLOQ at each pre-defined post-vaccination time point and participants with baseline values above LLOQ with a 4-fold increase in neutralizing antibody titers at each pre-defined post-vaccination timepoint	
Exploratory Efficacy		
2) To assess the clinical efficacy of the CoV2 preS dTM-AS03 vaccines in SARS-CoV-2 naïve participants by subgroups defined by age, high risk medical conditions, sex and race/ethnicity or a combination of those for: • Prevention of SARS-CoV-2 infection • Prevention of asymptomatic SARS-CoV-2 infection	<u>Endpoints for exploratory efficacy objective #2:</u> • Occurrences of SARS-CoV-2 infection • Occurrences of asymptomatic SARS-CoV-2 infection	Scope reduced. Deleted "by subgroups defined by age, high risk medical conditions, sex and race/ethnicity or a combination of those" from the objective.
3) To assess the clinical efficacy of the CoV2 preS dTM-AS03 vaccines in participants regardless of prior SARS-CoV-2 infection and by baseline prior SARS-CoV-2 infection (naïve and non-naïve) by subgroups defined by age, high risk medical conditions and race/ethnicity or a combination of those for: • Prevention of symptomatic COVID-19 • Reduction in duration of symptoms of COVID-19 • Prevention of severe COVID-19 • Prevention of hospitalized COVID-19	<u>Endpoints for exploratory efficacy objective #3:</u> • Occurrences of symptomatic COVID-19 • Days with symptoms associated with symptomatic COVID-19 • Occurrence of severe COVID-19 • Occurrences of CDC-defined COVID-19 • Occurrences of hospitalized COVID-19 • Days of hospitalization with symptomatic COVID-19	Scope reduced. Deleted "by subgroups defined by age, high risk medical conditions and race/ethnicity or a combination of those" from the objective.

Objectives and Endpoints: Initial double-blind primary series design (These apply to Stage 1 and Stage 2 of the initial, double-blind, primary series study design, unless otherwise specified)		
Objectives	**Endpoints**	**Changes**
• Reduction in duration of hospitalization with symptomatic COVID-19 • Reduction in severity of symptomatic COVID-19 on the 7-point ordinal scale • Prevention of symptomatic COVID-19 with severity of moderate COVID-19 or worse (composite endpoint of moderate or severe COVID-19) • Reduction in use of supplemental oxygen associated with symptomatic COVID-19 • Prevention of intensive care utilization associated with symptomatic COVID-19 • Reduction in use of mechanical ventilation or ECMO associated with symptomatic COVID 19 • Prevention of death associated with symptomatic COVID-19	• Occurrences of symptomatic COVID-19 in each severity rating on the 7-point ordinal scale • Occurrence of symptomatic COVID-19 with severity of moderate COVID-19 or worse (composite endpoint of at least one of moderate or severe COVID-19) • Occurrences of symptomatic COVID-19 requiring intensive care utilization • Occurrences of symptomatic COVID-19 requiring supplemental oxygen • Days of supplemental oxygen use in participants with symptomatic COVID-19 • Occurrences of intensive care utilization associated with symptomatic COVID-19 • Days of stay in an intensive care unit associated with symptomatic COVID-19 • Occurrences of symptomatic COVID-19 requiring mechanical ventilation or ECMO • Days of use of mechanical ventilation or ECMO over the course of symptomatic COVID-19 • Deaths associated with symptomatic COVID-19	

Objectives and Endpoints: Initial double-blind primary series design (These apply to Stage 1 and Stage 2 of the initial, double-blind, primary series study design, unless otherwise specified)		
Objectives	**Endpoints**	**Changes**
4) To assess the clinical efficacy of the CoV2 preS dTM-AS03 vaccines between the first and second injection in SARS-CoV-2 naïve participants for prevention of: • SARS-CoV-2 infection • Asymptomatic SARS-CoV-2 infection	Endpoints for exploratory efficacy objective #4: • Occurrences of SARS-CoV-2 infection • Occurrences of asymptomatic SARS-CoV-2 infection	Dropped.
5) To assess the clinical efficacy of the CoV2 preS dTM-AS03 vaccines between the first and second injection in all participants and by baseline SARS-CoV-2 infection for prevention of: • Symptomatic COVID-19 • Hospitalized COVID-19 • Prevention of severe COVID-19	Endpoints for exploratory efficacy objective #5: • Occurrences of symptomatic COVID-19 • Occurrences of hospitalized COVID-19 • Occurrence of severe COVID-19	Dropped.
9) To describe in each group the occurrence of events that may be classified as Long COVID syndrome.	Endpoints for exploratory efficacy objective #9: • Occurrence of Long COVID syndrome events	Dropped.
13) To assess if and how vaccine efficacy for the prevention of virologically-confirmed symptomatic COVID-19 depends on genotypic or neutralization phenotypic characteristics of SARS-CoV-2 (sieve analysis for disease).		Exploratory efficacy objective #13 will not be covered by this SAP but will be covered by either a separate SAP or a post-hoc analysis.
14) To conduct exploratory analyses related to furthering the understanding of SARS-CoV-2 / COVID-19, including analyses related to immunology, virology, vaccines, and clinical conduct.		Dropped.
Exploratory Immunogenicity		
The following objectives will be assessed in participants regardless of prior SARS-CoV-2 infection and in SARS-CoV-2 non-naïve and naïve participants. 2) To describe the association of binding antibody responses and the risk of symptomatic COVID-19. 3) To describe the association of binding antibody responses and the risk of SARS-CoV-2 infection.	Endpoints for exploratory immunogenicity objectives #2 - 4: Binding antibody concentration will be measured in participants for each study group against the homologous vaccine strains. • Individual antibody concentration at each pre-defined time point	Exploratory immunogenicity objectives #2 and #4 will not be covered by this SAP but will be covered by either a separate SAP or a post-hoc analysis. Dropped exploratory immunogenicity objective #3.

Objectives and Endpoints: Initial double-blind primary series design (These apply to Stage 1 and Stage 2 of the initial, double-blind, primary series study design, unless otherwise specified)		
Objectives	**Endpoints**	**Changes**
4) To describe the association of binding antibody responses and the risk of other COVID-19 disease endpoints.	• Individual antibody fold-rise post-vaccination relative to D01 at each pre-defined post-vaccination time point • 2-fold-rise and 4-fold-rise (foldrise in antibody concentration [post/pre] ≥ 2 and ≥ 4) at each pre-defined post-vaccination time point • Responders, defined as participants who had baseline values below LLOQ with quantifiable antibody concentration above assay LLOQ at each pre-defined post-vaccination timepoints and participants with baseline values above LLOQ with a 4-fold increase in antibody concentrations at each pre-defined post-vaccination timepoint. • Individual antibody concentration (≥ 2xLLOQ or ≥ 4xLLOQ) at each pre-defined time point	
6) To conduct exploratory analyses which may include (but are not limited to) testing of immune responses and other biomarkers in any subset of participants to inform further understanding of COVID-19 vaccines, including use as benchmarks for other studies.		Dropped.

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

A summary table of changes from SAP Core Body Version 4.0 is provided below.

Changes	Further Details
Removed the first 3 paragraphs in Section 1 (Introduction) from the Version 4.0 since they are not directly related to the statistical analysis and are included in the protocol already.	
Updated Figure 2.3 and 2.4 according to the Protocol Version 8.0 (Figure 1.3 and 1.4 in the protocol).	
For Stage 1 and Stage 2 Removed efficacy objectives focusing on the occurrence of endpoints during the following time periods: ≥ 14 days after the first injection; ≥ 7 days after the second injection; between the first and second injection. Dropped analyses for the related endpoints (e.g., symptomatic COVID-19 occurring ≥ 7 days after the second injection; symptomatic COVID-19 occurring ≥ 14 days after the first injection).	Removed the following efficacy objectives in Version 4.0: Secondary Efficacy Objective #3, #11; Exploratory Efficacy Objective #4, #5. Note: the numbers for each objective will be updated accordingly, e.g., Secondary Efficacy Objective "#4" in Version 4.0 will be updated to Secondary Efficacy Objective "#3" in the current version.
For Stage 1 and Stage 2 Removed efficacy analyses conducted on the following analysis sets: Per-Protocol Analysis Set (PPAS) (including PPAS all participants, PPAS Naïve-D01+D22, and PPAS Non-Naïve D01/D22); Modified full analysis set post-dose 1 (mFAS-PD1) (including mFAS-PD1 all participants, mFAS-PD1 Naïve D01 and mFAS-PD1 Non-Naïve D01). The definitions for PPAS and mFAS-PD1 were removed from Section 4.1 (Analysis Sets) but can be found in Version 4.0.	Removed all sensitivity/additional/survival analyses for efficacy endpoints conducted on PPAS and mFAS-PD1. For example, for Primary Efficacy and Key Secondary Efficacy (Stage 1 and 2), removed "Sensitivity Analysis 2" and "Survival Analysis" conducted on PPAS in Version 4.0.
Removed the definition for Full analysis set (FAS) from Section 4.1 (Analysis Sets) since no analyses will be conducted on FAS.	The definition for Modified full analysis set post-dose 2 (mFAS-PD2) was modified accordingly since the previous version was derived from FAS. But essentially, the mFAS-PD2 analysis set was defined same as before.

The point estimate of vaccine efficacy (VE) is calculated by the incidence rate ratio (IRR) when IRR is applicable. VE will be calculated based on relative risk (RR) only when IRR is not applicable.	Removed all sensitivity analyses for efficacy endpoints conducted with VE calculated by RR when IRR is applicable. For example, for Primary Efficacy and Key Secondary Efficacy (Stage 1 and 2), removed "Sensitivity Analysis 1" in Version 4.0.
No VE calculation (only descriptive numbers presented) for the following efficacy endpoints: • CDC-defined COVID-19 • Symptomatic COVID-19 with severity of moderate COVID-19 or worse • SARS-Cov-2 infection • Asymptomatic SARS-CoV-2 infection	
<u>For Stage 1 and Stage 2</u> Kaplan-Meier curves will be produced only for primary and key secondary efficacy endpoints (i.e., symptomatic COVID-19 and severe COVID-19), and not for the other efficacy endpoints (e.g., hospitalized COVID-19 and moderate or severe COVID-19). In case of an efficacy endpoint with less than 20 events in a corresponding population for both vaccine and placebo groups, the Kaplan-Meier curves will not be produced. Previously (in Version 4.0) the threshold for number of events was 5, not 20.	For subgroup analysis or analyses by variant – for each subgroup/variant, the Kaplan-Meier curves will not be produced if there are less than 20 events for both vaccine and placebo groups.
Removed all survival analyses with Cox model for efficacy endpoints	
Removed the area under the curve (AUC) analysis for Viral Burden	
<u>For Stage 1 and Stage 2</u> In case of an efficacy endpoint with less than 20 events in a corresponding population for both vaccine and placebo groups, the VE calculation will not be conducted.	For subgroup analysis or analyses by variant – for each subgroup/variant, the VE calculation will not be conducted if there are less than 20 events for both vaccine and placebo groups.
Removed the age group ">=65 years" in Section 3.2.4.1 since no analyses will be performed for this subgroup.	

Removed the definition for "High-risk Group" in Section 3.2.4.2 since no subgroup analyses will be performed by high-risk group.	
<u>For Stage 1 and Stage 2</u> Dropped the planned subgroup analyses for Exploratory Efficacy Objective #2.	Revised Exploratory Efficacy Objective #2 (Stage 1 and Stage 2) as shown below: To assess the clinical efficacy of the CoV2 preS dTM-AS03 vaccines in SARS-CoV-2 naïve participants for: • Prevention of SARS-CoV-2 infection • Prevention of asymptomatic SARS-CoV-2 infection
<u>For Stage 1 and Stage 2</u> Dropped the planned subgroup analyses for Exploratory Efficacy Objective #3.	Revised Exploratory Efficacy Objective #3 (Stage 1 and Stage 2) as shown below: To assess the clinical efficacy of the CoV2 preS dTM-AS03 vaccines in participants regardless of prior SARS-CoV-2 infection and by baseline prior SARS-CoV-2 infection (naïve and non-naïve) for: • Prevention of symptomatic COVID-19 • Reduction in duration of symptoms of COVID-19 • Prevention of severe COVID-19 • Prevention of hospitalized COVID-19 • Reduction in duration of hospitalization with symptomatic COVID-19 • Reduction in severity of symptomatic COVID-19 on the 7-point ordinal scale • Prevention of symptomatic COVID-19 with severity of moderate COVID-19 or worse (composite endpoint of moderate or severe COVID-19) • Reduction in use of supplemental oxygen associated with symptomatic COVID-19

	• Prevention of intensive care utilization associated with symptomatic COVID-19 • Reduction in use of mechanical ventilation or ECMO associated with symptomatic COVID 19 • Prevention of death associated with symptomatic COVID-19
For Stage 1 and Stage 2 Removed Exploratory Efficacy Objectives #4, #5, #9, #13, and #14 in Version 4.0.	
For Stage 1 and Stage 2 Revised statistical methods and analysis sets for Exploratory Efficacy Objectives #1-5.	For exploratory objective #1, #3 and #5, the analyses performed per naïve status will be conducted only if there are no less than 15% naïve participants enrolled. For exploratory objective #2 and #4, only descriptive numbers will be presented (no VE calculation).
For Stage 1 and Stage 2 Added details of statistical methods and analysis sets for Exploratory Efficacy Objectives #6-10.	In Version 4.0, "Analysis for these exploratory efficacy objectives will be described in supplementary SAP." See Section 4.2.3.1.1 for the added details.
For Stage 1 and Stage 2 Specified what subgroup analyses will be done for each of Primary and Secondary Efficacy Objectives. See details in Section 4.2.1.2.1 and 4.2.2.2.1.	
For Stage 1 and Stage 2 Revised Secondary Efficacy Objective #3 (which was Secondary Efficacy Objective #4 in Version 4.0) according to the Protocol Version 8.0 as shown below: Stage 1 only: To assess, in all participants regardless of prior SARS-CoV-2 infection, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for: • Prevention of symptomatic COVID-19 • Prevention of severe COVID-19	

Endpoints: specified as Stage 1 only.	
<u>For Stage 1 and Stage 2</u> Revised Secondary Efficacy Objective #10 (which was Secondary Efficacy Objective #12 in Version 4.0) according to the Protocol Version 8.0 as shown below: Stage 2 only: To assess, in participants who are SARS-CoV-2 naïve, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for: • Prevention of symptomatic COVID-19 • Prevention of severe COVID-19 Added "Occurrence of severe COVID-19" to the Endpoint for Secondary Efficacy Objective #10 accordingly.	
<u>For Stage 1 Only</u> Removed "Sensitivity Analysis 3 (Stage 1 only)" for "participants determined to be seronegative by the rapid diagnostic testing for SARS-CoV2 at enrollment" for Primary Efficacy Objective and Key Secondary Efficacy Objective #1.	
<u>For Stage 1 and Stage 2</u> Added two supplementary analyses – one is for multiple events and the other is for sequencing data (by variant), for Primary Efficacy Objective (Stage 1 and Stage 2), Key Secondary Efficacy Objective #2 (Stage 2 only), and Secondary Efficacy Objective #4 (Stage 1 only). Subgroup analyses will also be performed by age group (18-59 years or >=60 years) for these supplementary analyses.	The supplementary analysis for multiple events will produce the following summary statistics: 1) Number of participants experiencing only one, two, three, …, events of an endpoint will be counted, respectively, by treatment group (vaccine, placebo, vaccine + placebo). 2) Among participants experiencing multiple (>=2) events, the variant distribution will be summarized by treatment group, e.g., number of participants experiencing Omicron (BA.1.16) and Omicron (BA.4.1). 3) Summary statistics (mean, SD, median, min, max) of the time interval (in days) between two consecutive

	events (e.g., from the first event to the second event) will also be presented by treatment group. The supplementary analysis for sequencing data (by variant) will produce VE with CIs and Kaplan-Meier curves by variant type.
For Stage 1 and Stage 2 Revised statistical methods and analysis sets for Secondary Efficacy Objective #6.	No 95% CI calculation (by Wilson score method without continuity correction) for the difference of percentages of participant with positive viral load above the lower limit of quantitation of the assay. Dropped analysis on Area Under Curve. Added subgroup analyses by age group (18-59 years or >=60 years). For Stage 1, mFAS-PD2 Naïve-D01+D22 and mFAS-PD2 Non-Naïve-D01/D22 analysis sets will be used. For Stage 2, mFAS-PD2 analysis set will be used. The analyses performed per naïve status (on mFAS-PD2 Naïve-D01+D22 and mFAS-PD2 Non-Naïve-D01/D22 analysis sets, separately) will be conducted only if there are no less than 15% naïve participants enrolled.
For Stage 1 and Stage 2 Revised statistical methods and analysis sets for Secondary Efficacy Objective #8 and #9.	See Section 4.2.2.2.1 for details.
For Stage 1 and Stage 2 Revised the plan for subgroup analyses for Primary Safety Objective. Clearly stated that we will perform the subgroup analyses only for the safety overview table.	Subgroup analyses for Primary Safety Objective will be performed by age group (18-59 years or >=60 years), high-risk medical condition group (Yes or No), and prior SARS-CoV-2 infection status (Naïve-D01 or Non-Naïve-D01), combination of age group and high-risk medical condition, and combination of age group and prior SARS-CoV-2 infection status.

	In Version 4.0, subgroups for analyses are "age group, sex, high-risk group, high-risk medical condition group, race/ethnicity, and prior SARS-CoV-2 infection status (Naïve-D01 or Non-Naïve-D01)".
For Stage 1 and Stage 2 Reduced the number of subgroup analyses for Secondary Safety Objectives.	Subgroup analyses will be performed for age group (18-59 years or >=60 years) for Secondary Safety Objective #1. No subgroup analyses for Secondary Safety Objective #2. Removed subgroup analyses by "sex, high-risk medical conditions, high-risk group, and race/ethnicity" in Version 4.0.
For Stage 1 and Stage 2 Removed Secondary Immunogenicity Objectives #6-9 in Version 4.0.	
For Stage 1 and Stage 2 Removed complementary immunogenicity analysis (which will include participants receiving a non-study authorized/approved COVID-19 vaccine) for Secondary Immunogenicity Objectives.	
For Stage 1 and Stage 2 For Secondary Immunogenicity Objectives #1 to #4, added subgroup analyses by age group (18-59 years or >=60 years).	
For Stage 1 and Stage 2 Removed Exploratory Immunogenicity Objectives #2-4, and #6 in Version 4.0.	
Removed the definition for "Case-cohort immunogenicity analyses set (ccIAS)", "Crossover - Case-cohort immunogenicity analyses set (CR-ccIAS)", and "Booster - Case-cohort immunogenicity analyses set (BS-ccIAS)" from Section 4.1 (Analysis Sets) since no analyses covered by this SAP will be conducted on ccIAS/CR-ccIAS/BS-ccIAS.	

For Crossover / Booster Changed the study duration according to the Protocol Version 8.0.	In Section 2.1 Trial Design, "For participants who initially received placebo: 4 months post-last dose of the primary series + 6 months post-booster (ie, approximately 22 to 28 months)" has been changed to "For participants who initially received placebo: 4 months post-last dose of the primary series + 12 months post-booster (ie, approximately 28 to 34 months)"
For Crossover / Booster Removed Exploratory Immunogenicity Objectives #4 to #6 in Version 4.0.	
Removed sensitivity and complementary analyses for Safety Objectives.	Removed all the definitions provided for sensitivity and complementary analyses in Section 3.2.2 as well.
For Crossover Removed the definition for "Crossover – Full analysis set (CR-FAS)", and "Crossover - Modified Full Analysis Set post-primary series (CR-mFAS)" from Section 4.1 (Analysis Sets) since no analyses covered by this SAP will be conducted on CR-FAS/CR-mFAS.	
For Crossover / Booster Removed the definitions for "the prior SARS-CoV-2 infection status of all randomized participants for the crossover phase and booster phase" (Naïve-CRV01, Non-Naïve-CRV01, Naïve-BV01, and Non-Naïve-BV01) from Section 4.1 (Analysis Sets)	We'll use serostatus (anti-N) at crossover or booster to perform subgroup analysis instead of defining the naïve/non-naïve population for each objective, since we only collected anti-N assay for crossover/booster at baseline.
For Crossover / Booster Specified what subgroup analyses will be done for Secondary Immunogenicity Objectives	Subgroup analyses will be performed for age group, serostatus at Crossover / Booster, and combination of age group and serostatus.
For Crossover / Booster Specified what subgroup analyses will be done for each of the Secondary Safety Objectives	For Secondary Safety Objective #1, subgroup analysis will be performed for age group, serostatus at Crossover / Booster, and combination of age group and serostatus for main analysis.

	For Secondary Safety objective #2, subgroup analysis (only for the safety overview table) will be performed for age group, serostatus at Crossover / Booster, high-risk medical condition, combination of age group and serostatus, and combination of age group and high-risk medical condition.
<u>For Crossover / Booster</u> Added details of statistical methods and analysis sets for Exploratory Efficacy Objectives.	In Version 4.0, "Estimation and statistical methods on the observational efficacy endpoints for Crossover / Booster study will be as appropriate to the data collected." See Section 4.2.3.1.1 for details.
<u>For Crossover / Booster</u> Revised and added details of statistical methods and analysis sets for Exploratory Immunogenicity Objectives.	In Version 4.0, "The IAS, ccIAS will be applied for exploratory immunogenicity analyses." See Section 4.2.3.1.2 for details.

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List of Abbreviations

Ab	antibody
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
BL	blood sample
CDM	Clinical Data Management
CI	confidence interval
CLI	COVID-19 like-illness
CRF	case report form
CTL	Clinical Team Leader
CTM	Clinical Trial Manager
CSR	clinical study report
D	Day
DC	diary card
dil	Dilution
eCRF	electronic case report form
EDC	electronic data capture
EIA	enzyme immunosorbent assay
ELISA	enzyme linked immunosorbent assay
EMA	European Medicines Agency
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GM	geometric mean
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug (application)
ITT	intent-to-treat
IU	international unit
IVRS	interactive voice response system
IWRS	interactive web response system
LLOD	lower limit of detection

LLOQ	lower limit of quantification
LLN	lower limit of normal
MD	missing data
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not applicable
NSAID	non-steroidal anti-inflammatory drug
OG	Oversight Group
PC	phone call
PPAS	per-protocol analysis set
PSO	Product Safety Officer
PT	preferred term
PV	Pharmacovigilance
Q1; Q2; Q3	first quartile; second quartile (median); third quartile
RCDC	reverse cumulative distribution curve
SAE	serious adverse event
SafAS	safety analysis set
SAP	statistical analysis plan
SC	Screening
SD	standard deviation
SOC	system organ class (primary)
TLF	table(s), listing(s), and figure(s)
ULOD	upper limit of detection
ULOQ	upper limit of quantification
ULN	upper limit of normal
V	Visit
Vac	Vaccination
VE	Vaccine Efficacy
WHO	World Health Organization

1 Introduction

VAT00008 will be a Phase III, randomized, modified double-blind, placebo-controlled, multi-stage, multi-center, multi-country trial to assess the efficacy, safety, and immunogenicity of two CoV2 preS dTM-AS03 vaccines (monovalent and bivalent) in adults 18 years of age and older with 2 stages. In Stage 1, the monovalent vaccine with the adjuvanted prefusion S protein from the prototype D614 will be assessed against a placebo control. In Stage 2, the bivalent vaccine will be assessed against a placebo control. This bivalent vaccine will be introduced in this Phase III study when it is available and sufficient data have been generated to support its introduction including: preclinical data generated in animal models demonstrating non-deleterious interference between the 2 recombinant proteins, demonstration of similarity in manufacturing process for the two CoV2 preS dTM components of the bivalent products compared to the monovalent product, similar purity , safety and immunogenicity in the Phase II study of the monovalent vaccine.

The goal of this study is to generate data required for approval of each of the vaccines for use in prevention against SARS-CoV-2 infection and disease in adults. The data collected during this study will also support future development in other populations (eg, pediatrics, pregnant women). Based on the interim results from this study, participants in the Placebo group will be offered to participate in an unblinded Crossover / Booster design. Both participants in the Placebo and Vaccine groups will also be offered to receive Sanofi Pasteur's investigational CoV2 preS dTM-AS03 monovalent (B.1.351) vaccine to boost the immune response ≥ 4 months post-last dose of the primary vaccination series.

2 Description of the Overall Trial Design and Plan

2.1 Trial Design

VAT00008 will be a Phase III, randomized, modified double-blind, placebo-controlled, multi-stage, multi-center, multi-country trial to assess the efficacy, safety, and immunogenicity of two CoV2 preS dTM-AS03 vaccines (monovalent and bivalent) in adults 18 years of age and older as a primary series and open-label extension to assess immunogenicity, safety, efficacy of a monovalent booster dose of SARS-CoV2 Adjuvanted Recombinant Protein Vaccine with 2 stages. In Stage 1, the monovalent vaccine with the adjuvanted prefusion S protein from the prototype D614 will be assessed against a placebo control. In Stage 2, the bivalent vaccine will be assessed against a placebo control.

Participants will be screened for eligibility criteria at the time of inclusion and then randomized to either the investigational vaccine or placebo in a 1:1 ratio in each stage as shown below:

- Stage 1: eligible participants will be randomized to receive either CoV2 preS dTM-AS03 (D614) vaccine or Placebo 1 (participants who receive the placebo as part of Stage 1)

- Stage 2: eligible participants will be randomized to receive either CoV2 preS dTM-AS03 (D614 + B.1.351) vaccine or Placebo 2 (participants who receive placebo as part of Stage 2)

Randomization will be stratified by age groups (18-59 years of age and 60 years of age and older), baseline SARS-CoV-2 rapid serodiagnosis test positivity, and site. In the time period where the enrollment in Stage 1 overlaps with enrollment in Stage 2, participants will be randomly assigned to either Stage 1 or Stage 2 enrollment based on the enrollment eligibility and then continue to be randomly allocated to one of the investigational vaccine groups and their matched placebo group in a 1:1 ratio. There will be no sharing of the placebo participants between the two stages.

A total of approximately 21 046 participants are planned to be enrolled (5080 per study intervention group in Stage 1 and 5443 per study intervention group in Stage 2). If the crossover is not implemented, recruitment will continue until the minimally required number of naïve participants to assess efficacy is enrolled (even if the overall enrollment target is reached). Participants who are SARS-CoV-2 non-naïve at baseline will be capped to approximately 30% of the total study population in Stage 1 (up to ~1524 participants/arm). The target for SARS-CoV-2 non-naïves is ~1633 participants/arm in Stage 2. The objective is to ensure a sufficient number of participants/arms who are SARS-CoV-2 naïve at baseline are enrolled to achieve the power of the study.

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

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

- For participants who initially received vaccine: 6 months post-booster (ie, approximately 12 to 18 months)
- For participants who initially received placebo: 4 months post-last dose of the primary series + 6 months post-booster (ie, approximately 22 to 28 months)
- For participants who do not consent to continue in the unblinded Crossover / Booster part of the study, all study procedures will be stopped and participants will be discontinued from the study

Unblinded Crossover / Booster

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

Based on decisions of the Study OG, Stage 1 participants will be invited upon consent to continue participation as part of an unblinded crossover / booster study design. The participant unblinding and consent will trigger the end of the initial double-blind primary series design and the start of

the Crossover / Booster design, which includes a primary series vaccination for initial placebo recipients (ie, crossover vaccination) and a booster for both initial placebo and vaccine recipients (ie, booster vaccination).

Stage 1 participants who initially received placebo and are 18-59 years of age will be offered the opportunity to receive the investigational CoV2 preS dTM-AS03 monovalent (D614) vaccine if they choose not to receive an authorized/approved vaccine series.

Stage 1 participants who initially received placebo and are ⩾ 60 years of age will be strongly recommended to receive authorized/approved vaccination series and will only be offered the opportunity to receive the investigational CoV2 preS dTM-AS03 (D614) vaccine if they are unable or choose not to receive an authorized/approved vaccine series.

If initial placebo recipients of any age received at least 1 dose of an authorized/approved vaccine outside of the study or the investigational study vaccine as a primary series, they will also be offered the opportunity to receive Sanofi Pasteur's investigational Cov2 preS dTM-AS03 monovalent (B.1.351) booster vaccine ⩾ 4 months post-last dose of the primary series.

Stage 1 participants who initially received at least 1 dose of the CoV2 preS dTM-AS03 monovalent (D614) vaccine and are 18-59 years of age will be offered the opportunity to receive Sanofi Pasteur's investigational CoV2 preS dTM-AS03 monovalent (B.1.351) booster vaccine ⩾ 4 months post-last dose of the primary CoV2 preS dTM-AS03 monovalent (D614) injection.

Stage 1 participants who initially received at least 1 dose of the CoV2 preS dTM-AS03 monovalent (D614) vaccine and are ⩾ 60 years of age will be offered the Sanofi Pasteur's investigational CoV2 preS dTM-AS03 monovalent (B.1.351) booster vaccine ⩾ 4 months post-last dose of the primary CoV2 preS dTM-AS03 monovalent (D614) injection.

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

Based on an interim/final efficacy analysis and the recommendation of the Study OG, primary series followed by a booster dose will be offered to initial placebo recipients and a booster will be offered to initial vaccine recipients in Stage 2. The investigational product to be used in the Stage 2 unblinded crossover vaccinations was determined based on available efficacy data, which turns out to be the same as in Stage 1.

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

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

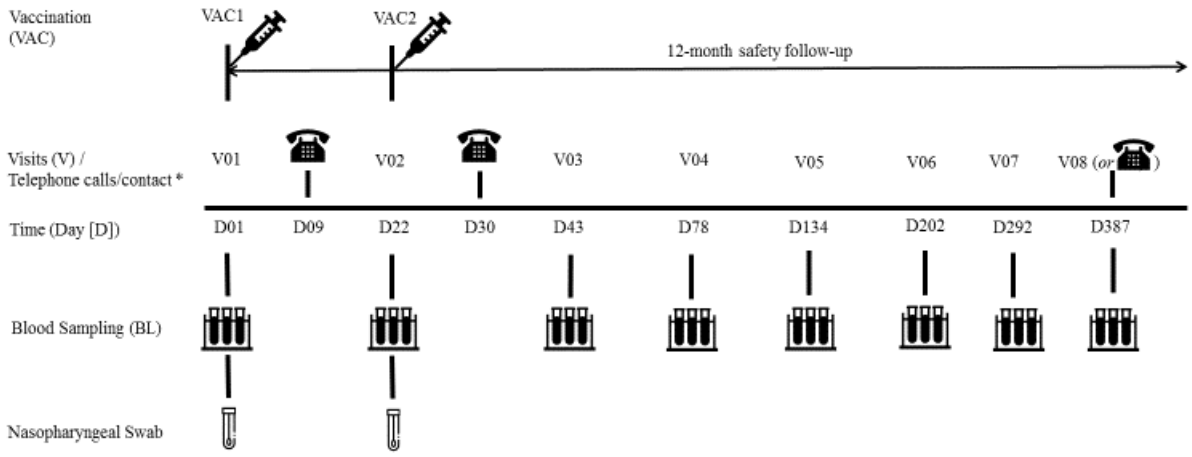
Participants in the Vaccine group who completed at least 1 dose of study vaccination and did not receive an authorized/approved vaccine will be eligible for a booster ⩾ 4 months post-last dose of the primary CoV2 preS dTM-AS03 vaccine.

Participants in the Placebo group who received at least 1 dose of either an authorized/approved vaccine or CoV2 preS dTM-AS03 vaccine will be eligible for a booster ⩾ 4 months post-last dose of the primary series.

2.2 Trial Plan

The graphical design of the VAT00008 study is presented in Figure 2.1, and the graphical design for the COVID-19-like illness follow-up is presented in Figure 2.2. For the graphical design of the Crossover / Booster, see Figure 2.3 through Figure 2.5.

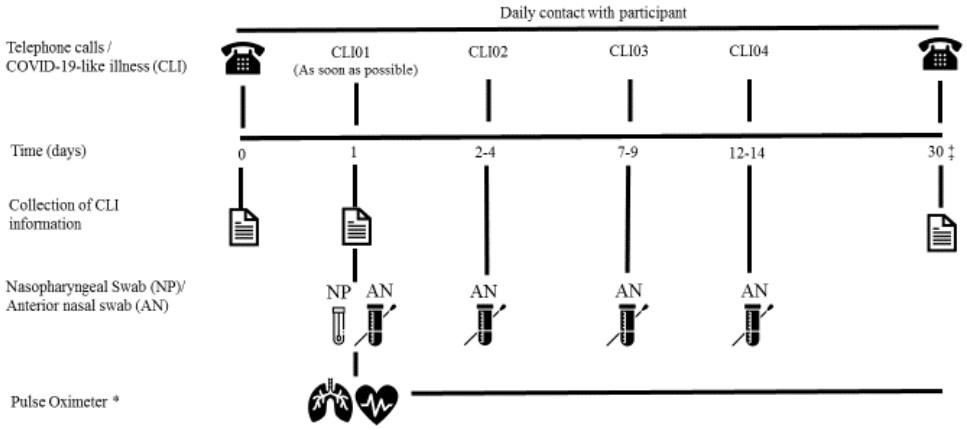
Figure 2.1: Graphical study design



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

For the V08 contact, all participants will be scheduled to attend V08 for blood sampling and 12-Month (post-VAC2) Safety Follow-up. However, if any participants discontinue the study early, they are still to be followed for safety and are to be contacted with a Safety Follow-up call to identify the occurrence of any SAEs and AESIs that had not yet been reported.

Figure 2.2: Follow-up of COVID-19-like illness

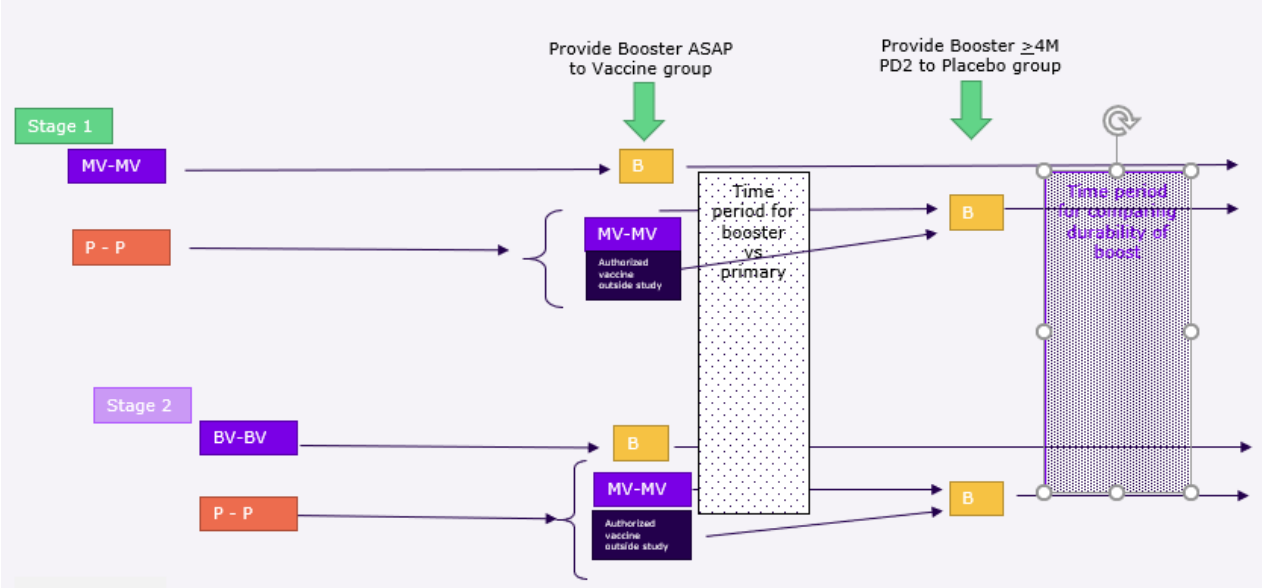


AN, anterior nasal; CLI, COVID-19-like illness, NP, nasopharyngeal

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

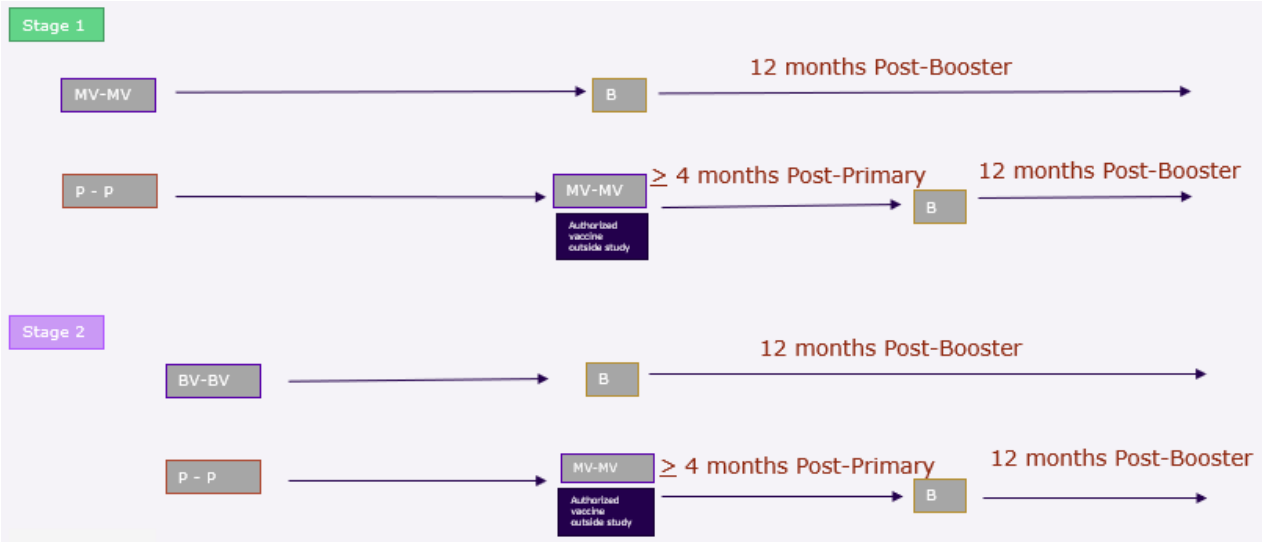
‡ Follow-up of telephone call approximately 30 days after illness onset. If symptoms are not resolved at this follow-up TC, a second TC will be needed approximately 60 days after illness.

Figure 2.3: Graphical design of unblinded crossover / booster design



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

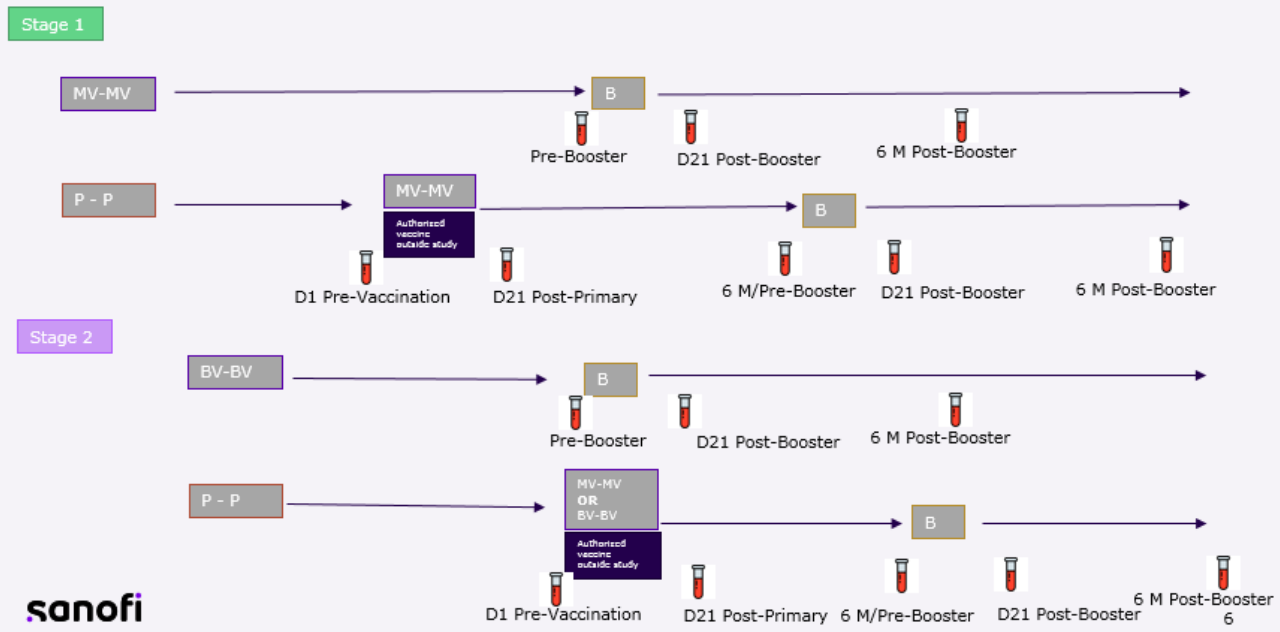
Figure 2.4: Crossover / booster efficacy and safety follow-up



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

Note: "≥ 4 months Post-Primary" means ≥ 4 months after the last dose of primary series. "12 months Post-Booster" should all be changed to "6 months Post-Booster".

Figure 2.5: Crossover / booster immunogenicity follow-up



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

Notes:

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

3 Protocol Defined Objectives, Endpoints and Assessment Methods

3.1 Objectives, Endpoints and Assessment Methods

The study objectives and the corresponding endpoints for the initial double-blind primary series design, prior to Crossover / Booster, are described in Table 1. The Crossover / Booster objectives and corresponding endpoints are described in Table 2.

In Table 1 and 2, the objective numbers may not correspond to those defined in Protocol Version 8.0 and SAP Core Body Version 4.0 because of the reduced scope (see the summary table of changes). The objectives that have been dropped or will be covered by a separate SAP will not listed in the following two tables.

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

Objectives	Endpoints	Assessment Methods for Endpoints
Primary Efficacy		
Stage 1 To assess, in participants who are SARS-CoV-2 naïve, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for the prevention of symptomatic COVID-19 occurring ≥ 14 days after the second injection.	• Occurrences of symptomatic COVID-19	• Symptomatic COVID-19 is defined as virologically-confirmed SARS-CoV-2 infection accompanied by protocol-defined COVID-19-like illness. Cases will be confirmed by adjudication committee. • Virologically-confirmed SARS-CoV-2 infection is defined as a positive result for SARS-CoV-2 by NAAT on at least one respiratory sample. Respiratory samples for NAAT testing are to be collected in participants with COVID-19 like illness (CLI) through the study. NAAT testing will be done using the protocol specified test in designated central laboratories. Genome sequencing of SARS-CoV-2 virus will be performed on NAAT positive samples to determine variant identity as protocol specified. NAAT testing based on other tests (not protocol defined) or/and done in local laboratories can account for virologic

Objectives	Endpoints	Assessment Methods for Endpoints
Stage 2: To assess, in all participants regardless of prior SARS-CoV-2 infection, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for prevention of symptomatic COVID-19 ≥ 14 days after the second injection.		confirmation if confirmed by an adjudication committee. • COVID-19-like illness (CLI) is defined per protocol as presented in Section 3.2.1.1.1. Surveillance and ascertainment of COVID-19-like illness will be performed through passive surveillance (participant reporting) and active surveillance (weekly contact from site to participant) and will be captured in the CRF based on participants reporting and other supportive documents (medical information when applicable). • Determination of naïve participants for the primary objective is based on negative NAAT at D01 and D22, negative by the anti-S immunoassay (Roche Elecsys) on D01 serum sample) as well as negative Nucleocapsid of SARS-CoV-2 electrochemiluminescence immunoassay (ECLIA) at D01 and D22. • Details on derivation person-years at risk, time to event are presented in Section 3.2.1.
Primary Safety		
To assess the safety of the CoV2 preS dTM-AS03 vaccines compared to placebo throughout the study.	For participants in the Reactogenicity Subset: • Presence of solicited (pre-listed in the participant's diary card / electronic diary card [DC/eDC] and [electronic] Case Report Form [CRF]) injection site reactions and systemic reactions occurring up to 7 days after each vaccination • Presence of non-serious unsolicited adverse events (AEs) reported up to 21 days after the last vaccination For all participants in the study:	• Solicited injection site (pain, erythema and swelling) and systemic (fever, headache, malaise, myalgia, arthralgia, chills) reactions are collected in the CRF based on participants reporting in study diary according to protocol definitions. Details on derivation of presence, intensity grading, time of onset, number of days of occurrence and ongoing status at end of solicited period are presented in Section 3.2.2.1 and Section 3.2.2.8. • Unsolicited adverse events are collected in the CRF based on participants reporting in study diary and other supportive documents (medical information when applicable). Details on derivation of presence, intensity, last vaccination

Objectives	Endpoints	Assessment Methods for Endpoints
	• Presence of unsolicited injection site and systemic AEs reported in the 30 minutes after each vaccination • Presence of medically-attended adverse events (MAAEs) throughout the study • Presence of serious adverse events (SAEs) throughout the study • Presence of adverse events of special interest (AESIs) throughout the study • Presence of virologically-confirmed SARS-CoV-2 infections and/or symptomatic COVID-19	associated with AE, time of onset, duration, causal relationship, seriousness, and outcomes are presented in Section 3.2.2.23.2.2.2 and Section 3.2.2.8. • Information on those events is collected in the CRF based on participants reporting in study diary and other supportive documents (medical information when applicable). • Information about derivation for unsolicited systemic AEs reported in the 30 minutes after each vaccination is in Section 3.2.2.23.2.2.2. • Additional information about derivations for MAAEs and related endpoints are presented in Section 3.2.2.5. • Additional information about derivations for SAEs is presented in Section 3.2.2.3. • Additional information about derivations for AESIs is presented in Section 3.2.2.4. • Additional information about derivations for virologically-confirmed SARS-CoV-2 infections and/or symptomatic COVID-19 is presented in Section 3.2.2.6. • Details on derivation for person-years at risk are presented in Section 3.2.2.8.
Secondary Efficacy		
Key Secondary Efficacy Objective (Stage 1): 1) To assess, in participants who are SARS-CoV-2 naïve, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for prevention of the following occurring ≥ 14 days after the second injection: • Prevention of SARS-CoV-2 infection	Endpoints for secondary efficacy objective #1 and #2: • Occurrences of SARS-CoV-2 infection • Occurrences of severe COVID-19	Occurrences of SARS-CoV-2 infection • SARS-CoV-2 infection is defined as a serologically-confirmed SARS-CoV-2 infection OR virologically-confirmed SARS-CoV-2 infection. • 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

Objectives	Endpoints	Assessment Methods for Endpoints
• Prevention of severe COVID-19 **Key Secondary Efficacy Objective (Stage 2):** 2) To assess: • Prevention of SARS-CoV-2 infection in participants who are SARS-CoV-2 naïve, occurring ⩾ 14 days after the second injection • Prevention of severe COVID-19 in participants regardless of prior SARS-CoV-2 infection occurring ⩾ 14 days after the second injection		electrochemiluminescence immunoassay (ECLIA). • Virologically-confirmed SARS-CoV-2 infection is defined as a positive result for SARS-CoV-2 by NAAT on at least one respiratory sample including NAAT tests that are not protocol-defined if confirmed by the adjudication committee. • NAAT testing on respiratory sample will be done in participants with COVID-19-like-illness, and it could be done in the absence of symptoms outside of study specific procedures (for example, as a result of contact tracing by health providers or authorities). • Serologic testing for SARS-CoV-2 infection will be performed at vaccination timepoints (D01 and D22) and serially at multiple timepoints during the study (D43, D78, D134, D202, D292 and D387) Occurrence of severe COVID-19 • Assessment methods are the same as those for the primary efficacy endpoint but applies the protocol definitions of severe (See Section 3.2.1.1.10 for details) for ascertainment of events. • Severity of COVID-19 events will be confirmed by an Adjudication Committee.
3) Stage 1 only: To assess, in all participants regardless of prior SARS-CoV-2 infection, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for: • Prevention of symptomatic COVID-19 • Prevention of severe COVID-19	Stage 1 only: Endpoints for secondary efficacy objective #3: • Occurrences of symptomatic COVID-19 • Occurrences of severe COVID-19	• Assessment methods are the same as those for the primary efficacy endpoint and for the second endpoint addressing this objective it applies the protocol definitions of severe (See Section 3.2.1.1.10 for details) for ascertainment of events. • Severity of COVID-19 events will be confirmed by an Adjudication Committee.
4) To assess, in participants who are SARS-CoV-2 non-naïve, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for:	Endpoints for secondary efficacy objective #4: • Occurrences of symptomatic COVID-19	• Assessment methods are the same as those for the primary efficacy endpoint and the second endpoint addressing secondary efficacy objective #1 but for the second endpoint addressing this objective it

Objectives	Endpoints	Assessment Methods for Endpoints
• Prevention of symptomatic COVID-19 • Prevention of severe COVID-19	• Occurrences of severe COVID-19	applies the protocol definitions of severe (See Section 3.2.1.1.10 for details) for ascertainment of events. • Severity of COVID-19 events will be confirmed by an Adjudication Committee.
5) To assess, in participants who are SARS-CoV-2 naïve, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for the prevention of asymptomatic SARS-CoV-2 infection.	Endpoint for secondary efficacy objective #5: • Occurrences of asymptomatic COVID-19 SARS-CoV-2 infection	• Asymptomatic SARS-CoV-2 infection is defined as SARS-CoV-2 infection, with no reported COVID-19-like illness episodes between enrollment and 14 days after the timepoint at which SARS-CoV-2 infection is ascertained.
6) To assess the impact of the CoV2 preS dTM-AS03 vaccines in the reduction of viral burden and shedding among participants with symptomatic COVID-19	Endpoints for secondary efficacy objective #6: • Viral copies/mL in respiratory samples collected at each follow-up timepoint • Number of days with positive NAAT • Occurrences of positive NAAT in respiratory samples at each follow-up timepoint during symptomatic COVID-19	• Real Time SARS-CoV-2 PCR assay will be used for quantitation of viral load on respiratory samples collected during COVID-19-like illness visits for participants who are determined to have virologically-confirmed SARS-CoV-2. • Anterior nasal samples collected at multiple time-points (4 time-points targeted for collection during a period of approximately 2 weeks from the onset of illness) during symptomatic COVID-19 illness will be tested by qualitative and quantitative PCR methods.
7) To assess, in all participants regardless of prior SARS-CoV-2 infection and in participants who are SARS-CoV-2 non-naïve and naïve, clinical efficacy of the CoV2 preS dTM-AS03 vaccines for: • Prevention of CDC-defined COVID-19 • Prevention of hospitalized COVID-19 • Prevention of symptomatic COVID-19 with severity of moderate COVID-19 or worse (composite endpoint of moderate or severe COVID-19)	Endpoints for secondary efficacy objective #7: • Occurrences of CDC-defined COVID-19 • Occurrences of hospitalized COVID-19 • Occurrences of symptomatic COVID-19 with severity of moderate COVID-19 or worse (composite endpoint of at least one of moderate or severe COVID-19)	• CDC-defined COVID-19 is defined based on virologic confirmation of SARS-CoV-2 by NAAT associated with symptoms presented in Section 3.2.1.1.7. • Hospitalized COVID-19 is defined as an episode of Symptomatic COVID-19 that requires inpatient hospitalization. • Assessment methods for symptomatic COVID-19 with severity of moderate COVID-19 or worse are the same as those for the primary efficacy endpoint but applies the protocol definitions of moderate and severe COVID-19 (See Section 3.2.1.1.13 for details) for ascertainment of events • Severity definitions are presented in Section 3.2.1.1; severity

Objectives	Endpoints	Assessment Methods for Endpoints
		classifications will be confirmed by an Adjudication Committee.
8) To assess the durability of clinical efficacy of the CoV2 preS dTM-AS03 vaccines over time in SARS-CoV-2 naïve participants against: • SARS-CoV-2 infection • Asymptomatic SARS-CoV-2 infection	Endpoints for secondary efficacy objective #8: • Occurrences of SARS-CoV-2 infection • Occurrences of asymptomatic SARS-CoV-2 infection	• Assessment methods are the same as those for secondary efficacy objective #1 and #4.
9) To assess the durability of clinical efficacy of the CoV2 preS dTM-AS03 vaccines over time in all participants and by prior SARS-CoV-2 infection (naïve and non-naïve) for: • Prevention of symptomatic COVID-19 • Prevention of severe COVID-19 • Prevention of CDC-defined COVID-19 • Prevention of hospitalized COVID-19	Endpoints for secondary efficacy objective #9: • Occurrences of symptomatic COVID-19 • Occurrences of severe COVID-19 • Occurrences of CDC-defined COVID-19 • Occurrences of hospitalized COVID-19	• Assessment methods are the same as those for secondary efficacy objective #7.
10) Stage 2 only: To assess, in participants who are SARS-CoV-2 naïve, the clinical efficacy of the CoV2 preS dTM-AS03 vaccines for: • Prevention of symptomatic COVID-19 • Prevention of severe COVID-19	Stage 2 only: Endpoint for secondary efficacy objective #10: • Occurrences of symptomatic COVID-19 • Occurrence of severe COVID-19	• Assessment methods are the same as those for primary efficacy objective of Stage 2, but in participants who are SARS-CoV-2 naïve.

Objectives	Endpoints	Assessment Methods for Endpoints
Secondary Immunogenicity		
1) To compare the neutralizing antibody response 21 days after last vaccination (D43) to the D614G variant between the monovalent and bivalent vaccines in SARS-CoV-2 naïve and non-naïve participants in the Random Immunogenicity Subcohort. 2) To compare the neutralizing antibody response 21 days after last vaccination (D43) to the B.1.351 variant between the monovalent and bivalent vaccines in SARS-CoV-2 naïve and non-naïve participants in the Random Immunogenicity Subcohort. 3) To compare the neutralizing antibody response 21 days after last vaccination (D43) to the B.1.351 variant in the bivalent vaccine group and the neutralizing antibody response to the D614G variant in the monovalent vaccine group in SARS-CoV-2 naïve and non-naïve participants in the Random Immunogenicity Subcohort.	<u>Endpoints for secondary immunogenicity objectives #1 - 3:</u> • Individual serum neutralizing titer at D01 and D43 • Responders, defined as participants who had baseline values below lower limit of quantification (LLOQ) with quantifiable neutralization titer above assay LLOQ at each pre-defined post-vaccination time point and participants with baseline values above LLOQ with a 4-fold increase in neutralizing antibody titers at each pre-defined post-vaccination time point • Seroresponse, defined as a 4-fold or greater rise in serum neutralization titer [pre/post] at D43 relative to D01	• Blood samples will be collected in all study participants at D01, D22, D43, D78, D134, D202, and D387. • Blood samples will be selected for testing in subsets of study participants in the Random Immunogenicity Subcohort, and by the occurrence of efficacy events (symptomatic COVID-19, SARS-CoV-2 infection, and other COVID-19 events). • Selected blood samples will be tested using pseudovirus neutralization assay, and may be supplemented by other assays. Descriptions of the assays and the timepoints for testing are presented in the Protocol.
The following objectives will be assessed in participants regardless of prior SARS-CoV-2 infection and in SARS-CoV-2 non-naïve and naïve participants. 4) To describe the neutralizing antibody profile at D01, D22, D43, D78, D134, D202, D292, and D387 in each study group for participants in the Random Immunogenicity Subcohort. 5) To describe the neutralizing antibody profile at D01, D22, D43, D78, D134, D202, D292, and D387 in each study group for participants aged 18-25 years in the Random Immunogenicity Subcohort.	<u>Endpoints for secondary immunogenicity objectives #4 - 5:</u> Neutralizing antibody titers will be measured in participants for each study group against the D614G and B.1.351 variants. • Individual serum neutralizing titer at each pre-defined time point • Individual serum neutralization titer fold-rise post-vaccination relative to D01 at each pre-defined time point • 2-fold rise and 4-fold-rise in serum neutralization titer	• Assessment methods are the same as those for secondary immunogenicity objectives #1-3, but additional immunological biomarkers/assays may be evaluated as correlates of risk/protection.

Objectives	Endpoints	Assessment Methods for Endpoints
	[post/pre] (fold rise ≥ 2 and ≥ 4) at each pre-defined post-vaccination timepoint • Responders, defined as participants who had baseline values below LLOQ with quantifiable neutralization titer above assay LLOQ at each pre-defined post-vaccination time point and participants with baseline values above LLOQ with a 4-fold increase in neutralizing antibody titers at each pre-defined post-vaccination timepoint	
Secondary Safety		
1) To describe the frequency and spectrum of disease in episodes of symptomatic COVID-19 in SARS-CoV-2 non-naïve adults in each study group.	Endpoints for secondary safety objective #1: For SARS-CoV-2 non-naïve participants in the study: • Severity of symptoms associated with symptomatic COVID-19 episode • Occurrences of hospitalized COVID-19 • Occurrence of severe COVID-19 • Occurrences of COVID-19 in each severity rating on the 7-point ordinal scale • Death associated with COVID-19	• Assessment methods will be similar as those utilized for addressing Efficacy Objective #4. • Additionally, description of COVID-19 symptom severity will be based on CRF reporting of each symptom present (see Section 3.2.2.7). • Death associated with symptomatic COVID-19 are presented in Section 3.2.1.1; and will be confirmed by an Adjudication Committee

Objectives	Endpoints	Assessment Methods for Endpoints
2) To assess the safety of the CoV2 preS dTM-AS03 vaccines compared to placebo in participants aged 18-25 years throughout the study.	Endpoints for secondary safety objective #2: For participants in the Reactogenicity Subset: • Presence of solicited (pre-listed in the participant's diary card / electronic diary card [DC/eDC] and [electronic] Case Report Form [CRF]) injection site reactions and systemic reactions occurring up to 7 days after each vaccination • Presence of non-serious unsolicited adverse events (AEs) reported up to 21 days after the last vaccination For all participants in the study: • Presence of unsolicited injection site and systemic AEs reported in the 30 minutes after each vaccination • Presence of medically-attended adverse events (MAAEs) throughout the study • Presence of serious adverse events (SAEs) throughout the study • Presence of adverse events of special interest (AESIs) throughout the study • Presence of virologically-confirmed SARS-CoV-2 infections and/or symptomatic COVID-19	• Assessment methods will be the same as primary safety objective
Exploratory Efficacy		
1) To assess in all participants regardless of prior SARS-CoV-2 infection and in SARS-CoV-2 non-naïve and naïve participants, clinical efficacy of the CoV2 preS dTM-AS03 vaccines for:	Endpoints for exploratory efficacy objective #1: • Days with symptoms associated with symptomatic COVID-19 • Days of hospitalization associated with COVID-19	• Information on occurrence and duration of COVID-19-like illness symptoms, hospitalization, supplemental oxygen use, intensive care utilization, requirement of mechanical ventilation or ECMO is collected in the CRF based on participants reporting in study diary and other supportive documents

Objectives	Endpoints	Assessment Methods for Endpoints
• Reduction in duration of symptoms of symptomatic COVID-19 • Reduction in duration of hospitalization with symptomatic COVID-19 • Reduction in severity of symptomatic COVID-19 on the 7-point ordinal scale • Reduction in use of supplemental oxygen associated with symptomatic COVID-19 • Prevention of intensive care utilization associated with symptomatic COVID-19 • Reduction in use of mechanical ventilation or ECMO associated with symptomatic COVID-19 • Prevention of death associated with symptomatic COVID-19	• Occurrences of symptomatic COVID-19 in each severity rating on the 7-point ordinal scale • Occurrences of symptomatic COVID-19 requiring supplemental oxygen • Days of use of supplemental oxygen over the course of symptomatic COVID-19 • Occurrences of intensive care utilization associated with symptomatic COVID-19 • Days of stay in an intensive care unit over the course of symptomatic COVID-19 • Occurrences of symptomatic COVID-19 requiring mechanical ventilation or ECMO • Days of use of mechanical ventilation or ECMO over the course of the symptomatic COVID-19 • Occurrence of death associated with symptomatic COVID-19	(medical information when applicable). • Death associated with symptomatic COVID-19 are presented in Section 3.2.1.1; and will be confirmed by an Adjudication Committee.
2) To assess the clinical efficacy of the CoV2 preS dTM-AS03 vaccines in SARS-CoV-2 naïve participants for: • Prevention of SARS-CoV-2 infection • Prevention of asymptomatic SARS-CoV-2 infection	<u>Endpoints for exploratory efficacy objective #2:</u> • Occurrences of SARS-CoV-2 infection • Occurrences of asymptomatic SARS-CoV-2 infection	• Assessment methods are the same as those for secondary efficacy objective #1 and #5.
3) To assess the clinical efficacy of the CoV2 preS dTM-AS03 vaccines in participants regardless of prior SARS-CoV-2 infection and by baseline prior SARS-CoV-2 infection (naïve and non-naïve) for: • Prevention of symptomatic COVID-19	<u>Endpoints for exploratory efficacy objective #3:</u> • Occurrences of symptomatic COVID-19 • Days with symptoms associated with symptomatic COVID-19 • Occurrence of severe COVID-19	• Assessment methods are the same as those for exploratory efficacy objective #1.

Objectives	Endpoints	Assessment Methods for Endpoints
• Reduction in duration of symptoms of COVID-19 • Prevention of severe COVID-19 • Prevention of hospitalized COVID-19 • Reduction in duration of hospitalization with symptomatic COVID-19 • Reduction in severity of symptomatic COVID-19 on the 7-point ordinal scale • Prevention of symptomatic COVID-19 with severity of moderate COVID-19 or worse (composite endpoint of moderate or severe COVID-19) • Reduction in use of supplemental oxygen associated with symptomatic COVID-19 • Prevention of intensive care utilization associated with symptomatic COVID-19 • Reduction in use of mechanical ventilation or ECMO associated with symptomatic COVID-19 • Prevention of death associated with symptomatic COVID-19	• Occurrences of CDC-defined COVID-19 • Occurrences of hospitalized COVID-19 • Days of hospitalization with symptomatic COVID-19 • Occurrences of symptomatic COVID-19 in each severity rating on the 7-point ordinal scale • Occurrence of symptomatic COVID-19 with severity of moderate COVID-19 or worse (composite endpoint of at least one of moderate or severe COVID-19) • Occurrences of symptomatic COVID-19 requiring intensive care utilization • Occurrences of symptomatic COVID-19 requiring supplemental oxygen • Days of supplemental oxygen use in participants with symptomatic COVID-19 • Occurrences of intensive care utilization associated with symptomatic COVID-19 • Days of stay in an intensive care unit associated with symptomatic COVID-19 • Occurrences of symptomatic COVID-19 requiring mechanical ventilation or ECMO • Days of use of mechanical ventilation or ECMO over the course of symptomatic COVID-19 • Occurrence of deaths associated with symptomatic COVID-19	
4) To assess the clinical efficacy of the CoV2 preS dTM-AS03	<u>Endpoints for exploratory efficacy objective #4:</u>	• Assessment methods are the same as for primary and secondary efficacy

Objectives	Endpoints	Assessment Methods for Endpoints
vaccines against all COVID-19 events (including all events regardless of adjudication committee decision)	• Occurrence of virologically-confirmed SARS-CoV-2 infections and COVID-19 events (including all events regardless of adjudication committee decision).	objectives but accounting for all COVID-19 events, regardless of Adjudication Committee decision.
5) To assess the clinical efficacy of the CoV2 preS dTM-AS03 vaccines in prevention of all-cause death	Endpoints for exploratory efficacy objective #5: • All-cause death	• Assessment method will be based on occurrence of death from any cause as reported in the CRF. • Details on derivation for person-years at risk, time to event are presented in Section 3.2.1.
6) To describe the occurrence of the following events temporally associated with symptomatic COVID-19 in each study group: • Rates of new onset or exacerbation of pre-existing cardio-respiratory conditions • Rates of health care utilization (hospitalizations, ER visits, or non-routine medical office visits [including urgent care visits]) • antibiotic and antiviral use • work absenteeism within 30 days of illness	Endpoints for exploratory efficacy objective #6: • Episodes of new onset or exacerbation of pre-existing cardio-respiratory conditions • Occurrences of health care utilization events (hospitalizations, ER visits, or non-routine medical office visits [including urgent care visits]) • Instances of antibiotic or antiviral use • Occurrence and number of days of work absenteeism	• The occurrence of these events will be captured in the CRF during symptomatic COVID-19 monitoring and follow-up. • Events occurring with 30 days of symptomatic COVID-19 onset will be counted. • Onset of symptomatic COVID-19 corresponds to the day of the first symptom contributing to the protocol definition of COVID-19-like illness.
7) To assess impact of vaccination on asymptomatic SARS-CoV-2 NAAT positivity at the time of the crossover set of vaccinations in naïve participants	Endpoints for exploratory efficacy objective #7: Occurrence of positive NAAT in respiratory samples at time of crossover	• Assessment methods will be further defined in a Supplemental Analysis Plan
8) To describe in each group virologically-confirmed respiratory viral infections as ascertained by real-time polymerase chain reaction (RT-PCR) for other respiratory viruses (eg, Influenza, RSV).	Endpoints for exploratory efficacy objective #8: • Occurrences of respiratory viral infections (other than SARS-CoV-2) associated with COVID-19-like illness (by RT-PCR)	• Other viral infections will be ascertained by real-time polymerase chain reaction (RT-PCR) on samples collected at time of COVID-19-like illness.
9) To assess clinical efficacy on prevention of symptomatic COVID-19 disease and SARS-COV-2 infection within the	Endpoints for exploratory efficacy objective #9: • Occurrences of symptomatic COVID-19	• Events in members of the same residence will be self-reported by the participant and captured in the CRF.

Objectives	Endpoints	Assessment Methods for Endpoints
same residence of study participants	and SARS-CoV-2 infection among members in the same residence self-reported by the participant	
10) To describe the relative efficacy against symptomatic COVID-19 by variants between the monovalent and bivalent vaccines.	<u>Endpoints for exploratory efficacy objective #10:</u> • Occurrences of symptomatic COVID-19	• Assessment methods are the same as those for primary efficacy objective.
Exploratory Immunogenicity		
The following objectives will be assessed in participants regardless of prior SARS-CoV-2 infection and in SARS-CoV-2 non-naïve and naïve participants. 1) To describe the binding antibody profile at D01, D22, D43, D78, D134, D202, D292, and D387 in each study group for participants in the Random Immunogenicity Subcohort. 2) To describe the neutralizing antibody profile at D01, D22, D43, D78, D134, D202, D292, and D387 against newly emergent variant strains for participants in the Random Immunogenicity Subcohort.	<u>Endpoints for exploratory immunogenicity objective #1:</u> Binding antibody concentration will be measured in participants for each study group against the homologous vaccine strains. • Individual antibody concentration at each pre-defined time point • Individual antibody fold-rise post-vaccination relative to D01 at each pre-defined post-vaccination time point • 2-fold-rise and 4-fold-rise (fold-rise in antibody concentration [post/pre] ≥ 2 and ≥ 4) at each pre-defined post-vaccination time point • Responders, defined as participants who had baseline values below LLOQ with quantifiable antibody concentration above assay LLOQ at each pre-defined post-vaccination timepoints and participants with baseline values above LLOQ with a 4-fold increase in antibody concentrations at each pre-defined post-vaccination timepoint. • Individual antibody concentration (≥ 2xLLOQ or ≥ 4xLLOQ) at each pre-defined time point	• Blood samples will be collected in all study participants at D01, D22, D43, D78, D134, D202, and D387. • Blood samples will be selected for testing in subsets of study participants in the Random Immunogenicity Subcohort, and by the occurrence of efficacy events (symptomatic COVID-19, SARS-CoV-2 infection, and other COVID-19 events). • Selected blood samples will be tested using anti-S protein IgG ELISA and electrochemiluminescence immunoassay (ECLIA). Descriptions of the assays and the timepoints for testing are presented in the Protocol.

Objectives	Endpoints	Assessment Methods for Endpoints
	<u>Endpoints for exploratory immunogenicity objective #2:</u> Neutralizing antibody titers will be measured in participants against newly emergent variants of concern (VOCs). • Individual serum neutralization titer at each pre-defined time point • Individual serum neutralization titer fold-rise post-vaccination relative to D01 at each pre-defined time point • 2-fold-rise and 4-fold-rise in serum neutralization titer [post/pre] (fold-rise ≥ 2 and ≥ 4) at each pre-defined post-vaccination timepoint • Responders, defined as participants who had baseline values below LLOQ with quantifiable neutralization titer above assay LLOQ at each pre-defined post-vaccination timepoint and participants with baseline values above LLOQ with a 4-fold increase in neutralizing antibody titers at each pre-defined post-vaccination timepoint.	

Table 2: Objectives and Endpoints: Crossover / Booster design

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

Objectives	Endpoints	Assessment Methods for Endpoints
vaccines after the crossover or booster vaccinations	For all participants in the study: • Presence of unsolicited injection site and systemic AEs reported in the 30 minutes after each vaccination • Presence of non-serious unsolicited AEs reported up to 21 days after the booster vaccination • Presence of MAAEs throughout the study • Presence of SAEs throughout the study • Presence of AESIs throughout the study	objective prior to Crossover/Booster design
Exploratory Efficacy		
1) To describe the relative efficacy ≥ 6 months after a booster dose among participants initially in the Vaccine group (earlier booster) versus the efficacy ≥ 14 days after a booster dose in participants initially in the Placebo group (later booster).	Endpoints for exploratory efficacy objective #1: • Occurrences of symptomatic COVID-19 • Occurrences of hospitalized COVID-19 • Occurrence of severe COVID-19	• Assessment methods are the same as the primary and secondary efficacy endpoints prior to Crossover/Booster design
2) To describe the relative efficacy ≥ 14 days after a booster dose among initial vaccine recipients versus ≥ 14 days after the primary series among initial placebo recipients.	Endpoints for exploratory efficacy objective #2: • Occurrences of symptomatic COVID-19 • Occurrences of hospitalized COVID-19 • Occurrence of severe COVID-19	• Assessment methods are the same as the primary and secondary efficacy endpoints prior to Crossover/Booster design
3) To describe the relative efficacy ≥ 14 days after a booster dose among participants initially vaccinated with the monovalent CoV2 preS dTM-AS03 (D614) vaccine (Vaccine group Stage 1) versus the efficacy ≥ 14 days after a booster dose in participants initially vaccinated with the bivalent CoV2 preS dTM-AS03 (D614+B.1351) vaccine (Vaccine group Stage 2).	Endpoints for exploratory efficacy objective #3: • Occurrences of symptomatic COVID-19 • Occurrences of hospitalized COVID-19 • Occurrence of severe COVID-19	• Assessment methods are the same as the primary and secondary efficacy endpoints prior to Crossover/Booster design
4) To describe the relative efficacy≥ 14 days after a booster dose among	Endpoints for exploratory efficacy objective #4:	• Assessment methods are the same as the primary and secondary

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

Objectives	Endpoints	Assessment Methods for Endpoints
and booster (initial Placebo group).	above assay LLOQ at each pre-defined post-vaccination time point and participants with baseline values above LLOQ with a 4-fold increase in antibody concentrations at each pre-defined post-vaccination timepoint	

3.2 Definition, Derivation, and Calculation of Endpoints

3.2.1 Efficacy

This section will include all definitions of efficacy endpoints. Start and stop dates are also defined for some efficacy endpoints if applicable.

An adjudication committee will be assembled for the purpose of reviewing potential cases to determine if the criteria for the efficacy endpoints have been met. An adjudication database including all information adjudicated will be applied for analysis. Some efficacy endpoints listed in this section will be analyzed based on the adjudicated database from the adjudication committee instead of based on CRF information. Details will be provided below under each endpoint.

3.2.1.1 COVID-19 Efficacy Endpoints, Start/Stop Date (if applicable)

3.2.1.1.1 COVID-19-like illness

COVID-19-like illness (CLI) symptoms will be graded by the intensity grade and here are the listed symptoms/conditions of CLI.

New onset or exacerbation of any ONE of the following:

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

OR

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

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

OR

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

- Sore throat
- Chills
- Myalgia
- Fatigue
- Malaise
- Headache
- Rhinorrhea or nasal congestion
- Abdominal pain
- At least one of nausea, diarrhea, vomiting

Each COVID-19 like illness (CLI) will be collected in a CLI page in the CRF with an identical episode number. Respiratory samples for NAAT testing are collected in participants with any identified CLI throughout the study. NAAT testing will be done using the protocol specified test in designated central laboratories. NAAT testing done using assays different than those specified in the protocol or performed at laboratories other than the designated central laboratories will be assessed by an adjudication committee.

The start and stop date of each illness episode will be derived based on information collected in the CRF.

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 within 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 COVID-19-like-illness symptoms or occurrences of new symptoms during an ongoing COVID-19-like-illness which is not associated with a positive NAAT for SARS-CoV-2 (missing or negative test), a new COVID-19-like-illness visit and subsequent schedule of events should be generally triggered if the new symptom or exacerbation

of symptom occurs more than 7 days from the onset of the initial COVID-19-like-illness. In these cases, the onset of illness will correspond to the date of onset of the new symptom(s) or the date of the worsening of the pre-existing symptom(s).
In these instances of overlapping CLIs, 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.

3.2.1.1.2 Virologically-confirmed SARS-CoV-2 infection

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

3.2.1.1.3 Serologically-confirmed SARS-CoV-2 infection

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

3.2.1.1.4 SARS-CoV-2 infection

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

3.2.1.1.5 Symptomatic COVID-19

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

Analysis will be only based on events identified in the adjudicated database instead of by the CRF.

3.2.1.1.6 Asymptomatic SARS-CoV-2 infection

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

3.2.1.1.7 CDC-defined COVID-19

CDC-defined COVID-19 is defined as virologically-confirmed SARS-CoV-2 infection with at least one of:

- Fever or chills
- Cough
- Shortness of breath or difficulty breathing

- Fatigue
- Muscle or body aches
- Headache
- New loss of taste or smell
- Sore throat
- Congestion or runny nose
- Nausea or vomiting
- Diarrhea

3.2.1.1.8 Hospitalized COVID-19

Hospitalized COVID-19 is defined as an episode of symptomatic COVID-19 that requires inpatient hospitalization (as collected in CRF where subjects are admitted to hospital).

The start date or stop date of the hospitalized COVID-19 endpoint is the same than that of the corresponding symptomatic COVID-19.

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.

3.2.1.1.9 Moderate COVID-19

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

- Shortness of breath that persists for at least 12 hours

OR

- Clinical signs of moderate illness measured at least on two occasions separated by 30 mins (respiratory rate ≥ 20 breaths per minute at rest, heart rate ≥ 90 beats per minute at rest)

AND

- No clinical signs indicative of Severe COVID-19.

Although the information will be collected in the CRF, analysis will be based on adjudication of severity by the adjudication committee and reflected in the adjudication database rather than the CRF.

Similarly, for analyses of moderate or severe COVID-19, adjudicated results will be used.

The start date and stop date is the same with that of the corresponding symptomatic COVID-19.

3.2.1.1.10 Severe COVID-19

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

- Any clinical signs of severe illness measured at least on 2 occasions separated by 30 minutes (saturation of oxygen [SpO2] ≤ 93% on room air (corrected for altitude),

PaO2/FiO2 < 300 mm Hg, 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

Although the information will be collected in the CRF, analysis will be based on adjudication of severity by the adjudication committee and reflected in the adjudication database rather than the CRF.

The start date and stop date is the same with that of the corresponding symptomatic COVID-19.

3.2.1.1.11 COVID-19 severity scale

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

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

The above 7 scales for all COVID-19 events will be analyzed as collected in the CRF page.

The start date and the stop date of symptomatic COVID-19 with a scale is the same with that of the corresponding symptomatic COVID-19.

3.2.1.1.12 Death associated with COVID-19

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

as an immediate or underlying cause of death on the death certificate if association confirmed by adjudication committee.
Although the information will be collected in the CRF, analysis will be based on adjudication of association by the adjudication committee and reflected in the adjudication database rather than the CRF.

The start date and stop date is the same as that of the corresponding symptomatic COVID-19.

3.2.1.1.13 Moderate or severe COVID-19

This is defined as a participant as at least one of moderate COVID-19 or severe COVID-19.

3.2.1.1.14 Other Efficacy Events

All events regardless of adjudication committee decision

This endpoint is defined as any SARS-CoV-2 infections or symptomatic COVID-19 events identified in the database including those identified by local lab test or by central laboratory (protocol) testing, regardless of adjudication committee decision.

All cause death

This endpoint is defined as any death event collected in CRF for all participants during the study regardless of relationship to CLI or not.

3.2.1.2 Person-years at Risk

The 1000 person-years at risk for efficacy evaluation will be calculated for each population (as defined in Section 4.1), each analysis period (eg, from 14 days post-dose 2) and for each definition of efficacy endpoints independently (as listed below):

- Symptomatic COVID-19
- Severe COVID-19
- CDC-defined COVID-19
- Hospitalized COVID-19
- Death associated with COVID-19
- Moderate or severe COVID-19
- Symptomatic COVID-19 with a severity scale or worse in 7-point ordinal scales
- Symptomatic COVID-19 requiring intensive care utilization
- Symptomatic COVID-19 requiring mechanical ventilation or ECMO
- Symptomatic COVID-19 requiring supplemental oxygen

The 1000 person-years at risk are calculated as the addition of “person-years at risk for each participant” which is the accumulating time (in years) until the participant is diagnosed with an event corresponding to each efficacy endpoint, or until another time-point by which the

participant has not experience an event (censored). The situations of censoring and calculation of censoring date are defined below.

Event date (start date of an event) will be used for calculation if a participant has an event during the analysis period. Details are:

1. If a participant has one event within the analysis period, the event date will be used.
2. If a participant has more than one event corresponding to the same endpoint during the analysis period, the first event date will be used.
3. Events occurring outside the analysis period will not be considered as an event for the corresponding calculation.

The calculation of 1000 person-years at risk for a participant having an event is:

(Start date of the event corresponding to an endpoint – start date of an analysis period +1)/ (365.25 * 1000)

Censoring date will be used for calculation if a participant has not/did not experienced an event during the analysis period and the calculation of 1000 person-years at risk is

(Participant censoring date – start date of an analysis period +1) / (365.25 * 1000)

Details of censoring date are:

1. If a participant has early termination during the analysis period, then the termination date will be the censoring date. Early termination reasons include withdrawal by the participant, discontinuation due to an AE (including death), discontinuation and loss to follow-up.

   Note: If a participant is unblinded due to any reason (AE or by participant's request) during the analysis period, the unblinding date will be considered as the censoring date. Participants are considered as having an early termination due to the unblinding although safety follow-up of these participants would continue over the duration of the study.
2. If a participant receives another SARS-CoV-2 vaccine outside the protocol during the analysis period, the date of vaccination with the other SARS-CoV-2 vaccine is considered as the censoring date.
3. If a participant is terminated early (including unblinding) or receives another SARS-CoV-2 vaccine (outside the protocol), or has an event (either CDC-defined event or symptomatic COVID-19 event for CDC-defined endpoint; or symptomatic COVID-19 event for other endpoints) and either of these conditions occur before the analysis period (if applicable), then the day before the start date of the planned analysis is considered as the censoring date. If this situation is met, the person-years will be 0 for the corresponding analysis.

4. If a participant does not meet any of the situations above (early terminated, receives another vaccine outside of the protocol, unblinded), then the cutoff date of the planned analysis will be the censoring date.

3.2.1.3 Time to event

For survival analysis, time to event will be calculated in days based on the same rule utilized for calculation of 1000 person-years at risk (Section 3.2.1.2) for each population, each analysis period and each efficacy endpoint. Time to event will be calculated in days instead of in years.

Time to event for a participant with an event is:

(Start date of the event corresponding to an endpoint – start date of an analysis period+1)

Time to event for a participant without an event is:

(Participant censoring date – start date of an analysis period +1)

The endpoints with time to event available are listed as below but not all of them will be used for statistical analysis based on time to event data (details please see Section 4.1):

- Symptomatic COVID-19
- Severe COVID-19
- CDC-defined COVID-19
- Hospitalized COVID-19
- Death associated with COVID-19
- Moderate or severe COVID-19

For participants with adjudicated symptomatic COVID-19 events, the censoring time for each the following endpoint, will be the onset time of the 1st adjudicated symptomatic COVID-19 event. That is to say, once participants have a symptomatic COVID-19 event, they are no longer at risk and therefore should be censored. Exploratory analyses to assess efficacy in participants with multiple events will be performed.

- Severe COVID-19
- Hospitalized COVID-19
- Death associated with COVID-19
- Moderate or severe COVID-19

For the CDC-defined COVID-19 event, if the 1st CDC-defined COVID-19 event occurs after the primary adjudicated symptomatic event, it will be censored at the onset time of the 1st adjudicated symptomatic COVID-19 event. If 1st CDC-defined COVID-19 event occurs before the primary adjudicated symptomatic event, then 1st CDC-defined event date will be used for the CDC-defined event date.

Some post-hoc analysis to look at multiple events on those efficacy endpoints will be considered.

3.2.1.4 Duration of event

Duration of an efficacy event is defined as the total number of days of the corresponding event related to a single endpoint.

For any symptomatic COVID-19, the duration is calculated by the definition of start/stop date (Section 3.2.1):

(The stop date – the start date +1)

For any of the following:

- Use of supplemental oxygen over the course of symptomatic COVID-19. This includes use of supplemental oxygen regardless of delivery device or system and includes mechanical ventilation and ECMO.
- Use of mechanical ventilation or ECMO over the course of symptomatic COVID-19. This includes us of both invasive and non-invasive mechanical ventilation as well as ECMO.

The number of days with either usage will be collected in the CRF by the investigator.

Duration of the hospitalization associated with a single symptomatic COVID-19 is calculated as:

The hospital discharge date - the hospital admission date +1

Duration of stay in an intensive care unit (ICU) is calculated as:

The ICU discharge date - ICU admission date +1

Duration of work absenteeism is the reported days away from work as collected in the CRF.

If a participant has multiple hospitalizations, ICU stays, or work absenteeism related to the same CLI, the duration is the sum of the durations of the single events.

Duration of positive NAAT results within the protocol collection period corresponding to a single symptomatic COVID-19 event is calculated as:

The date of last swab tested positive – The date of 1st swab tested positive + 1

3.2.1.5 Viral Burden

The viral copies in protocol-defined respiratory swabs collected during an illness episode are reported as positive continuous values with unit of log copies/ml.

Results that are detected but below the LLOQ will be reported as detected, < 2.00 Log copies/mL. Results that are above the ULOQ will be reported as detected, > 7.00 Log copies/mL. Positive results are defined as values > LLOQ. Results not detected will be recorded as not detected.

Duration of viral shedding as defined by a positive NAAT is defined in Section 3.2.1.4.

3.2.1.6 Episodes of new onset or exacerbation of pre-existing cardio-respiratory conditions

This endpoint is defined as those CLI episodes adjudicated as symptomatic COVID-19 cases meeting the following criteria:

- Either a new onset of cardio-respiratory conditions temporally related to the corresponding symptomatic COVID-19 occurring within 30 days following the onset of a symptomatic COVID-19 episode ([start day of the symptomatic COVID-19, the start day + 29 days])
- Or an exacerbation of cardio-respiratory conditions temporally related to the corresponding symptomatic COVID-19 occurring within 30 days following the onset of a symptomatic COVID-19 episode ([start day of the symptomatic COVID-19, the start day + 29 days])

This endpoint will be analyzed as collected in the CRF.

3.2.1.7 Instances of antibiotic or antiviral use

This endpoint is defined as the use of antibiotics or antivirals collected in the corresponding symptomatic COVID-19 within 30 days following the symptomatic COVID-19 ([start day of the symptomatic COVID-19, the start day + 29 days]) as collected in CRF.

3.2.1.8 Health care utilization events

The endpoint of health care utilization events including hospitalizations, ER visits, or nonroutine medical office visits (including urgent care visits) will be analyzed as collected in CRF page of health care resource. This includes health care utilization events related to the corresponding symptomatic COVID-19 occurring within 30 days following the symptomatic COVID-19 ([start day of the symptomatic COVID-19, the start day + 29 days]):

- Emergency room
- General Practitioner
- Hospital
- Pharmacy
- Telemedicine

3.2.2 Safety

Main analysis will be undertaken based on safety analysis set. Main safety analysis will be performed as the key safety results (no sensitivity or complementary analysis).

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). For all 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. Details of conducting main analysis for those endpoints including censored data are further clarified in the following subsections.

3.2.2.1 Solicited Reactions

Solicited reactions are collected within 7 days after each injection.

3.2.2.1.1 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 will have all daily intensities derived as None.
2) For non-measurable solicited reactions, daily intensities will correspond to daily records reported in the clinical database. For measurable solicited reactions the daily measurements reported in the clinical database will be converted based upon the intensity scales defined in the protocol; this assumes a reaction that is too large to measure (non-measurable, "NM") is Grade 3. Note the intensity could be considered "None" (not a reaction) in the analysis despite being considered a reaction by the investigator (e.g., swelling measurement > 0 mm but < 25 mm in adults).

3.2.2.1.2 Time of Onset

Time of onset is derived from the daily intensities computed as described in Section 3.2.2.1.1. It corresponds to the first day with intensity of Grade 1, Grade 2, or Grade 3.

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

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

3.2.2.1.3 Maximum Overall Intensity

Maximum intensity is derived from the daily intensities computed as described in Section 3.2.2.1.1 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). 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.

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.

3.2.2.1.4 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

Participants with at least one non-missing presence for a specific endpoint will be included in the analysis.

The time period will be categorized into and displayed as 1-4 days, 5-8 days for each injection.

3.2.2.1.5 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 3.2.2.1.1. It corresponds to the number of days with daily intensities of Grade 1, Grade 2, or Grade 3. Number of days of presence on the solicited period with a specified intensity may also be derived.

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.

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.

3.2.2.1.6 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 presence is derived from the daily intensities and the end date of the reaction after the end of the solicited period. The overall number of days of presence is:

(End date - last vaccination date) + (number of days of presence within the solicited period) - length of the solicited period + 1

If the end date is missing or incomplete (contains missing data), the overall number of days of presence will be considered as Missing.

Main analysis will be applied by overall number of days of occurrence. 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.

3.2.2.1.7 Ongoing

Ongoing is derived from the last daily intensity of the solicited period computed as described in Section 3.2.2.1.1 and the maximum intensity on 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).

3.2.2.2 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.

3.2.2.2.1 Presence

An observation will be considered an event if it has at least a verbatim term and is not a Grade 0 intensity event.

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

3.2.2.2.2 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:

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 field, 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.

3.2.2.2.3 Intensity

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

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

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

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.

3.2.2.2.4 Last Vaccination

Last vaccination before an unsolicited AE is derived from the start date of the unsolicited AE provided in the CRF 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.

3.2.2.2.5 Duration

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

Duration = (End date of unsolicited AE - start date of unsolicited AE + 1).

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

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.

3.2.2.3 Serious Adverse Event (SAE)

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:

- 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 (ie, V01 to V06 or D202 if V06 is not performed)

- During the planned analysis follow-up period (ie, the cutoff date will correspond to the date of any planned analysis including periodic DSMB analysis, interim analysis and final analysis)
- During the entire study (ie, all SAEs occurred until the end of the trial including the period after claiming success from primary objective)

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

3.2.2.4 Adverse Events of Special Interest (AESI)

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:

- 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 (ie, V01 to V06 or D202 if V06 is not performed)
- During the planned analysis follow-up period (i.e. the cutoff date will be the date of any planned analysis including periodic DSMB analysis, interim efficacy and final analysis)
- During the entire study (ie, all AESIs occurred until the end of the trial including the period after claiming success from primary objective)

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

3.2.2.5 Medically-Attended Adverse Event (MAAE)

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:

- 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 (ie, V01 to V06 or D202 if V06 is not performed)
- During the planned analysis follow-up period (i.e. the cutoff date will be the date of any planned analysis including periodic DSMB analysis, interim efficacy and final analysis)
- During the entire study (ie, all MAAEs occurred until the end of the trial including the period after claiming success from primary objective)

Note: MAAEs with date of onset before first vaccination (negative time of onset) will not be included in analysis but will be listed separately.

3.2.2.6 Virologically-Confirmed SARS-CoV-2 Infections and/or Symptomatic COVID-19

This safety endpoint is defined similarly as virologically-confirmed SARS-CoV-2 infections presented in Section 3.2.1.1.2 (with or without symptoms) but regardless of adjudication. Any event identified as positive either from protocol defined tests or tests not defined within protocol (COVID local test) will be included in the analysis (the positive test cases from either the protocol defined testing or CRF including COVID local test page).

Main safety analysis will include those virologically-confirmed SARS-CoV-2 infections with start date before a participant received a non-study authorized/approved COVID-19 vaccine if applicable. All virologically-confirmed SARS-CoV-2 infections with start date reported in participants after the receipt of an authorized/approved COVID-19 vaccine will be listed separately.

3.2.2.7 Severity of symptoms associated with symptomatic COVID-19 episode

The severity of symptoms is determined by the intensities collected daily for each symptom corresponding to a single CLI. Multiple derived endpoints are defined as follows and will be derived from data collected from CRF:

Intensity of a symptom: The intensity is collected as Grade 1, Grade 2 or missing for Anosmia and Ageusia. For all other symptoms collected, the intensity is Grade 1, Grade 2, Grade 3 or missing. Missing intensity will not be imputed and will be presented as missing.

Maximum intensity of a symptom is defined as the maximum intensity of the corresponding symptom related to a single CLI.

Maximum intensity of any symptom is defined as the highest value of Maximum intensity of any of the symptoms related to a single CLI.

Presence of a symptom is defined as symptoms recorded with at least Grade 1 (or missing) intensity for at least 1 day related to a single CLI.

Number of symptoms counts all symptoms presented related to a single CLI with certain intensity or any intensity based on different calculations. The categories analyzed are 1-3 symptoms, 4-6 symptoms, 7-9 symptoms and >=10 symptoms.

Duration of a symptom
Duration of a symptom counts the total number of days with at least Grade 1 (or missing) related to a single CLI regardless of the continuous or intermittent symptoms.

Maximum duration of any symptom: The longest duration of a symptom among all symptoms for each single CLI. The maximum duration of any symptom will be analyzed with categories of 1-3 days, 4-6 days, 7-9 days, 10-30 days and 30 days or more. Missing end of day (or a symptom

ongoing at the end of the study) of a symptom will not be imputed and the last day of the corresponding symptom collection will be used as the stop date of the symptom.

Duration of a CLI: Last date of the last symptom - First date of the first symptom corresponding to a single CLI. Please go to Section 3.2.1.1.1 for the details of CLI definition.

3.2.2.8 The 1000 Person-years at Risk

The 1000 person-years at risk for safety analysis will be calculated for each analysis period and for each definition of safety endpoints independently (as listed below) in SafAS (Section 0).

Safety analysis based on 1000 person-years is applied to:

- SAEs, AESIs, MAAEs
- Virologically-confirmed SARS-CoV-2 infections and/or symptomatic COVID-19
- Hospitalized COVID-19
- Severe COVID-19
- COVID-19 severity scale
- Death associated with COVID-19

And the 1000 person-years will only be applied to longer duration of analysis period such as the 6 months follow-up period, from D01 to any planned analysis with a cut-off date (if applicable) and during the entire study period.

The calculation of 1000 person-years at risk are the addition of the person-years at risk for each participant which is calculated as below regardless of the participants with an event or without an event:

(Censoring date of safety analysis – start date of an analysis period +1) / (365.25 * 1000)

The censoring date of safety analysis for each participant is defined as:

Minimum (death, withdrawal by subject, loss to follow-up, vaccination date of non-study COVID-19 vaccine, subject unblinding date, study analysis cutoff date, study end date).

3.2.2.9 Other Safety Endpoints

3.2.2.9.1 Pregnancy

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

3.2.2.9.2 Action Taken

Solicited injection site/systemic reactions and unsolicited AEs after any vaccine injection(s) will be summarized, by action taken (none, medication, health care provider contacts and hospitalized).

3.2.2.9.3 Seriousness

This information will be summarized as collected in SAEs (listed as below). No derivation or imputation will be done.

- Congenital anomaly or birth defect
- Significant disability
- Death
- Hospitalization
- Life threatening
- Other medically important event

3.2.2.9.4 Outcome

This information will be summarized in unsolicited AEs as collected (listed as below). No derivation or imputation will be done.

- Recovered or resolved
- Recovered or resolved with sequalae
- Recovering or resolving
- Not recovered or not resolved
- Fatal
- Unknown

3.2.2.9.5 Causality

This information will be summarized as collected in unsolicited AEs. Missing causality (relationship to investigational product) will be handled as described in Section 4.3.1.2.

3.2.2.9.6 AEs Leading to Study Discontinuation

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

In general, the items that are counted are:

- For participant disposition: if participant did not complete the study due to AE as recorded in Completion at End of Study form
- For safety overview: if participant 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 AEs leading to study discontinuation by system organ class (SOC) / PT: A solicited AE that has "Caused Study Termination" checked and is at least Grade 1 or an unsolicited AE that has "Caused Study Discontinuation" checked and is at least Grade 1 or missing. Any AE included in this analysis should be within the time period indicated.

3.2.3 Immunogenicity

3.2.3.1 Computed Values for Analysis

In order to appropriately manage extreme values (< lower limit of quantification (LLOQ) or > Upper limit of quantification (ULOQ) if applicable), 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 virus neutralization assay at USG, LLOQ is 40 and no ULOQ.

For SARS-CoV-2 neutralizing antibody assay at SP (GCI lab), LLOQ is 10 and ULOQ is 10240 with unit of 1/dil.

For SARS-CoV-2 spike protein antibody serum IgG ELISA (Nexelis), LLOQ is 18.9, no ULOQ.

3.2.3.2 Fold-rise

The derived endpoint fold-rise is driven by both pre-vaccination and post-vaccination computed values as described in Section 3.2.3.1 and is computed as individual titer ratio:

- Post-vaccination value divided by pre-vaccination value.

Note: If any of the pre-vaccination or post-vaccination values is missing, then fold-rise is missing for the corresponding timepoint(s).

3.2.3.3 Responders

The responder's endpoint is determined by both baseline and post-baseline computed values with detectable 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 (D22, D43, D202, D387)

- Baseline computed values >= LLOQ and <ULOQ with a 4-fold increase in post-baseline titers at each pre-defined timepoint (D22, D43, D202, D387).
- 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.

3.2.3.4 Seroresponse

Seroresponse is defined as a 4-fold or greater rise in serum neutralization titer [pre/post] at D43 relative to D01.

3.2.4 Other Variables

3.2.4.1 Age

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 59 years" means from the day of the 18th birthday to the day before the 60th birthday.
- "≥ 60 years" means from the day of the 60th birthday.
- "18 to 25 years" means from the day of the 18th birthday to the day before the 25th birthday.

All 3 age groups may be applied for safety, efficacy, and immunogenicity subgroup analysis.

3.2.4.2 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.

High-Risk Medical Conditions Group

- Yes: at least one high-risk medical conditions as defined in the protocol present. Participants who are current or former 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 in the protocol present. Participants who are or never smoked (neither tobacco use nor electronic cigarette use) will be considered as not in high-risk medical conditions group.

3.2.4.3 Duration of the Study

The duration of the study is defined as the number of days from the first day of first participant to the last day of the last contact of all participants. It is computed in days as follows:

Maximum (latest date of Visit, Termination date, Vaccination date out of the protocol, 12 Month Post-dose 2 follow-up end date, study cutoff date/end date) – minimum (date of V01) +1.

The termination date is collected in the end of study page from CRF including reasons of withdrawal by subject, discontinuation due to AE, discontinuation due to a protocol deviation, loss to follow-up.

3.2.4.4 Subject Duration

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

Maximum (Visit dates, Termination date, Non-study COVID-19 vaccine injection date, 12 Month Post-dose 2 follow-up end date, study cutoff date/end date) - V01 date + 1.

The termination date is collected in the end of study page from CRF.

4 Statistical Methods and Determination of Sample Size

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

The results of the statistical analysis will be available in the final clinical study report (CSR). For descriptive purposes, the following statistics will be presented:

Table 3. Descriptive statistics produced

Baseline characteristics and follow-up description	**Categorical data**	Number of participants. Percentage of participants.
	Continuous data	Mean, standard deviation, quartiles, minimum, and maximum.
Efficacy results	**Categorical data**	Efficacy endpoints without person-years data available: Number and percentage (95% CIs) of participants with events, vaccine efficacy (VE) and 95% CIs. Efficacy endpoints with person-years data available: Number of participants with events and incidence rates (by person-years) with 95% CIs, vaccine efficacy (VE) and 95% CIs.

		Viral Burden: percent of participants with positive results and 95% CI.
	Continuous data	Duration of endpoints: summary statistics (min, max, mean, median, Q1, Q3), difference of mean days with 95% CIs. Viral Copies/ml: Mean, standard deviation, median, quartiles, minimum, and maximum.
	Time-to-event data	Efficacy endpoints with time-to-event data available: Survival function with 95% CI. Graphical representation by Kaplan–Meier curves.
Clinical safety results	**Categorical data**	Solicited: Number and percentage (95% confidence intervals (CIs)) of participants. Unsolicited AEs, Immediate unsolicited AEs, Severity of symptoms with symptomatic COVID-19 episode: Number and percentage (95% CIs) of participants, and number of events. SAEs, AESIs, MAAEs, Virologically-confirmed SARS-CoV-2 infections and/or symptomatic COVID-19, Hospitalized COVID-19, severe COVID-19, Death associated with COVID-19, COVID-19 in each severity scale on the 7-point ordinal scale: Number of participants and percentages with 95% CI, number of subjects with at least one event with incidence rates (by number of events and person-years) with 95% CI.
Immunogenicity results	**Categorical data**	Responders, fold-rise, titers >=cutoff values: Number and percentage (95% CIs) of participants.
	Continuous data	Titers/Concentrations: Log10: Mean and standard deviation. Anti-Log10 (work on Log10 distribution, and anti-Log10 applied): Geometric mean, 95% CI of the geometric mean, quartiles, minimum, and maximum. Graphical representation by Reverse Cumulative Distribution Curve (RCDC).

The CI for the single proportion will be calculated using the exact binomial method (Clopper-Pearson method, quoted by Newcombe (4), i.e., using the inverse of the beta integral with SAS®. The CI for incidence rate (by person-years) will be calculated using the Poisson method.

The CI of VE will be derived by exact binomial method assuming the number of cases in vaccine group follows a binomial distribution conditional on the total number of cases in both groups, taking into account the ratio of person-year between groups.

The CI of survival probabilities is based on the Greenwood formula (5).

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

4.1 Analysis Sets

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

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

SARS-CoV-2 Non-Naïve at second injection (Non-Naïve -D01/D22)	• Positive by the anti-S immunoassay (Roche Elecsys) on D01 serum sample OR • Positive by the anti-N immunoassay on D01 or D22 serum samples OR • Positive NAAT for SARS-CoV-2 on respiratory samples collected on D01 or D22

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

Population	Description
Screened	All participants screened for potential study enrollment will be included regardless of being enrolled or not being enrolled. The screening includes the SARS-CoV-2 rapid serodiagnosis test results, demographic information (age, ethnic/racial population, high-risk medical conditions), and inclusion/exclusion criteria. The participants reaching the enrollment cap identified in IRT will be excluded from the study enrollment and will have no participant ID assigned.
Randomized	All participants with a randomized group that has been allocated by IRT
Safety Analysis Set (SafAS)	All randomized participants who have received at least one dose of the study vaccine or placebo. For safety analysis, all participants will have their safety analyzed after each dose according to the vaccine they actually received, and after any dose according to the vaccine received at the first dose. For harm monitoring, analysis on SafAS will be described in detail in Section 4.4.3. Safety data recorded for participants not administered a study intervention will be excluded from the analysis (and listed separately).
Reactogenicity safety analysis subset (RSafAS)	Subset of the SafAS and comprising all participants who receive at least one study injection and are randomized into the reactogenicity subset.
Modified full analysis set post-dose 2 (mFAS-PD2)	All randomized participants who receive at least one study injection excluding: • Participants who did not complete the vaccination schedule (2 injections) • Participants with onset of symptomatic COVID-19 episode between the date of the first injection and before 14 days after the second injection

	• Participant received the second injection despite meeting any of the definitive contraindication criteria • Participant discontinued from study before 14 days after the second injection Participants will be analyzed according to the intervention to which they were randomized.
Immunogenicity analysis set (IAS)	All randomized participants assigned to the Random Immunogenicity Subcohort (either allocation at enrollment OR supplemental selection after enrollment [details see below]). Participants not compliant with the protocol will be excluded from IAS: • Participants who did not complete the vaccination schedule (2 doses) • Participant did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria • Participant received a vaccine / placebo other than the one that he / she was randomized to receive • Preparation and / or administration of vaccine was not done as per-protocol • Participant did not receive vaccine / placebo in the protocol-defined time window • Participants who did not collect D43 blood sample • Participant received the second injection despite meeting any of the definitive contraindication criteria • Participant receives an authorized/approved COVID-19 vaccine prior to D43 The definition may be complemented with additional criteria for exclusion after the review of protocol deviations reported on site.

The following analysis sets are defined and will be applied for crossover phase receiving primary vaccine series among initial placebo recipients at each stage:

Crossover-Safety Analysis Set (CR-SafAS)	All participants who have received at least one dose of CoV2 preS dTM-AS03 vaccine during crossover study phase. All participants will have their safety analyzed after each dose, and after any dose. Safety data recorded from participants not administered CoV2 preS dTM-AS03 vaccines will be excluded from the analysis (only listed separately).
Crossover - Immunogenicity Analysis Set (CR-IAS)	All randomized participants assigned to the Random Immunogenicity Subcohort (either allocation at enrollment OR supplemental selection after enrollment). Participants not compliant with the protocol will be excluded from CR-IAS: • Participants who did not complete the primary series vaccination schedule (CoV2 preS dTM-AS03 vaccine or external approved vaccine)

	• Preparation and / or administration of vaccine was not done as per-protocol (only for CoV2 preS dTM-AS03 vaccine) • Participant did not receive vaccine in the protocol-defined time window (only for CoV2 preS dTM-AS03 vaccine) • Participants who did not collect any blood sample post primary series and before Booster • Participant received the second injection despite meeting any of the definitive contraindication criteria (only for CoV2 preS dTM-AS03 vaccine) The definition may be complemented with additional criteria for exclusion after the review of protocol deviations reported on site.

The following analysis sets are defined and will be applied for booster phase at each stage:

Booster - Safety Analysis Set (BS-SafAS)	All participants who have received one dose of CoV2 preS dTM-AS03 vaccine during booster study phase.
Booster - Modified Full Analysis Set (BS-mFAS)	Subset of the BS-SafAS excluding: • Participants with onset of symptomatic COVID-19 episode between the date of the booster injection and 14 days after the booster injection • Participant discontinued from study before 14 days after the booster injection • Participant received the booster injection despite meeting any of the definitive contraindication criteria
Booster - Immunogenicity Analysis Set (BS-IAS)	All participants assigned to the Random Immunogenicity Subcohort (either allocation at enrollment OR supplemental selection after enrollment). Participants not compliant with the protocol will be excluded from BS-IAS: • Participants who did not receive one dose of CoV2 preS dTM-AS03 vaccine during booster study phase. • Preparation and / or administration of the booster vaccine was not done as per-protocol • Participant did not receive booster vaccine in the protocol-defined time window • Participants who did not collect any blood sample after the booster • Participant received the booster injection despite meeting any of the definitive contraindication criteria The definition may be complemented with additional criteria for exclusion after the review of protocol deviations reported on site.

4.1.1 Populations Used in Analyses

Analysis populations used for each individual objective are indicated in Section 4.2. A summary table is provided in Table 6 in Appendix 1.

4.2 Statistical Methods

All statistical analysis described in this section will be applied for each stage based on the same methodology independently, unless otherwise specified. No formal multiplicity adjustment will be done in the statistical analysis of vaccine efficacy between the 2 stages. The analysis for each vaccine will be conducted against placebo controls enrolled contemporaneously.
A table of the objectives, endpoints, statistical methodologies, and population used is summarized in Appendix 1.

USG COVID-19 vaccine efficacy trial marker SAP is developed to mainly address the correlates analysis related to trials immunogenicity markers. Supplementary SAP will be developed to address some exploratory objectives which will be conducted after the primary analysis.

4.2.1 Hypotheses and Statistical Methods for Primary Objectives

4.2.1.1 Hypotheses and VE estimation

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

Primary objective

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

H0: VE $\leqslant$ 30%

HA: VE > 30%

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

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

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

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

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

Let $q = \frac{C_V}{C_V+C_P}$ represent the proportion of cases belonging to vaccine group among the total number of cases, and let $\theta = \frac{E(C_V)}{E(C_V)+E(C_P)} = \frac{1-VE}{1-VE+PY_P/PY_V}$. Given the total number of cases, C_V

has a binomial distribution (C_V+C_P, θ). Thus, a CI for θ may be constructed using the exact Clopper-Pearson method for binomial proportions (exact method) (10).

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

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

which is a strictly decreasing function of q.

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

When IRR is not applicable, the point estimate of VE is based on relative risk (RR) of COVID-19 case occurrence shown below:

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

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

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

The CI of VE by RR is calculated with the same method as described above for the CI of VE by IRR by replacing the 1000 person-years to number of participants in the denominators, respectively.

For participants experiencing multiple events of symptomatic COVID-19 during the duration of the study, the first event will be counted for the analyses of VE of the primary efficacy endpoint.

Hypothesis testing for primary efficacy objective is only applied for VE estimated by IRR.

4.2.1.2 Statistical Methods

4.2.1.2.1 Efficacy

Hypothesis Testing based on Incidence Rate

The hypothesis testing against symptomatic COVID-19 will be based on the estimation of VE by IRR (Formula 1) with adjusted CI applied. The detailed alpha adjustment will be described in Interim analysis plan (Section 4.4).

The primary analysis will be conducted in the mFAS-PD2 Naïve-D01+D22 analysis set for Stage 1 and in the mFAS-PD2 analysis set for Stage 2 to conclude on demonstration of the primary objective.

Survival Analysis

Kaplan-Meier curves will be applied with 95% CI calculated by Greenwood formula.

Survival analysis will be conducted in the mFAS-PD2 Naïve-D01+D22 analysis set for Stage 1 and in the mFAS-PD2 analysis set for Stage 2.

In case of the primary endpoint (symptomatic COVID-19) with less than 20 events in the corresponding population, the Kaplan-Meier curves will not be produced.

Supplementary Analysis 1 for Multiple Events

Number of participants experiencing only one, two, three, …, events of symptomatic COVID-19 will be counted, respectively, by treatment group (vaccine, placebo, vaccine + placebo).

Among participants experiencing multiple (>=2) events, the variant distribution will be summarized by treatment group, e.g., number of participants experiencing Omicron (BA.1.16) and Omicron (BA.4.1).

Summary statistics (mean, SD, median, min, max) of the time interval (in days) between two consecutive events (e.g., from the first event to the second event) will also be presented by treatment group.

This analysis will be conducted in the mFAS-PD2 Naïve-D01+D22 analysis set for Stage 1 and in the mFAS-PD2 analysis set for Stage 2. Additional subgroup analyses will be performed by age group (18-59 years or >=60 years).

Supplementary Analysis 2 for Sequencing Data (by Variant)

VE (by IRR) with CIs will be calculated by variant type. The VE against each variant will be calculated in two ways: 1) the first case tested out by each variant will be counted; 2) the first variant tested out will be counted (may not be the first case).

Kaplan-Meier curves will be applied with 95% CI calculated by Greenwood formula.

This analysis will be conducted in the mFAS-PD2 Naïve-D01+D22 analysis set for Stage 1 and in the mFAS-PD2 analysis set for Stage 2. Additional subgroup analyses will be performed by age group (18-59 years or >=60 years).

4.2.1.2.2 Safety

All safety endpoints will be described for each vaccine group with the statistics as presented in Table 3. The corresponding 95% CIs for incidence rates will be calculated based on the Poisson method, and 95% CI for percentages or proportions will be calculated based on Clopper-Pearson method. Number of subjects with at least one event per 1000 person years will be provided for SAEs, AESIs, MAAEs and endpoints related to SARS-CoV-2 infection and/or symptomatic COVID. The analysis period using person-years will be applied to any planned analysis with a

study cut-off date, up to the 6 month follow-up (if applicable) and throughout the trial (Section 3.2.2.8).

This analysis to calculate incidence rate of events using person-time as a denominator for the safety endpoints listed above will be complementary analysis to the primary safety analysis using cumulative frequency. This analysis is planned as participants in this study are given the option of unblinding to receive approved/authorized COVID-19 vaccines during the conduct of the study. In this situation, it is possible that the safety follow-up of the placebo group may be shorter than the one of the vaccine groups. In this situation we believe that the duration of follow-up should be integrated in the presentation of the safety data, i.e. using the person-time denominator to calculate the incidence rate of the events in addition to the cumulative frequency analysis (number of events with the number of participants as the denominator). This minimizes the likelihood of biased assessment given the potential for shorter duration of follow-up for the participants in the placebo group.

RSafAS will be used for safety analyses for the following endpoints:

- Presence, time of onset, number of days of occurrence, intensity, action taken, and whether the reaction led to early termination from the study, of solicited (pre-listed in the participant's DC/eDC and CRF) injection site reactions and systemic reactions occurring up to 7 days after each vaccination.
- Presence, nature (Medical Dictionary for Regulatory Activities [MedDRA] system organ class [SOC] and preferred term [PT]), time of onset, duration, intensity, relationship to vaccination and whether the event led to early termination from the study of non-serious unsolicited AEs reported up to 21 days after last vaccination.

SafAS will be used for the safety analysis for the following endpoints:

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

In addition to the analysis above, subgroup analyses (only for the safety overview table) will be performed by age group (18-59 years or >=60 years), high-risk medical condition group (Yes or No), prior SARS-CoV-2 infection status (Naïve-D01 or Non-Naïve-D01), combination of age group and high-risk medical condition, and combination of age group and prior SARS-CoV-2 infection status.

4.2.2 Hypotheses and Statistical Methods for Secondary Objective(s)

4.2.2.1 Hypotheses and VE Estimation

The following hypotheses will be tested for the key secondary efficacy objectives (secondary efficacy objective #1):

H_0: VE $\leq$ 0%

H_A: VE > 0%

The VE of severe COVID-19 is computed by IRR (Formula 1) and CI by exact binomial method (Section 4.2.1.1).

The VE of SARS-CoV-2 infection is computed by RR (Formula 2) and CI by exact binomial method (Section 4.2.1.1). It is proposed to use RR for evaluating SARS-CoV-2 infection as the ascertainment of serological infection using blood samples collected at serial intervals does not enable robust assessments of person-time at risk for each individual.

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

- The primary objective is demonstrated
- 22 severe cases and 162 infections are collected

The criteria of 22 severe COVID-19 and 162 SARS-CoV-2 infections are calculated based on 80% of power with assumed VEs (80% for VE against severe COVID-19 and 40% for VE against SARS-CoV-2 infection) and one-side alpha 0.0125.

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

If either criterion is not met, hypothesis testing for the key secondary endpoints will be performed with final data available in comparison to a placebo control, (i.e., at the time of the analysis with data prior to the cross-over) if at least a minimum of 11 severe events or 70 infections are collected. In this case, if only the minimum number of events are met for only one of the key secondary endpoints, the corresponding hypothesis testing will be performed without alpha splitting. If the minimum numbers of events are met for both key secondary endpoints, the Holm's procedure will be applied for the testing of the 2 key secondary endpoints.

For planning of situation that not meeting the number of planned number of cases upon the availability of final data described above, a base case is planned for the minimum numbers of severe COVID-19 (11) and SARS-CoV-2 infections (70), which are calculated based on at least 70% of power and assumed VEs (90% for VE against severe COVID-19 and 50% for VE against SARS-CoV-2 infection) and one-side alpha 0.0125.

4.2.2.2 Statistical Methods

4.2.2.2.1 Efficacy

Secondary Efficacy Objective #1:

Hypothesis Testing for Both Key Secondary Endpoints in Objective #1 and #2

In the context of the pandemic, prevention of SARS-CoV-2 infection is considered a key secondary endpoint given the high proportion of asymptomatic infections (30% to 50%) and the evidence of asymptomatic and presymptomatic transmission. Prevention of infection will result in prevention of illness and can also contribute to pandemic control by decreasing transmission of infection. Severe COVID-19 illness represents an endpoint associated with high individual and public health burden as well as high burden for the healthcare system. Both are defined as key secondary endpoints which are more critical so hypothesis testing with control of family-wise error rate (FWER) will be applied.

Hypothesis testing for the key secondary objectives in the SARS-CoV-2 naïve participants will be performed for the SARS-CoV-2 infection endpoint and severe COVID-19 occurring >=14 days after the second vaccination. The hypothesis tests for the two key secondary endpoints is conditional on the success of the primary endpoint compared to a LB of 0% as described in the Section 4.2.2.1. The success criteria align the statistical considerations of regulatory guidance on the development and of vaccines to prevent COVID-19.

To control the FWER of the hypothesis tests of the entire study conclusion, we have two steps to control alpha. Conditional on the success of primary objective, gate-keeping method is applied to move two-sided alpha of 0.05 to the key secondary endpoints. Within the two key secondary objectives, the Holms procedure [12] is applied. The testing procedure are based on the p-values of the two hypothesis tests and will start from the smaller p-value. If the smaller p-value demonstrates efficacy compared to 0.025 (equivalent to using a 2-sided 97.5% CI with the LB compared to 0%) then the other p-value will be compared to 0.05 to assess efficacy (equivalent to the 2-sided 95% CI with the LB compared to 0%).

For Stage 1, the hypothesis testing and corresponding conclusions against each of the secondary endpoints will be made in mFAS-PD2 Naïve-D01+D22 analysis set. For Stage 2, the hypothesis testing and corresponding conclusions against the SARS-COV-2 infection endpoint and the severe COVID-19 endpoint will be made in mFAS-PD2 Naïve-D01+D22 and mFAS-PD2 analysis sets, respectively.

Survival Analysis for Severe COVID-19 in Objective #1 and #2

Survival analysis will be applied as an additional analysis for the severe COVID -19 only. The methods are the same as those described in primary objective (Kaplan-Meier curves).

Survival analysis will be conducted in the mFAS-PD2 Naïve-D01+D22 analysis set for Stage 1, and mFAS-PD2 analysis set for Stage 2.

Supplementary Analysis 1 for Multiple Events for Objective #2 (Stage 2 only)

This analysis will be conducted for the SARS-COV-2 infection endpoint and the severe COVID-19 endpoint in mFAS-PD2 Naïve-D01+D22 and mFAS-PD2 analysis sets, respectively, with the same summary statistics produced for the primary efficacy endpoint. Additional subgroup analyses will be performed by age group (18-59 years or >=60 years).

Supplementary Analysis 2 for Sequencing Data (by Variant) for Objective #2 (Stage 2 only)

This analysis will be conducted for the SARS-COV-2 infection endpoint and the severe COVID-19 endpoint in mFAS-PD2 Naïve-D01+D22 and mFAS-PD2 analysis sets, respectively, using the same methods (VE calculations and Kaplan-Meier curves) for the primary efficacy endpoint. Additional subgroup analyses will be performed by age group (18-59 years or >=60 years).

Secondary Efficacy Objective #3, #4, #5, #7, and #10:

To evaluate the secondary objectives of prevention of occurrence of events, the point estimates of VE with CIs (by an exact method) will be calculated against each of the defined secondary endpoints in the vaccine group versus the placebo group.
For those endpoints with person-years available (see Section 3.2.1.2), the point estimate of VE will be calculated by IRR (Formula 1) with 95% CI. Kaplan-Meier curves with 95% CI will be applied for severe COVID-19. In case of less than 20 events in a corresponding population, the Kaplan-Meier curves will not be produced.

For those endpoints without person-years available, the point estimate of VE will be calculated by RR (Formula 2). Details of the related endpoints are defined in Section 3.2.1.2.

For the objective #3, mFAS-PD2 will be used. Subgroup analyses will also be performed by age group (18-59 years or >=60 years).

For the objective #4, mFAS-PD2 Non-Naïve-D01/D22 will be used. Subgroup analyses will also be performed by age group (18-59 years or >=60 years). Supplementary analyses for multiple events and sequencing data (by variant) will be conducted for the two endpoints (symptomatic COVID-19 and severe COVID-19), respectively, using the same methods for the primary efficacy endpoint. For these two supplementary analyses, subgroup analyses will also be performed by age group (18-59 years or >=60 years).

For the objective #5 and #10, mFAS-PD2 Naïve-D01+D22 will be used. For the objective #5 (endpoint – asymptomatic SARS-CoV-2 infection), only descriptive numbers will be presented (no VE calculation). For the objective #10, subgroup analyses will be performed for age group (18-59 years or >=60 years).

For the objective #7, mFAS-PD2 Naïve-D01+D22 and mFAS-PD2 Non-Naïve at D01/D22 analysis sets will be used. For hospitalized COVID-19, VE (with CIs) will be calculated, and subgroup analyses will be performed for age group (18-59 years or >=60 years). For the other two endpoints (CDC-defined COVID-19 and symptomatic COVID-19 with severity of moderate COVID-19 or worse), only descriptive numbers will be presented (no VE calculation).

Secondary Efficacy Objective #6:

Viral copies/ml will be described for each time point when respiratory samples are collected during a symptomatic COVID-19 episode with summary statistics (min, max, mean, median, Q1, Q3) by trial intervention groups. The 95% CI of mean value of viral copies assuming the log10 transformation of values follows Normal distribution. Percentage of participants with positive viral copies will be calculated for each time point by trial intervention groups. Difference of percentages of participant with positive viral load above the lower limit of quantitation of the assay will also be provided. Subgroup analyses will be performed for age group (18-59 years or >=60 years).

For Stage 1, mFAS-PD2 Naïve-D01+D22 and mFAS-PD2 Non-Naïve-D01/D22 analysis sets will be used.

For Stage 2, mFAS-PD2 analysis set will be used. The analyses performed per naïve status (on mFAS-PD2 Naïve-D01+D22 and mFAS-PD2 Non-Naïve-D01/D22 analysis sets, separately) will be only conducted if there are no less than 15% naïve participants enrolled in Stage 2.

Secondary Efficacy Objective #8 and #9:

To assess the durability of VE over time against occurrence of events, point estimates of VE with 95% CI will be described (same method stated in objective #3, #4) for different time periods (eg, events occurring every 3 months: within 3 months, 4-6 months, 7-9 months, and over 9 months based on data availability; and events occurring every 6 months: within 6 months, 7-12 months depending on the availability of the data). Details of time to event and person-years at risk are described in Section 3.2.1.2 and Section 3.2.1.3.

For the objective #8, mFAS-PD2 Naïve-D01+D22 analysis set will be used. Only descriptive numbers will be presented (no VE calculations).

For objective #9, mFAS-PD2, mFAS-PD2 Naïve-D01+D22, and mFAS-PD2 Non-Naïve at D01/D22 analysis sets will be used. Analyses per Naïve status will be conducted only if there are 15% naïve participants enrolled. Subgroup analyses will be performed for age group (18-59 years or >=60 years). For CDC-defined COVID-19, only descriptive numbers will be presented (no VE calculation).

4.2.2.2.2 Immunogenicity

Secondary Immunogenicity Objectives (Stage 1 and Stage 2) #1 to #5:

Immunogenicity results will be described for each vaccine or placebo group with the statistics as presented in Table 3.

The percentage of participants defined as responders, participants with 2-fold rise (2FR), 4-fold rise (4FR) and concentrations ≥ 2x LLOQ or ≥ 4 x LLOQ (for binding antibodies by ELISA only) will be provided against each endpoint with the corresponding 95% CIs using the Clopper-Pearson method. Geometric mean titers (GMTs) or geometric mean value of concentrations (GMCs) will be summarized along with their 95% CIs using the normal approximation of log-transformed titers/concentrations. Geometric mean titer ratios (GMTRs) or geometric mean concentration ratios (GMCRs) are defined as geometric mean of individual titers/concentration ratios (post-vaccination/pre-vaccination for each injection) for each strain. GMTR/GMCRs will

be summarized with 95% CI (Normal approximation) for any post-dose values compared to D01 or D22. The ratios of GMTs/GMCs will be obtained between groups with the two-sided 95% CIs calculated using normal approximation of log-transformed titers/concentrations. The differences in the responder rates, 2FRs, 4FRs between groups will be computed along with the two-sided 95% CIs by the Wilson-Score method without continuity correction (11).

Reverse cumulative distribution curves (RCDC) will be generated for baseline (D01) and post-vaccination immunogenicity.

Secondary objective #1, #2, #3 and #5 will be conducted in IAS Naïve-D01 and IAS Non-Naïve-D01.

Secondary objective #4 will be conducted in IAS, IAS Naïve-D01 and IAS Non-Naïve-D01.

For secondary objective #1 to #4, subgroup analyses will be performed by age group (18-59 years or >=60 years) for main immunogenicity analyses.

Main immunogenicity analyses will be performed in those BL collected on or before receiving a non-study authorized/approved COVID-19 vaccine. Other immunogenicity results will be listed separately.

Secondary Immunogenicity Objectives (Crossover / Booster):

For objectives post-Crossover / Booster, analyses will be conducted in the CR-IAS and BS-IAS, with the same methods described above for immunogenicity analyses for neutralizing antibody.

Main immunogenicity analyses will be performed in those BL collected on or before receiving a non-study authorized/approved COVID-19 vaccine. Subgroup analyses will be performed for age group (18-59 years or >=60 years), serostatus (positive or negative by the anti-N immunoassay) at Crossover / Booster, and combination of age group and serostatus.

4.2.2.2.3 Safety

All secondary safety endpoints will be described by percentages with 95% CI (by Clopper-Pearson methods). Analysis will also be provided by number of subjects with at least one event per 1000 person-years for all endpoints except for the severity of symptoms. Subgroup analyses will be performed by age group (18-59 years or >=60 years) for Secondary Safety Objective #1 (Stage 1 and Stage 2).

SafAS Non-Naïve-D01 will be utilized for the following endpoints:

- Severity of symptoms associated with symptomatic COVID-19 episode
- Occurrences of hospitalized COVID-19
- Occurrences of severe COVID-19
- Occurrences of COVID-19 in each severity scale on the 7-point ordinal scales
- Death associated with COVID-19

Percentages with 95% CI and number of subjects with at least one event per 1000 person-years against symptomatic COVID-19 will be calculated in each scale or worse of the 7-point ordinal scales.

For severity of symptoms (intensity of symptoms), percentages with 95% CI will be calculated against symptomatic COVID-19 categorized by Number of symptoms, Maximum intensity of any symptom, Maximum duration of any symptom, as well as the Duration of CLI.

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

For objectives post-Crossover / Booster, analyses will be conducted in the CR-SafAS and BS-SafAS. For the secondary safety objective #1, subgroup analysis will be performed for age group (18-59 years or >=60 years), serostatus (positive or negative by the anti-N immunoassay) at Crossover / Booster, and combination of age group and serostatus for main analysis. For the secondary safety objective #2, subgroup analysis (only for the safety overview table) will be performed for age group (18-59 years or >=60 years), serostatus (positive or negative by the anti-N immunoassay) at Crossover / Booster, high-risk medical condition (Yes or No), combination of age group and serostatus, and combination of age group and high-risk medical condition.

4.2.3 Statistical Methods for Exploratory Objectives

No hypotheses will be tested.

4.2.3.1.1 Efficacy

Exploratory Efficacy Objective (Stage 1 and Stage 2) #1, #2, #3, #4, #5:

To evaluate the exploratory objectives of prevention of occurrence of events, the point estimates of VE with CIs (by exact method) will be calculated against each of the defined exploratory endpoints in the vaccine group versus the placebo group.

To evaluate the reduction of number of days related to an event, duration of the event will be analyzed with summary statistics (min, max, mean, median, Q1, Q3) by trial intervention groups. Details of the related events are defined in Section 3.2.1.4. In addition to that, the difference of mean days between groups is calculated with 95% CI by Normal approximation.

To evaluate the reduction of severity of symptomatic COVID-19 on a 7-point ordinal scale, VE will be calculated for endpoints with each scale or worse using formula 1 with corresponding 95% CI calculated (by exact method).

Exploratory objective #1, #3 and #5, will be conducted in mFAS-PD2 Naïve-D01+D22, mFAS-PD2 Non-Naïve-D01/D22 and mFAS-PD2. The analyses performed per naïve status will be conducted only if there are no less than 15% naïve participants enrolled.

Exploratory objective #2 will be conducted in mFAS-PD2 Naïve-D01+D22. Only descriptive numbers will be presented (no VE calculation).

Exploratory objective #4 will be conducted in mFAS-PD2 Naïve-D01+D22, mFAS-PD2 Non-Naïve-D01/D22 and mFAS-PD2. Only descriptive numbers will be presented (no VE calculation).

No subgroup analyses will be conducted for exploratory efficacy objectives #1 to #5.

Exploratory Efficacy Objective (Stage 1 and Stage 2) #6, #7, #8, #9, #10:

Exploratory objective #6, #8, #9, and #10 will be conducted in mFAS-PD2 Naïve-D01+D22, mFAS-PD2 Non-Naïve-D01/D22 and mFAS-PD2, while the objective #7 will be conducted in mFAS-PD2 Naïve-D01+D22.

For exploratory objectives #6, #7, and #8, percentage and 95% CI of participants experienced each endpoint will be summarized.

For exploratory objectives #9, VE will be estimated as 1-RR among those who get symptomatic COVID-19 in study.

No subgroup analyses will be conducted for exploratory efficacy objectives #6 to #9.

For exploratory objectives #10, relative efficacy will be estimated as {1-IRR} of MV divided by {1- IRR} of BV. Subgroup analyses will be performed by age group (18-59 years or >=60 years).

Exploratory Efficacy Objective (Crossover / Booster):

Estimation and statistical methods on the observational efficacy endpoints for Crossover / Booster study will be as appropriate to the data collected.

For the exploratory efficacy objective #1, RE will be estimated as {1-IRR} of {SP primary series + MV (B.1.351)} divided by {1-IRR} of {Placebo + MV (D614) / External + MV (B.1.351)}.

For the exploratory efficacy objective #2, RE will be estimated as {1-IRR} of {SP primary series + MV (B.1.351)} divided by {1-IRR} of {Placebo + MV (D614) / External}.

For the exploratory efficacy objective #3, RE will be estimated as {1-IRR} of {MV (D614) + MV (B.1.351)} divided by {1-IRR} of {BV (D614 + B.1.351) + MV (B.1.351)}.

For the exploratory efficacy objective #4, RE will be estimated as {1-IRR} of {Placebo + MV (D614) + MV (B.1.351)} divided by {1-IRR} of {Placebo + External + MV (B.1.351)}.

For the exploratory efficacy objective #5, RE will be estimated as {1-IRR} of {SP primary series + MV (B.1.351)} divided by {1-IRR} of {Placebo + MV (D614) / External + MV (B.1.351)}.

For all exploratory efficacy objectives post-Booster, analyses will be conducted in the BS-mFAS. Subgroup analysis will be performed for age group (18-59 years or >=60 years), serostatus (positive or negative by the anti-N immunoassay) at Booster, and combination of age group and serostatus. In case of an endpoint with less than 20 events in a corresponding subgroup for both vaccine and placebo, the VE calculation will not be conducted.

4.2.3.1.2 Immunogenicity

Exploratory Immunogenicity Objective (Stage 1 and Stage 2):

The same methods described in Section 4.2.2.2.2 for immunogenicity analyses for neutralizing antibody will be applied for the exploratory immunogenicity objective #1 and #2.

Exploratory immunogenicity objective #1 and #2 will be conducted in IAS, IAS Naïve-D01 and IAS Non-Naïve-D01. Subgroup analyses will be performed by age group (18-59 years or >=60 years) for main analyses.

Exploratory Immunogenicity Objective (Crossover / Booster):

The same methods described in Section 4.2.2.2.2 for immunogenicity analyses for neutralizing antibody will be applied for the exploratory immunogenicity objective #1, #2, and #3.

Exploratory immunogenicity objective #1, #2 and #3 will be conducted in BS-IAS. Subgroup analyses will be performed by age group (18-59 years or >=60 years), serostatus (positive or negative by the anti-N immunoassay) at Booster, and combination of age group and serostatus.

For the exploratory immunogenicity objective #1, data will be summarized by MV (D614) + MV (B.1.351) / BV (D614 + B.1.351) + MV (B.1.351).

For the exploratory immunogenicity objective #2, data will be summarized by Placebo + MV (D614) + MV (B.1.351) / Placebo + External + MV (B.1.351).

For the exploratory immunogenicity objective #3, data will be summarized by SP primary series + MV (B.1.351) vs Placebo + MV (D614) / External + MV (B.1.351).

4.3 Handling of Missing Data and Outliers

4.3.1 Safety

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

In all subject listings, partial and missing data will be clearly indicated as missing.

4.3.1.1 Immediate

Unsolicited systemic AEs with a missing response to the “Immediate” field will be assumed to have not occurred within the 30-minute surveillance period.

4.3.1.2 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. Missing causality for unsolicited non-serious AEs and SAEs will be considered at the time of analysis as related to vaccination.

4.3.1.3 Measurements

Partially missing temperatures will be handled as described in Section 3.2.2.1.

4.3.1.4 Intensity

For solicited reactions, missing intensities will be handled as described in Section 3.2.2.1.1. For unsolicited non-serious AEs, missing intensities will remain missing and will not be imputed.

4.3.1.5 Start Date and Stop Date

Missing or partially missing start dates for unsolicited AEs will remain missing and not be imputed. If either the start or stop date is missing or partially missing, the time of onset will be considered to be missing.

Nevertheless, unsolicited AEs with missing time of onset will be included in analyses according to the visit collected.

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

4.3.2 Immunogenicity

No imputation of missing values and no search for outliers will be performed. LLOQ management will be performed as described in Section 3.2.3.1.

4.3.3 Efficacy

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

If a participant performed a visit but did not get BL draw (or swab collected) at a visit, or if the test results were not available or did not produce a valid result for a BL collected (swab collected), it is considered as missing data for efficacy endpoints. Based on each population applied, the participants with missing efficacy endpoints will still be included in the analysis and will not be considered as a confirmed case. As long as the participant is not considered as having an event, the participant will continue contributing to time of follow-up.

4.4 Interim / Preliminary Analysis

The monitoring plan for interim efficacy, futility and harm described in this section will be performed with data collected in each stage, respectively.

An interim analysis will be triggered with all the criteria listed below. At the interim analysis, planned analyses of efficacy, futility, and safety will be performed by an independent statistical group and evaluated by the DSMB. The database will be cleaned and locked for the interim analysis.

1) Observed cases are within the range of 40 to 55 symptomatic COVID-19 cases (from 50% to 70% data)

2) All participants enrolled have a median 2-month follow-up after 2 injections
3) Injection site and systemic reactogenicity data after the second vaccination is available on at least 50% participants assigned in the reactogenicity subset.
4) A minimum of 5 severe COVID-19 cases
5) A minimum of 3000 vaccine recipients have been followed for at least 1 month after the second vaccination for collection of safety data on MAAE, AESI and SAEs

The Sponsor, in collaboration with independent committees, as well as the study Oversight Group (OG), may decide to accelerate the interim analysis or skip the interim analysis before unblinding (eg, based on Regulatory considerations of emerging knowledge about expectations related to vaccine approval). In either case of skipping the planned interim analysis, or if the information fraction is different than planned (not within the range of 50% to 70% data), alpha splitting will be adjusted based on the Lan-DeMets O'Brien-Fleming approximation spending function approach for interim and final efficacy analysis, if applicable.
In the event that the interim analysis of the Stage 1 is reached prior to the initiation of enrollment of Stage 2, the protocol may be amended based on the recommendations of the DSMB and discussion with the regulatory authorities.

4.4.1 Monitoring for Efficacy

At either interim or final analysis for efficacy, the point estimate of vaccine efficacy and associated 2-sided CI for the primary efficacy endpoint will be provided. The confidence level of the CI is determined by the Lan-DeMets O'Brien-Fleming approximation spending function with one-sided adjusted nominal level 0.025 at corresponding information fraction at the time of analysis. The primary analysis population is the mFAS-PD2 Naïve-D01+D22 for Stage 1 and the mFAS-PD2 analysis set for Stage 2. The success criteria for demonstration of efficacy include: 1) the LB of CI is > 30%, and 2) the point estimate of VE is > 50%.

If the planned interim analysis happens with information fraction at 50%, 60% or 70% as stated above, the adjusted one-sided nominal alpha for the interim and final analysis are (0.0015, 0.0245), (0.0038, 0.0238) or (0.0074, 0.0228) for the interim and final analysis, respectively. The corresponding adjusted CIs calculated for hypothesis testing at the interim and final analysis will be (99.7%, 95.1%), (99.24%, 95.24%) or (98.52% CI, 95.44%), respectively.

The DSMB may also consider supportive data such as secondary endpoints and other key information described above, to aid for assessment of totality of safety and efficacy data at the interim analysis.

4.4.2 Monitoring for Futility

At each interim analysis, a non-binding futility analysis may be performed. Hypothesis testing is used for futility analysis at each interim based on 95% CI (one-sided unadjusted alpha 0.025):

H0: VE ≥ 50%

HA: VE < 50%

Futility or low probability of having a positive trial outcome may be concluded if the upper bound of the CI < 50%, based on the PPAS Naïve-D01+D22 for Stage 1 and PPAS for Stage 2. Bayesian predictive power (see appendix 3) to demonstrate the primary objective at the end of the trial based on observed VE at each interim may also be calculated as supportive information.

The Sponsor will carefully evaluate the DSMB recommendation and take appropriate action for the study.

4.4.3 Monitoring for Harm

Continuous monitoring for harm will be conducted by assessing the frequency of symptomatic COVID-19 cases (primary endpoint) and severe COVID-19 separately. For each endpoint, the number of cases will be examined comparing vaccine group versus placebo group as each case accrues. Once a case occurs, a one-sided conditional exact binomial test is applied as follows:

H0: $p \leq 0.5$

HA: $p > 0.5$

Where p is the binomial probability that a case participant is assigned to the vaccine group conditional on the total observed number of cases at that moment. Each test is performed at the same one-sided nominal unadjusted alpha of 0.05. The non-binding harm monitoring for symptomatic COVID-19 will start when at least 10 symptomatic COVID-19 cases are observed. The non-binding harm monitoring for severe COVID-19 will start when the first severe COVID-19 case is observed.

The population used for harm monitoring will be SafAS in all participants. Once the results of testing of the D01 samples are available to determine the participants prior SARS-CoV-2 infection status, harm monitoring will also be evaluated in the SafAS Naïve-D01 and the SafAS Non-Naive-D01 analysis sets respectively for each endpoint. Harm monitoring will be analyzed based on the following criteria in SafAS population:

- If participant only received one injection, the harm monitoring will be analyzed based on the vaccine/placebo group injected
- If participants received both injections and the dose injected are from the same group, the harm monitoring will be analyzed based on the vaccine/placebo group injected
- If participants received both injections and the dose injected are from difference groups, the harm monitoring will be analyzed based on the vaccine group injected

If a null hypothesis is rejected for any one of the endpoints in any one of the population tested (based on the availability of baseline serostatus information), the DSMB will be notified immediately of the potential harm signal and will carefully review all unblinded case information to make recommendations on study conduct.

4.4.4 Monitoring for Potential Disease Enhancement

Additional disease enhancement analysis will be conducted at the interim analysis by the evaluation of severity of symptomatic COVID-19 on the 7-point ordinal scale analysis (as stated in Section 4.2.2.2.3). The primary (including efficacy and safety) and secondary safety analyses described in Section 4.2.1.2.2 and Section 4.2.2.2.3 will be conducted as supportive information at the interim analysis.

4.5 DSMB Monitoring Plan

The Coronavirus Disease 2019 (COVID-19) Vaccine Data and Safety Monitoring Board (DSMB) established by the US National Institutes of Health, National Institute of Allergy and Infectious Diseases (NIAID) will monitor all randomized COVID-19 vaccine studies supported by the United States Government (USG), including the VAT00008 study. The primary role of the DSMB is to make certain that appropriate safeguards are in place to ensure the safety of all study participants and that the study is conducted with scientific rigor. To accomplish these goals, the DSMB will review enrollment, data completeness, and accumulating safety and outcome data on a regular basis while the study is ongoing. The DSMB will review unblinded analyses of accumulating efficacy and safety data for the study in order to assess the risk-benefit ratio of the vaccine. The DSMB will make recommendations concerning the conduct of the study.

The DSMB will be supported by an independent Statistical Support Group (SSG) that will serve as a liaison between the DSMB and the Sponsor and the study OG, and will prepare the reports for the DSMB. Blinded data will be presented in Open reports, which will be shared with the study OG and designated Protocol Team members. Unblinded data will be presented in Closed reports, only available to the DSMB members.

The DSMB will be provided data in an expedited basis as well as in a periodic basis.

4.5.1 Expedited Monitoring

Data provided in an expedited fashion will allow the DSMB to assess any potentially emerging safety issues in due diligence. These data will include the description of specified event categories at the participant level as well as the crossing of harm monitoring boundaries.

4.5.1.1 Participant-level expedited data

Data on participant level events will be provided by the study Sponsor/OG to the SSG and the SSG will then provide the information to the DSMB Executive Secretary. If the need arises, the chair of the study OG may also communicate the information to the DSMB Executive Secretary. Participant-level events triggering expedited data sharing to the DSMB include:

Fatal events (including information of death due to COVID-19)

Related SAEs

Severe COVID-19 events

COVID-19 events meeting the definition of an SAE

AESIs

4.5.1.2 Harm monitoring

The non-binding harm monitoring will be based on multiple endpoints in different populations:

- Symptomatic COVID-19 in all participants in FAS
- Severe COVID-19 in all participants in FAS
- Symptomatic COVID-19 in naïve-D01 participants in FAS
- Symptomatic COVID-19 in non-naïve-D01 participants in FAS
- Severe COVID-19 in naïve-D01 participants in FAS
- Severe COVID-19 in non-naïve-D01 participants in FAS

Harm monitoring based on all participants will be started at 10 cases for symptomatic COVID-19 and after the first severe COVID-19 case. Harm monitoring in naïve-D01 or non-naïve-D01 participants will start when naïve-D01/non-naïve-D01 status data (described in Section 4.1) becomes available and at least 10 cases for symptomatic COVID-19 or 1 case for severe COVID-19 in each of the naïve/non-naïve at D01 reached, respectively. Statistical methods are described in Section 4.4.3. The boundary to trigger an alert to inform DSMB is displayed in Appendix 2.

4.5.1.3 Criteria to trigger an alert

An alert will be triggered based on either one of the criteria:

Any event observed in the list of participant-level expedited data

Boundary is crossed for any endpoint in any population in harm monitoring

DSMB will be informed immediately if there is an alert. Detailed evaluation on unblinded safety information related to the alert will be carefully reviewed to support a suggestion to Sponsor.

4.5.2 Periodic Monitoring

Periodic data will be provided to the DSMB for the purpose of monitoring study conduct, overall safety, efficacy, and futility. Periodic monitoring for aspects related to study conduct and overall safety will occur monthly. Periodic monitoring for efficacy and efficacy futility will be triggered based on pre-specified information fractions for events corresponding to the primary endpoint of the study.

4.5.2.1 Periodic Monitoring for Study Conduct

The SSG will generate monthly reports covering various aspects related to study conduct. These reports will include the following information:

Subject Disposition (randomized, vaccinated, terminated and reason for termination)

Adherence to Study Procedures (compliance with injection visits, compliance with D01, D22 and D43 blood draw, compliance with D01 and D22 NAAT sample, compliance with NAAT sample collection in the context of COVID-19-like illness)

Participants in analysis sets (Randomized, FAS, mFAS-PD2, PPAS, reason for exclusion from per-protocol analysis set [including eligibility violations]).

Demographic characteristics (age, sex, race/ethnicity, racial/ethnic minority, high-risk medical conditions at baseline, naïve/non-naïve at D01)

4.5.2.2 Periodic Monitoring for Overall Safety

The SSG will generate monthly reports containing overall safety data. The data presented in these reports will include:

- Immediate reactions
- Solicited (injection site and systemic) reactions with intensity
- Grade 3 Unsolicited AEs (by SOC and PT)
- Related unsolicited AEs (by SOC and PT)
- AEs leading to study discontinuation
- MAAEs
- AESIs (including potential immune-mediated diseases)
- SAEs
- Pregnancies
- Summaries of COVID-19 events (Severe symptomatic COVID-19

4.5.2.3 Periodic Monitoring for Operational Futility

Monitoring for Operational Futility

The DSMB monitors the study for operational futility. The objective is to monitor the projected number of treatment arm-pooled symptomatic COVID primary endpoints by each of a set of calendar dates to aid ascertainment of whether the study is on target to meet the study objective regarding the evaluation of VE. The monitoring is done separately for Stage 1 and Stage 2, using the same approach.

The operational futility monitoring report is based on treatment-blinded data and is provided to the DSMB as well as to the Study OG and the Trial Leadership Group starting at the second data review DSMB meeting to be held in September 2021, depending on the adjudication data available. The report will include the following:

a) The enrollment rate
b) The accrual rate of symptomatic COVID-19 cases for the primary efficacy endpoint
c) The right censoring rate to date, including participants early terminated and received approved COVID-19 vaccine

d) The mean projected number of treatment arm-pooled primary symptomatic COVID-19 endpoints in the mFAS-PD2 naive D01+D22 cohort for Stage 1 and in the mFAS-PD2 cohort for Stage 2, with a Wald 95% CI for the mean by each calendar date 15 November 2021, 15 December 2021, and 15 January 2022
e) The estimated distribution of the total treatment arm-pooled number of primary symptomatic COVID-19 endpoints in the mFAS-PD2 naïve D01+D22 cohort, with corresponding power to reject H0: VE ≤ 30% using a 1-sided 0.025-level Wald test from a Cox model under the alternative hypotheses VE = 70%, 80%, and 90% by each calendar date 15 /November 2021, 15 December 2021, and 15 January 2022.

The estimation procedures in (d) and (e) above will be conducted under each of the following 3 scenarios:

1) The treatment arm-pooled symptomatic COVID-19 endpoint rate in (d) and (e) used for generating future data are based on a Bayesian model and the prior assumption that VE=70% (the design alternative)
2) The treatment arm-pooled symptomatic COVID-19 endpoint rate in (d) and (e) used for generating future data are based on a Bayesian model and the prior assumption that VE= 30% (the null hypothesis)
3) The treatment arm-pooled symptomatic COVID-19 endpoint rate in (d) and (e) used for generating future data is based on a Bayesian model and the prior assumption that the COVID-19 endpoint rate equals to the observed-to-date symptomatic COVID-19 endpoint rate.

The Bayesian model in (d) and (e) will be conditioned on the observed data to-date, more specifically, to-date data in (a), (b), and (c). Right censoring in (c) occurs due to a variety of events including early termination, unblinding for any reason and receipt authorized/approved COVID-19 vaccine.

While it is the primary responsibility of the Study OG with the Trial Leadership Group to make decisions regarding trial operations and modifications based on the monitoring of the treatment-blinded primary endpoints, given the resource issues involved, DSMB review is also needed because issues of scientific integrity are also involved. Upon request, the statisticians will provide the DSMB and the Study OG with additional information, as appropriate, for use in their consideration of whether to recommend early trial completion.

The details of the Bayesian model and projected number of COVID endpoints of this operational futility statistical analysis is available in Appendix 4. .

4.5.2.4 Periodic (Sequential) Monitoring for Efficacy and Futility

Monitoring for efficacy and futility are planned as described in Section 4.4. For the interim analysis to occur (including both efficacy and futility), conditions other than the specified range for information fraction will have to be met. If these conditions are not met at the time the upper bound of the information fraction is reached, then the interim efficacy and futility analysis will be skipped or postponed. These conditions are:

- Observed cases are within the range of 40 to 55 symptomatic COVID-19 cases (from 50% to 70% data)
- All participants enrolled have a median 2-month follow-up after 2 injections
- Injection site and systemic reactogenicity data after the second vaccination is available on at least 50% participants assigned in the reactogenicity subset
- A minimum of 5 severe COVID-19 cases
- A minimum of 3000 vaccine recipients have been followed for at least 1 month after the second vaccination for collection of safety data on MAAE, AESI and SAEs

In addition to the conditions above, the study OG may decide to skip or postpone the interim efficacy analysis for other reasons, based on Regulatory considerations at the time the specified information fraction is reached (ie, emerging knowledge about expectations related to vaccine approval, etc.). The interim non-binding futility analysis will still be conducted as planned if the conditions listed above are met but interim efficacy is skipped due to other reasons.

Once the interim efficacy analysis is skipped or postponed, the alpha will be readjusted based on the Lan-DeMets O'Brien-Fleming approximation spending function. The real information fraction based on the number of symptomatic COVID-19 events over 78 (100% information) will be used to adjust alpha.

4.5.2.5 Sequential Monitoring Criteria informing DSMB actions

The DSMB may consider recommending the presentation of unblinded data to Regulatory Authorities supporting demonstration of efficacy and associated study modifications based on the following criteria:

The LB of the alpha-adjusted CI of VE (by IRR) against symptomatic COVID-19 in mFAS-PD2 Naïve D01+D22 is >30%

AND

The point estimate of VE is >=50%

The DSMB may consider recommending the presentation of unblinded data to Regulatory Authorities supporting efficacy futility and associated study modifications based on the following criterion:
Upper bound of 95% CI (unadjusted alpha) of VE (by IRR) against symptomatic COVID-19 in PPAS Naïve D01+D22 is <50% and point estimate of VE <= 0
The DSMB may consider pausing the study for potential safety issues if a harm monitoring boundary is crossed. In addition to this criterion related to sequential harm monitoring, the DSMB may consider recommending study pause based on the details (nature, severity, frequency, etc.) associated with expedited events described in Section 4.5.1.1 upon Committee review. The DSMB can make recommendations about study modifications based on any safety outcome.

4.5.2.6 Analysis after interim efficacy or futility demonstrated

The Sponsor will prepare the Regulatory documents presenting the data generated related to interim efficacy or futility.

In the case of interim efficacy demonstration, Sponsor representatives will be unblinded in order to prepare the Regulatory file, but the study will continue per protocol. Investigators, testing laboratories, and Sponsor study staff not involved in Regulatory file preparation will remain blinded at the subject-level. Additional efficacy analyses will be conducted at later timepoints accounting for longer follow-up time inclusive of events occurring after the data cut-off point utilized for the analysis resulting in efficacy demonstration.

In the case of futility demonstration, Sponsor representatives will be unblinded in order to prepare Regulatory communications. While the study will continue monitoring for safety, the Sponsor may take additional decisions based on DSMB recommendations (unblinding of investigators or/and participants, communications to IRBs/ECs, etc.).

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

- The primary objective is demonstrated
- 22 severe cases and 162 infections are collected

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

If either criteria are not met, hypothesis testing for the key secondary endpoints will be performed with final data available in comparison to a placebo control, (ie, at the time of the analysis with data prior to the cross-over) if at least a minimum of 11 severe events or 70 infections are collected. If only one of the minimum number of events met, the corresponding hypothesis testing will be performed without alpha splitting. If both of the minimum numbers of events met, the Holm's procedure will be applied for the testing of the two key secondary endpoints.

In the event this minimum number of events are not met at the time of the analysis in comparison to a placebo control prior to the crossover, vaccine efficacy will be estimated without hypothesis testing.

4.6 Determination of Sample Size and Power Calculation

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

primary endpoint for Stage 2, including both naïve and non-naïve participants, was changed after enrollment of Stage 2 was already completed; therefore, all sample size calculations were based on a primary endpoint that considered only naïve participants. The power of primary efficacy analysis is driven by the total number of symptomatic COVID-19 events.

Assumptions for sample size calculation are listed as follows[1]:

- The LB of adjusted CI for the VE estimate is > 30% for both stages
- The expected true VE for symptomatic COVID-19 is 70%
- The one-sided type I error for each stage is 0.025 with the sample size calculated based on adjusted alpha of one-sided 0.02276 for final analysis including one interim at 70% data
- The incidence rate of symptomatic COVID-19 in Placebo is assumed as 2.25% illness rate in both stages per 2-months follow-up period
- Power = 90%

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

- Attrition rate = 25% in Stage 1 and 30% in Stage 2

The attrition rate is assumed to be higher for Stage 2 as larger parts of the population are eligible to receive vaccine. Table 3 shows the sample size for different incidence rate from 2% to 2.2.5%, with the power of 90%.

Table 4. Sample size for different incidence rate

Incidence rate	2%	2.25%	2.50%
Stage 1	11428	10160	9142
Stage 2	12244	10886	9796

For each stage, the type I error of hypothesis testing is controlled as one-sided 0.025, and the Lan-DeMets O'Brien-Fleming approximation spending function is applied to adjust for multiplicity of interim analysis for efficacy with one potential interim analysis when accrual of approximately 50%-70% of the total number of events is reached (see Section 4.4). The sample size calculated based on the adjusted final alpha of 0.02276 will ensure at least 90% power to conclude on primary objective when the interim analysis is conducted between 50% - 70% range of data. Adjusted alpha by spending function is applied and the corresponding adjusted CI will be used for

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

hypothesis testing (by exact method as described in Section 4.2) at the interim and the final analysis against symptomatic COVID-19 in each stage independently.

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

Because Omicron is the prevalent variant during case accrual for Stage 2 and the expected vaccine efficacy against Omicron is expected to be lower than the original assumption of 70%, the expected true VE for symptomatic COVID-19 for Stage 2 was estimated at 60%. Therefore, a total of approximately 125 symptomatic COVID-19 events will be required to achieve 80% power with 1-side type I error rate of 0.025, assuming no interim analysis. If any interim analysis is planned for Stage 2, type I error rate will be adjusted appropriately.
Table 4 provides information of number of events calculated based on a range of assumed VE (70% to 75%) and power (80% to 90%) with OBF adjusted one-side type-I-error specified above and VE LB >30% as success criteria. While 78 cases are required to reach 90% power and the basis of the sample size estimation, ≥61 cases provide ≥ 80% power assuming the true VE is 70%.

Table 5. Number of events required with VE range 70% - 75% and power 80% – 90%

Power	80%	85%	90%
VE=70%	61	70	78
VE=75%	44	50	56

* The type-I-error one-side alpha=0.02276 is used.

In each stage, hypothesis testing for key secondary objectives will only be applied conditional on achieving the predefined success criteria for the primary objective of the corresponding stage. It is considered success for the key secondary endpoints if the LB of the CI for the corresponding VE is > 0% against either the SARS-CoV-2 infection endpoint, or the severe COVID-19. The Holm's procedure (8) will be applied to control the overall 1-sided alpha 0.025 against key secondary objectives. Assuming the VE against SARS-CoV-2 infection endpoint is at least 40%, a total of 162 infections will have at least 80% power to conclude at 0% LB. Assuming the VE against the severe COVID-19 is 80%, a total of 22 events will provide at least 80% power to conclude at 0% LB.

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

4.7 Data Review for Statistical Purposes

A blind review of the data has been anticipated through the data review process led by data management before database lock. This review of the data includes a statistical review.

- **Changes in the Conduct of the Trial or Planned Analyses**

Based on the evolving nature of the pandemic during the conduct of this trial as detailed below, SP plans to conduct early primary efficacy analysis when approximately 61 events for the primary efficacy analyses (participants with adjudicated symptomatic COVID-19 events in the modified full analysis set mFAS post-dose 2 (mFAS-PD2) Naïve population) are accrued instead of the planned 78 events of the primary efficacy endpoint for stage 1. Hypotheses testing and statistical methods for primary and secondary efficacy endpoints are not being changed.

The protocol planned sample size of stage 1 naïve participants is 7112. Naïve participants for the purposes of the protocol-defined efficacy analyses were defined by a negative result in N-ELECSYS, S-ELECSYS and PCR at time of each vaccination visit. The protocol planned to cap the number of non-naïve participants in the study using a rapid serodiagnostic test (RDT). However, due to the lower-than-expected sensitivity of the RDT test used at enrollment, the number of SARS-CoV-2 naïve participants contributing to the primary efficacy population was ~ 2000. In addition, the incidence rate of COVID disease in the countries where the study is being conducted has been decreasing lately, probably related to the increasing COVID vaccination coverage combined with increasing rates of prior SARS-CoV2 exposure. The limited number of SARS-CoV-2 naïve individuals in the study, reflective of the true global epidemiological situation, in combination with lower incidence rates in countries makes case accrual of 78 events in the primary efficacy population unlikely in a reasonable time frame.

With delayed case accrual, true vaccine efficacy estimates are likely to be impacted by waning immunity and the emergence of the Omicron VOC making it very challenging to meet FDA requirements of efficacy for emergency authorization established at a time when highly mutated variants were yet to emerge.

Under current protocol-defined assumptions of VE (70%), achieving a readout of approximately 61 endpoints would provide >80% power compared to the original 78 endpoints (>90% power) as shown in Table 4. We propose that the risk of falsely not being able to conclude on efficacy is not significantly impacted and mitigates the risk of not being able to accrue the original 78 events in a reasonable timeframe.

Taken together, conducting primary analysis with approximately 61 cases provides an appropriate balance between risk and timely successful conclusion for Stage 1.

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

5 Appendix

Appendix 1: Analysis Methods and Populations Applied for Each Endpoint

Table 6: Summary of Analysis Methods and Populations Applied for Each Endpoint

Endpoints	Analysis Methods	Analysis Sets
Efficacy endpoints with objectives after any injection for the initial double-blind primary series design		
• Occurrences of symptomatic COVID-19	• VE (1-IRR) with CI using the exact method. • Kaplan-Meier curves	**<u>Hypothesis Testing:</u>** mFAS-PD2 Naïve-D01+D22 for Stage 1 and mFAS-PD2 for Stage 2 VE (1-IRR) only **<u>Additional:</u>** mFAS-PD2 Non-Naïve D01/D22 mFAS-PD2 All participants
• Occurrence of severe COVID-19	• VE (1-IRR) with CI using the exact method. • Kaplan-Meier curves	
• Occurrences of hospitalized COVID-19	• VE (1-IRR) with CI using the exact	mFAS-PD2 Naïve D01+D22

	method.	mFAS-PD2 Non-Naïve D01/D22 mFAS-PD2 All participants
• Occurrences of SARS-CoV-2 infection	• Descriptive Method (Percentages of participants experiencing events with 95% CI, # of events, percentage of events)	**Hypothesis Testing:** mFAS-PD2 Naïve-D01+D22
• Occurrences of CDC-defined COVID-19 • Occurrences of symptomatic COVID-19 in each severity scale on the 7-point ordinal scale • Occurrence of symptomatic COVID-19 with severity of moderate COVID-19 or worse (composite endpoint of at least one of moderate or severe COVID-19) • Occurrences of symptomatic COVID-19 requiring supplemental oxygen • Occurrences of intensive care utilization associated with symptomatic COVID 19 • Occurrences of symptomatic COVID-19 requiring mechanical ventilation or ECMO • Death associated with symptomatic COVID-19 • Occurrences of positive NAAT in respiratory samples at each follow-up timepoint during	• VE (1-IRR) with CI using the exact method.	mFAS-PD2 Naïve D01+D22 mFAS-PD2 Non-Naïve D01/D22 mFAS-PD2 All participants

symptomatic COVID-19 • Occurrence of virologically-confirmed SARS-CoV-2 infections and COVID-19 events (including all events regardless of adjudication committee decision). • All-cause death		
• Occurrences of asymptomatic SARS-CoV-2 infection	• Descriptive Method (Percentages of participants experiencing events with 95% CI, # of events, percentage of events)	mFAS-PD2 Naïve D01+D22
• Days with symptoms associated with symptomatic COVID-19 • Days of hospitalization associated with COVID-19 • Days of use of supplemental oxygen over the course of symptomatic COVID-19 • Days of stay in an intensive care unit over the course of symptomatic COVID-19 • Days of use of mechanical ventilation or ECMO over the course of symptomatic COVID-19 • Occurrence and number of days of work absenteeism • Number of days with positive NAAT	• Descriptive Method (min, max, mean with 95% CI, median, Q1, Q3) • Differences of mean days with 95% CI (Normal approximation)	mFAS-PD2 Naïve D01+D22 mFAS-PD2 Non-Naïve D01/D22 mFAS-PD2 All participants

• Episodes of new onset or exacerbation of pre-existing cardio-respiratory conditions • Occurrences of health care utilization events (hospitalizations, ER visits, or nonroutine medical office visits [including urgent care visits]) • Instances of antibiotic or antiviral use • Occurrence of work absenteeism • Occurrences of COVID-19 and SARS-CoV-2 infection among members in the same residence self-reported by the participant	• Descriptive Method (Percentages of participants experiencing events with 95% CI, # of events, percentage of events)	mFAS-PD2 Naïve-D01+D22 mFAS-PD2 All participants
• Viral copies/mL in respiratory samples collected at each follow-up timepoint	• Summary statistics (min, max, mean with 95% CI, median, Q1, Q3)	mFAS-PD2 Naïve-D01+D22 mFAS-PD2 Non-Naïve-D01/D22 mFAS-PD2 in all participants
Safety endpoints for the initial double-blind primary series design		
• Presence of solicited (pre-listed in the participant's diary card / electronic diary card [DC/eDC] and [electronic] Case Report Form [CRF]) injection site reactions and systemic reactions occurring up to 7 days after each vaccination • Presence of non-serious unsolicited adverse events (AEs) reported up to 21 days after each vaccination	• Descriptive Method (Percentages of participants experiencing events with 95% CI, # of events, percentage of events)	RSafAS

• Presence of unsolicited injection site and systemic AEs reported in the 30 minutes after each vaccination • Presence of serious adverse events (SAEs) throughout the study • Presence of medically-attended adverse events (MAAEs) throughout the trial • Presence of adverse events of special interest (AESIs) throughout the study • Presence of virologically-confirmed SARS-CoV-2 infections and/or symptomatic COVID-19	• Descriptive Method (Percentages of participants experiencing events with 95% CI) • Incidence by number of subjects with at least one event per 1000 person-years	SafAS
• Occurrences of hospitalized COVID-19 • Occurrence of severe COVID-19 • Occurrences of COVID-19 in each severity scale on the 7-point ordinal scale • Death associated with COVID-19	• Descriptive Method (Percentages of participants experiencing events with 95% CI) • Incidence by number of subjects with at least one event per 1000 person-years	SafAS
• Severity of symptoms associated with symptomatic COVID-19 episode	• Descriptive Method (Percentages of participants experiencing events with 95% CI)	SafAS
Immunogenicity endpoints for the initial double-blind primary series design		
Neutralizing antibody titers will be measured in participants for each study group against the D614G	• Descriptive statistics with 95% CIs (GMT, GMTR, 2FR, 4FR, percentage of	IAS (All, Naïve-D01 and Non-Naïve-D01)

and B.1.351 variants. All corresponding endpoints described in Table 1.	responders, difference of participants of responders/2FR/4FR)	
Binding antibody concentration will be measured in participants for each study group against the homologous vaccine strains. All corresponding endpoints described in Table 1.	• Descriptive statistics with 95% CIs (GMT, GMTR, 2FR, 4FR, percentage of responders, difference of participants of responders/2FR/4FR, concentrations >= 2/4 X LLOQ for Binding antibodies only)	IAS (All, Naïve -D01 and Non-Naïve-D01)
Immunogenicity endpoints with objectives for the crossover and booster design		
Neutralizing antibody titers will be measured in participants for each study group against the D614G and B.1.351 variants. All corresponding endpoints described in Table 2.	• Descriptive statistics with 95% CIs (GMT, GMTR, 2FR, 4FR, percentage of responders, difference of participants of responders/2FR/4FR)	CR-IAS BS-IAS
Safety endpoints with objectives for the crossover and booster design		
• Occurrences of hospitalized COVID-19 • Occurrence of severe COVID-19 • Occurrences of COVID-19 in each severity rating on the 7-point ordinal scale • Death associated with COVID-19	• Descriptive Method (Percentages of participants experiencing events with 95% CI) • Incidence by number of subjects with at least one event per 1000 person-years	CR-SafAS, BS-SafAS
• Severity of symptoms associated with symptomatic COVID-19 episode	• Descriptive Method • (Percentages of participants experiencing events with 95% CI)	CR-SafAS, BS-SafAS

• Presence of unsolicited injection site and systemic AEs reported in the 30 minutes after each vaccination • Presence of non-serious unsolicited AEs reported up to 21 days after the booster vaccination • Presence of MAAEs throughout the study • Presence of SAEs throughout the study • Presence of AESIs throughout the study	• Descriptive Method (Percentages of participants experiencing events with 95% CI) • Incidence by number of subjects with at least one event per 1000 person-years	CR-SafAS, BS-SafAS
Efficacy endpoints with objectives for the booster design only		
• Occurrences of symptomatic COVID-19 • Occurrences of hospitalized COVID-19 • Occurrence of severe COVID-19	• VE (1-IRR) with CI using the exact method.	BS-mFAS
Immunogenicity endpoints with objectives for the booster design only		
Binding antibody concentration will be measured in participants for each study group against the homologous vaccine strains. All corresponding endpoints described in Table 2.	• Descriptive statistics with 95% CIs (GMT, GMTR, 2FR, 4FR, percentage of responders, difference of participants of responders/2FR/4FR, concentrations >= 2/4 X LLOQ for Binding antibodies only)	BS-IAS

Appendix 2: Boundary of Harm Monitoring

Table 7: Boundary of Harm Monitoring - The Case Split to Trigger the Alert based on the observed total number of events

Total	SARS-CoV-2 Recombinant Protein Vaccine with Adjuvant (Equal or greater than)	Placebo	Relative Risk
5*	5	0	Inf
6	6	0	Inf
7	7	0	Inf
8	7	1	7
9	8	1	8
10	9	1	9
11	9	2	4.5
12	10	2	5
13	10	3	3.33
14	11	3	3.67
15	12	3	4
16	12	4	3
17	13	4	3.25
18	13	5	2.6
19	14	5	2.8
20	15	5	3
21	15	6	2.5
22	16	6	2.67
23	16	7	2.29
24	17	7	2.43
25	18	7	2.57
26	18	8	2.25
27	19	8	2.38
28	19	9	2.11
29	20	9	2.22
30	20	10	2

31	21	10	2.1
32	22	10	2.2
33	22	11	2
34	23	11	2.09
35	23	12	1.92
36	24	12	2
37	24	13	1.85
38	25	13	1.92
39	26	13	2
40	26	14	1.86
41	27	14	1.93
42	27	15	1.8
43	28	15	1.87
44	28	16	1.75
45	29	16	1.81
46	30	16	1.88
47	30	17	1.76
48	31	17	1.82
49	31	18	1.72
50	32	18	1.78
51	32	19	1.68
52	33	19	1.74
53	33	20	1.65
54	34	20	1.7
55	35	20	1.75
56	35	21	1.67
57	36	21	1.71
58	36	22	1.64
59	37	22	1.68
60	37	23	1.61
61	38	23	1.65
62	38	24	1.58
63	39	24	1.62
64	40	24	1.67
65	40	25	1.6

66	41	25	1.64
67	41	26	1.58
68	42	26	1.62
69	42	27	1.56
70	43	27	1.59
71	43	28	1.54
72	44	28	1.57
73	45	28	1.61
74	45	29	1.55
75	46	29	1.59
76	46	30	1.53
77	47	30	1.57
78	47	31	1.52

*The boundary starts as 5 cases as total cases below 5 cannot be rejected based on the current hypothesis testing

Appendix 3: Bayesian Predictive Power

One method to perform the futility analysis is the Bayesian predictive power which can be interpreted as the probability of rejecting the null hypothesis at the end of the trial conditional on the interim data.

Let x_v^1, x_c^1, x_T^1 denote the observed number of cases at interim in vaccine, control group and total ($x_T^1 = x_v^1 + x_c^1$). Similarly, let x_v^2, x_c^2, x_T^2 denote the future number of new cases to be observed in the remaining part of the trial.

Bayesian posterior distribution

Assuming the number of cases in vaccine group is binomially distributed conditionally on the total number of cases in both groups, the likelihood of the data at interim is:

$$f(x_v^1|P, x_T^1) = C_{x_T^1}^{x_v^1} P^{x_v^1}(1-P)^{x_c^1}$$

Based on Bayes's theorem, the Bayesian posterior distribution is then determined using the results of the interim analysis (likelihood data) combined with the prior (generally uniform) as follows:

$$f(P|x_v^1, x_T^1) = \frac{f(x_v^1|P, x_T^1) f(P)}{f(x_v^1|x_T^1)}, \text{ where } f(P) = 1 \text{ (prior uniform) for } P \in [0,1];$$

$$f(x_v^1|x_T^1) = \int_0^1 f(x_v^1|P, x_T^1) f(P) dP = \int_0^1 C_{x_T^1}^{x_v^1} P^{x_v^1}(1-P)^{x_c^1} dP = C_{x_T^1}^{x_v^1} \frac{\Gamma(x_v^1+1)\Gamma(x_c^1+1)}{\Gamma(x_T^1+2)}$$

Therefore, $f(P|x_v^1, x_T^1) = \frac{f(x_v^1|P, x_T^1) f(P)}{f(x_v^1|x_T^1)} = \frac{\Gamma(x_T^1+2)}{\Gamma(x_v^1+1)\Gamma(x_c^1+1)} P^{x_v^1}(1-P)^{x_c^1}$

Predictive Distribution

The predictive distribution gives the probability distribution of the future cases in vaccine group occurring until the end of the trial:

$$Pr(X_v^2 = x_v^2|x_v^1, x_T^1) = \int_0^1 Pr(X_v^2, P|x_v^1, x_T^1) dP = \int_0^1 Pr\,(X_v^2 = x_v^2|P)\, f(P|x_v^1, x_T^1) dP$$

where $Pr\,(X_v^2 = x_v^2|P)$ is the likelihood of the future data:

$$Pr(X_v^2 = x_v^2|P) = C_{x_T^2}^{x_v^2} P^{x_v^2}(1-P)^{x_c^2}$$

$f(P|x_v^1, x_T^1)$ is the posterior distribution previously defined:

$$f(P|x_v^1, x_T^1) = \frac{\Gamma(x_T^1+2)}{\Gamma(x_v^1+1)\Gamma(x_c^1+1)} P^{x_v^1}(1-P)^{x_c^1}$$

Put everything together, the predictive distribution of the future cases in vaccine group occurring in the trial conditional on the observed interim data is:

$$Pr(X_v^2 = x_v^2 | x_v^1, x_T^1) = \int_0^1 Pr\,(X_v^2 = x_v^2 | P)\, f(P | x_v^1, x_T^1) dP$$
$$= \int_0^1 C_{x_T^2}^{x_v^2} P^{x_v^2} (1-P)^{x_c^2} \frac{\Gamma(x_T^1 + 2)}{\Gamma(x_v^1 + 1)\Gamma(x_c^1 + 1)} P^{x_v^1} (1-P)^{x_c^1} dP$$
$$= C_{x_T^2}^{x_v^2} \frac{\Gamma(x_T^1 + 2)}{\Gamma(x_v^1 + 1)\Gamma(x_c^1 + 1)} \int_0^1 P^{x_v^2 + x_v^1} (1-P)^{x_c^2 + x_c^1} dP$$
$$= C_{x_T^2}^{x_v^2} \frac{\Gamma(x_T^1 + 2)}{\Gamma(x_v^1 + 1)\Gamma(x_c^1 + 1)} \frac{\Gamma(x_v^1 + x_v^2 + 1)\Gamma(x_c^1 + x_c^2 + 1)}{\Gamma(x_T^1 + x_T^2 + 2)}$$

Bayesian predictive power

Based on the above formula, the predictive probability of rejecting the null hypothesis at the end of the trial, the Bayesian predictive power, is then obtained by integrating the predictive distribution over a pre-defined region of future cases, on which the overall data will lead to reject the null hypothesis, as follow:

- To obtain x_T^f ($x_T^f = x_T^1 + x_T^2$) (a total number of cases for the final analysis) from x_T^1 (the total cases are observed at interim), and x_T^2 (the total future new cases are needed during remaining part of the trial)
- The future cases x_T^2 are split into the vaccine and placebo group (x_v^2, x_c^2), all combinations of (x_v^2, x_c^2) are determined with the associated predictive probability.
- The cases in each group obtained at the interim look are pooled with the future cases given the following combination ($x_v^1 + x_v^2,\ x_c^2 + x_c^2$), the vaccine efficacy and the associated CI is determined for each combination. For the considered combination the null hypothesis (H_0: VE≤ VE_0) is rejected if the lower bound of the CI is greater than VE_0.
- The Bayesian predictive power is then the sum of the predictive probability over the set of all combination of cases for which the null hypothesis is rejected at end of the trial.

Appendix 4: Statistical Modelling Method for Operational Futility

Estimation of the number of COVID endpoint

The method for estimating the probability distribution of the number of COVID endpoints by a given calendar date is based on the following approach to simulating this trial. The trial is modeled as a combination of three process – enrollment, right censoring, and COVID primary endpoint – and a large number of trials are simulated. The three process are assumed to be independent, and their distribution are taken to be Poisson, exponential and exponential, respectively. Data are generated at the level of the individual participant, such that, for each participant, we obtain an enrollment time, a right censoring time, and a COVID endpoint time. Only the minimum of the COVID and right censoring times is observable, and the average value for this minimum is beyond the duration of the trial, such that neither event will be observed for most participants.

In the absence of observed trial data, the treatment arm-pooled parameters for the COVID and right-censoring process are chosen to match our pre-trial assumptions about these rates. In addition, the COVID endpoint rate considers both the design alternative of VE=70% and the null hypothesis of VE=30% in the calculation of the total number of endpoints. More specifically, treatment arm-pooled calculations in (a) assume the following prior distribution parameters:

(i) Pooled COVID endpoint rate (VE=70% scenario): ((1/2)(1-0.7)× AnnInc + (1/2)× AnnInc COVID endpoints) / person-year at-risk, and
(ii) Pooled COVID endpoint rate (VE=30% scenario): ((1/2)(1-0.3)× *AnnInc* + (1/2)× *AnnInc* COVID endpoints) / person-year at-risk.

Here the background/placebo incidence rate *AnnInc* is computed based on surveillance data if available; if not, it will be based on the most recent protocol assumption of 2.25 COVID-19 endpoints per 100 participants each followed for 2 months in either Stage 1 and 2 (as stated in Section 9.2 of the study protocol v5.0). For prior distributions, we use the protocol specified treatment arm-pooled dropout rate of 25 and 30 dropouts per 100 participants each followed for 2 months in Stage 1 and 2, respectively (as stated in Section 9.2 of the study protocol v5.0).

The first step in simulating each trial is to enroll a certain number of baseline SARS-COV-2 negative participants per week according to a random draw from a Poisson distribution with rate parameter as listed above. Enrollment continues week-by-week until a total of 7112 participants is reached (this would occur with 10 160 total enrollees if 70% are baseline SARS-COV-2 negative). Second, each participant is assigned an exact enrollment day, uniformly distributed within their enrollment week. following enrollment, the COVID endpoint and right-censoring times are drawn from their respective exponential distributions, and the lesser of the two is recorded as occurring at the given time (possibly outside the time-window of the trial). We consider right-censoring events to have occurred at the right-censoring time that was generated (assuming it was less than the COVID endpoint time).

A modification of the above procedure for simulating an efficacy trial is used for estimating metrics of futility to assess VE at a given interim analysis. The modification entails using the observed trial data to estimate parameters of the processes, rather than relying entirely on protocol assumptions. In particular:

- Enrollment rate: if enrollment is incomplete, this parameter is estimated based on the treatment arm-pooled rate observed in approximately the last 2 weeks of the study prior to the data lock for the DSMB meeting,
- COVID endpoint rate: drawn from a posterior distribution of the COVID endpoint rate formed by combining the observed data with our prior specification about the COVID endpoint rate based on the protocol assumptions, and
- Right-censoring rate: estimated based on the treatment arm-pooled rate observed to date.

The rationale for a Bayesian approach for the COVID endpoint rate is to help stabilize the COVID endpoint rate early in the trial when insufficient time will have passed to accrue many COVID endpoints. If we were to rely solely on the observed COVID endpoints, we might by chance obtain very low rates, which would lead to an unrealistic prediction of the number of endpoints.

We consider three different Gamma prior distributions for the COVID endpoint rate in each of the scenarios (1) – (3) in Section 4.5.2.3 reflecting different weights assigned to the prior distribution. Gamma distributions are considered because they are conjugate to the exponential distribution used for generating future infection data.

At a given monitoring time, 10^5 trials are simulated using the above procedure, including generation of the treatment arm-pooled COVID endpoint rates and right-censoring rates, for computing the estimates in (a). Each of these trials yields a projected number of COVID endpoint cases by each specified calendar date. These projected numbers of COVID endpoints from each trial will be used to estimate the entire distribution of the number of COVID endpoints. For a given fixed number of cases, the probability of reaching at least this number will be estimated as the proportion of trials with the projected number of COVID endpoints greater than or equal to the target.

Figures on enrollment, COVID endpoint incidence, and right-censoring over time will also be included to aid interpretation of the results. In addition to showing estimates of the probability of right-censoring over time (Kaplan-Meier nonparametric estimation), competing risk analysis (Aalen-Johansen nonparametric estimation) will be used to estimate the cumulative incidence of cause-specific right-censoring with 3 mutually exclusive and exhaustive causes: (1) unblinding; (2) receipt of an authorized/approved COVID-19 vaccine; and (3) all other causes, which are generally early termination events such as loss to follow-up.

A Bayesian model for the COVID endpoint incidence rate

Let n_k and T_k denote, respectively, the COVID endpoint count and the observed total person-time at risk at the time of the k-th futility analysis, pooling over both treatment arms. Additionally, let T^* denote the estimated total person-time at risk for the vaccine efficacy analysis counting COVID endpoints through the target calendar date. Let the prior distribution of the pooled COVID endpoint incidence rate p be Ga(α, β) parameterized such that the prior mean E p = α / β.

Generally, assuming that, conditional on p, the times to COVID follow Exp(p), the posterior mean of p at the time of the k-th analysis equals

$$E[p|data] = \frac{\alpha+n_k}{\beta+T_k} = \frac{\alpha}{\beta}\frac{\beta}{\beta+T_k} + \frac{n_k}{T_k}\frac{T_k}{\beta+T_k} \qquad (1)$$

i.e., the posterior mean can be interpreted as a convex combination of the prior mean and the observed incidence rate. For a given β > 0, the weight on the prior mean at the first analysis depends on the accumulated person-time at risk T_1, and the weight will decrease in subsequent analyses because $\beta/(\beta + T_k)$ is a decreasing function of T_k , which is a desirable Bayesian property.

In order to identify α and β, it is desirable that the prior mean equals the pre-trial assumed treatment arm-pooled incidence rate p^*, i.e.,

$$\frac{\alpha}{\beta} = p^*$$

Furthermore, we propose to consider three values of β that correspond to the weights ω=1/2, 1/3, and 1/4 on the prior mean at the time when 50% of the estimated total person-time at risk has been accumulated, i.e., for each value of ω, β is defined as the solution to the equation

$$\frac{\beta}{\beta + T^*/2} = \omega$$

It follows that $\beta = \beta(\omega, T^*) = \frac{\omega T^*}{2(1-\omega)}$, and the estimation of T^* is described in the following Section . For $\omega = \frac{1}{2}, \frac{1}{3}, \text{and} \frac{1}{4}$, we obtain $\beta = \frac{T^*}{2}, \frac{T^*}{4}, \text{and } \frac{T^*}{6}$, respectively.

At the *k*-th futility analysis and for each of the three values of β, we will sample the COVID endpoint incidence rate from Ga($\alpha + n_k, \beta + T_k$) for generating future data and report the weight $\frac{\boldsymbol{\beta}}{\boldsymbol{\beta}+T_k}$ on the prior mean in the convex combination (1)

Estimation of the total person-years at risk T^*

We consider the standard right-censored failure time analysis framework. Denoting the failure and censoring times as T and C, respectively, we assume that T is dependent of C, $T \sim Exp(p^*)$, and $C \sim Exp(d^*)$. It follows that $X \coloneqq \min(T, C) \sim Exp(p^* + d^*)$ and

$$\begin{aligned} T^* &= N \times E[\min(X, \tau)] \\ &= N \times E[X|X \le \tau]P(X \le \tau) + \tau P(X > \tau) \\ &= N \times \left\{ (p^* + d^*) \int_0^\tau x \, exp^{-(p^*+d^*)x} \, dx \; + \tau exp^{-(p^*+d^*)\tau} \right\} \\ &= N \times \frac{1 - exp^{-(p^*+d^*)\tau}}{p^* + d^*} \end{aligned}$$

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