CLINICAL STUDY REPORT

Protocol Number:	CLO-SCB-2019-003
Long Title:	Protocol Title: A Double-blind, Randomized, Controlled, Phase 2/3 Study to Evaluate the Efficacy, Immunogenicity, and Safety of CpG 1018/Alum-Adjuvanted Recombinant SARS-CoV-2 Trimeric S-protein Subunit Vaccine (SCB-2019) for the Prevention of SARS-CoV-2-mediated COVID-19 in Participants Aged 12 Years and Older
Short Title:	A controlled phase 2/3 study of adjuvanted recombinant SARS-CoV-2 trimeric S-protein vaccine (SCB-2019) for the prevention of COVID-19
Sponsor:	Clover Biopharmaceuticals AUS Pty Ltd. Level 17, HWT Tower, 40 City Road, Southbank VIC 3006, Australia
IND Number:	Not applicable **EUDRACT Number:** 2020-004272-17
NCT Number:	NCT04672395
Investigational Medicinal Product(s):	• CpG 1018/Alum-adjuvanted SCB-2019 vaccine • Placebo
Indication Studied:	Prophylactic vaccine for the prevention of COVID-19 in subjects 12 years and above
Study Phase:	Phase 2/3
Study Dates:	Date first subject signed informed consent form: 24 March 2021 Date of last subject's last visit/contact: 11 September 2024 Data lock points for this report: 13 Sep 2021, 17 Dec 2021, 11 Sep 2024
Early Study Termination Date:	Not applicable.
Sponsor's Responsible Medical Officer:	Htay Htay Han, MBBS CMO, Vaccine Clinical Development Clover Biopharmaceuticals
Report Date:	21 October 2024 (V2.0)

This study was performed in accordance with Good Clinical Practice.

2.0 SYNOPSIS

Name of company: Clover Biopharmaceuticals. **Name of finished product:** SCB-2019 **Name of active substance:** Recombinant SARS-CoV-2 Spike [S]-Trimer Fusion Protein	**TABULAR FORMAT REFERRING TO PART OF THE DOSSIER** **Volume:** **Page:**	(for national authority only)

Title of the study:

Protocol Title: A Double-blind, Randomized, Controlled, Phase 2/3 Study to Evaluate the Efficacy, Immunogenicity, and Safety of CpG 1018/Alum-Adjuvanted Recombinant SARS-CoV-2 Trimeric S-protein Subunit Vaccine (SCB-2019) for the Prevention of SARS-CoV-2-mediated COVID-19 in Participants Aged 12 Years and Older.

Investigators:

This study was conducted by 31 principal investigators. A coordinating investigator was designated for each country.

Study sites:

This study was multi-site: 31 sites in 5 countries (3 sites in Belgium, 5 sites in Brazil, 9 sites in Colombia, 10 sites in the Philippines, and 4 sites in South Africa).

Publication (reference):

Bravo L, Smolenov I, Han HH, Li P, Hosain R, Rockhold F, et al. Efficacy of the adjuvanted subunit protein COVID-19 vaccine, SCB-2019: a phase 2 and 3 multicentre, double-blind, randomised, placebo-controlled trial. Lancet. 2022 Jan 29;399(10323):461-472.

Smolenov I, Han HH, Li P, Baccarini C, Verhoeven C, Rockhold F et al. Impact of prior exposure to SARS-CoV-2 and the SCB-2019 COVID-19 vaccine candidate on re-infection; a randomised, controlled phase3 trial. Lancet Infectious Disease. 2022 (DOI:https://doi.org/10.1016/S1473-3099(22)00144-X published online).

Study period:	**Clinical phase:**
Date first subject signed informed consent form: 24 March 2021. Date of last subject's last visit/contact: 11 September 2024. Data lock points: 13 September 2021, 17 December 2021, 11 September 2024.	Phase 2/3

Background and rationale:

This study assessed the efficacy against coronavirus disease 2019 (COVID-19), immunogenicity, reactogenicity, and safety of CpG 1018/alum-adjuvanted recombinant, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) trimeric spike (S) protein subunit vaccine (SCB-2019) in adults (aged 18 years and above) and adolescents (12-17 years of age). The COVID-19 pandemic has resulted in high morbidity and mortality, caused major disruption to healthcare systems, and has had significant socioeconomic impacts. Currently, only limited treatment options are available against COVID-19 and accelerated vaccine development is urgently needed. Several COVID-19 vaccines have been authorized in some countries, but the global supply remains insufficient for pandemic control. Additional safe and effective vaccines for COVID-19 prevention would have significant public health impact.

Objectives:

*Primary Efficacy Objective (**H1**) - vaccine efficacy (VE) against RT-PCR-confirmed COVID-19 of any severity:*

- To demonstrate the efficacy of CpG 1018/alum-adjuvanted SCB-2019 vaccine for the prevention of any RT-PCR-confirmed COVID-19 of any severity in subjects without evidence of prior SARS-CoV-2 infection.

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Primary Safety and Reactogenicity Objective:

- To assess the safety and reactogenicity of CpG 1018/alum-adjuvanted SCB-2019 vaccine compared to placebo.

*Key Secondary Efficacy Objective #1 (**H2b**) - VE against any RT-PCR-confirmed moderate-to-severe COVID-19:*

- To evaluate the efficacy of CpG 1018/alum-adjuvanted SCB-2019 vaccine for the prevention of any RT-PCR-confirmed moderate to severe COVID-19 in subjects without evidence of prior SARS-CoV-2 infection.

*Key Secondary Efficacy Objective # 2 (**H2a**) – VE against any laboratory-confirmed SARS-CoV-2 infection:*

- To evaluate the efficacy of CpG 1018/alum-adjuvanted SCB-2019 vaccine for the prevention of any laboratory-confirmed SARS-CoV-2 infection in subjects without evidence of prior SARS-CoV-2.

*Key Secondary Efficacy Objective #3 (**H4**) - VE against any RT-PCR-confirmed severe COVID-19:*

- To evaluate the efficacy of CpG 1018/alum-adjuvanted SCB-2019 vaccine for the prevention of any RT-PCR-confirmed severe COVID-19 in subjects without evidence of prior SARS-CoV-2 infection.

*Key Secondary Efficacy Objective #4 (**H3**) - VE against any laboratory-confirmed asymptomatic SARS-CoV-2 infection:*

- To evaluate the efficacy of CpG 1018/alum-adjuvanted SCB-2019 vaccine for the prevention of any laboratory-confirmed asymptomatic SARS-CoV-2 infection in subjects without evidence of prior SARS-CoV-2 infection.

Secondary Efficacy Objective #1 – VE against burden of disease (BOD):

- To evaluate the efficacy of CpG 1018/alum-adjuvanted SCB-2019 vaccine for the reduction of BOD, in subjects without evidence of prior SARS-CoV-2 infection.

Secondary Efficacy Objective #2 – VE against any RT-PCR-confirmed COVID-19 of any severity, associated with hospitalization:

- To evaluate the efficacy of CpG 1018/alum-adjuvanted SCB-2019 vaccine for the prevention of any RT-PCR-confirmed COVID-19 of any severity, associated with hospitalization, in subjects without evidence of prior SARS-CoV-2 infection.

Secondary Efficacy Objective #3 – VE by evidence of prior SARS-CoV-2 infection and risk of severe COVID-19:

- To describe the efficacy of CpG 1018/alum-adjuvanted SCB-2019 vaccine in subgroup population: subjects with and without evidence of prior SARS-CoV-2 infection (yes/no); and subjects at risk of severe COVID-19 (high/ low risk).

Secondary Efficacy Objective #4 - VE after the first dose:

- To evaluate the efficacy of CpG 1018/alum-adjuvanted SCB-2019 vaccine, after the first study vaccination.

Secondary efficacy objective #5 – VE against SARS-CoV-2 variants of concern (VOCs):

- To evaluate the efficacy of CpG 1018/alum-adjuvanted SCB-2019 vaccine for the prevention of RT-PCR-confirmed COVID-19 of any severity caused by SARS-CoV-2 VOCs, including but not limited to B.1.1.7, B.1.351, B.1.1.28.1 (P1), etc.

Secondary Immunogenicity Objective:

- To assess the immunogenicity of CpG 1018/alum-adjuvanted SCB-2019 vaccine in Phase 2 adult subjects and adolescents.

Secondary Safety Objective:

- To assess the immune response against Trimer-Tag domain of SCB-2019 in Phase 2 adult subjects and adolescents.

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The exploratory objectives are listed in Section 8.3.

Study design/Methodology:

Overall study design: CLO-SCB-2019-003 was a double-blind, randomized, controlled, multi-country study of CpG 1018/alum-adjuvanted SCB-2019 to assess the efficacy, immunogenicity, reactogenicity, and safety compared with control (placebo).

Stages of the Study:

- Phase 2 of the study was to include approximately 1600 adult subjects (800 subjects in the CpG 1018/alum/SCB-2019 group and 800 subjects in the Placebo arm) to assess reactogenicity, safety and immunogenicity of the study vaccine. Safety and reactogenicity data were to be reviewed by the data safety monitoring board (DSMB) to provide recommendations regarding the study continuation, modification, or termination. Efficacy data were to be collected during the Phase 2 stage and analyzed along with the data collected in Phase 3.
- Phase 3 of the study was to include the remaining subjects to assess efficacy and safety of study vaccine.

Staggered recruitment:

- Initially, only healthy adults 18 to 64 years of age were to be recruited in the study. After the review of post-Dose 1 safety data of approximately 200 healthy adult subjects 18 to 64 years of age, the DSMB was to make a recommendation regarding the extension of recruitment and inclusion of the overall study population, including older adults aged ≥65 years and individuals with comorbidities.
- After recruiting approximately 200 additional adult subjects, including older adults aged ≥65 years and individuals with comorbidities, the DSMB was to review available safety data necessary to recommend the initiation of recruitment in Phase 3 part of the study.
- In addition, the DSMB could authorize the enrollment of adolescent subjects 12 to less than 18 years of age to assess reactogenicity, safety, efficacy, and immunogenicity. These subjects were to follow study procedures for the Phase 2 stage of the study. The volume of blood samples was to be reduced according to their age. The immunogenicity and safety results for adolescent subjects are presented in a separate report.

Study visits:

Five planned study visits for all subjects, at Days 1, 22, 36, 205, and 389.

Safety call:

One safety call for subjects in the Phase 2 study and adolescents on Day 43 (-2/+7 days) to collect information about unsolicited adverse events (AEs), serious adverse events (SAEs,) AEs leading to early study termination, medically attended AEs (MAAEs), and AEs of special interest (AESIs).

Blood sampling:

Five blood draws from each adult subject and adolescent enrolled.

Duration of the study:

The study duration was to be approximately 13 months (approximately 12 months after the second study vaccination) for each subject.

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Planned number of subjects:

Approximately 30 000 adult subjects and 1200 adolescents were planned to be included in this study and distributed (1:1) as follows:

- **CpG 1018/alum/SCB-2019 group**: approximately 15 000 adult subjects and 600 adolescents;
- **Placebo arm**: approximately 15 000 adult subjects and 600 adolescents.

Main criteria for inclusion:

1. Male or females ≥12 years of age, inclusive.
2. Subjects willing and able to comply with study requirements, including all scheduled visits, vaccinations, laboratory tests, the electronic completion of the COVID-19 electronic patient-reported outcome (ePRO) and other study procedures.
3. Healthy adults or adolescents, or adults with pre-existing but stable medical conditions.
4. Not-pregnant, non-breastfeeding female subjects.
5. Male subjects willing to employ acceptable contraception from the day of first dose of the study vaccine/placebo until 6 months after the last dose of the study vaccine/placebo and also willing to refrain from donating sperm during this period.
6. Individuals [or their legally acceptable representative (LAR) based on local regulations] willing and able to give an informed consent, prior to screening. For adolescent subjects: informed assent signed by adolescents and informed consent signed by the parent(s) or LAR(s) as per local requirements.

The full list of criteria is provided in Section 9.3.1.

Investigational product, dose, mode of administration, batch no.:

CpG 1018/Alum-adjuvanted SCB-2019 vaccine for intramuscular (i.m.) administration is formulated with the following components:

- **SCB-2019**: prefilled syringe (720 µg in 1.0 mL) for preparation of 20 doses of study vaccine. Batch numbers 202103001, 202103003, 202104012, 202104006, 202105014, 200902002, X210001, and 202104010.
- **CpG 1018 Adjuvant**: a vial (2.0 mL) containing 12 mg/mL of a 22-mer phosphorothioate oligodeoxynucleotide in Tris buffered saline (24 mg per vial). Batch number 1-FIN-3840.
- **Alhydrogel®**: a vial or bottle containing 10 mg/mL of aluminum hydroxide. Batch number 202103002.

Placebo, dose and mode of administration, batch no.:

Placebo (0.9% saline solution) for i.m. administration is provided as a 10 mL ampoule. Batch number 003502.

Dosing schedule:

Two i.m. injections, at Days 1 and 22.

Criteria for evaluation:

*Estimand for the primary efficacy objective (**H1**):*

- 1 minus incidence rate ratio (IRR) of the vaccine to placebo in subjects with any RT-PCR-confirmed COVID-19 of any severity per cumulative follow-up person time by PPS for efficacy.

Estimand for the primary safety and reactogenicity objective:

- Proportion of subjects with local and systemic solicited AEs reported within 7 days after each study vaccine (in Phase 2 subjects);

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- Proportion of subjects with unsolicited AEs reported from Visit 1 (Day 1) through Safety Call Day 43 (in Phase 2 subjects);
- Proportion of subjects with SAEs, AEs leading to early termination from the study, MAAEs, and AESIs during the entire study period.

*Estimand for the key secondary efficacy objective #1 (**H2b**):*

- 1 minus IRR of the vaccine to placebo in subjects with any RT-PCR-confirmed SARS-CoV-2 moderate to severe COVID-19 per cumulative follow-up person time by PPS for efficacy.

*Estimand for the key secondary efficacy objective #2 (**H2a**):*

- 1 minus IRR of the vaccine to placebo in subjects with any laboratory-confirmed SARS-CoV-2 infection per cumulative follow-up person time by PPS for efficacy.

*Estimand for the key secondary efficacy objective #3 (**H4**):*

- 1 minus IRR of the vaccine to placebo in subjects with any RT-PCR-confirmed SARS-CoV-2 severe COVID-19 per cumulative follow-up person time by PPS for efficacy.

*Estimand for the key secondary efficacy objective #4 (**H3**):*

- 1 minus IRR of the vaccine to placebo in subjects with laboratory-confirmed asymptomatic SARS-CoV-2 infection per cumulative follow up person time by PPS for efficacy.

Estimand for the secondary efficacy objective #1:

- 1 minus relative risk in terms of BOD (refer to BOD score definition) from the vaccine and placebo in subjects with any BOD by PPS for efficacy.

Estimand for the secondary efficacy objective #2:

- 1 minus IRR of the vaccine to placebo in subjects with RT-PCR-confirmed COVID-19 of any severity, associated with hospitalization per cumulative follow up person time by PPS for efficacy.

Estimand for the secondary efficacy objective #3:

- 1 minus IRR of the vaccine to placebo:
  - in subjects with RT-PCR-confirmed COVID-19 of any severity;
  - in subjects with RT-PCR-confirmed moderate-to-severe COVID-19;
  - in subjects with RT-PCR-confirmed severe COVID-19;
  - in subjects with RT-PCR-confirmed COVID-19 of any severity associated with hospitalization;
  - in subjects with any laboratory-confirmed SARS-CoV-2 infection;
  - in subjects with laboratory-confirmed asymptomatic SARS-CoV-2 infection;

  per cumulative follow up person time by PPS for efficacy.

Estimand for the secondary efficacy objective #4:

- 1 minus IRR of the vaccine to placebo:
  - in subjects with RT-PCR-confirmed COVID-19 of any severity;
  - in subjects with RT-PCR-confirmed moderate-to-severe COVID-19;
  - in subjects with RT-PCR-confirmed severe COVID-19;
  - in subjects with RT-PCR-confirmed COVID-19 of any severity associated with hospitalization;

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- in subjects with any laboratory-confirmed SARS-CoV-2 infection;
- in subjects with laboratory-confirmed asymptomatic SARS-CoV-2 infection;

per cumulative follow up person time by FAS (for 1 dose) for efficacy.

Estimand for the secondary efficacy objective #5:

- 1 minus IRR of the vaccine to placebo in subjects with RT-PCR-confirmed COVID-19 of any severity by individual VOC, per cumulative follow up person time by PPS for efficacy.

Estimand for the secondary immunogenicity objective:

- GMTs, GMFRs (post/pre-vaccination), proportion of subjects with seroconversion, and proportion of subjects with antibody titer above a pre-specified threshold (Limit of Quantification) for each type of serological assays by PPS for immunogenicity.

Estimand for the secondary safety objective:

- GMTs and GMFRs from Baseline by PPS for immunogenicity.

The estimands for the exploratory objectives are listed in Section 9.5.9.3.

Statistical methods:

This study had two stages: Phase 2 and Phase 3.

The primary endpoint for this study was defined as first occurrence of RT-PCR-confirmed COVID-19 of any severity, with onset at least 14 days after the second vaccination. The null ($H1_0$) and alternative ($H1_a$) hypotheses for the primary endpoint are:

$H1_0$: VE ≤30% vs $H1_a$: VE >30%.

The VE was to be calculated as 100×[1 – incidence rate ratio (IRR)]. The incidence rate (IR) for this study was defined as the number of subjects with any RT-PCR-confirmed COVID-19 of any severity divided by cumulative follow-up person time among all subjects at risk. VE at the final analysis would be demonstrated if the lower limit (LL) of Type I-adjusted confidence interval (CI) for VE against COVID-19 of any severity exceeded 30%.

The study sample size was driven by the primary efficacy objective. The final target of 150 any RT-PCR-confirmed COVID-19 events would provide approximately 90% power to reject the null hypothesis (VE ≤30% for any COVID-19), assuming the true VE to be at least 60%, considering one interim analysis (IA). Considering an attack rate of 0.60% per month (in the Placebo arm) for any COVID-19, and approximately 2 months follow-up or the primary efficacy endpoint, a total of 22 000 subjects, with randomization ratio 1:1, were to be enrolled assuming non-evaluability of 20% or less.

The IA for the primary endpoint evaluation was to be conducted only when 50% of the target events was reached and was to be performed by an independent team after observing 75 *any COVID-19* events for the primary efficacy endpoint within the Per Protocol Set.

Attack rate estimations were to be performed in a blinded manner under the efficacy assumptions used for planning the study. If the average underlying attack rate was substantially lower than 0.60% for any COVID-19 as expected, or baseline SARS-CoV-2 seropositivity rate was higher than anticipated, the sample size was to be reassessed or the duration of follow-up for the primary endpoint may have been adjusted and the maximum number of study subjects increased up to 30 000.

All analyses, summaries, and listings were to be performed using SAS® software (version 9.4 or higher).

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Analyses were performed according to protocol.

Results - Summary:

This compiled clinical study report (CSR) includes data obtained between 24 March 2021 (study start) and 1 December 2021.

This trial was conducted at 31 sites, in 5 countries (3 sites in Belgium, 5 sites in Brazil, 9 sites in Colombia, 10 sites in the Philippines, and 4 sites in South Africa). Initially, and for the Phase 2 part, subjects were recruited from the Philippines, Colombia, and Belgium. The Phase 3 part of the study was launched on 12 April 2021, from when the recommendation to proceed to that stage of the protocol was received from the DSMB's review of the safety and reactogenicity data of the first 400 study participants. For the Phase 3 part, subjects were also recruited from Brazil and South Africa.

In the Results section of the synopsis, the "round half to the nearest even" rounding convention has been applied to the data in certain cases to aid clarity. In this convention, a value exactly halfway between two digits is rounded to the nearest even digit (e.g., 1.5 is halfway between 1 and 2 and is rounded to 2); and all other values are rounded to the nearest digit.

Disposition: Overall

Subject disposition and demographic and baseline characteristics for all analysis cohorts are presented in the body of the CSR. This section focuses on the Primary efficacy analysis period.

In total, 31201 individuals were screened, and 30174 subjects were included in the Randomized set of the study, initially for the Phase 2 and then as part of the Phase 3 (**Table S1**). Hence the Phase-3 Randomized set included the Phase-2 Randomized set (see below). After random allocation the SCB-2019 arm included 15092 subjects and the Placebo arm included 15082 subjects.

In each arm, 15064 subjects received at least 1 dose of SCB-2019 or Placebo and were included in the Exposed set and SAF. In the Efficacy (Dose 1) FAS, the SCB-2019 arm included 14684 subjects, and the Placebo arm included 14670 subjects (**Table S1**). In the Efficacy (Dose 2) FAS, the SCB-2019 arm included 12989 subjects, and the Placebo arm included 12823 subjects.

The SCB-2019 arm and Placebo arm in the Efficacy (Dose 1) FAS and the Efficacy (Dose 2) FAS included similar sized subsets of baseline-SARS-CoV-2-naïve and baseline SARS-CoV-2-exposed subjects (i.e., those subjects without/with evidence of prior SARS-CoV-2 infection; **Table S1**). In the Efficacy (Dose 1) FAS, the SCB-2019 arm was split 7331:7353, and the Placebo arm was split 7331:7339, respectively. In the Efficacy (Dose 2) FAS, the SCB-2019 arm was split 6283:6706. and the Placebo arm was split 6140:6683, respectively.

In the Efficacy PPS, the SCB-2019 arm included 6251 subjects, and the Placebo arm included 6104 subjects (**Table S1**). Subjects were excluded from the Efficacy PPS with respect to the SAF, for one or more reasons. Most subjects were excluded because they had evidence of prior SARS-CoV-2 infection, and covered 7315 subjects in the SCB-2019 arm and 7307 subjects in the Placebo arm. The second most frequent reason for exclusion was the absence of a second dose, and covered 1386 subjects in the SCB-2019 arm and 1524 subjects in the Placebo arm. The third most frequent reason for exclusion was that the randomization code was broken, and covered 375 subjects in the SCB-2019 arm and 394 subjects in the Placebo arm. The breaking of the randomization code was mainly due to requests by subjects who preferred to receive an authorized COVID-19 vaccine during the study conduct.

In the Exposed set/SAF, the median duration of subjects in the study was 74 days (mean 82 days), and was similar between arms (75 days SCB2019 arm; 74 days Placebo arm; **Table 14.1.1.3**).

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Overall, 1070 subjects discontinued from the vaccination schedule, 513/15064 (3.4%) of subjects in the SCB-2019 arm and 557/15064 (3.7%) of subjects in the Placebo arm (**Table 14.1.1.2**). The most frequent reason for discontinuation was not specified (other) and was reported by a similar percentage of subjects in the SCB-2019 and Placebo arms (both 1.3%). The most frequent reason for discontinuation that was categorized was an adverse event (AE), and was reported by a similar percentage of subjects in the SCB-2019 and Placebo arms (1.1% and 1.3%, respectively). Eight subjects in the SCB-2019 arm and six subjects in the Placebo arm discontinued based on the decision of the physician. One subject in the SCB-2019 arm and three subjects in the Placebo arm discontinued because of death; and eight subjects in the SCB-2019 arm and seven subjects in the Placebo arm discontinued because of pregnancy.

Overall, 851 subjects discontinued from the study, 392/15064 (2.6%) of subjects in the SCB-2019 arm and 459/15064 (3.0%) of subjects in the Placebo arm (**Table 14.1.1.2**). The most frequent reason for discontinuation was not specified (other) and was reported by a similar percentage of subjects in the SCB-2019 and Placebo arms (1.3% and 1.5%, respectively). The most frequent reason for discontinuation that was categorized was withdrawal-by-subject, and was reported by a similar percentage of subjects in the SCB-2019 and Placebo arms (0.9% and 1.0%, respectively). Three subjects in the SCB-2019 arm and four subjects in the Placebo arm discontinued based on the decision of the physician. Three subjects in the SCB-2019 arm and seven subjects in the Placebo arm discontinued because of death; and two subjects in the Placebo arm discontinued because of pregnancy.

Table S1: Disposition of subjects in the entire study cohort of the primary efficacy analysis

	Number of subjects	
Enrolled Set	31201	
Randomized set	30174	
	SCB-2019 arm	**Placebo arm**
Randomized	15092	15082
Exposed set & SAF	15064	15064
Efficacy (Dose 1) - FAS	14684	14670
Efficacy (Dose 2) - FAS	12989	12823
Efficacy - PPS	6251	6104

Source: Table 14.1.1.1.

Disposition: Phase 2

In total, 1660 individuals were screened, and 1601 subjects were included in the Phase-2 Randomized set of the study **Table S2**. After random allocation the SCB-2019 arm included 808 subjects and the Placebo arm included 793 subjects. All subjects received at least 1 dose and were included in the Phase-2 Exposed set and Phase 2 SAF. In the Immunogenicity subset, the SCB-2019 arm included 759 subjects, and the Placebo arm included 95 subjects (randomly selected from Phase 2 SAF). In the Immunogenicity FAS, the SCB-2019 arm included 636 subjects, and the Placebo arm included 84 subjects. In the Immunogenicity PPS, the SCB-2019 arm included 381 subjects, and the Placebo arm included 47 subjects.

Subjects were excluded from the Immunogenicity PPS with respect to the Phase 2 SAF, for one or more reasons. Most subjects were excluded because they had evidence of prior SARS-CoV-2 infection, and covered 248 subjects in the SCB-2019 arm and 32 subjects in the Placebo arm.

The second most frequent reason for exclusion was missing serology at Day 36, and covered 57 subjects in the SCB-2019 arm and 7 subjects in the Placebo arm. The third most frequent reason for exclusion was that the absence of a second dose, and covered 30 subjects in the SCB-2019 arm and 3 subjects in the Placebo arm.

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Table S2: Disposition of subjects in the Phase-2 cohort

	Number of subjects	
Enrolled Set	1660	
Randomized set	1601	
	SCB-2019 arm	**Placebo arm**
Randomized set	808	793
Exposed set & SAF	808	793
Immunogenicity - Subset	759	95
Immunogenicity - FAS	636	84
Immunogenicity - PPS	381	47

Source: Table 14.1.1.1.1.

As of 1 December 2021, 31483 individuals were screened, and 30338 subjects 12 years of age and above were included in the Randomized set. Overall, 30299 subjects received at least one dose of the study vaccine or placebo, including 30137 adult study participants and 162 adolescents (**Table 14.1.1.1_P6m**). The disposition for subjects analyzed for the Six-month Follow-up is provided in the body of the CSR.

Demographics:

SAF, Efficacy FAS (Dose 1), Efficacy FAS (Dose 2), and Efficacy PPS (Phase 3)

The demographic and baseline characteristics were generally balanced between arms in the SAF (**Tables 14.1.2.1 and 14.1.3.1**). In the SCB-2019 and Placebo arms, 47% of subjects were female (7086/15064 and 7033/15064, respectively). The mean age was 32 years in both arms, with most subjects (99%) being between the ages of 18 to 64. Mean height and mean weights were 164 cm and 68 kg, respectively, in both arms. Most subjects in both arms were from the Philippines (45%), followed by Brazil (26%), Colombia (22%), South Africa (4%) and Belgium (2%). Most subjects in both arms identified as Asian (46%).

In both the SCB-2019 and Placebo arms, the percentage of subjects with high risk of severe COVID-19 was 18%. The most prevalent of those risks were obesity, hypertension and asthma, being reported by 13%, 4.5% and 1.3% respectively, in both the SCB-2019 arm and the Placebo arm.

In both the SCB-2019 and Placebo arms, 49 to 50% of subjects had no evidence of prior SARS-CoV-2 infection and/or were SARS-CoV-2 seronegative at baseline (baseline seronegative).

In the Efficacy-FAS (Dose 1; **Tables 14.1.2.1.10** and **14.1.3.1.10**), and Efficacy FAS (Dose 2; **Table 14.1.2.1.7** and **14.1.3.1.7**), the demographic and baseline characteristics were generally balanced between arms. The demographic and baseline characteristics were also similar to those in the SAF.

The demographic and baseline characteristics were generally balanced between arms in the Efficacy-PPS (**Tables 14.1.2.1.1** and **14.1.3.1.1**). The demographic and baseline characteristics were also similar to those in the SAF, except that all subjects had no evidence of prior SARS-CoV-2–infection at baseline in the Efficacy-PPS.

Phase 2 SAF (Reactogenicity Subset) and Immunogenicity PPS

In the Phase- 2 SAF, the demographic and baseline characteristics were generally balanced between arms. In the SCB-2019 and Placebo arms, 46% (373/808) and 43% (342/793) of subjects were female, respectively. The mean age was 37 years in both arms, with most subjects (97%) being between the ages of 18 to 64. Mean height and mean weights were 165 cm and 70 kg, respectively, in both arms. Most subjects in both arms were from the Philippines (57 or 56%), followed by Belgium (24 or 25%) and Colombia (19%). Most subjects in both arms

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identified as Asian (57%). No subjects were from Brazil or South Africa (unlike in the remainder of the Phase 3 SAF.

In both the SCB-2019 and Placebo arms, the percentage of subjects with high risk of severe COVID-19 was 21%. The most prevalent of those risks were obesity and hypertension, being reported by 13% and 8% of subjects, respectively, in the SCB-2019 arm, and both by 10% of subjects in the Placebo arm.

In both the SCB-2019 and Placebo arms, 60 to 65% of subjects had no evidence of prior SARS-CoV-2 infection or were SARS-CoV-2 seronegative at baseline.

In the Immunogenicity FAS, the demographic and baseline characteristics were generally balanced between arms (**Table 14.1.2.1.3** and **Table 14.1.3.1.3**). The demographic and baseline characteristics were also similar to those in the Phase 2 SAF.

In the Immunogenicity-PPS, the demographic and baseline characteristics were generally balanced between arms. The demographic and baseline characteristics were also similar to those in the Phase 2 SAF, except that all subjects in the Immunogenicity PPS had no evidence of prior SARS-CoV-2–infection at baseline. Also, in the Immunogenicity PPS SCB-2019 or Placebo arms, there were proportionally more subjects from Belgium (34% or 49%) and subjects who identified as White (32% or 49%) than in the Phase 2 SAF (24 or 25%, and 23% or 24%, respectively).

The demographic characteristic for the populations analyzed in the Six-month Follow-up, analysis of cross-neutralizing antibodies against variants of SARS-CoV-2, analysis of cell-mediated immune response, and analyses of specific populations (elderly subjects, individuals with HIV infection, subjects of Chinese origin, and subjects participated in analysis of comparability of SCB-2019 manufactured at different scales) are presented in the body of the report.

Efficacy/Immunogenicity Results:

Efficacy

All efficacy objectives (except key secondary #2 [any laboratory-confirmed SARS-CoV-2 infection], #4 [any laboratory-confirmed asymptomatic SARS-CoV-2 infection], and secondary #1 – [BOD]) are based on the primary analysis (data lock point 13 September 2021, efficacy cutoff date 10 Aug 2021). Cutoff date for key secondary #2, #4 and secondary #1 is 1 December 2021.

Primary Efficacy Objective (H1) - VE against COVID-19 of any severity

Vaccine efficacy against COVID-19 of any severity in the Efficacy PPS was 67.2% (95.72% CI: 54.3–76.8), and the lower limit of the CI was above the pre-specified success threshold of 30%. In the SCB-2019 arm, 52 endpoint cases were reported among the 5935 subjects at risk; whereas in the Placebo arm, 155 endpoint cases were reported among 5806 subjects at risk (**Table S3**).

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Table S3: Vaccine Efficacy against COVID-19 of Any Severity (Efficacy-PPS)

	No. of subjects at risk of endpoint	Cumulative follow up period (person.years)	No. of subjects with endpoint case	% VE (95.72% CI)
SCB-2019 (N=6251)	5935	517.3	52	67.2 (54.3–76.8)
Placebo (N=6104)	5806	506.1	155	

Source: **Table 14.2.1.1**. Follow-up period was from 14 days after Dose 2 to the cutoff date of the 10 August 2021.
Vaccine efficacy (VE) = 100×(1 minus the ratio of incidence rates [IR] in the Vaccine and Placebo arms). IR = number (No.) of subjects with endpoint case per cumulative follow-up.

Key Secondary Efficacy Objectives #1 (H2b) and #3 (H4) - VE against moderate-to-severe and severe COVID-19

Vaccine efficacy against moderate-to-severe COVID-19 in the Efficacy PPS was 83.7% (97.86% CI 55.9–95.4), and the lower limit of the CI was above the pre-specified success threshold of 0% (**Table S4**). In the SCB-2019 arm, 6 endpoint cases were reported among the 5935 subjects at risk, whereas in the Placebo arm, 36 endpoint cases were reported among 5806 subjects at risk. Vaccine efficacy against severe COVID-19 was 100% (97.86% CI 25.3–100.0), and the lower bound of the CI was above the pre-specified success threshold of 0% (**Table S4**). In the SCB-2019 arm, no endpoint case was reported among the 5935 subjects at risk, whereas in the Placebo arm, 8 endpoint cases were reported among 5806 subjects at risk.

Therefore SCB-2019 had statistically significant efficacy against moderate-to-severe COVID-19 and had statistically significant efficacy against severe-COVID-19 in the PPS.

Table S4: Vaccine Efficacy against moderate-to-severe COVID-19 and severe COVID-19 (Efficacy-PPS)

	No. of subjects at risk of endpoint	Cumulative follow up period (person.years)	No. of subjects with endpoint case	% VE (97.86% CI)
	Endpoint: moderate-to-severe COVID-19			
SCB-2019 (N=6251)	5935	517.3	6	83.7 (55.9–95.4)
Placebo (N=6104)	5806	506.1	36	
	Endpoint: severe COVID-19			
SCB-2019 (N=6251)	5935	517.3	0	100 (25.3–100.0)
Placebo (N=6104)	5806	506.1	8	

Source: **Table 14.2.2.1**. Follow-up period was from 14 days after Dose 2 to the cutoff date of 10 August 2021. Vaccine efficacy (VE) = 100×(1 minus the ratio of incidence rates [IR] in the Vaccine and Placebo arms). IR = number (No.) of subjects with endpoint case per cumulative follow-up.

Key Secondary Efficacy Objectives #2 (H2a) and #4 (H3) – VE against any laboratory-confirmed SARS-CoV-2 infection and any laboratory-confirmed asymptomatic SARS-CoV-2 infection

From 14 days after Dose 2 to the cutoff date of 1 December 2021, vaccine efficacy against any laboratory-confirmed SARS-CoV-2 infection was 34.4% (95% CI: 27.1–41.0) in the Efficacy PPS, with endpoint cases reported by 593 SCB-2019 recipients and 851 placebo recipients. The lower limit (LL) of 95% CI for vaccine efficacy (27.1%) is above 0 (**Table 14.2.2.2_P6m**).

Vaccine efficacy against any laboratory-confirmed asymptomatic SARS-CoV-2 infection was 12.9% (95% CI: -1.4–25.2) in the Efficacy PPS, with endpoint cases reported by 333 SCB-2019 recipients and 360 placebo recipients. The LL of 95% CI for vaccine efficacy (-1.4%) is below 0 (**Table 14.2.2.2_P6m**).

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Other secondary efficacy objectives

Secondary Efficacy Objective #1 - Vaccine efficacy against BOD

From 14 days after Dose 2 to the cutoff date of 1 December 2021, the number of subjects with RT-PCR-confirmed COVID-19 of any severity was 260 for SCB-2019 recipients and 489 for placebo recipients in the Efficacy PPS. None of the subjects presented RT-PCR-confirmed severe COVID-19 in SCB-2019 group. Twenty subjects presented RT-PCR-confirmed severe COVID-19 in placebo group. During this period, vaccine efficacy against BOD was 48.9% (95% CI: 40.5–56.0), with a BOD score of 260 for SCB-2019 recipients and 509 for placebo recipients (**Table 14.2.3.1_P6m**).

Secondary Efficacy Objective #2 – VE against any COVID-19 of any severity, associated with hospitalization

In the Efficacy PPS, vaccine efficacy against COVID-19 leading to hospitalization was 100% (95% CI 42.7–100; **Table 14.2.3.2**). In the SCB-2019 arm, no endpoint case was reported among the 5935 subjects at risk; whereas in the Placebo arm, 8 endpoint cases were reported among 5806 subjects at risk.

In SARS-CoV-2-naïve subjects in the Efficacy FAS (Dose 2), vaccine efficacy against COVID-19 leading to hospitalization was 100% (95% CI 42.7–100; **Table 14.2.3.2.1**), and was consistent with the Efficacy PPS.

Secondary Efficacy Objective #3 – VE by evidence of prior SARS-CoV-2 infection and by risk of severe COVID-19

- VE by evidence of prior SARS-CoV-2 infection

In SARS-CoV-2-exposed subjects in the Efficacy-FAS (Dose 2), and from 14 days after the 2nd dose to the cutoff date (10 August 2021), vaccine efficacy against COVID-19 of any severity was 64.2% (95% CI 26.5–83.8; **Table 14.2.3.7.2**). In the SCB-2019 arm, 11 endpoint cases were reported among the 6195 subjects at risk; whereas in the Placebo arm, 30 endpoint cases were reported among 6147 subjects at risk.

In SARS-CoV-2-exposed subjects in the Efficacy-FAS (Dose 2), and from 14 days after the 2nd dose, vaccine efficacy against moderate-to severe COVID-19 was 67.5% (95% CI −305.2 to 99.4; **Table 14.2.3.7.2**). In the SCB-2019 arm, 1 endpoint case was reported among the 6195 subjects at risk; whereas in the Placebo arm, 3 endpoint cases were reported among 6147 subjects at risk.

In SARS-CoV-2-exposed subjects in the Efficacy-FAS (Dose 2), and from 14 days after the 2nd dose, no severe COVID-19 case, or a COVID-19 case leading to hospitalization was reported (**Table 14.2.3.7.2**).

- VE by risk of severe COVID-19

In the Efficacy PPS (cutoff date 10 August 2021), in adults at high risk of severe COVID-19, vaccine efficacy against COVID-19 of any severity was 65.9% (95% CI 35.7–82.9; **Table 14.2.3.4.4**). In the SCB-2019 arm, 14 endpoint cases were reported among the 1027 subjects at risk; whereas in the Placebo arm, 38 endpoint cases were reported among 949 subjects at risk. In adults at low risk of severe COVID-19, vaccine efficacy against COVID-19 of any severity was 67.9% (95% CI 53.3–78.3; **Table 14.2.3.4.4**). In the SCB-2019 arm, 38 endpoint cases were reported among the 4908 subjects at risk; whereas in the Placebo arm, 117 endpoint cases were reported among 4857 subjects at risk.

Secondary Efficacy Objective #4 – VE against COVID-19 cases with onset after the 1st dose

In SARS-CoV-2–naïve subjects in the Efficacy-FAS (Dose 1), vaccine efficacy against COVID-19 of any severity was 7.8% (95% CI −16.7 to 27.3) from 14 days after Dose 1 through to Dose 2 (**Table 14.2.3.7.7**). In the SCB-2019 arm, 140 endpoint cases were reported among the 7311 subjects at risk, whereas in the Placebo arm, 152

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endpoint cases were reported among 7312 subjects at risk.

In SARS-CoV-2–naïve subjects in the Efficacy-FAS (Dose 1), vaccine efficacy against moderate-to-severe COVID-19 was 16.1% (95% CI −46.1 to 52.1) (**Table 14.2.3.7.7**). In the SCB-2019 arm, 26 endpoint cases were reported among the 7311 subjects at risk, whereas in the Placebo arm, 31 endpoint cases were reported among 7312 subjects at risk. Regarding severe COVID-19, one endpoint case was reported in the SCB-2019 arm and one endpoint case in the Placebo arm.

In SARS-CoV-2–exposed subjects in the Efficacy-FAS (Dose 1), vaccine efficacy against COVID-19 of any severity was 49.9% (95% CI 1.5–75.6; **Table 14.2.3.7.8**). In the SCB-2019 arm, 14 endpoint cases were reported among the 7325 subjects at risk; whereas in the Placebo arm, 28 endpoint cases were reported among 7305 subjects at risk. Regarding moderate-to-severe COVID-19, three endpoint cases were reported in each arm. No severe endpoint cases were reported in SARS-CoV-2-exposed adults in the interval from 14 days after Dose 1 to Dose 2.

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Secondary Efficacy Objective #5 – VE against SARS-CoV-2 VOCs (Efficacy PPS)

In the Efficacy PPS, the three most frequent lineages of SARS-CoV-2 detected in the COVID-19 cases of any severity were the Delta, Mu and Gamma lineages (**Table 14.2.3.6.1**). The Delta and Gamma lineages represent VOCs, whereas the Mu lineage represents variants of interest (VOIs).

Vaccine efficacy against COVID-19 of any severity associated with Delta lineage was 78.7% (95% CI 57.3–90.4; **Table 14.2.3.7**). In the SCB-2019 arm, 10 endpoint cases were reported among the 5935 subjects at risk; whereas in the Placebo arm, 46 endpoint cases were reported among 5806 subjects at risk.

Vaccine efficacy against COVID-19 of any severity associated with Mu lineage was 58.6% (95% CI 13.3–81.5; **Table 14.2.3.7**). In the SCB-2019 arm, 11 endpoint cases were reported among the 5935 subjects at risk; whereas in the Placebo arm, 26 endpoint cases were reported among 5806 subjects at risk.

Vaccine efficacy against COVID-19 of any severity associated with Gamma lineage was 91.8% (95% CI 44.9–99.8; **Table 14.2.3.7**). In the SCB-2019 arm, 1 endpoint case was reported among the 5935 subjects at risk; whereas in the Placebo arm, 12 endpoint cases were reported among 5806 subjects at risk.

For all other lineages, except the Beta lineage, there were more cases in the Placebo arm than in the SCB-2019 group (**Table 14.2.3.7**). For the Beta lineage, 7 endpoint cases were reported among the 5935 subjects at risk in the SCB-2019 arm; whereas in the Placebo arm, 4 endpoint cases were reported among 5806 subjects at risk. Regarding the vaccine efficacy in the cases for which no lineage could be defined or for cases where biological samples were not available for sequencing (missing), a similar vaccine efficacy as in the primary endpoint was observed (57.5 and 67.4%, respectively; **Table 14.2.3.7**).

Six-month follow up efficacy

Results of the six-month follow up efficacy (cutoff date 1 December 2021) are provided in the body of the CSR.

A re-analysis (sensitivity analysis) was performed upon the request from Chinese regulatory a

uthority for the primary efficacy analysis (cut-off date of 10 August 2021) and the 6-month follow-up analysis (cut-off date of 1 Dec 2021). Efficacy results for the Efficacy PPS and the Efficacy FAS populations for both the primary analysis and the 6-month follow-up analysis were similar to the original results for the primary endpoint. For the primary analysis, vaccine efficacy against COVID-19 of any severity in the Efficacy PPS was 64.4% (95.72% CI: 50.3–74.9) (**Table 14.2.1.1_S)**; and, for the 6-month follow-up analysis, vaccine efficacy was 50.4% (95.72% CI: 42.0–57.6) (**Table 14.2.1.1_P6m_S).**

Secondary immunogenicity objective – To assess the immunogenicity of SCB-2019 vaccine

Two doses of SCB-2019 were immunogenic in the adult study population (Immunogenicity PPS), in terms of the induction of SARS-CoV-2–specific antibodies (Abs). These Abs included; neutralizing Abs (measured by wild-type SARS-CoV-2 neutralization assay [WT-VNA] and pseudovirus neutralizing assay [pseudo-VNA]); Abs that specifically block SCB-2019 spike protein from binding to hACE-2 (ACE2-receptor-binding Abs); and Abs specific for the SCB-2019 spike protein (SCB-2019–binding Abs) (**Table S5**).

For WT-VNA titers (in IU/ml) and in the SCB-2019 recipients at Day 36, 2-weeks after the 2nd dose, the GMT was 224 (N=220) and higher than a GMT of 13 (N=219) at baseline (Day 1; **Table S5**). The corresponding GMFR at Day 36 was 17.5 (N=217; **Table 14.3.3.2.1**), and the percentage of SCB-2019 recipients who seroconverted (i.e. the SCR) was 82% (179/217; **Table S6**). At Day 36, 97% (213/220) of SCB-2019 recipients had titers ≥LLoQ (**Table 14.3.3.4.4**). At Day 22, 3-weeks after the 1st dose, the GMT was 16 (N=215), the GMFR was 1.2 (N=212)

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and the SCR was 4% (9/212; **Table S5** and **S6**). By contrast, in the placebo recipients, the GMTs at Days 1, 22 and 36 were 12 (N=27), 13 (N=28) and 13 (N=28), respectively; were similar to each other, and were similar to the baseline titer in the SCB-2019 recipients (13, N=219; **Table S5**).

Similar patterns of SARS-CoV-2–specific NAb induction in SCB-2019 recipients were observed for pseudo-VNA titers (**Table S5**, **Table S6** and **Tables 14.3.3.1.1**, **14.3.3.2.1**, **14.3.3.3.1** and **14.3.3.4.4**). For pseudo-VNA titers (in IU/ml) at Day 36, the GMT was 540 (N=220) and higher than a GMT of 16 (N=219) at baseline (Day 1; **Table S5**). The corresponding GMFR at Day 36 was 34.1 (N=218; **Table 14.3.3.2.1**), and the SCR was 94% (204/218; **Table S6**). At Day 36, 98% (216/220) of SCB-2019 recipients had titers ≥LLoQ (**Table 14.3.3.4.4**). At Day 22, 3-weeks after the 1st dose, the GMT was 23 (N=214), the GMFR was 1.5 (N=212) and the SCR was 8% (16/212; **Table S5** and **Table S6**).

For ACE2-receptor-binding titers (in CP50) and in the SCB-2019 recipients at Day 36, 2-weeks after the 2nd dose, the GMT was 258 (N=183) and higher than a GMT of 13 (N=213) at baseline (Day 1; **Table S5**). The corresponding GMFR at Day 36 was 20.1 (N=182; **Table 14.3.3.2.1**), and the SCR was 63% (115/182; **Table S6**). At Day 36, 65% (119/183) of SCB-2019 recipients had titers ≥LLoQ (**Table 14.3.3.4.4**). At Day 22, 3-weeks after the 1st dose, the GMT was 17 (N=213), the GMFR was 1.4 (N=212) and the SCR was 6% (13/212; **Table S6**).

Similar patterns of SARS-CoV-2–specific Ab induction in SCB-2019 recipients were observed for SCB-2019–binding titers (**Table S5**, **Table S6**, and **Tables 14.3.3.1.1**, **14.3.3.2.1**, and **14.3.3.3.1**). For SCB-2019–binding titers (in IU/ml) at Day 36, the GMT was 8.4 (N=378) and higher than a GMT of 0.5 (N=375) at baseline (Day 1; **Table S5**). The corresponding GMFR at Day 36 was 16.6 (N=375; **Table 14.3.3.2.1**), and the SCR was 78% (291/375; **Table S6**). At Day 36, 94% (356/378) of SCB-2019 recipients had titers ≥LLoQ (**Table 14.3.3.4.4**). At Day 22, 3-weeks after the 1st dose, the GMT was 0.7 (N=367), the GMFR was 1.4 (N=364) and the SCR was 4% (15/364; **Table S5** and **Table S6**).

Table S5: Geometric mean titers (GMTs; Immunogenicity PPS)

	SCB-2019	(N=381)	Placebo	(N=47)
Day	**N**	**GMT (95% CI)**	**N**	**GMT (95% CI)**
WT-VNA (IU/ml; i)				
Day 1	219	13 (13–13)	27	12 (–)
Day 22	215	16 (14–18)	28	13 (12–13)
Day 36	220	224 (194–259)	28	13 (12–13)
Pseudo-VNA (IU/ml; ii)				
Day 1	219	16 (16–16)	27	16 (–)
Day 22	214	23 (20–26)	28	16 (15–17)
Day 36	220	540 (473–618)	28	20 (15–28)
ACE2-receptor-binding Abs (CP50; iii)				
Day 1	213	13 (12–13)	27	12 (–)
Day 22	213	17 (15–20)	27	13 (12–14)
Day 36	183	258 (178–373)	27	12 (–)
SCB-2019-binding Abs (IU/ml; iv)				
Day 1	375	0.5 (0.5–0.5)	46	0.5 (0.5–0.5)
Day 22	367	0.7 (0.6–0.8)	46	0.6 (0.5–0.6)
Day 36	378	8.4 (7.5–9.5)	47	0.5 (0.5–0.6)

Source: **Table 14.3.3.1.1**. GMTs and 95% confidence intervals (95% CIs) by arm for (i) neutralizing Abs (measured by wild-type SARS-CoV-2 neutralization assay [{i} WT-VNA] and pseudovirus neutralizing assay [{ii} pseudo-VNA]); (iii) Abs that specifically block SCB-2019 spike protein from binding to hACE-2 (ACE2-receptor-binding Abs); and (iv) Abs specific for the

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SCB-2019 spike protein (SCB-2019–binding Abs). GMTs were calculated at Day 1 (baseline), at Day 22 (21 days after Dose 1) and Day 36 (14 days after Dose 2). A titer value measured below the lower limit of quantification (LLoQ) of the assay was assigned the value LLoQ/2. Titers were obtained from the Immunogenicity Per-Protocol set (PPS).

Table S6 Seroconversion rates (SCRs; Immunogenicity PPS)

	SCB-2019 (N=381)		Placebo (N=47)	
Assay	**n/N**	**% (95% CI)**	**n/N**	**% (95% CI)**
Day 22				
• WT-VNA (IU/ml; i)	9/212	4 (2–8)	0/27	0 (0–13)
• Pseudo-VNA (IU/ml; ii)	16/212	8 (4–12)	0/27	0 (0–13)
• ACE2-receptor-binding Abs (CP50; iii)	13/212	6 (3–10)	0/27	0 (0–13)
• SCB-2019-binding Abs (IU/ml; iv)	15/364	4 (2–7)	1/45	2 (0–12)
Day 36				
• SARS-CoV-2-specific NAbs (IU/ml; i)	179/217	82 (77–87)	0/27	0 (0–13)
• Pseudovirus-specific NAbs (IU/ml; ii)	204/218	94 (90–96)	1/27	4 (0–19)
• ACE2-receptor-binding Abs (CP50; iii)	115/182	63 (56–70)	0/27	0 (0–13)
• SCB-2019-specific Abs (IU/ml; iv)	291/375	78 (73–82)	0/46	0 (0–8)

Source: **Table 14.3.3.3.1**. The percentages (and 95% CIs) by arm of subjects seroconverted for (i) neutralizing Abs (measured by wild-type SARS-CoV-2 neutralization assay [{i} WT-VNA] and pseudovirus neutralizing assay [{ii} pseudo-VNA]); (iii) Abs that specifically block SCB-2019 spike protein from binding to hACE-2 (ACE2-receptor-binding Abs); and (iv) Abs specific for the SCB-2019 spike protein (SCB-2019–binding Abs); i.e., the seroconversion rates (SCRs). SCRs were calculated at Day 22 and Day 36. Seroconversion was defined as ≥4-fold rise in the titer at the post-baseline time point from the baseline titer (Day 1) or from the lower limit of quantification (LLoQ) of the assay if that baseline titer was below the LLoQ. Titers were obtained from the Immunogenicity Per-Protocol set (PPS).

Antibody persistence results at 6 months post-vaccination, cross-neutralization immune response data against SARS-CoV-2 variants of concern, cell-mediated immune response, immune response in specific populations (elderly subjects, individuals with HIV infection, subjects of Chinese origin) and immunological comparability data for SCB-2019 drug substance manufactured at different scales are presented in the body of the CSR.

Safety Results:

All summaries and analyses of safety data were based on subjects in the Phase-2 SAF for reactogenicity and unsolicited AEs in the 6-week period after the first dose; in the SAF (including Phase 2 and Phase 3 subjects) for SAEs, MAAEs, AESIs, AE leading to study termination, and unsolicited AEs in the 6-week period after the first dose; and in the Immunogenicity PPS for the measurement of Trimer-Tag–specific serum antibodies. In both SAF and Phase-2 SAF, subjects were grouped according to the vaccine/placebo they received at least the first dose. The SAF adults, from Dose 1 up to 1 December 2021 included 15070 adult recipients of at least 1 dose of SCB-2019, and 15067 adult recipients of at least 1 dose of placebo (**Table 14.1.1.1_P6m**). Of those, 14011 subjects (93.0%) received 2 doses of SCB-2019, and 13861 subjects (92.0%) received 2 doses of placebo (**Table 14.1.1.2.1_P6m**).

Primary objective: the safety and reactogenicity of SCB-2019

Solicited Local Reactions (Phase 2 SAF)

Solicited local AEs were reported more frequently by SCB-2019 recipients than placebo recipients (**Table S7**). Within the 7-day periods after either dose, these solicited AEs were reported by 44% (349/803) of SCB-2019 recipients and 15% (119/787) of placebo recipients. The majority of solicited local AEs reported were mild in intensity. Moderate intensity AEs were reported by 4.4% (35/803) SCB-2019 recipients and 0.1% (1/787) of

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placebo recipients; and severe intensity AEs (PTs: injection site pain, erythema and swelling) were reported by 0.9% (7/803) SCB-2019 recipients and 0.1% (1/787) of placebo recipients.

Injection-site pain was the most frequent local symptom, being reported by 42% (340/803) of SCB-2019 recipients and 14% (107/787) of placebo recipients (**Table S7**).

Frequencies of solicited local AEs were generally lower after the 2nd dose than after the 1st dose (**Table S7**). After the 2nd and 1st doses, solicited local AEs were reported by 28% (198/702) and 36% (290/803) of SCB-2019 recipients, respectively, and 8% (57/699) and 11% (89/786) of placebo recipients, respectively. A similar pattern was observed with severe solicited local AEs, even though very few subjects reported severe AEs. Notably, after the 2nd and 1st doses, severe solicited local AEs were reported by 0.4% (3/702) and 0.6% (5/803) of SCB-2019 recipients, respectively.

Solicited local AEs were transient, generally resolved in the 7-day period after dosing; and the duration of these AEs were similar between the SCB-2019 arm and the Placebo arm (**Table 14.3.1.2**). For SCB-2019 recipients, the mean duration of symptoms ranged from 1.5 days (erythema, N=14; Dose 1) to 2.0 days (injection-site pain, N=189; Dose 2). The mean duration of injection-site pain – the most frequent symptom – was 1.9 days after Dose 1 (N=287), and 2.0 days after Dose 2 (N=189). For Placebo recipients, the mean duration of symptoms ranged from 1.2 day (swelling, N=9, Dose 1) to 2.7 days (erythema, N=10; Dose 2). The mean duration of injection-site pain – the most frequent symptom – was 1.5 days after Dose 1 (N=81), and after Dose 2 (N=52).

Table S7: Solicited Local Adverse Events (Phase 2 SAF)

After Dose	Solicited Local Adverse Event (AE)	Ne	Any intensity		Moderate		Severe	
			n	% (95%CI)	N	% (95%CI)	n	% (95%CI)
SCB-2019 (N=808)								
1	**Any Symptom**	803	290	36 (33–40)	24	3.0 (1.9–4.4)	5	0.6 (0.2–1.4)
2	**Any Symptom**	702	198	28 (25–32)	15	2.1 (1.2–3.5)	3	0.4 (0.1–1.2)
1 or 2	**Any Symptom**	803	349	44 (40–47)	35	4.4 (3.1–6.0)	7	0.9 (0.4–1.8)
	• Injection-site pain		340	42 (39–46)	30	3.7 (2.5–5.3)	6	0.7 (0.3–1.6)
	• Erythema		48	6.0 (4.4–7.8)	5	0.6 (0.2–1.4)	2	0.2 (0.0–0.9)
	• Swelling		41	5.1 (3.7–6.9)	5	0.6 (0.2–1.4)	1	0.1 (0.0–0.7)
Placebo (N=793)								
1	**Any Symptom**	786	89	11 (9–14)	1	0.1 (0.0–0.7)	1	0.1 (0.0–0.7)
2	**Any Symptom**	699	57	8 (6–10)	0	0.0 (0.0–0.5)	0	0.0 (0.0–0.5)
1 or 2	**Any Symptom**	787	119	15 (13–18)	1	0.1 (0.0–0.7)	1	0.1 (0.0–0.7)
	• Injection-site pain		107	14 (11–16)	1	0.1 (0.0–0.7)	0	0.0 (0.0–0.5)
	• Erythema		22	2.8 (1.8–4.2)	0	0.0 (0.0–0.5)	1	0.1 (0.0–0.7)
	• Swelling		16	2 (1.2–3.3)	0	0.0 (0.0–0.5)	0	0.0 (0.0–0.5)

Source: **Table 14.3.1.1**. Solicited local AEs were recorded within 7 days after each dose. For a given subject and when more than one AE was reported for a given symptom within the 7-day period, the most severe AE in intensity grading was included in the calculations of percentages. Percentages were calculated as 100×n/Ne. Some values have been rounded to 2 significant figures or to the nearest integer to aid comprehension.

Solicited Systemic Adverse Events (Phase 2 SAF)

Solicited systemic AEs were reported by SCB-2019 recipients at a similar frequency to that reported by placebo recipients (**Table S8**). Within the 7-day periods after either dose, these solicited AEs were reported by 43%

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(347/803) of SCB-2019 recipients and 40% (312/787) of placebo recipients. The majority of solicited systemic AEs were mild in intensity. Solicited systemic AEs of moderate intensity were reported by 11% (89/803) of SCB-2019 recipients and 11% (89/787) of placebo recipients; and solicited systemic AEs of severe intensity were reported by 3.6% (29/803) SCB-2019 recipients and 2.3% (18/787) of placebo recipients.

Fatigue and headache were the most frequent systemic symptoms; fatigue being reported by 27% (219/803) of SCB-2019 recipients and 24% (189/787) of placebo recipients; and headache being reported by 27% (219/803) of SCB-2019 recipients and 26% (201/787) of placebo recipients (**Table S8**).

Frequencies of solicited systemic AEs were generally lower after the 2nd dose than after the 1st dose (**Table S8**). After the 2nd and 1st doses, solicited systemic AEs were reported by 23% (162/702) and 36% (288/803) of SCB-2019 recipients, respectively, and 21% (147/699) and 34% (268/786) of placebo recipients, respectively. A similar pattern was observed with severe solicited systemic AEs. Notably, after the 2nd and 1st doses, severe solicited systemic AEs were reported by 1.4% (10/702) and 2.4% (19/803) of SCB-2019 recipients, respectively.

Solicited systemic AEs were transient, generally resolved in the 7-day period after dosing; and the duration of these AEs were similar between the SCB-2019 arm and the Placebo arm (**Table 14.3.1.5**). For SCB-2019 recipients, the mean duration of symptoms ranged from 1.3 days (loss of appetite, N=39; fever, N=8; Dose 1) to 2.4 days (loss of appetite, N=19; Dose 2). The mean duration of headache – the most frequent symptom – was 2.1 days after Dose 1 (N=170), and 2.0 days after Dose 2 (N=98). For Placebo recipients, the mean duration of symptoms ranged from 1.0 day (fever, N=2, Dose 2) to 2.4 days (fatigue, N=74; Dose 2). The mean duration of headache – the most frequent symptom – was 2.1 days after Dose 1 (N=166), and after Dose 2 (N=89).

Table S8: Solicited Systemic Adverse Events (Phase-2 SAF)

After Dose	Solicited Systemic Adverse Event (AE)	Ne	Any intensity		Moderate		Severe	
			n	% (95%CI)	n	% (95%CI)	n	% (95%CI)
SCB-2019 (N=808)								
1	**Any Symptom**	803	288	36 (32–39)	71	8.8 (7.0–11.0)	19	2.4 (1.4–3.7)
2	**Any Symptom**	702	162	23 (20–26)	39	5.6 (4.0–7.5)	10	1.4 (0.7–2.6)
1 or 2	**Any Symptom**	803	347	43 (40–47)	89	11.1 (9.0–13.5)	29	3.6 (2.4–5.1)
	• Fatigue		219	27 (24–30)	53	6.6 (5.0–8.5)	19	2.4 (1.4–3.7)
	• Headache		219	27 (24–30)	54	6.7 (5.1–8.7)	5	0.6 (0.2–1.4)
	• Myalgia		119	15 (12–18)	29	3.6 (2.4–5.1)	5	0.6 (0.2–1.4)
	• Arthralgia		75	9.3 (7.4–11.6)	19	2.4 (1.4–3.7)	2	0.2 (0.0–0.9)
	• Loss of appetite		51	6.4 (4.8–8.3)	11	1.4 (0.7–2.4)	3	0.4 (0.1–1.1)
	• Nausea		54	6.7 (5.1–8.7)	15	1.9 (1.0–3.1)	2	0.2 (0.0–0.9)
	• Chills		53	6.6 (5.0–8.5)	5	0.6 (0.2–1.4)	5	0.6 (0.2–1.4)
	• Fever		12	1.5 (0.8–2.6)	5	0.6 (0.2–1.4)	3	0.4 (0.1–1.1)
Placebo (N=793)								
1	**Any Symptom**	786	268	34 (31–38)	65	8.3 (6.4–10.4)	16	2.0 (1.2–3.3)
2	**Any Symptom**	699	147	21 (18–24)	39	5.6 (4.0–7.5)	5	0.7 (0.2–1.7)
1 or 2	**Any Symptom**	787	312	40 (36–43)	89	11.3 (9.2–13.7)	18	2.3 (1.4–3.6)
	• Fatigue		189	24 (21–27)	50	6.4 (4.8–8.3)	10	1.3 (0.6–2.3)
	• Headache		201	26 (22–29)	53	6.7 (5.1–8.7)	8	1.0 (0.4–2.0)
	• Myalgia		109	14 (12–16)	27	3.4 (2.3–5.0)	3	0.4 (0.1–1.1)
	• Arthralgia		66	8.4 (6.5–10.5)	19	2.4 (1.5–3.7)	2	0.3 (0.0–0.9)
	• Loss of appetite		56	7.1 (5.4–9.1)	10	1.3 (0.6–2.3)	3	0.4 (0.1–1.1)

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• Nausea	51	6.5 (4.9–8.4)	12	1.5 (0.8–2.6)	5	0.6 (0.2–1.5)
• Chills	41	5.2 (3.8–7.0)	6	0.8 (0.3–1.7)	2	0.3 (0.0–0.9)
• Fever	9	1.1 (0.5–2.2)	2	0.3 (0.0–0.9)	2	0.3 (0.0–0.9)

Source: **Table 14.3.1.4**. Solicited systemic AEs were recorded within 7 days after each dose. For a given subject and when more than one AE was reported for a given symptom within the 7-day period, the most severe AE in intensity grading was included in the calculations of percentages. Percentages were calculated as 100×n/Ne. n_e= number of events. Some values have been rounded to 2 significant figures or to the nearest integer to aid comprehension.

Unsolicited AEs between Day 1 and Day 43 (Phase 2 SAF)

Unsolicited AEs were reported by SCB-2019 recipients at a similar frequency to that reported by placebo recipients (**Table S9**, **Table S10** and **Table S11**). Within the 6-week period after receiving the 1st dose, these unsolicited AEs were reported by 12% (94/808) of SCB-2019 recipients and 14% (112/793) of placebo recipients. Similarly, unsolicited AEs considered related to vaccination were reported by SCB-2019 recipients at a similar frequency to that reported by placebo recipients (**Table S9** and **Table S10**). These related unsolicited AEs were reported by 3.1% (25/808) of SCB-2019 recipients and 3.3% (26/793) of placebo recipients; and were mostly classified under General disorders and administration site conditions or Nervous system disorders (primarily headaches; **Table S11**).

Table S9: Unsolicited AEs in the Phase 2 SAF (Day 1 to 43)

Adverse event (AE)	**SCB-2019 (N=808)**		**Placebo (N=793)**	
	n_s (n_e)	**% subjects (95% CI)**	**n_s (n_e)**	**% subjects (95% CI)**
Any AE	94 (123)	11.6 (9.5–14.0)	112 (140)	14.1 (11.8–16.7)
Any related AE	25 (31)	3.1 (2.0–4.5)	26 (33)	3.3 (2.2–4.8)
Any severe AE	1 (1)	0.1 (0–0.7)	2 (2)	0.3 (0.0–0.9)

Source **Table 14.3.2.2**, **Table 14.3.2.3** and **Table 14.3.2.4.** Percentage of subjects was calculated as 100×n_s/N, where n_s=number of subjects reporting the AE, n_e= number of events and N=number of subjects in the Phase-2 SAF by arm. Unsolicited AEs were collected from Day 1 and Day 43 for the primary endpoint. A related AE was an AE which the investigator considered to be probably or possibly caused by the study vaccine. CI, confidence interval.

Table S10: Unsolicited AEs with prevalence of >1% subjects by SOC in the Phase 2 SAF (Day 1 to 43)

Unsolicited adverse event (AE) by system organ class (preferred term)	**SCB-2019 (N=808)**		**Placebo (N=793)**	
	n_s (n_e)	**% subjects (95% CI)**	**n_s (n_e)**	**% subjects (95% CI)**
Infections and infestations	45 (48)	5.6 (4.1–7.4)	62 (65)	7.8 (6.0–9.9)
• (COVID-19)	18 (18)	2.2 (1.3–3.5)	26 (26)	3.3 (2.2–4.8)
General disorders & admin. site conditions	21 (23)	2.6 (1.6–3.9)	16 (20)	2.0 (1.2–3.3)
Nervous system disorders	10 (14)	1.2 (0.6–2.3)	20 (24)	2.5 (1.5–3.9)
• (Headache)	4 (5)	0.5 (0.1–1.3)	7 (7)	0.9 (0.4–1.8)

Source **Table 14.3.2.2**. Percentage of subjects was calculated as 100×n_s/N, where n_s=number of subjects reporting the AE, n_e= number of events and N=number of subjects in the Phase-2 SAF by arm. Unsolicited AEs were collected from Day 1 and Day 43 for the primary endpoint. Admin., administration; and CI, confidence interval.

Table S11: Related unsolicited AEs with prevalence of >0.5% subjects by SOC in the Phase 2 SAF (Day 1 to 43)

Related unsolicited adverse event (AE)	**SCB-2019 (N=808)**	**Placebo (N=793)**

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by system organ class (preferred term)	**n_s (n_e)**	**% subjects (95% CI)**	**n_s (n_e)**	**% subjects (95% CI)**
General disorders and admin. site conditions	13 (15)	1.6 (0.9–2.7)	9 (12)	1.1 (0.5–2.1)
Nervous system disorders	4 (6)	0.5 (0.1–1.3)	7 (8)	0.9 (0.4–1.8)
• (Headache)	3 (4)	0.4 (0.1–1.1)	4 (4)	0.5 (0.1–1.3)

Source **Table 14.3.2.3**. Percentage of subjects was calculated as $100 \times n_s/N$, where n_s=number of subjects reporting the AE, n_e= number of events and N=number of subjects in the Phase-2 SAF by arm. A related AE was an AE which the investigator considered to be probably or possibly caused by the study vaccine. Unsolicited AEs were collected from Day 1 and Day 43 for the primary endpoint. Admin., administration; and CI, confidence interval.

Severe unsolicited AEs between Day 1 and Day 43 (Phase 2 SAF)

The majority of reported unsolicited AEs were mild or moderate in intensity and resolved within short duration. Only three severe unsolicited AEs were reported in the Phase 2 – SAF: two cases of hypertension (one in each arm) and one case of stab wound in the Placebo arm (**Table 14.3.2.4**).

Unsolicited AEs between Day 1 and Day 43 (SAF)

In the SAF, from Dose 1 to 3-weeks after Dose 2 (Day 43), unsolicited AEs were reported by 10.2% (1543/15070) of SCB-2019 recipients and 9.4% (1414/15067) of placebo recipients. At least one related unsolicited AE was reported from Day 1 to Day 43 by 4.6% (690/15070) of SCB-2019 recipients and 3.0% (459/15067) of placebo recipients.

The most frequently reported related unsolicited AEs by SOC in the SCB-2019 and Placebo arms were General disorders and administration site conditions (reported by 3.4% and 1.7% of subjects, respectively), and Nervous system disorders (reported by 0.9% of subjects in both arms). The most frequently reported related unsolicited AEs by PT in the SCB-2019 and Placebo arms were vaccination site pain (reported by 2.0% and 0.6% of subjects, respectively), and headache (reported by 0.8% and 0.7%, of subjects respectively) (**Table 14.3.2.3_P6m**).

Severe unsolicited AEs between Day 1 and Day 43 (SAF)

At least one severe unsolicited AE was reported from Day 1 to Day 43 by 0.2% (33/15070) of SCB-2019 recipients and 0.2% (33/15067) of placebo recipients (**Table 14.3.2.4_P6m**). The most frequently reported severe unsolicited AEs by SOC in the SCB-2019 and Placebo arms were Infections and infestations (reported by 8/15070 and 12/15067 subjects, respectively), and by PT were COVID-19 reported by 4 subjects in the SCB-2019 arm and 5 subjects in the Placebo arm.

Secondary Safety Objective: Assessment of Trimer-Tag-Specific Antibodies

There was no evidence in the adult recipients of SCB-2019 of the induction of Abs specific for the Trimer-Tag domain of the SCB-2019 antigen. A total of 2589 serum samples collected from 863 subjects after 1 dose (Day 22) or 2 doses (Day 36) and no Trimer-Tag-specific Ab titer above the LLoQ was observed in any SCB-2019 recipient in the Immunogenicity subset of the PPS (i.e. GMTs = LLoQ/2 and GMFRs =1; **Table 14.3.3.1.1** and **14.3.3.1.2**).

Safety: Brief Summary of AEs

SAEs, MAAEs, AESIs and AE leading to study termination (SAF)

From Dose 1 to 1 December 2021, overall, 90 (0.6%) subjects in the SCB-2019 arm and 114 (0.8%) subjects in the Placebo arm reported at least one SAE (**Table S12**). The number of SAEs reported in subjects appeared to be lower in the SCB-2019 arm (114) than in the Placebo arm (176), possibly reflecting a lower frequency of AEs categorized under preferred terms related to COVID-19 (**Table 14.3.2.6_P6m**). SAEs were most frequently reported in the SOCs Infections and infestations (reported by 23 [0.2%] of subjects in SCB-2019 arm and 46 [0.3%] in the Placebo

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arm).

From Dose 1 to 1 December 2021, eight SAEs considered by the investigator as related to vaccination were reported by 4 SCB-2019 recipients (4 events) and 2 placebo recipients (4 events).

The four related SAEs reported by the four SCB-2019 recipients were hypersensitivity (2 events), Bell's palsy, and spontaneous abortion (**Appendix 14.3.2.2_P6m**). Three related SAEs were reported by one placebo recipient and were (i) COVID-19 and (ii) pneumonia, and (iii) acute respiratory distress syndrome. A fourth related SAE was reported by one placebo recipient and was spontaneous abortion.

Overall, 323 (2.1%) subjects in the SCB-2019 arm and 496 (3.3%) subjects in the Placebo arm reported at least one AESI (**Table S12**). The number of AESIs reported in subjects appeared to be lower in the SCB-2019 arm (509) than in the Placebo arm (791), reflecting a difference in the number of Anosmia (252 vs 386) and Ageusia (201 vs 327) AEs in the SCB-2019 and Placebo arms. AESIs were most frequently reported in the SOCs Nervous system disorders (reported by 288 [1.9%] subjects in the SCB-2019 arm and 463 [3.1%] subjects in the Placebo arm).

At least one MAAE was reported by 7.1% (1071/15070) of SCB-2019 recipients and 8.0% (1211/15067) of placebo recipients (**Table S12**). The most frequently reported MAAEs by SOC in the SCB-2019 and Placebo arms were Infections and infestations (5.0% and 5.9% of subjects, respectively).

Fewer SCB-2019 recipients than placebo recipients reported AEs that led to early termination from the study (**Appendix 14.3.2.7_P6m**). From Day 1 to the cutoff date for this report, 10 of these AEs were reported by 9/15070 SCB-2019 recipients, whereas 30 of these AEs were reported by 24/15067 placebo recipients.

Deaths: From Dose 1 to the cutoff date for this addendum (1 December 2021), 32 deaths associated with 38 AEs were reported; 9 (0.1%) deaths were reported in the SCB-2019 arm (N=15070) and 23 (0.2%) deaths were reported in the Placebo arm (N=15067; **Table S12**). No death was considered to be associated with the study vaccine.

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Table S12: Overall Summary of Unsolicited AEs, SAEs MAAEs, AESIs and AEs Leading to Study Termination (SAF)

Adverse event (AE) type	SCB-2019 (N=15070)		Placebo (N=15067)	
	Number of subjects, (n_s) (number of events, n_e)	% subjects (95% CI)	Number of subjects, (n_s) (number of events, n_e)	% subjects (95% CI)
Unsolicited AE*	1543 (2293)	10.2 (9.8–10.7)	1414 (2040)	9.4 (8.9–9.9)
• Related	690 (1024)	4.6 (4.3–4.9)	459 (616)	3.0 (2.8–3.3)
• Severe	33 (39)	0.2 (0.2-0.3)	33 (37)	0.2 (0.2-0.3)
Serious AE (SAE)	90 (114)	0.6 (0.5–0.7)	114 (176)	0.8 (0.6–0.9)
• Related	4 (4)	0 (0.0–0.1)	2 (4)	0 (0.0–0.0)
Medically attended AE (MAAE)	1071 (1697)	7.1 (6.7–7.5)	1211 (1910)	8.0 (7.6–8.5)
AE of special interest (AESI)	323 (509)	2.1 (1.9–2.4)	496 (791)	3.3 (3.0–3.6)
AE leading to early study termination	9 (10)	0.1 (0.0–0.1)	23 (29)	0.2 (0.1–0.2)
Death	9 (9)	0.1 (0.0–0.1)	23 (29)	0.2 (0.1–0.2)

Source **Tables 14.3.2.1_P6m**, **14.3.2.2_P6m** and **14.3.2.3_P6m and 14.3.2.4_P6m**. The percentage of subjects was calculated as $100 \times n_s/N$, where n_s=number of subjects reporting the AE, and N=number of subjects in the SAF by arm. A related AE was an AE which the investigator considered to be probably or possibly caused by the study vaccine. CI, confidence interval. AEs were excluded if occurring after other COVID-19 vaccine. *Any unsolicited AEs were collected from Day 1 up to 3 weeks after Dose 2 (Day 43). Other AE types were collected from Day 1 up to 1 December 2021.

Pregnancies

From Dose 1 up to 1 December 2021, 125 pregnancies were reported; 60 pregnancies were reported by SCB-2019 recipients and 65 were reported by Placebo recipients. Nine (0.06 %) spontaneous abortions were reported in SCB-2019 vaccine arm and 10 (0.07 %) in the placebo arm. Overall, no imbalance in the number of subjects with abnormal pregnancy outcomes was observed between the study arms (**Listing 16.2.8.4_P6m**).

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Efficacy Conclusions

- The primary efficacy objective was met in demonstrating that two doses of the SCB-2019 vaccine protected against COVID-19 of any severity in SARS-CoV-2 naïve adults.
- The key secondary efficacy objectives were met in demonstrating significant efficacy of two doses of the SCB-2019 vaccine against moderate-to-severe COVID-19 and against severe COVID-19 in SARS-CoV-2–naïve adults.
- SCB-2019 vaccine induces protection against laboratory-confirmed SARS-CoV-2 infection of any severity and reduces the burden of COVID-19 disease in SARS-CoV-2-naïve adults. Protection against asymptomatic RT-PCR-confirmed SARS-CoV-2 infection was observed in SARS-CoV-2-exposed adults, but not in SARS-CoV-2 naïve adults.
- Two doses of the SCB-2019 vaccine protected against COVID-19 caused by various lineages of SARS-CoV-2 variants.
- In SARS-CoV-2 naïve subjects, VE against severe COVID-19 and COVID-19-associated hospitalizations remain high at 6 months after vaccination.
- In subjects previously infected with SARS-CoV-2, SCB-2019 induces protection against any COVID-19, with no reduction in the efficacy of SCB-2019 vaccine for at least 6 months after vaccination.
- SCB-2019 vaccine induces protection against COVID-19 in healthy subjects and individuals with co-morbidities associated with high risk of severe COVID-19 across the entire age range, including subjects 60 years of age and above.
- A re-analysis (sensitivity analysis) performed for the primary and 6-month follow-up efficacy objectives has shown SCB-2019 vaccine efficacy to be consistent with the original efficacy analysis results.

Immunogenicity Conclusions

- Two doses of the SCB-2019 vaccine were immunogenic in SARS-CoV-2–naïve adults, in terms of the induction of functional Abs specific for SARS-CoV-2.
- In SARS-CoV-2 exposed subjects, a single dose induced a rapid, significant and specific humoral response at 21 days after vaccination. The second dose was associated with further increase in antibody titers.
- Neutralizing antibody persist for at least 6 months after the primary immunization series in SARS-CoV-2-naïve and SARS-CoV-2 exposed individuals.
- In SARS-CoV-2 naïve study participants, a robust cross neutralizing response was observed against Alpha, Beta, Gamma, Delta, Mu and Omicron BA.2 and BA.5 variants but not against Omicron BA.1 and BA.4. In SARS-CoV-2 exposed study participants, a cross neutralizing response was observed against all variants at antibody levels associated with clinical protection.
- A Th1 CD4+ T cell response was observed against S1 subunit peptide pool in PBMCs from subjects who received 2 doses of SCB-2019. This Th1 response tended to be lower against S2 subunit peptide and was not observed with Trimer-tag, Gly repeats or CICP. No Th2 or Th17 type responses were detected with any of the stimulating pools of peptides.

Safety Conclusions

- The SCB-2019 vaccine had an acceptable safety profile with no major safety concerns in the adult study population.

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4.0 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACE2	angiotensin-converting enzyme 2
AE	adverse event
AESI	adverse events of special interest
BOD	burden of disease
CI	confidence interval
CMI	cell-mediated immunity
COVID-19	coronavirus disease 2019
CSR	clinical study report
DSMB	data safety monitoring board
EAC	endpoint adjudication committee
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
ePRO	electronic patient-reported outcome
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMFR	geometric mean fold rise
GMT	geometric mean titer
$H1_0$	null hypothesis
$H1_a$	alternative hypothesis
HIV	human immunodeficiency virus
IA	interim analysis
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
Ig	Immunoglobulin
i.m.	Intramuscular
IMP	investigational medicinal product
IRR	incidence rate ratio
LAR	legally acceptable representative
LL	lower limit
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle-East respiratory syndrome
N	Nucleocapsid
NAb	neutralizing antibody
NEWS2	National Early Warning Scoring 2
PaO_2	partial pressure of arterial oxygen
PBMC	peripheral blood mononuclear cell
PD	protocol deviation
PI	principal investigator

pIMD	potential immune-mediated diseases
PPS	per-protocol set
PT	Preferred Term
RBD	receptor-binding domain
RR	relative risk
RT-PCR	reverse transcription-polymerase chain reaction
S	spike (protein)
SAE	serious adverse event
SAF	safety (set)
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCB-2019	CpG 1018/alum-adjuvanted recombinant, SARS-CoV-2 trimeric S-protein subunit vaccine
SOC	System Organ Class
SOP	standard operating procedure
SpO_2	oxygen saturation
TNE	target number of events
VE	vaccine efficacy
VNA	virus-neutralizing assay
VOC	variant of concern
VOI	variant of interest
WOCBP	women of childbearing potential

5.0 ETHICS

5.1 Independent Ethics Committee

The trial protocol, protocol amendments, informed consent form (ICF), and other information that required approval were reviewed and approved by the ethics committee of each clinical site.

Details of the independent ethics committees (IECs) are provided in **Appendix 16.1.3**.

5.2 Ethical Conduct of the Study

This study was conducted in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 - Good Clinical Practice (GCP) ethical principles that have their origin in the Declaration of Helsinki, Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) and applicable local regulations.

5.3 Subject Information and Consent

Written informed consent was obtained prior to screening from each subject prior to performing any study-specific procedures.

A sample ICF is provided in **Appendix 16.1.3.** Representative written information for subjects is provided in **Appendix 16.1.3**.

6.0 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The administrative structure of the study is described briefly in the following sections. Information about investigators and other important participants in the study is provided in **Appendix 16.1.4**.

6.1 Study Sites

This was a multi-site trial conducted at 31 trial sites, in 5 countries (3 sites in Belgium, 5 sites in Brazil, 9 sites in Colombia, 10 sites in the Philippines, and 4 sites in South Africa). The Phase 2 part of the study was conducted at 10 out of the 31 trial sites (3 sites in Belgium [sites 151, 153, 155], 2 sites in Colombia [sites 301 and 306] and 5 sites in the Philippines [sites 602, 606, 610, 614 and 615]).

Selection of the trial sites was based on expertise in the therapeutic area and the conduct of clinical research trials.

6.2 Sponsor Information and Delegated Study-related Activities

The sponsor or delegate was to perform all study-related activities. The PI at each site was responsible for ensuring that monitoring findings were addressed to ensure compliance with the protocol.

Information concerning the investigators is provided in **Appendix 16.1.4**. A list of organizations or institutions that conducted key study-related activities is provided in **Appendix 16.1.4**.

6.3 Study-specific Committees

An independent data safety monitoring board (DSMB) was to be convened to assess the progress of the clinical study, the safety data, and critical efficacy endpoints (if appropriate), and provide recommendations to the sponsor during the entire study period.

An independent endpoint adjudication committee (EAC) was to review in an independent, unbiased, blinded-to-treatment way all potential coronavirus disease 2019 (COVID-19) cases and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection events corresponding to the primary and secondary efficacy endpoints.

The composition, roles and responsibilities of the DSMB and the EAC are described in the DSMB charter (**Appendix 16.1.13**) and EAC charter (**Appendix 16.1.14**).

6.4 Principal Investigator and Coordinating Investigator Selection

Selection criteria for the investigators included significant knowledge of the trial protocol, the investigational vaccine, expertise in the therapeutic area and conduct of clinical research as well as trial participation. A principal investigator was designated for each of the 31 sites. A coordinating investigator was designated for each country and was required to review and sign this clinical study report (CSR) and by doing so agreed that it accurately describes the results of the trial. The signatures for the coordinating investigators are provided in **Appendix 16.1.5**.

7.0 INTRODUCTION

This study assessed the efficacy against COVID-19, immunogenicity, reactogenicity, and safety of CpG 1018/alum-adjuvanted recombinant, SARS-CoV-2 trimeric spike (S) protein subunit vaccine (SCB-2019) in adults (aged 18 years and above) and adolescents (12-17 years of age).

The COVID-19 pandemic has resulted in high morbidity and mortality, caused major disruption to healthcare systems, and has had significant socioeconomic impacts. Currently, only limited treatment options are available against COVID-19 and accelerated vaccine development is urgently needed. Several COVID-19 vaccines have been authorized in some countries, but the global supply remains insufficient for pandemic control. Additional safe and effective vaccines for COVID-19 prevention would have significant public health impact.

SCB-2019 is a recombinant SARS-CoV-2 S protein (Wuhan-Hu1 strain) fused to Trimer-Tag and produced in Chinese hamster ovary (CHO) cells. SCB-2019 preserves the native trimeric structure of S-protein in the prefusion form and induces neutralizing antibodies to SARS-CoV-2. Trimer-Tag is derived from the human C-propeptide domain of pro-collagen and is capable of self-trimerization by fusing any soluble receptor or biologically-active proteins in-frame of Trimer-Tag[1]. The resulting fusion proteins expressed in mammalian cells are secreted as disulfide bond-linked homotrimers. SCB-2019 is adjuvanted with CpG 1018/alum.

Immunogenicity and safety of different dose levels (3, 9, and 30 µg) of CpG 1018/alum-adjuvanted SCB-2019 vaccine, administered as 2-dose series 21 days apart was assessed in a Phase 1 clinical study. All dose levels were well-tolerated and induced neutralizing antibodies against S protein of the SARS-CoV-2 virus[1]. The SARS-CoV-2-specific neutralizing antibodies persisted for at least 6 months after a 2-dose vaccination series with SCB-2019 CpG/alum[2]. Based on the results of the Phase 1 clinical study, Clover selected the formulation containing 30 µg of SCB-2019 in combination with CpG1018/alum adjuvant for further clinical development.

This study of CpG 1018/alum-adjuvanted SCB-2019 included two clinical phases: Phase 2 in adults and adolescents and Phase 3 in adults. Subjects received two doses, 21 days apart. The study was placebo-controlled to allow a direct comparison with placebo and for a precise estimation of clinical efficacy of SCB-2019. In this report, the term *study vaccine* refers to both SCB-2019 and placebo.

The design, conduct, and analysis of this study complied with international and regional standards for clinical research in humans, and for investigating the efficacy, immunogenicity, and safety of COVID-19 investigational vaccines.

The study was conducted in accordance with the protocol, ICH-GCP Guidelines, and applicable regulatory requirements.

7.1 Scope of this Report

The data presented in this report is a compilation of the second CSR (V2.0) and selected addenda. The list of addenda included in this report is presented in Table 1.

Table 1 CLO-SCB-2019-003 Compiled CSR

CSR Name	Date	Data Reported	Data Lock Point
CLO-SCB-2019-003 CSR V1.0	10 November 2021	Primary efficacy, immunogenicity and safety	13 September 2021*
CLO-SCB-2019-003 Six-month Follow-up	22 April 2022	Efficacy, immunogenicity and safety (6 months)	17 December 2021**
CLO-SCB-2019-003 Additional Secondary Efficacy	16 September 2022	Efficacy	17 December 2021**
CLO-SCB-2019-003 Elderly	23 December 2021	Immunogenicity and safety	13 September 2021*
CLO-SCB-2019-003 HIV	25 April 2022	Immunogenicity and safety	13 September 2021*
CLO-SCB-2019-003 Chinese Origin	8 December 2022	Immunogenicity and safety	13 September 2021*
CLO-SCB-2019-003 Cross-neutralization	7 September 2022	Cross-neutralization	13 September 2021*
CLO-SCB-2019-003 CMI	29 April 2022	Cell-mediated immunity	13 September 2021*
CLO-SCB-2019-003 Manufacturing Scales	13 December 2022	Immunogenicity and safety	13 September 2021*
CLO-SCB-2019-003 CSR V2.0	21 October 2024	Pregnancy follow-up	11 September 2024

*The cutoff date for efficacy analysis is 10 August 2021 and for safety analysis is 20 August 2021.

**The cutoff date for efficacy and safety analysis is 1 December 2021. The data lock point is 17 December 2021.

***The data lock point of pregnancy follow-up and the whole study is 11 September 2024.

8.0 STUDY OBJECTIVES

This study assessed the efficacy against COVID-19, immunogenicity, reactogenicity, and safety of CpG 1018/alum-adjuvanted SCB-2019.

8.1 Primary Objectives

*Primary Efficacy Objective (**H1**) – vaccine efficacy (VE) against reverse transcription polymerase chain reaction (RT-PCR)-confirmed COVID-19 of any severity:*

- To demonstrate the efficacy of CpG 1018/alum-adjuvanted SCB-2019 vaccine for the prevention of any RT-PCR-confirmed COVID-19 of any severity in subjects without evidence of prior SARS-CoV-2 infection.

Primary Safety and Reactogenicity Objective:

- To assess the safety and reactogenicity of CpG 1018/alum-adjuvanted SCB-2019 vaccine compared to placebo.

8.2 Secondary Objectives

*Key Secondary Efficacy Objective #1 (**H2b**) – VE against any RT-PCR-confirmed moderate-to-severe COVID-19:*

- To evaluate the efficacy of CpG 1018/alum-adjuvanted SCB-2019 vaccine for the prevention of any RT-PCR-confirmed moderate to severe COVID-19 in subjects without evidence of prior SARS-CoV-2 infection.

*Key Secondary Efficacy Objective # 2 (**H2a**) – VE against any laboratory-confirmed SARS-CoV-2 infection:*

- To evaluate the efficacy of CpG 1018/alum-adjuvanted SCB-2019 vaccine for the prevention of any laboratory-confirmed SARS-CoV-2 infection in subjects without evidence of prior SARS-CoV-2.

*Key Secondary Efficacy Objective #3 (**H4**) – VE against any RT-PCR-confirmed severe COVID-19:*

- To evaluate the efficacy of CpG 1018/alum-adjuvanted SCB-2019 vaccine for the prevention of any RT-PCR-confirmed severe COVID-19 in subjects without evidence of prior SARS-CoV-2 infection.

*Key Secondary Efficacy Objective #4 (**H3**) – VE against any laboratory-confirmed asymptomatic SARS-CoV-2 infection:*

- To evaluate the efficacy of CpG 1018/alum-adjuvanted SCB-2019 vaccine for the prevention of any laboratory-confirmed asymptomatic SARS-CoV-2 infection in subjects without evidence of prior SARS-CoV-2 infection.

Secondary Efficacy Objective #1 – VE against burden of disease (BOD):

- To evaluate the efficacy of CpG 1018/alum-adjuvanted SCB-2019 vaccine for the reduction of BOD, in subjects without evidence of prior SARS-CoV-2 infection.

Secondary Efficacy Objective #2 – VE against any RT-PCR-confirmed COVID-19 of any severity, associated with hospitalization:

- To evaluate the efficacy of CpG 1018/alum-adjuvanted SCB-2019 vaccine for the prevention of any RT-PCR-confirmed COVID-19 of any severity, associated with hospitalization, in subjects without evidence of prior SARS-CoV-2 infection.

Secondary Efficacy Objective #3 – VE by evidence of prior SARS-CoV-2 infection and risk of severe COVID-19:

- To describe the efficacy of CpG 1018/alum-adjuvanted SCB-2019 vaccine in subgroup population: subjects with and without evidence of prior SARS-CoV-2 infection (yes/no); and subjects at risk of severe COVID-19 (high/ low risk).

Secondary Efficacy Objective #4 – VE after the first dose:

- To evaluate the efficacy of CpG 1018/alum-adjuvanted SCB-2019 vaccine, after the first study vaccination.

Secondary Efficacy Objective #5 – VE against SARS-CoV-2 variants of concern (VOCs):

- To evaluate the efficacy of CpG 1018/alum-adjuvanted SCB-2019 vaccine for the prevention of RT-PCR-confirmed COVID-19 of any severity caused by SARS-CoV-2 VOCs, including but not limited to B.1.1.7, B.1.351, B.1.1.28.1 (P1), etc.

Secondary Immunogenicity Objective:

- To assess the immunogenicity of CpG 1018/alum-adjuvanted SCB-2019 vaccine in Phase 2 adult subjects and adolescents.

Secondary Safety Objective:

- To assess the immune response against Trimer-Tag domain of SCB-2019 in Phase 2 adult subjects and adolescents.

8.3 Exploratory Objectives

Exploratory Efficacy Objectives:

- To explore the effect of CpG 1018/alum-adjuvanted SCB-2019 vaccine on the severity of COVID-19 using the National Early Warning Scoring 2 (NEWS2) score in subjects with COVID-19-associated hospitalization.
- To explore the effect of CpG 1018/alum-adjuvanted SCB-2019 vaccine on SARS-CoV-2 viral load in infected individuals.

- To explore the effect of CpG 1018/alum-adjuvanted SCB-2019 vaccine on the prevention of COVID-19 long-term sequelae.
- To explore the effect of CpG 1018/alum-adjuvanted SCB-2019 vaccine on the risk of disease enhancement, including but not limited to enhanced respiratory disease.
- To perform characterization of SARS-CoV-2 isolates by genetic sequencing (in a subset of samples).

Exploratory Immunogenicity Objectives:

- To assess the cell-mediated immunity (CMI) of CpG 1018/alum-adjuvanted SCB-2019 vaccine in a subset of Phase 2 adult subjects.
- To explore neutralization of new emergent mutants of SARS-CoV-2 by SCB-2019 vaccine-elicited sera.
- To explore potential immune correlates of protection based on binding antibody enzyme-linked immunosorbent assay (ELISA) and/or other immunological assays.

9.0 INVESTIGATIONAL PLAN

The information provided in Sections 9.1 to 9.6 reflects the conduct of the study based on protocol Version 5.1 dated 27 September 2021. Any global differences between the planned and actual methods are described in Section 9.8. Significant individual protocol deviations are described in Section 10.2.

9.1 Overall Study Design and Plan

9.1.1 Description

CLO-SCB-2019-003 was a double-blind, randomized, controlled, multi-country study of CpG 1018/alum-adjuvanted SCB-2019 to assess the efficacy, immunogenicity, reactogenicity, and safety compared with control (placebo). The study was to include adult subjects aged 18 years and older, and adolescents 12 to less than 18 years of age, enrolled at selected sites.

Approximately 30 000 adult subjects and 1200 adolescents were to be randomized 1:1 to one of the treatment groups as shown in Table 2. Each subject was to receive 2 doses of their assigned treatment on Days 1 and 22. The treatment was to be administered IM in the deltoid region of the upper arm.

Table 2 Treatment Groups

Group	Treatment	Adult	Adolescent	Total
CpG 1018/Alum/SCB-2019	SCB-2019 + CpG 1018/Alum adjuvant	15 000	600	15 600
Placebo	Placebo; 0.9% saline	15 000	600	15 600
Total		30 000	1200	31 200

This was a case-driven study which required 150 cases to trigger the analysis of the primary efficacy endpoint. The total number of subjects was to be based on the attack rate of COVID-19 of any severity in the study (see Section 9.7.2) and anticipated baseline SARS-CoV-2 seropositivity rate; additional subjects may have been recruited to reach the required number of COVID-19 cases.

For each subject, the study duration was to be approximately 13 months (approximately 12 months after the second study vaccination). There were to be 5 study visits for all subjects, at Days 1, 22, 36, 205, and 389 and one safety call at Day 43 (for Phase 2 subjects only).

9.1.2 Stages of the Study

- Phase 2 of the study was to include approximately 1600 adult subjects (800 subjects in CpG 1018/alum/SCB-2019 group and 800 subjects in Placebo arm) to assess reactogenicity, safety, and immunogenicity of the study vaccine. Safety and reactogenicity data were to be reviewed by the DSMB who was to provide recommendations regarding the study continuation, modification, or termination. Efficacy data were also to be also collected during the Phase 2 stage and analyzed along with the data collected in Phase 3.

- Phase 3 of the study was to include the remaining subjects to assess efficacy and safety of study vaccine.

Initially only healthy adult individuals 18 to 64 years of age were to be recruited in the study. After the review of post-Dose 1 safety data of approximately 200 healthy subjects aged 18 to 64 years, the DSMB was to make a recommendation regarding the extension of recruitment and inclusion of older adults aged ≥65 years and individuals with comorbidities.

After recruiting approximately 200 additional adult subjects, including older adults aged ≥65 years and individuals with comorbidities, the DSMB was to review available safety data and may have recommend the initiation of recruitment in the Phase 3 part of the study.

In addition, the DSMB could authorize the enrollment of adolescent subjects 12 to less than 18 years of age may have been enrolled in the study to assess reactogenicity, safety, efficacy and immunogenicity. These subjects were to follow study procedures for a Phase 2 stage of the study for evaluation of efficacy, immunogenicity, safety, and reactogenicity. The volume of blood samples was to be reduced according to their age. The immunogenicity and safety results for adolescent subjects are presented in a separate report.

9.1.3 Subjects with Suspected COVID-19 Signs and Symptoms

Starting at 2 weeks after Visit 1 (Day 1), subjects were to receive weekly reminders via electronic patient-reported outcome (ePRO) to report any symptoms or signs of suspected COVID-19, as specified in Table 3. The purpose of these reminders was to identify potential episodes of COVID-19 and trigger SARS-CoV-2 testing and daily reporting of associated symptoms.

Table 3 COVID-19 Signs and Symptoms

New onset of one of the following clinical symptoms/signs:

• Fever (>37.8°C; irrespective of method) or chills;
• New onset or has worsened from Baseline of any of below:
  • Nonproductive cough;
  • Shortness of breath or difficulty breathing;
  • Fatigue;
  • Loss of taste or smell.
• Radiologicallyconfirmed lower respiratory tract infection;
• Acute diarrhea (≥3 loose stools/24 hours period);
• Close contact with a person with confirmed symptomatic or asymptomatic COVID-19 in the past 14 days.

Table 3 COVID-19 Signs and Symptoms (continued)

At least two of the following symptoms of COVID-19 that is of new onset or has worsened from Baseline:
• Muscle or body aches; • Arthralgia; • Headache; • Sore throat; • Congestion or runny nose; • Nausea or vomiting; • Loss of appetite/skipped meals; • Dizzy/light-headed.

In case of appearance of suspected symptoms or signs, these were to be documented in the ePRO by the subject. The symptoms and signs were to be verified, and, if they met the definition in Table 3, the subject was to receive instructions regarding SARS-CoV-2 testing.

9.1.4 Assessment of Immunogenicity and Reactogenicity

The first approximately1600 recruited adult subjects were to be included in the Phase 2 portion of the study to compose the immunogenicity/reactogenicity subset (Table 4). The 12 to less than 18 year-old adolescents enrolled in the study were also to follow the Phase 2 procedures for assessment of immunogenicity, safety and reactogenicity.

Table 4 Immunogenicity/Reactogenicity and Cell-mediated Immunity Adult Subsets

Subset	**Subject Numbers**	**Total**
Immunogenicity/reactogenicity	Number per group	800
	Total number	1600
Cell-mediated (a part of immunogenicity/reactogenicity)	Number per group	75
	Total number	150

For the adult subjects in the immunogenicity/reactogenicity subset and adolescents , blood (sera) was to be collected for analysis of humoral immune responses before each vaccination (Visits 1 and 2), and 14 days (Visit 3 Day 36), 183 days (Visit 4 Day 205), and 367 days (Visit 5, Day 389) after the second vaccination. Depending on the type of assay [e.g., ELISA or virus neutralizing assay (VNA)] and active/placebo status, all or randomly-selected set of serum samples collected in the immunogenicity/reactogenicity subset were to be analyzed for humoral immunity. The remaining samples may have been analyzed post-hoc based on emerging data and regulatory requirements.

Initially, the number of subjects in each study group from which samples were planned to be tested for each humoral immunity analysis were the following:

- Humoral (ELISAs):
  - SCB-2019-binding antibody ELISA:
    - Adults: 800 subjects in study vaccine group/100 subjects in Placebo arm;
    - Adolescents: 300 subjects in the study vaccine group/100 subjects in the Placebo arm.

  - Angiotensin-converting enzyme 2 (ACE2)-competitive ELISA: 400 adult subjects in study vaccine group/50 subjects in the Placebo arm.

- Trimer-Tag binding antibody ELISA:
  - Adult: 800 subjects in study vaccine group/100 subjects in the Placebo arm.
  - Adolescents: 300 subjects in the study vaccine group/100 subjects in the Placebo arm.

- Humoral (VNAs):
  - Wild-type SARS-CoV-2 VNA:
    - Adults: 400 subjects in study group/50 subjects in the Placebo arm.
    - Adolescents: 300 subjects in the study group/100 subjects in the Placebo arm.
  - SARS-CoV-2 pseudo-VNA:
    - 400 adult subjects in study group/50 subjects in the Placebo arm.

In addition, randomly selected subset of subjects may have been used for further characterization of vaccine-induced immune response (e.g. in older adults, subjects with certain comorbidities), or based on specific requests from regulatory authorities. The description of additional testing and associated statistical analysis was to be presented in the SAP.

All adult subjects in the immunogenicity/reactogenicity subset and the adolescent subjects were to record solicited adverse events (AEs) within 7 days after each vaccination and unsolicited AEs from Day 1 to Day 43.

Approximately 150 adult subjects (75 subjects in CpG 1018/alum/SCB-2019 group and 75 subjects in the Placebo arm) from the immunogenicity/ reactogenicity subset were to compose the CMI subset. For subjects included in this subset, 32 mL of whole blood were to be collected for analysis of CMI at Baseline (Visit 1 Day 1) and 14 days after the second vaccination (Visit 3 Day 36). An additional 2 mL of whole blood were to be collected at each study visit for exploratory evaluation of T-cell receptor mapping.

No CMI responses was to be assessed in adolescents as it was expected that the results of these evaluations would be similar in this age group and adults and such no substantial significant data was to be generated to describe the immune response in adolescents versus adults.

In all subjects, a baseline testing for SARS-CoV-2 seropositivity to the receptor-binding domain (RBD) of the S protein using anti-SARS-CoV-2 ELISA immunoglobulin (IgG) test kit (anti-S ELISA test kit) was to be performed in all subjects.

In all subjects, blood was to be collected at Baseline (Day 1), Day 22 (Visit 2), Day 36 (Visit 3), and 205 days (Visit 4) and 389 days (Visit 5) after completion of the vaccination regimen for SARS-CoV-2 seropositivity testing against N protein. In subjects of interest (including but not limited to having confirmed COVID-19 or relevant AEs), blood samples may also have been used for the evaluation of humoral immunogenicity (e.g., ELISA and VNA).

All subjects were also to provide post-Dose 2 serum sample (Visit 3) to explore potential correlates of protection.

In case of early study termination (e.g., if VE is demonstrated at primary efficacy analysis), subjects were to have blood collected at time of early termination for immunogenicity evaluations.

The protocol and protocol amendments are provided in **Appendix 16.1.1**. A sample case report form (CRF) is provided in **Appendix 16.1.2**.

9.2 Discussion of the Study Design

It is known that older adults and people with co-morbidities are at risk of severe symptoms of COVID-19. This study aimed to include subjects representative of these populations.

The Phase 2 portion of the study in adults aimed to provide additional reactogenicity and safety data, and an assessment of vaccine immunogenicity.

To ensure the safety of the enrolled subjects, safety monitoring was to be performed in a blinded fashion by the study medical monitoring team, with an unblinded review by the DSMB planned to occur on a regular basis. Established stopping criteria for subsequent vaccination for individual subjects were also to be applied.

To assess the nature and duration of the immune response after natural infection with SARS-CoV-2 or administration of investigational COVID-19 vaccines the kinetics of the immune response after the first and second vaccination and antibody persistence were to be assessed within 12 months after the last vaccination.

To be able to assess the vaccine benefits within a reasonable timeframe, this study was designed to show VE against COVID-19 of any severity. The efficacy against moderate-to-severe COVID-19, severe COVID-19, any SARS-CoV-2 infection, and asymptomatic SARS-CoV-2 infection were to be assessed as key secondary objectives. In addition, VE against any COVID-19 associated with hospital admission were to be described.

This was a case-driven study. The total number of subjects was based on COVID-19 attack rate in the study and anticipated baseline SARS-CoV-2 seropositivity rate; and additional subjects may have been recruited to reach the required number of COVID-19 cases.

Placebo was included in the study design to allow a precise estimation of clinical efficacy of the study vaccines.

The selected efficacy endpoints and case definitions are consistent with FDA guidance ‘Development and Licensure of Vaccines to Prevent COVID-19’, May 2020 FDA guidance ‘COVID-19: Developing Drugs and Biological Products for Treatment or Prevention’9, and recommendations of International Coalition of Medicines Regulatory Authorities (ICMRA) SARS-CoV-2 Vaccines Workshop.

9.2.1 Justification for Dose

Safety and immunogenicity data from the CLO-SCB-2019-001 Phase 1 study, showed 30 µg SCB-2019 adjuvanted with CpG1018/alum induced high antibody titers in young and older adult subjects after a 2-dose vaccination series, with evidence of functional immune response after the

first dose in adult subjects. SCB-2019 dose of 30 µg was well-tolerated and appeared to be safe when administered with CpG 1018/alum adjuvant.

9.3 Selection of Study Population

All entry criteria, including test results, were to be confirmed prior to randomization.

9.3.1 Inclusion Criteria

Subjects were eligible to be included in the study only if all of the following criteria were met:

Type of Subject

1. Male or females ≥12 years of age, inclusive*.
2. Subjects willing and able to comply with study requirements, including all scheduled visits, vaccinations, laboratory tests, the electronic completion of the COVID-19 ePRO and other study procedures.
3. Healthy adult or adolescent subjects or adult subjects with pre-existing medical conditions who were in stable condition.

A stable medical condition was defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 3 months before enrollment*.

*Note: The first 200 individuals enrolled in the Phase 2 part of the study were to be healthy subjects 18 to 64 years or age without comorbidities associated with a high risk of severe COVID-19.

Pregnancy and Contraception

4. Female subjects were eligible to participate in the study if not pregnant, not breastfeeding, and at least 1 of the following criteria applied:

- Women of childbearing potential (WOCBP) were to have had a negative urine pregnancy test prior to each vaccination. A confirmatory serum pregnancy test may have been conducted at the investigator's discretion. They were to have used a highly effective licensed method of birth control for 30 days prior to the first vaccination and must have agreed to continue such precautions during the study until 90 days after the second vaccination.

5. Male subjects must have agreed to employ acceptable contraception from the day of first dose of the study vaccine/placebo until 6 months after the last dose of the study vaccine/placebo and also to refrain from donating sperm during this period.

Informed Consent

6. Individuals [or their legally acceptable representative (LAR) based on local regulations] willing and able to give an informed consent, prior to screening. For adolescent subjects: informed assent signed by adolescents and informed consent signed by the parent(s) or LAR(s) as per local requirements.
7. Applicable for human immunodeficiency virus (HIV)-positive individuals only:

HIV positive individuals could participate in the study only if:

- They were medically stable at screening, as determined by the investigator, and free of opportunistic infections in the 1 year prior to first study vaccination, and
- They had an HIV-1 viral load <1000 copies/mL within 45 days of randomization in the study, and
- They were receiving highly active antiretroviral therapy (HAART) for at least 3 months before screening. Changes in antiretroviral dosage within 3 months of entering the study were allowed, as were exchanges in pharmacological formulations.

Note: No HIV screening was required except subjects in South Africa due to the high prevalence of HIV, prior to study enrollment, individuals without recent HIV testing (within the previous 6 months), were to undergo screening for HIV using an approved method, as per site standard medical practice to determine if they could participate in the study.

9.3.2 Exclusion Criteria

Subjects were excluded from the study if any of the following criteria applied:

1. Individuals with laboratory-confirmed SARS-CoV-2 infection (e.g., a positive RT-PCR* or Rapid COVID-19 Antigen test) at screening or within 14 days prior to enrollment.

*Note: A confirmation of SARS-CoV-2 infection by RT-PCR was required for subjects recruited in Brazil.

2. Individuals with behavioral or cognitive impairment (including drug and alcohol abuse) in the opinion of the investigator.
3. Individuals with any progressive or severe neurologic disorder, seizure disorder, or history of Guillain-Barré syndrome (GBS).
4. Individuals who had received treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, e.g., for cancer or an autoimmune disease, or planned receipt during the study period. If a short-term course of systemic corticosteroids had been administered for treatment of an acute illness, subjects were not to be enrolled into the study until corticosteroid therapy had been discontinued for at least 30 days before the first study vaccination. A unique dose of systemic steroids on a single day was allowed, as well as inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids.
5. Individuals who were pregnant, or breastfeeding, or planning to become pregnant during the study period.
6. Individuals with a history of severe adverse reaction associated with a vaccine or severe allergic reaction (e.g., anaphylaxis) to any component of the study vaccine (SCB-2019, CpG 1018 adjuvant and aluminum hydroxide components as outlined in the latest IB).

7. Individuals with a history of malignancy within 1 year before screening (exceptions were squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix which had been cured, or other malignancies with minimal risk of recurrence).
8. Individuals who had received any other investigational product within 30 days prior to Day 1 or intended to participate in another clinical study at any time during the conduct of this study.
9. Individuals who had received previous vaccination with any coronavirus vaccine.
10. Individuals who had received any other licensed vaccines within 14 days prior to enrollment in this study or were planning to receive any vaccine up to 14 days after the second vaccination.
11. Individuals with known bleeding disorder that would, in the opinion of the investigator, contraindicate intramuscular (i.m.) injection.
12. Individuals who had received any blood/plasma products or immunoglobulins within 60 days prior to Day 1 or were planning to receive it during the study period.
13. Individuals with any condition that, in the opinion of the investigator, may have increased the risk of study participation or interfered with the assessment of the primary study objectives.
14. Individuals with fever >37.8°C (irrespective of method), or any acute illness at Baseline (Day 1) or within 3 days of randomization. Subjects meeting this criterion may have been rescheduled within the relevant window. A febrile subject with minor illness could have been enrolled at the discretion of the investigator.

9.3.3 Individual Subject and Study Stopping Criteria

The following criteria applied during the trial.

9.3.3.1 Contraindications to the Second Vaccination

If subjects met any of the criteria listed below, they were not to receive the second vaccination. However, these subjects were to be encouraged to continue study participation.

- Subjects who experienced any allergic reaction within 24 hours after the previous study vaccination;
- Subjects who experienced any serious adverse event (SAE) judged to be related to study vaccination, including hypersensitivity reactions;
- Subjects who developed any clinically significant medical condition which, in the opinion of the investigator, may have posed additional risk to the subject if he/she continued to participate in the study;
- Subject who became pregnant;
- Subjects who developed RT-PCR -confirmed SARS-CoV-2 infection prior to the second vaccination.

9.3.3.2 Criteria for Delay of the Second Vaccination

After enrollment, subjects may have encountered clinical circumstances that warranted a delay in subsequent study vaccination. These situations are listed below.

If any of the following events occurred at the time scheduled for the study vaccine administration, the subject may have received the second dose once the window for delay had passed as long as the subject was otherwise eligible for study participation:

- Acute disease and/or fever at the time of vaccination:
  - Fever was defined as temperature >37.8°C (irrespective of method);
  - Subjects with a minor illness (such as mild diarrhea, mild upper respiratory infection, etc.) without fever could have been administered the second vaccination if not suspected of having SARS-CoV-2 infection and/or COVID-19 by the investigator.
- Any acute clinically relevant disease that in the judgment of the investigator would have contraindicated vaccination;
- Receipt of an immunosuppressant drug or any other treatment that in the judgment of the investigator would have increased the risk to the subject.

9.3.3.3 Discontinuation of Study vaccine

A "withdrawal" from the study vaccine refers to any subject who did not receive the complete treatment, i.e., when no further planned dose was administered from the date of withdrawal. A subject withdrawn from the study vaccine may have continued further study procedures (safety or immunogenicity) if planned in the study protocol, as deemed appropriate by the investigator.

Primary reason relative to premature discontinuation of the study vaccine/control was to be documented in the electronic case report form (eCRF):

- AE(s);
- Subject decision, not due to an AE;
- Pregnancy;
- Lost to follow-up (Section 9.3.3.5);
- Sponsor study termination;
- Positive for SARS-CoV-2 infection prior to Day 22 visit (prior to the second vaccination);

If a subject who did not meet enrollment criteria was inadvertently enrolled, that subject was to be discontinued from study and the sponsor or sponsor designee contacted. An exception may have been granted in rare circumstances for which there was a compelling safety reason to allow the subject to continue and the investigator was to document this.

9.3.3.4 Subject Withdrawal from the Study

- A subject may have withdrawn from the study at any time at his/her own request, or may have been withdrawn, at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- If the subject withdrew consent for disclosure of future information, the sponsor may have retained and continued to use any data collected before such a withdrawal of consent.
- If a subject withdrew from the study, he/she may have requested destruction of any samples taken and not tested, and the investigator was to document this in the study center study records and inform sponsor's representative.

9.3.3.5 Lost to Follow-up

A subject was to be considered lost to follow-up if he or she repeatedly failed to return for scheduled visits and was unable to be contacted by the study center.

The following actions were to be taken if a subject failed to return to the clinic for a required study visit:

- The study site was to attempt to contact the subject and/or parent/LAR and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wished to and/or should continue in the study.
- Before a subject was deemed lost to follow up, the investigator or designee was to make every effort to regain contact with the subject and/or parent/LAR (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts were to be documented in the subject's medical record.

Should the subject and/or parent/LAR have continued to be unreachable, the subject was to be considered to have withdrawn from the study.

9.3.3.6 Criteria for Study Pause

In the Phase 2 part of the study, the following event would pause the study recruitment and administration of study vaccination until the review by the DSMB and associated recommendations:

- If any subject developed an SAE assessed by the investigator as related to study vaccine, or for which there was no alternative, plausible, attributable cause.

In the Phase 3 part of the study, all related SAEs were to be escalated for the DSMB to review within 24 hours without study pause.

9.4 Study Vaccines

SCB-2019 adjuvanted with CpG 1018/alum and placebo used in this study were to be stored separately from other vaccines and medications in a secure location under appropriate storage conditions with temperature monitoring. All vaccines associated with this study were to be checked for expiry date prior to use. Expired study vaccines were not to be administered to subjects.

9.4.1 Study Vaccines Administered

SCB-2019 was supplied in a prefilled syringe containing 720 µg of SCB-2019 as a sterile, clear colorless solution for injection and to be stored at 2°C to 8°C in a dark and dry environment prior to reconstitution. Each dose contained 30 µg SCB-2019.

CpG 1018 adjuvant was also to be stored at 2°C to 8°C in a dark and dry environment.

Alhydrogel® was to be stored upright at 15°C to 25°C in a dark and dry environment.

Further details of preparation, handling, storage, and accountability of the study vaccine were provided in the pharmacy manual.

Notes:

- The investigator or designee was to confirm appropriate temperature conditions were maintained during transit for all study vaccine received and any discrepancies reported and resolved before use of the study vaccine.
- Only subjects enrolled in the study were eligible to receive study vaccine and only authorized study staff was to supply or administer the study vaccine. All study vaccines were to be stored in a secure, environmentally-controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study center staff.
- The investigator, institution, or the head of the medical institution (where applicable) was to be responsible for study vaccine accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

9.4.2 Identity of Investigational Vaccine(s)

The identities of CpG 1018/alum/SCB-2019 and Placebo are summarized in Table 5.

The list of lot numbers given to each subject is provided in **Appendix 16.1.6**.

Table 5 Identity of the CpG 1018/alum/SCB-2019 and Placebo

Group Name	CpG 1018/alum/SCB-2019	Control group
Intervention name	CpG 1018/alum-adjuvanted SCB-2019 vaccine	Placebo, 0.9% sodium chloride
Formulation:	**SCB-2019**: prefilled syringe (720 µg in 1.0 mL) for preparation of 20 doses of study vaccine) **CpG 1018 Adjuvant**: vial (2.0 mL) containing 12 mg/mL of a 22-mer phosphorothioate oligodeoxynucleotide in Tris buffered saline (24 mg/vial) **Alhydrogel®**: vial or bottle containing 10 mg/mL of aluminum hydroxide.	Ampoule, 10 mL[a]
Presentation	SCB-2019: solution CpG 1018 adjuvant: solution Alhydrogel®: a gel-like aqueous suspension	Solution
Manufacturer	SCB-2019: Sichuan Clover Biopharmaceuticals, Inc CpG 1018 adjuvant: Dynavax Technologies Alhydrogel®: Croda Health Care	Various manufacturers
Route of Administration	i.m. in the deltoid region of the upper non-dominant arm (preferable)	
Volume (final)	0.5 mL	0.5 mL
IMP	Yes	No
Packaging	The study vaccines were to be packaged and labeled according to GCP and local regulations. The study vaccine was not to be packed in individual subject kits; one kit was be used for multiple subjects. One kit was to include one prefilled syringe with SCB-2019, two vials with CpG 1018, and one ampoule with 0.9% sodium chloride. Alhydrogel® was to be supplied separately for matching one kit.	

[a] Volume of saline and presentation (vial or ampoule) may have been different. GCP = Good Clinical Practice; i.m. = intramuscular; IMP = investigational medicinal product.

9.4.3 Method of Assigning Subjects to Study Arms

This study was to be double blind, i.e., the study subjects and those responsible for the evaluation of any study endpoint were to be blinded to the administered treatment (study vaccine or control).

After signing the ICF or the assent form (for adolescents) each subject was to be given a screening number according to the screening order. On Day 1, following confirmation of eligibility, a subject number was to be assigned, and subjects allocated to the study arms using an interactive voice response system (IVRS)/interactive web response system (IWRS).

The randomization for adults enrolled in the study was to be stratified by site, age group (≥18 to <65 years of age versus ≥65 years of age), absence/presence of comorbidities associated with a high risk of severe COVID-19, and a known history of COVID-19. Approximately 25% of enrolled subjects were to be either ≥65 years of age or <65 years of age and at high risk of severe COVID-19.

The randomization scheme and codes are included in **Appendix 16.1.7**.

9.4.4 Selection of Doses in the Study

In nonclinical studies, SCB-2019 (at doses of 3 to 30 µg) administered with CpG 1018/alum adjuvant demonstrated a robust immune response (as measured by ELISA binding and neutralizing antibodies) in mice, rats, and non-human primates (NHPs), that was comparable to or higher than the level of antibodies in human convalescent serum. Because there are no well-characterized allometric scaling guidelines for vaccines from animals to humans, and such scaling can range from 0.5- to 100-fold, 3 SCB-2019 doses of 3, 9, and 30 µg administered with CpG 1018/alum were evaluated in a Phase 1 first in human clinical study (CLO-SCB-2019-001). Based on preliminary safety and immunogenicity data from this Phase 1 study, a SCB-2019 dose of 30 µg with CpG1018/alum adjuvant induced high antibody titers in young and older adult subjects after a 2-dose vaccination series, with evidence of functional immune response after the first dose in adult subjects. SCB-2019 dose of 30 µg was well-tolerated and appeared to be safe when administered with CpG 1018/alum adjuvant.

9.4.5 Selection and Timing of Doses for Each Subject

In the first-in-human clinical study (CLO-SCB-2019-001), highest immune responses were observed after completion of the two-dose series at Day 36, justifying the two-dose regimen of the study vaccine given at least 21 days apart.

9.4.6 Blinding

Due to the visual differences between the study vaccine and placebo, the subjects were to be blinded before receiving the study vaccine or placebo. An unblinded dosing team, not involved with study subject's evaluation, was to prepare and administer the study vaccine/placebo doses. The investigational product syringe was to be opacified to avoid unblinding of the subject. The administration of the study vaccine was also to be performed behind a closed curtain to ensure that the other blinded staff members would not become unblinded. The investigative study center personnel, as well as the sponsor personnel involved in the monitoring or conduct of the study, were to be blinded to the study vaccine code.

The laboratories in charge of immunogenicity and efficacy testing were also to be blinded, so that associating the sample with an assigned treatment or study visit would not be possible.

The treatment code was to be broken only if the investigator/physician in charge of the subject felt that the case could not be treated without knowing the identity of the study vaccine.

Except in cases of medical necessity, a subject's treatment was not to be unblinded without the approval of the sponsor. In case of unblinding (by either accidental unblinding or emergency unblinding) before completion of the study, the investigator was to promptly contact the sponsor and document the circumstances on the appropriate forms. Instructions regarding emergency unblinding were to be provided to the investigator and be available in the CLO-SCB-2019-003 Site User and Investigator User Guide.

9.4.7 Prior and Concomitant Medication

Prior medications, vaccines, and blood products are described in the exclusion criteria were to be recorded on the eCRF, when they were administered, including:

- Use of systemic (oral or parenteral) corticosteroids within 30 days prior to Day 1;
- Receipt of cancer chemotherapy (e.g., cytotoxic agents) within 60 days prior to Day 1;
- Receipt of immunosuppressants (e.g., for an autoimmune disease treatment) within 60 days prior to Day 1;
- Receipt of blood/plasma products or parenteral immunoglobulin within 60 days prior to Day 1;
- Receipt of any investigational product within 30 days prior to Day 1;
- Receipt of any prior coronavirus vaccine [e.g., against SARS-CoV, SARS-CoV-2, or Middle-East respiratory syndrome (MERS)-CoV];
- Receipt of any licensed vaccines within 14 days prior to Day 1.

Concomitant medications include medications and vaccines taken by/administered to the subject at and after enrollment and were to be documented on the eCRF. The following were considered concomitant medications:

- All medications administered from Visit 1 to Visit 3 (or from Visit 1 to Day 43 in Phase 2 subjects);
- All medications associated with SAEs, adverse events of special interest (AESIs), medically-attended AEs (MAAEs), and AEs leading to early study termination, during the entire study period (from Visit 1 to study completion);
- All medications administered for treatment of COVID-19 or SARS-CoV-2 infection;
- Any investigational and non-licensed medications (other than the study vaccine) during the entire study period (from Visit 1 to study completion).

Any medication that met the reporting criteria (including over-the-counter or prescription medicines, and/or herbal supplements) was to be recorded on the eCRF along with:

- Reason for use;
- Dates of administration including start and end dates;
- Dosage information including dose and frequency.

The use of antipyretics (e.g., paracetamol) was to be allowed as treatment for fever and pain or other post-vaccination reactions; subjects were not to be encouraged to use antipyretics prophylactically. The medical monitor was to be contacted if there are any questions regarding concomitant or prior therapy. The use of an excluded medication/therapy was a protocol violation and was to be recorded in the eCRF. The use of an excluded medication did not require withdrawal of subject from the study. Prohibited medications are presented below:

- Systemic (oral or parenteral) corticosteroids within 30 days prior to Day 1 and from Visit 1 (Day 1) to Visit 3 (Day 36). A unique dose of systemic steroids on a single day would be allowed, as well as inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids was permitted;
- Receipt of cancer chemotherapy (e.g., cytotoxic agents) within 60 days prior to Day 1 or during the study period;
- Receipt of immunosuppressants (e.g., for an autoimmune disease treatment) within 60 days prior to Day 1 or during the study period;
- Receipt of blood/plasma products or parenteral immunoglobulin within 60 days prior to Day 1 or during the study period;
- Receipt of any investigational product within 30 days prior to Day 1 and during the study period;
- Receipt of any prior coronavirus vaccine (e.g., against SARS-CoV, SARS-CoV-2, or MERS-CoV) or any other coronavirus vaccine during the study period;
- Receipt of any licensed vaccines within 14 days prior to Day 1, and from Day 1 up to 14 days after the second vaccination.

9.4.8 Compliance to Vaccine Administration

The prescribed dosage, timing, and mode of administration was not to be changed. Any departures from the intended regimen were to be recorded in the eCRFs. All dose administrations were to be performed at the study center by appropriately trained staff.

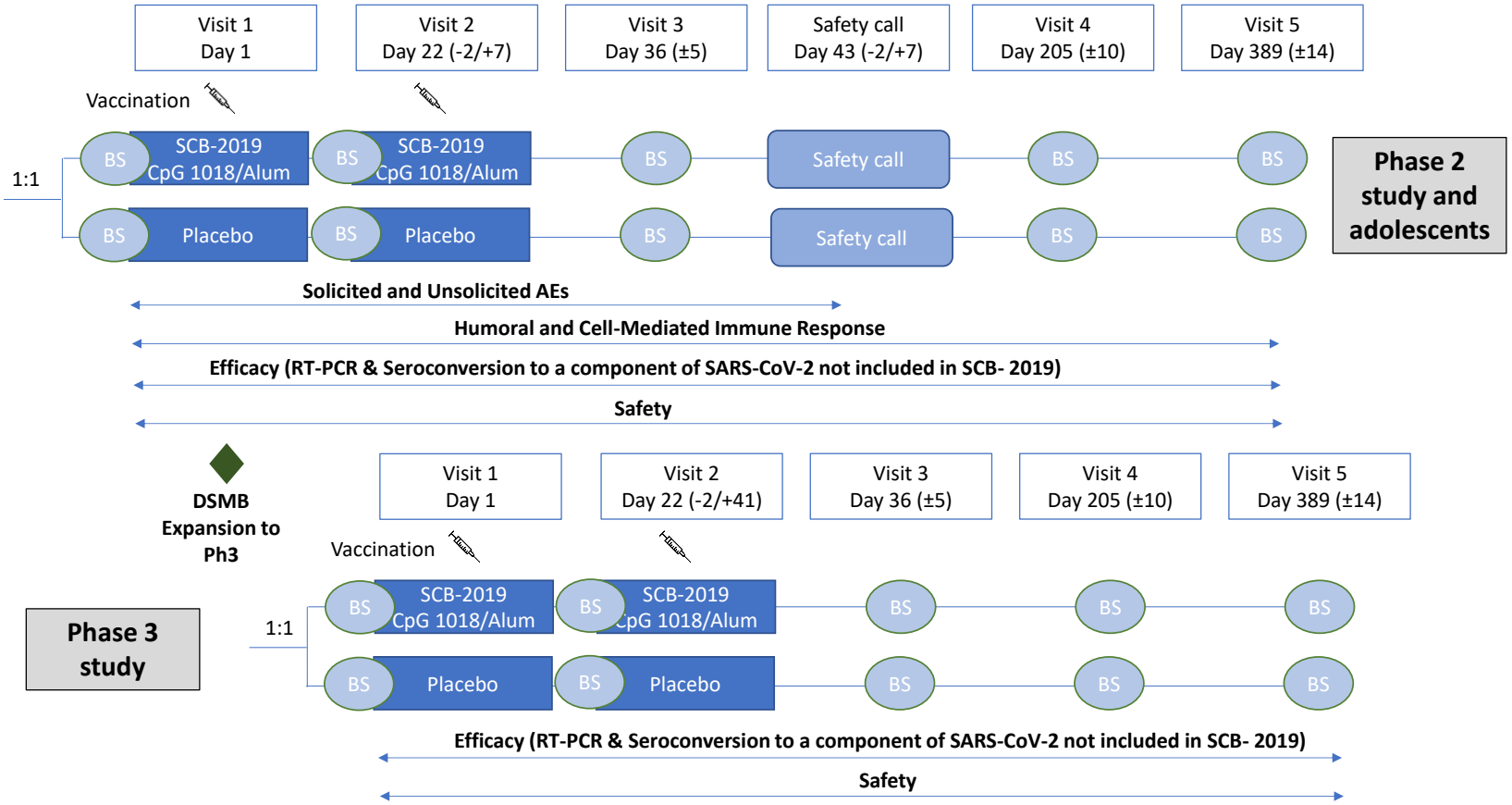
9.5 Efficacy, Immunogenicity and Safety Variables

The variables used to assess the efficacy, immunogenicity, reactogenicity, and safety of CLO-SCB-2019-003 compared with control (placebo) are described in the following sections.

9.5.1 Measurements Assessed and Flow Chart

The study design is presented in Figure 1 and the schedule of activities (SoA) is presented in Table 6 and Table 7.

Figure 1 Study Design



AE = adverse event; BS = blood sample; DSMB = data safety monitoring board; Ph3 = Phase 3; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Table 6 Overall Schedule of Activities

Phase	**Treatment Intervention and Follow-up**					
Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**ET**
Timing relative to vaccination	**Pre-Vac1 & Vac1**	**Vac1+21d**	**Vac2+14d**	**Vac2+183d**	**Vac2+367d**	
Target Visit Study Day (± window)	**D1**	**D22 (-2d/+7d)[m]**	**D36 (±5d)[n]**	**D205 (±10d)**	**D389 (±14d)**	
Visit Type	**Screening & Vaccination 1**	**Vaccination 2**	**Safety & Immuno.**	**Safety & Immuno.**	**Safety & Immuno.**	**Early Withdrawal**
Informed consent/informed assent (adolescents)	X					
Demography	X					
Medical history[o] and prior medication	X					
Physical examination[a]	X	X	X	X	X	X
Vital signs[b]	X	X				
Pregnancy test[c]	X	X				
Rapid COVID-19 Antigen test[d]	X	X				
Inclusion and exclusion criteria	X					
Risk Assessment of SARS-CoV-2 infection acquisition [p]	X					
Randomization	X					
Eligibility for 2nd vaccination/criteria of vaccination delay[e]		X				
Vaccination	X	X				
30 minutes post vaccination observation[f]	X	X				
ePRO training	X					
Training and distribution of Rapid COVID-19 Antigen test	X	Continuous				
Surveillance for suspected COVID-19 cases (ePRO)[g]	Continuous					
Self-collection of nasal swabs and testing using Rapid COVID-19 Antigen by subjects[h]	Continuous					
Provide Rapid COVID-19 Antigen results to the study site	Continuous					
Interpretation of Rapid COVID-19 Antigen results by trained study staff	Continuous					
Solicited AE reporting[i] — Immunogenicity/ Reactogenicity subset and adolescents – ONLY	X	X				
Unsolicited AE reporting[i] – Immunogenicity/ Reactogenicity subset and adolescents – ONLY	X	X	X[i]			
SAE reporting	X	X	X	X	X	X
AEs leading to early termination from study or vaccination	X	X	X	X	X	X
AESI reporting	X	X	X	X	X	X
MAAE reporting	X	X	X	X	X	X

Table 6 Overall Schedule of Activities (continued)

Phase	**Treatment Intervention and Follow-up**					
Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**ET**
Timing relative to vaccination	**Pre-Vac1 & Vac1**	**Vac1+21d**	**Vac2+14d**	**Vac2+183d**	**Vac2+367d**	
Target Visit Study Day (± window)	**D1**	**D22(-2d/+7d)[m]**	**D36 (±5d)[n]**	**D205 (±10d)**	**D389 (±14d)**	
Visit Type	**Screening & Vaccination 1**	**Vaccination 2**	**Safety & Immuno.**	**Safety & Immuno.**	**Safety & Immuno.**	**Early Withdrawal**
Concomitant medication reporting	X	X	X	X	X	X
Serum sample for baseline SARS-CoV-2 seropositivity testing using anti-S ELISA test – *ALL SUBJECTS*	X					
Serum sample for SARS-CoV-2 seropositivity testing against N-protein (or other immune markers of wild SARS-CoV-2 infection) – ALL SUBJECTS	X[j]	X[j]	X[k]	X	X	X
Serum samples for assessment of humoral immune response – Immunogenicity/ Reactogenicity subset and adolescents – ONLY	X[j]	X[j]	X	X	X	X
Blood sample for PBMCs isolation to evaluate the CMI – CMI subset- ONLYl	X[j]		X			
Blood sample for TCR mapping analysis – CMI subset-ONLY[l]	X[j]	X[j]	X	X	X	
Study conclusion					X	X

AE = adverse event; AESI = adverse event of special interest; CMI = cell-mediated immunity; d = days; D = day; eCRF = electronic case report form; ELISA = enzyme-linked immunosorbent assay; ePRO = electronic patient-reported outcome; ET = early termination; Immunogen. = immunogenicity; MAAE = medically attended adverse event; N protein = nucleocapsid protein; PBMC = peripheral blood mononuclear cell; S = spike (protein); SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TCR, T-cell receptor; Vac = vaccination; WOCBP = women of childbearing potential.

Safety call on Day 43 (-2/+7 days) was to be performed for all adult subjects in the Phase 2 part of the study (immunogenicity/reactogenicity subset) and in adolescents to collect unsolicited AEs, SAEs, MAAEs, AESIs and AEs leading to early termination. Visit 3 and Safety Call Day 43 could have been combined if the visit windows overlapped.

The informed consent and assent (if applicable) process and pre-vaccination procedures (except SARS-CoV-2 testing, vital signs and pregnancy testing, if applicable) may have been conducted earlier, but within 3 days prior to Day 1. In the event that the individual had a mild illness that prevented his/her participation in the study, he/she could have been re-screened once.

Notes on the next page.

[a] Physical examination was to be performed by a qualified health professional in accordance with local regulations.

[b] Vital signs collection (systolic/diastolic blood pressure, respiratory rate, body temperature, and heart rate).

[c] A urine pregnancy test was to be conducted in WOCBP prior to each vaccination. Blood pregnancy test may have been performed at investigator discretion.

[d] The subject was to be also trained on how to perform nasal self-swabbing, testing, and reporting the test outcome. Rapid COVID-19 Antigen test was to be conducted by the subject under guidance of trained study personnel. If the subject had difficulties performing the test, the study personnel could assist as necessary to ensure adequate sample collection for testing.

[e] Prior to the second vaccination, the investigator was to check eligibility criteria for the second vaccination and criteria for vaccination delay.

[f] Any AEs reported within 30 minutes after vaccination were to be recorded in the eCRF.

[g] The surveillance was to include evaluation of suspected COVID-19 symptoms and signs.

[h] Rapid COVID-19 Antigen test was to be performed weekly by study subjects.

i Assessment of solicited symptoms within 7 days after each vaccination and unsolicited AEs from Visit 1 (Day 1) to Safety Call (Day 43) was to be performed in all adult subjects included in the immunogenicity/reactogenicity subset and in adolescents.

[j] Collected prior to vaccination.

[k] Blood draw at Visit 3 was to include a serum sample to explore correlates of protection against COVID-19 and/or SARS-CoV-2 infection.

[l] Blood samples of 30 mL at Visits 1 and 3, and blood samples of 2 mL at Visits 1, 2, 3, 4 and 5 (adults only).

[m] Visit 2 window for Phase 3 subjects was Day 22 (-2d/+41d).

[n] Visit 3 was to be scheduled 14 days (±5 days) after Visit 2.

[o] Information about COVID-19 history was to be collected by interview during the screening procedure.

[p] Collection of information on the risk of a SARS-CoV-2 infection including attending work or school in person, living conditions, household information.

Table 7 Schedule of Activities for Subjects with a Positive Rapid COVID-19 Antigen Test or Suspected COVID-19 Symptoms

Timing Relative to Onset of Signs and Symptoms	**Day 1**	**Days 2-3**	**Days 4+**	**Day 29 (±7 days)[a]**
Subject Location	**Home**	**Local Clinic or Home**	**Home**	**Local Clinic or Home**
Confirmation of symptoms and signs of suspected COVID-19 or a positive result of Rapid COVID-19 Antigen test[b]	X			
Setup ePRO to collect symptoms and signs of COVID-19[c]	X	Daily		
Pulse oximetry for measurement of oxygen saturation and heart rate[d]	X	Daily		X
Nasopharyngeal swab for SARS-CoV-2 RT-PCR[e]		X		
Vital signs[f]		X		X
Details of COVID-19 episode[g]		X		
Review of COVID-19 symptoms and complications (ePRO) by study staff[h]		X	Daily	
For hospitalized patients only: NEWS2 will be calculated daily until resolution[i]		Daily		
Assessment of COVID-19 episode as severe, moderate-to-severe or other[j]				X
Final review of ePRO data and concomitant medications				X
Healthcare Resource Utilization associated with COVID-19 and complications				X

eCRF = electronic case report form; ePRO = electronic patient-reported outcome; NEWS2 = National Early Warning Score 2; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Notes on the next page.

[a] The visit on Day 29 could have been combined with a regular study visit. In case COVID-19 was not yet resolved, the Day 29 visit may have been postponed until resolution.

[b] Symptom evaluation and confirmation.

[c] Subjects were to be encouraged by the study center to complete the ePRO daily, preferably in the evening around the same time each day, starting on the day of suspected COVID-19 symptoms appearance, or positive Rapid COVID-19 Antigen test. In case of non-compliance with daily reporting, study centers were to remind the subject to complete the ePRO, unless special circumstances occurred such as hospitalization or ventilation, in which case the reason for not completing the ePRO was to be recorded by study center staff in the eCRF. The subject was to be asked to record their symptoms in ePRO until resolution (for symptomatic cases) or for a period of 10 days for asymptomatic infection. If the result of the RT-PCR test was negative, the collection of symptoms and signs of COVID-19 was to be stopped.

[d] Pulse oximetry was to be performed daily until resolution of COVID-19 episode (for symptomatic cases) or within 10 days in asymptomatic subjects; and the results reported using ePRO.

[e] A nasopharyngeal swab sample for RT-PCR testing was to be collected from the subject as soon as suspected COVID-19 symptoms were reported, or a positive result of Rapid COVID-19 Antigen test was received (preferably within 2 days but no more than 5 days).

[f] Systolic and diastolic blood pressure, heart rate, respiratory rate, oxygen saturation (after at least 5 minutes rest), oxygen status, consciousness status, pulse oximeter, and body temperature. Vital signs were to be measured before collection of nasopharyngeal samples.

[g] Collected by interview with the subject and recorded in the eCRF.

[h] Based on the information collected through the ePRO or, for the more severe symptoms, through notification to the study center directly.

[i] For hospitalized patients with COVID-19, the investigator was to obtain records to assess severity of disease using NEWS2.

[j] Assessment to be completed by the investigator or delegate.

9.5.2 Informed Consent

Written informed consent was to be obtained at the time of randomization from each subject prior to performing any study-specific procedures.

A representative ICF is provided in **Appendix 16.1.3**. Site-specific versions are available upon request. Other written information given to the subjects is included in **Appendix 16.1.3**.

9.5.3 Demographics

Information about sex, age, ethnic origin (race, ethnicity), and risk of severe COVID-19, was to be collected for each subject.

9.5.4 Safety Measurements

9.5.4.1 Physical Examination

A detailed physical examination was to be performed only at screening and may have included the examination of the following: general appearance, weight, and height, abdomen; head and neck; eyes, ears, nose, throat, chest/respiratory, heart/cardiovascular, gastrointestinal/liver, musculoskeletal/extremities, dermatological/skin, thyroid, lymph nodes, and neurological.

A brief symptom-directed physical examination may have been performed during study visits if necessary, according to symptoms the subject reported. The physical assessment was to be conducted by the investigator or designee, who was to be qualified to perform a physical assessment in accordance with their institutional policy. These data were to be written in the source document. Should the symptom-directed physical examination have revealed any abnormal values or events, these were to be documented in the eCRF AE form.

Treatment of any abnormality observed during this examination was to be performed according to local medical practice outside this study or by referral to an appropriate healthcare provider.

9.5.4.2 Vital Signs

Prior to each study vaccination, vital signs evaluations (systolic/diastolic blood pressure, respiratory rate, body temperature, and heart rate) were to be performed after at least 5 minutes of rest.

9.5.4.3 Adverse Events

AEs were to be graded and analyzed according to the FDA Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.[3]

Collection and reporting of AEs was to be performed as follows:

- *All subjects:* any AEs were to be collected within 30 minutes after each study vaccination, and all SAEs, AESIs, MAAEs, and AEs leading to early termination from the study or from vaccination, were to be collected during the entire study period.
- *Adult subjects enrolled in the Phase 2 part of the study (immunogenicity/reactogenicity subset) and adolescents:* in addition, local and systemic solicited AEs were to be recorded daily within 7 days after each study vaccination using ePRO, and all unsolicited AEs were to be collected from the time of first vaccination until 21 days post-second vaccination

[from Visit 1 (Day 1) to Safety Call (Day 43)]. Unsolicited AEs were to be collected by query in ePRO followed by interviewing the subjects during the site visits or phone contacts, and by review of available medical records. ePRO training was to be directed at the individual(s) performing the measurements of AEs and entering the information into ePRO.

Solicited Adverse Events

Solicited local (injection site) AEs

- Injection site pain;
- Erythema;
- Swelling.

Solicited systemic AEs

- Fatigue;
- Headache;
- Myalgia;
- Arthralgia;
- Loss of appetite;
- Nausea;
- Chills;
- Fever (≥38.0°C; irrespective of method).

Unsolicited Adverse Events

An unsolicited AE was an AE not listed as 'solicited'.

Adverse Events of Special Interest

Potential immune-mediated diseases (pIMDs) include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune etiology. However, the investigator was to exercise his/her medical and scientific judgment in deciding whether other diseases had an autoimmune origin (i.e., pathophysiology involving systemic or organ-specific pathogenic autoantibodies) and was also to be recorded as a pIMD. A list of pIMDs was provided in the protocol (**Appendix 16.1.1**; Section 8.3.7).

Medically-attended Adverse Event

MAAEs were defined as AEs with medically-attended visits including hospital, emergency room, urgent care clinic, or other visits to or from medical personnel for any reason but did not fulfill seriousness criteria. Routine study visits were not to be considered medically attended visits.

Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator was required to proactively follow each subject at subsequent visits/contacts. All AEs/SAEs were to be followed until resolution, stabilization, the event was otherwise explained, or the subject was lost to follow-up.

9.5.4.4 Pregnancy

A urine pregnancy test was to be conducted for WOCBP prior to each vaccination.

9.5.4.5 Clinical Safety Laboratory Assessments

A urine pregnancy test was to be conducted for WOCBP prior to each vaccination.

9.5.5 Efficacy Measurements

The surveillance for COVID-19 of any severity and SARS-CoV-2 infection was to be based on two parallel approaches:

- Reporting of suspected cases of COVID-19 (symptomatic cases) by study subjects and confirmation by RT-PCR;
- Identification of asymptomatic and pre-symptomatic cases of SARS-CoV-2 infection by weekly use of Rapid COVID-19 Antigen test, and confirmation of positive cases, using an RT-PCR test.

Subjects were to be encouraged to report symptoms and signs of suspected COVID-19, to the study site using ePRO. The reported symptoms and signs were to be verified, and, if they met the definition, the subject was to receive instructions regarding SARS-CoV-2 RT-PCR testing and daily reporting of COVID-19 symptoms and signs until resolution of the COVID-19 episode.

The weekly surveillance for COVID-19 cases (starting approximately 2 weeks after each vaccination) was to be based on regular contacts with study subjects and collection of the information about symptoms and signs of suspected COVID-19. In addition, weekly self-testing using the Rapid COVID-19 Antigen test was to be implemented. This testing was to be performed regardless of the presence of suspected COVID-19 symptoms. The implementation of weekly testing using the Rapid COVID-19 Antigen test may have been done on the study, country, or region level. The sponsor may also have defined the duration of this testing based on epidemiological and other relevant data.

In case of COVID-19 or SARS-CoV-2 infection diagnosis outside the study, site staff was to obtain a copy of the laboratory report and follow-up the subject according to the protocol (including RT-PCR testing and post-episode evaluation). The RT-PCR testing was to be performed by the study staff as soon as possible. In the case of a negative RT-PCR result, an additional RT-PCR test may have been performed in case the subject remains symptomatic.

The results of RT-PCR tests, or other equivalent nucleic acid amplification–based tests were to be considered acceptable if obtained using:

- European Medicines Agency- or FDA-cleared assay; or
- An assay conducted in a Clinical Laboratory Improvement Amendments certified laboratory; or
- An assay performed by a laboratory accredited according to the ISO 15189 standard by a national or regional accreditation body.

9.5.5.1 Reporting of Symptoms or Signs of Suspected COVID-19 by Subjects

Subjects were to be asked to actively report symptoms and signs of suspected COVID-19 to the sites using ePRO. Based on the information collected through ePRO or received directly by study staff, an automatic check was to be performed whether the reported signs and symptoms were qualified as suspected using the protocol definition.

Once the symptoms and signs met the protocol definition of suspected COVID-19, the study personnel were to trigger the daily collection of COVID-19 symptoms and signs using ePRO including measuring and recording body temperature, heart rate, and SpO_2.

For symptomatic subjects, a nasopharyngeal swab sample was to be collected from the subject at home or at the study center preferably within 2 days after the onset of suspected COVID-19 symptoms but no more than 5 days (to allow for weekends). This sample was to be sent to a designated laboratory for RT-PCR testing.

In case the result of RT-PCR test is negative, site staff was to stop daily collection of COVID-19 symptoms.

In case the RT-PCR result was positive, subject was to continue follow-up until the resolution of COVID-19 episode.

Preferably, nasopharyngeal swabs for RT-PCR testing were to be collected in all subjects, who met the criteria for testing, to confirm SARS-CoV-2 infection. Other RT-PCR-positive respiratory tract samples collected outside of the study (e.g., nasal swab sample, sputum sample, throat swab sample, saliva sample) were to be considered for efficacy evaluation as well. These cases were to be assessed by the EAC.

Active surveillance for SARS-CoV-2 infection and COVID-19

The active surveillance for SARS-CoV-2 infection and COVID-19 was to include weekly collection of clinical symptoms and signs of suspected COVID-19 and self-testing using Rapid COVID-19 Antigen test.

Starting approximately 2 weeks after Visit 1, subjects were to receive weekly reminders via ePRO to perform routine reporting of symptoms and signs of suspected COVID-19 and self-testing for SARS-CoV-2 using a Rapid COVID-19 Antigen test at home. The testing was to be conducted regardless of the presence of suspected COVID-19 symptoms. The initial training on nasal swabbing procedure and the use of the Rapid COVID-19 Antigen test was to be done at Visit 1. The subsequent training was to be performed at Visit 2.

The outcome of the Rapid COVID-19 Antigen test was to be transferred to the study site using ePRO. The image was to be interpreted by site staff as positive, negative, or invalid.

In case of a positive Rapid COVID-19 Antigen test, site staff were to arrange a home or clinic visit to collect a nasopharyngeal swab for RT-PCR testing preferably within 2 days but no more than 5 days (to allow for weekend). The subject was to be instructed to start daily reporting of suspected symptoms and signs of COVID-19. If the RT-PCR result was positive, the subject was to continue reporting the symptoms for total of 10 days (if asymptomatic) or until resolution.

In case of a negative result of RT-PCR test, the subject was to return to routine weekly surveillance. The reporting of daily symptoms using ePRO was to be stopped.

In case of a symptomatic subject with the negative Rapid Antigen test, no action from the site was required. However, the investigator could perform the RT-PCR test at his/her discretion.

9.5.5.2 Assessment of Subjects with Laboratory-confirmed SARS-CoV-2 Infection and COVID-19

The subject was to be asked to complete the ePRO and document the presence and intensity of COVID-19 symptoms on a daily basis; this was to include measuring and recording their body temperature, heart rate, and SpO_2.

Also, at the time of nasopharyngeal swab collection, the subject was to be interviewed by a member of the study staff for details of the COVID-19 episode.

The subject may have been requested to remain at home and not visit the study center. If necessary, study center personnel was to visit the subject at home (or at the hospital or other location, as applicable), if allowed by local regulations. Under these circumstances, the subject was to be contacted by the study center at least once per week and the subject's medical care provider was to be notified.

A follow-up visit of COVID-19 episodes was to be performed at Day 29 (±7 days) at the clinic or at home; this was to include assessment of vital signs (including targeted physical examination if the visit was conducted at the study center), pulse oximetry, and a concluding interview for the subject with study center staff. This visit may have been combined with a regular study visit if within the applicable visit windows. In case the COVID-19 episode had not resolved within the window (Day 29 ±7 days), the visit may have been postponed until resolution of the episode.

The following assessments were to be performed during a concluding interview by the investigator or delegate:

- Review of the final diagnosis and any complications of COVID-19, including respiratory, cardiac, renal, hepatic, coagulation or other disorders;
- Assess the severity of COVID-19 as severe, moderate-to severe or none;
- Review the ePRO and any medications taken during the COVID-19 episode. Concomitant medications were to be recorded on the eCRF;
- Capture information on healthcare utilization associated with the COVID-19 episode (such as hospitalizations, emergency room visits, unplanned visits to/from healthcare providers).

The subject was to be reminded to contact the site immediately if he/she experienced a new COVID-19-like episode. A new event was only to be counted after at least 45 symptom-free days. If a new event occurred, a nasopharyngeal swab was again to be collected for evaluation of the presence of SARS-CoV-2. In case of a positive RT-PCR result, the confirmation of reinfection was to be done based on comparative evaluation of viral sequences from both episodes.

9.5.5.3 Assessment of Hospitalized Subjects with Laboratory-confirmed COVID-19

For study subjects who contracted COVID-19 and were hospitalized, the NEWS2 was to be calculated every day during hospitalization. (Table 8) The NEWS2 was to be calculated on a daily basis, and the maximum daily score (including the scores of the individual parameters)

reported in the eCRF. This information may have been collected prospectively (during hospitalization) or retrospectively (after discharge, based on medical records). As an exploratory objective, the NEWS2 score (or other similar) was to be used to assess the effect of CpG 1018/alum-adjuvanted SCB-2019 on the degree of illness of hospitalized subjects compared with control, based on the NEWS2 scores upon hospitalization and the subsequent changes in the scores.

Six physiological parameters form the basis of the scoring system:

1. Respiration rate (from 0 to 3);
2. Peripheral oxygen saturation (SpO_2, from 0 to 3; Scale 1 used for all subjects, except patients with hypercapnic respiratory failure [usually chronic obstructive pulmonary disease (COPD], where Scale 2 should be applied);
3. Systolic blood pressure (from 0 to 3);
4. Pulse rate (from 0 to 3);
5. Level of consciousness or new confusion (0 or 3);
6. Temperature (from 0 to 3).

A score was to be allocated to each parameter, with the magnitude of the score reflecting how extremely the parameter varies from the norm. The score was then to be aggregated and increased by 2 points for people requiring supplemental oxygen to maintain their recommended oxygen saturation.

Table 8 National Early Warning Score 2 System

Physiological Parameter	Score						
	3	**2**	**1**	**0**	**1**	**2**	**3**
Respiratory rate (pm)	≤8		9 to 11	12 to 20		21 to 24	≥25
Peripheral capillary O_2 saturation, Scale 1 (%)	≤91	92 to 93	94 to 95	≥96			
Peripheral capillary O_2 saturation, Scale 2 (%)	≤83	84 to 85	86 to 87	• 88 to 92 • ≥93 on air	93 to 94 on O_2	95 to 96 on O_2	≥97 on O_2
Air or O_2?		O_2		Air			
Systolic BP (mmHg)	≤90	91 to 100	101 to 110	111 to 219			≥220
Pulse (bpm)	≤40		41 to 50	51 to 90	91 to 110	111 to 130	≥131
Consciousness				Alert			Drowsiness Lethargy Coma Confusion
Temperature (°C)	≤35.0		35.1 to 36.0	36.1 to 38.0	38.1 to 39.0	≥39.1	

Abbreviations: BP = blood pressure; bpm = beats per minute; pm = per minute.
Note: Scale 2 of oxygen saturation section was to be specific to patients with hypercapnic respiratory failure [usually chronic obstructive pulmonary disease (COPD)] who require their 'usual' oxygen saturations to be set at 88% to 92% in accordance with respective guidelines.

9.5.5.4 Case Definitions

COVID-19 of any severity was defined as an episode of RT-PCR-confirmed SARS-CoV-2 infection associated with at least one symptom/sign of COVID-19, observed within 7 days prior and 14 days after the first positive RT-PCR result.

COVID-19 associated symptoms/signs include fever (>37.8°C; irrespective of method), chills, nonproductive cough, shortness of breath or difficulty breathing, fatigue, new loss of taste or smell, acute diarrhea (≥3 loose stools/24 hour period), radiologically confirmed lower respiratory tract infection, or a combination of at least two symptoms (muscle or body aches, arthralgia, headache, sore throat, congestion or runny nose, nausea or vomiting, loss of appetite/skipped meals, and dizzy/light-headed).

Asymptomatic SARS-CoV-2 infection was defined as:

- Occurrence of RT-PCR-confirmed SARS-CoV-2 infection in absence of any of COVID-19 associated symptoms/signs, within 7 days prior and 14 days after the first positive laboratory result for SARS-CoV-2, or
- Occurrence of seroconversion to a component of SARS-CoV-2 not included in CpG 1018/alum-adjuvanted SCB-2019 [including nucleocapsid (N)-protein and/or other relevant SARS-CoV-2 proteins) between Visit 1 (Day 1) and Visit 2 (Day 22), Visit 3 (Day 36), Visit,4 (Day 205), or Visit 5 (Day 389). Seroconversion was defined as change of negative test result at Baseline to positive result at any time point during the study period.

Severe COVID-19 was defined as COVID-19 associated with at least one of the following symptoms/signs, observed within 7 days prior and 14 days after the first positive RT-PCR result:

- Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥30 breaths per minute, heart rate ≥125 beats per minute, oxygen saturation [SpO_2] ≤93% on room air at sea level or partial pressure of arterial oxygen [PaO_2]/fraction of inspired oxygen [FiO2] <300 mm Hg);
- Respiratory failure (defined as needing high flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation);
- Evidence of shock (systolic blood pressure <90 mm Hg, diastolic blood pressure <60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction;
- Admission to an intensive care unit (ICU);
- Death.

Moderate-to-Severe COVID-19 was defined as the COVID-19 associated with any of symptoms/signs associated with severe COVID-19, OR at least one of the following symptoms/signs, observed within 7 days prior and 14 days after the first positive RT-PCR result:

- Fever (≥39.0°C or ≥102.2°F) for at least 2 consecutive days;
- New onset of shortness of breath (with exertion), not requiring oxygen, and meeting the definition of "moderate" as set forth by the May 2020 Food and Drug Administration (FDA) Guidance for Industry: COVID-19: Developing Drugs and Biological Products for Treatment or Prevention (FDA, 2020)[4], which includes all of the following criteria:
  - Respiratory rate: ≥20 breaths/minute;
  - SpO_2: >93% on room air at sea level, and
  - Heart rate: ≥90 beats/minute;
  - COVID-19 will be assessed as moderate if shortness of breath and at least 2 out of the 3 abnormal vital signs (respiratory rate, heart rate, and oxygen saturation) are present.
- Clinical or imaging-confirmed pneumonia (or lower respiratory disease) with a saturation of oxygen (SpO_2) >93% on room air at sea level;
- Radiologic evidence of deep vein thrombosis;
- Diarrhea (>3 episodes a day) for at least 2 consecutive days (in absence of any other diagnosed gastrointestinal infection).

Any SARS-CoV-2 infection was defined as:

- Occurrence of RT-PCR-confirmed COVID-19 of any severity, or
- Occurrence of laboratory-confirmed asymptomatic SARS-CoV-2 infection.

Burden of Disease Score was defined as shown in Table 9.

Table 9 Burden of Disease Score

Subject-level clinical outcome	Binary Efficacy Endpoint Scores			BOD Score
	SARS-CoV-2	COVID-19?	Severe	

	infection? No=0, Yes=1	**No=0, Yes=1**	**COVID-19? No=0, Yes=1**	
Non-infected (negative SARS-CoV-2 tests)	0	0	0	0
Infected, but no COVID-19 (asymptomatic)	1	0	0	0
Infected, non-severe COVID-19	1	1	0	1
Infected, severe COVID-19	1	1	1	2

BOD = burden of disease; COVID-19, coronavirus disease 2019; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Subject without evidence of prior SARS-CoV-2 infection was defined as

- Individual with a negative result of anti-SARS-CoV-2 ELISA Ig test to RBD of the S protein (anti-S ELISA test), and (if applicable) a negative result of SARS-CoV-2 IgG test to the N protein (anti-N test) at Baseline, and
- Individual with a negative Rapid COVID-19 Antigen test at Baseline, and
- Individual without documented history of SARS-CoV-2 infection.

Subject with evidence of prior SARS-CoV-2 infection was defined as

- Individual with a positive result of anti-SARS-CoV-2 ELISA Ig test to RBD of the S protein (anti-S ELISA test) or (if applicable) a positive result of SARS-CoV-2 IgG test to the N protein (anti-N test) at Baseline, or
- Individual with documented history of SARS-CoV-2 infection.

Subject with high risk of severe COVID-19 was defined as an individual with history of at least one medical condition that constitutes a high risk for COVID-19 as defined by US Centers for Disease Control and Prevention (cancer, chronic kidney disease, chronic obstructive pulmonary disease, immunocompromised state, obesity with body mass index ≥30 kg/m2, serious heart conditions such as hypertension, heart failure, coronary artery disease or cardiomyopathies, sickle cell disease and Type 2 diabetes mellitus).

COVID-19-associated hospitalization was defined as a hospitalization due to any medical condition associated with a positive RT-PCR SARS-CoV-2 laboratory result (obtained within 14 days prior to hospitalization or during the hospital stay). Hospital stay for isolation or quarantine purpose was not to be considered as COVID-19 associated hospitalization.

COVID-19-associated death was defined as any death reported within 30 days after the first RT-PCR-confirmed SARS-CoV-2 infection, or any death assessed as COVID-19 related based on subject medical records or death certificate.

Duration of COVID-19: from the first day of the initial clinical symptom or sign [fever (>37.8°C; irrespective of method), chills, nonproductive cough, shortness of breath or difficulty breathing, fatigue, new loss of taste or smell, acute diarrhea, muscle or body aches, arthralgia, headache, sore throat, congestion or runny nose, nausea or vomiting, loss of appetite/skipped meals, dizzy/light-headed, or radiologically confirmed lower respiratory tract infection] until the event resolution defined as the first day when the following conditions were met simultaneously:

- Subject discharged from the hospital (if applicable);

- No clinical symptoms or signs that indicate severe systemic illness, respiratory failure, shock, significant acute renal, hepatic or neurological dysfunction;
- All COVID-19 associated symptoms either absent or mild during 2 consecutive days.

If COVID-19 associated symptoms or signs reappeared or worsened, the duration of the episode was to be calculated until the first time that the above listed conditions were met after worsening of these symptoms.

A new event was only to be counted after at least 45 symptom-free days. If a new event occurred, a nasopharyngeal swab was to be collected for evaluation of the presence of SARS-CoV-2 virus. In case of positive RT-PCR result, the confirmation of reinfection was to be done based on comparative evaluation of viral sequences from both episodes.

Variant of Concern

A VOC was defined as SARS-CoV-2 isolate, associated with an increase in transmissibility or detrimental change in COVID-19 epidemiology, or an increase in virulence or change in clinical disease presentation; or a decrease in the effectiveness of public health and social measures or available diagnostics, vaccines, and therapeutics (WHO, February 2021). The VOCs include but are not limited to Alpha, Beta, Gamma, Lambda, Mu.

9.5.6 Immunogenicity Measurements

Humoral and cell mediated immunity assessments were to be performed at time points detailed in Section 9.1.4.

Whole blood was to be drawn for analysis of humoral immune response at each predefined time point specified in Section 9.5.1.

Serum samples were also to be collected at the final visit from subjects withdrawn from the study. These samples may have been tested by the sponsor or sponsor's designee.

The detection and characterization of antibodies was to be performed by or under the supervision of the sponsor or the sponsor's designee. Samples may have been stored for a maximum of 20 years (or according to local regulations) following the last subject's last visit for the study at a facility selected by the sponsor to enable further analysis of immune responses to the study vaccine.

The analyses performed on the samples collected for assessment of immunogenicity may have been expanded as more knowledge regarding COVID-19 became available.

9.5.6.1 Humoral Immunogenicity

As a secondary objective, in a subset of adult and adolescent subjects, the humoral immune response of CpG 1018/alum-adjuvanted SCB-2019 was to be compared with control using the following methods:

- VNA (analysis of neutralizing antibodies to the wild-type* SARS-CoV-2 virus and pseudovirus);
- ACE2-competitive ELISA (analysis of antibodies competing for binding of S protein to the human ACE2 receptor);

- SCB-2019 binding antibody ELISA (analysis of antibodies binding to SCB-2019).*

* immunogenicity assessments in adolescents were to be based only on these methods.

For these assays, geometric mean titers (GMTs), geometric mean fold rise (GMFR post- to pre vaccination), proportion of subjects with seroconversion and other relevant endpoints were to be evaluated.

In addition, Trimer-Tag binding antibody ELISA was to be analyzed in the subset of adult and adolescent subjects.

All analyses were to be performed at a laboratory designated by the sponsor or the sponsor's designee using qualified or/and validated procedures.

9.5.6.2 Cell Mediated Immunity

In a CMI subset of adult subjects, as an exploratory analysis, the number of lymphocyte and intracellular cytokine staining (ICS) of peripheral blood mononuclear cells (PBMCs) was to be conducted to characterize the T-cell responses to 2 doses of SCB-2019. The analysis was to include responses to S1 and S2 subunit of SARS-CoV-2 S protein) and Trimer-Tag. Post-vaccination results (Day 36) was to be compared with Baseline (Day 1 pre vaccination), and results for active vaccine were to be compared with placebo for CMI based on cytokine production after in vitro stimulation, including but not limited to, type 1 T-helper cells [interferon γ, interleukin (IL)-2], type 2-helper cells (IL-4, IL-5) and type 17 T-helper cells (IL 17). Additional exploratory analyses of CMI response may also have been conducted.

9.5.6.3 Immunological Markers of SARS-CoV-2 Infection

The identification of antibodies to the N protein of SARS-CoV-2 in serum samples was to be an indication of immune response to SARS-CoV-2 natural infection.

The sequence of samples testing to identify the seroconversion to N protein was to be as follows:

- All samples collected at Visit 1 (Day 1) were to be tested for the presence of anti-N IgG.
- If subject's test was negative at Visit 1, then his/her Visit 4 (Day 205), then Visit 3 (Day 36) and Visit 2 (Day 22) samples were also to be tested to assess when the natural infection occurred.

9.5.7 Other Measurements

9.5.7.1 SARS-CoV-2 Surveillance:

- Subjects were to be asked to actively report symptoms and signs of suspected COVID-19 to the sites using ePRO. A nasopharyngeal swab for SARS-CoV-2 RT-PCR testing was to be collected in all subjects with suspected symptoms.
- In addition, active surveillance for SARS-CoV-2 infection and COVID-19, including weekly collection of clinical symptoms and signs of suspected COVID-19 and self-testing using Rapid COVID-19 Antigen test, were to be performed. The sponsor may have defined the duration of weekly testing using Rapid CoVID-19 Antigen test based on epidemiological and other data.

- Serological samples to assess seroconversion to a component of SARS-CoV-2 not included in CpG 1018/alum-adjuvanted SCB-2019 vaccine (e.g., N-protein) were to be collected at Baseline (Day 1), Visit 2 (Day 22), Visit 3 (Day 36), Visit 4 (Day 205), and Visit 5 (Day 389).

COVID-19 (e)Booklet: subjects with RT-PCR-confirmed COVID-19 or SARS-CoV-2 infection were to be asked to record symptoms in ePRO until the case resolution (for symptomatic cases) or for period of 10 days (for asymptomatic infection).

Post COVID-19 visit: All subjects were to be asked to return to the site or receive a home visit after COVID-19 episode to examine the subject for possible COVID-19-related complications and to assess health care utilization during the episode. Any medication packages were to be checked during the visit.

9.5.7.2 Medical Resource Utilization and Health Economics

Information about utilization of healthcare resources associated with COVID-19 was to be collected in the study.

9.5.7.3 Risk of Disease Enhancement

Enhancement of disease, where a vaccinated individual who subsequently becomes infected with a natural infection develops a more severe form of the disease than people who have never been vaccinated, has been observed in patients for vaccines against other respiratory viruses such as respiratory syncytial virus (RSV).

In this study, to assess the effect of CpG 1018/alum-adjuvanted SCB-2019 compared to control on the incidence of disease enhancement, including but not limited to enhanced respiratory disease, the ratio of severe COVID-19 to COVID-19 of any severity for CpG 1018/alum-adjuvanted SCB-2019 vaccine was to be compared with the control group. Furthermore, the ratio of severe COVID-19 to all SARS-CoV-2 infection (symptomatic + asymptomatic) was to be assessed, between Baseline (Day 1) and Visit 4 (Day 205) and Visit 5 (Day 389), in all study groups. Deaths associated with COVID-19 for subjects receiving CpG 1018/alum-adjuvanted SCB-2019 vaccine was to be compared with the control group.

9.5.8 Appropriateness of Measurements

The model assumptions were examined to ensure the appropriateness of the methods.

9.5.9 Endpoints and Estimands

The primary, secondary, and exploratory endpoints and associated estimands of this trial are listed in the following sections.

9.5.9.1 Primary Endpoints and Estimands

Efficacy (H1)

First occurrence of any RT-PCR-confirmed COVID-19 of any severity (refer to case definition) with onset at least 14 days after the second study vaccination in subjects without evidence of prior SARS-CoV-2 infection:

- 1 minus incidence rate ratio (IRR) of the vaccine to placebo in subjects with any RT-PCR confirmed COVID-19 of any severity per cumulative follow-up person time by Per Protocol Set (PPS) for efficacy.

Safety and reactogenicity

Local and systemic solicited AEs reported within 7 days after each study vaccination (in Phase 2 adult subjects and adolescents):

- Proportion of subjects with local and systemic solicited AEs reported within 7 days after each study vaccine (in Phase 2 subjects).

Unsolicited AEs reported from Visit 1 (Day 1) through Safety Call Day 43 (in Phase 2 adult subjects and adolescents):

- Proportion of subjects with unsolicited AEs reported from Visit 1 (Day 1) through Safety Call Day 43 (in Phase 2 subjects).

SAEs, AEs leading to early termination from the study, MAAEs, and AESIs during the entire study period (in all subjects):

- Proportion of subjects with SAEs, AEs leading to early termination from the study, MAAEs, and AESIs during the entire study period.

9.5.9.2 Secondary Endpoints and Estimands

Key secondary #1 (H2b): First occurrence of RT-PCR-confirmed moderate-to-severe COVID-19 (refer to case definition) with onset at least 14 days after the second vaccination in subjects without evidence of prior SARS-CoV-2 infection:

- 1 minus IRR of the vaccine to placebo in subjects with any RT-PCR-confirmed SARS-CoV-2 moderate-to-severe COVID-19 per cumulative follow-up person time by PPS for efficacy.

Key secondary #2 (H2a): Occurrence of any laboratory-confirmed SARS-CoV-2 infection (refer to case definition) with onset at least 14 days after the second study vaccination in subjects without evidence of prior SARS-CoV-2 infection:

- 1 minus IRR of the vaccine to placebo in subjects with any laboratory-confirmed SARS-CoV-2 infection per cumulative follow-up person time by PPS or efficacy.

Key secondary #3 (H4): First occurrence of RT-PCR-confirmed severe COVID-19 (refer to case definition) with onset at least 14 days after the second vaccination in subjects without evidence of prior SARS-CoV-2 infection:

- 1 minus IRR of the vaccine to placebo in subjects with any RT-PCR-confirmed SARS-CoV-2 severe COVID-19 per cumulative follow-up person time by PPS for efficacy.

Key secondary #4 (H3): Occurrence of laboratory-confirmed asymptomatic SARS-CoV-2 infection (refer to case definition), with onset at least 14 days after the second vaccination in subjects without evidence of prior SARS-CoV-2 infection.

- 1 minus IRR of the vaccine to placebo in subjects with laboratory-confirmed asymptomatic SARS-CoV-2 infection per cumulative follow-up person time by PPS* for efficacy.

See Figure 2 for the order in which key secondary objectives were to be evaluated.

Secondary efficacy #1: Occurrence of any SARS-CoV-2 infection, any RT-PCR COVID-19 and any RT-PCR-confirmed severe COVID-19 with onset at least 14 days after the second vaccination in subjects without evidence of prior SARS-CoV-2 infection:

- 1 minus relative risk (RR) in terms of BOD (refer to BOD score definition) from the vaccine and placebo in subjects with any BOD by PPS for efficacy.

Secondary efficacy #2: First occurrence of RT-PCR confirmed COVID-19 of any severity, associated with hospitalization (refer to case definition), with onset at least 14 days after the second vaccination in subjects without evidence of prior SARS-CoV-2 infection:

- 1 minus IRR of the vaccine to placebo in subjects with RT-PCR confirmed COVID-19 of any severity, associated with hospitalization per cumulative follow up person time by PPS for efficacy.

Secondary efficacy #3: First occurrence of RT-PCR confirmed COVID-19 or laboratory-confirmed SARS-CoV-2 infection (refer to endpoints below) by evidence of prior SARS-CoV-2 infection and risk of severe COVID-19

First occurrence of RT-PCR confirmed COVID-19 of any severity:

- 1 minus IRR of the vaccine to placebo in subjects with RT-PCR confirmed COVID-19 of any severity.

First occurrence of RT-PCR confirmed moderate-to-severe COVID-19:

- 1 minus IRR of the vaccine to placebo in subjects with RT-PCR-confirmed moderate-to-severe COVID-19.

First occurrence of RT-PCR confirmed severe COVID-19:

- 1 minus IRR of the vaccine to placebo in subjects with RT-PCR-confirmed severe COVID-19.

First occurrence of RT-PCR confirmed COVID-19 of any severity, associated with hospitalization:

- 1 minus IRR of the vaccine to placebo in subjects with RT-PCR-confirmed COVID-19 of any severity associated with hospitalization.

Occurrence of any laboratory-confirmed SARS-CoV-2 infection:

- 1 minus IRR of the vaccine to placebo in subjects with any laboratory-confirmed SARS-CoV-2 infection.

Occurrence of laboratory-confirmed asymptomatic SARS-CoV-2 infection:

- 1 minus IRR of the vaccine to placebo in subjects with laboratory-confirmed asymptomatic SARS-CoV-2 infection.

with onset at least 14 days after the second vaccination (refer to case definitions) per cumulative follow-up person time by PPS for efficacy.

Secondary efficacy #4: First occurrence of RT-PCR confirmed COVID-19 or laboratory-confirmed SARS-CoV-2 infection (refer to endpoints below) after the first vaccine dose

First occurrence of RT-PCR confirmed COVID-19 of any severity:

- 1 minus IRR of the vaccine to placebo in subjects with RT-PCR confirmed COVID-19 of any severity.

First occurrence of RT-PCR confirmed moderate-to-severe COVID-19:

- 1 minus IRR of the vaccine to placebo in subjects with RT-PCR-confirmed moderate-to-severe COVID-19.

First occurrence of RT-PCR confirmed severe COVID-19:

- 1 minus IRR of the vaccine to placebo in subjects with RT-PCR-confirmed severe COVID-19.

First occurrence of RT-PCR confirmed COVID-19 of any severity, associated with hospitalization:

- 1 minus IRR of the vaccine to placebo in subjects with RT-PCR-confirmed COVID-19 of any severity associated with hospitalization.

Occurrence of any laboratory-confirmed SARS-CoV-2 infection:

- 1 minus IRR of the vaccine to placebo in subjects with any laboratory-confirmed SARS-CoV-2 infection.

Occurrence of laboratory-confirmed asymptomatic SARS-CoV-2 infection:

- 1 minus IRR of the vaccine to placebo in subjects with laboratory-confirmed asymptomatic SARS-CoV-2 infection.

with onset at least 14 days after the first vaccination to the second vaccination per cumulative follow-up person time by FAS (for 1 dose) for efficacy.

Secondary efficacy #5: First occurrence of RT-PCR confirmed COVID-19 of any severity (refer to case definition), caused by SARS-CoV-2 VOCs, with onset at least 14 days after the second vaccination in subjects without evidence of prior SARS-CoV-2 infection:

- 1 minus IRR of the vaccine to placebo in subjects with RT-PCR confirmed COVID-19 of any severity by individual VOC, per cumulative follow up person time by PPS for efficacy.

Secondary immunogenicity:

At each of Visits 1, 2, 3, 4 and 5 (in a subset of subjects):

- VNA (analysis of neutralizing antibodies to wild-type SARS-CoV-2 and pseudovirus);
- ACE2-competitive ELISA (analysis of antibodies competing for binding of S protein to the human ACE2 receptor);
- SCB-2019 binding antibody ELISA (analysis of antibodies binding to SCB-2019).

GMTs, GMFRs (post/pre-vaccination), proportion of subjects with seroconversion, and proportion of subjects with antibody titer above a pre-specified threshold (Limit of Quantification) for each type of serological assays by PPS for immunogenicity.

Secondary safety: At each blood sample collection time point (Visits 1, 2, 3, 4 and 5),

Trimer-Tag binding antibody as measured by ELISA assay:

- GMTs and GMFRs from Baseline by PPS for immunogenicity.

9.5.9.3 Exploratory Endpoints and Estimands

Exploratory efficacy

NEWS2 score in subjects who were hospitalized with COVID-19 of any severity:

- Distribution/average NEWS2 score in subjects who were hospitalized with COVID-19 of any severity by FAS (dose 2) for efficacy.

Viral genome copies in nasopharyngeal swabs collected at SARS-CoV-2 infection episode as determined by quantitative RT-PCR:

- Distribution of viral genome copies in nasopharyngeal swabs collected at SARS-CoV-2 infection episode as determined by RT-PCR by PPS for efficacy.

Long-term sequelae of COVID-19, including but not limited to respiratory disorders, neurologic disorders, and other organ dysfunctions (as adjudicated by the DSMB):

- Percentage of subjects with at least one long-term sequela of COVID-19, including but not limited to respiratory disorders, neurologic disorders, and other organ dysfunctions, by safety set.

Severe COVID-19; all COVID-19 of any severity; all SARS-CoV-2 infection; total number of deaths and case fatality rate associated with COVID-19:

- Ratio of severe COVID-19 to all COVID-19 of any severity PPS for efficacy;
- Ratio of severe COVID-19 to all SARS-CoV-2 infection PPS for efficacy;
- Total number and percentage of deaths and case fatality rate associated with COVID-19 by safety set population.

Full-length genome sequence:

- Phylogenetic analysis of full-length genome sequences.

Exploratory immunogenicity:

Lymphocytes and ICS of PBMCs specific to proteins related to SCB-2019 (including but not limited to SARS-CoV-2 S protein and Trimer-Tag), and secreting cytokines including but not limited to Th1 (IFNγ, IL-2), Th2 (IL 4, IL-5), and Th17 (IL 17):

- Number and percentage of lymphocytes and ICS of PBMCs specific to proteins related to SCB-2019 (including but not limited to SARS-CoV-2 S protein and Trimer-Tag), and secreting cytokines including but not limited to Th1 (IFNγ, IL-2), Th2 (IL-4, IL-5), and Th17 (IL-17) by PPS for immunogenicity.

VNA (analysis of neutralizing antibodies to new emergent mutants of SARS-CoV-2):

- GMTs, GMFRs (post/pre-vaccination), and proportion of subjects with seroconversion, by PPS for immunogenicity.

Correlate of protection:

- The endpoints will be presented in the statistical analysis plan (SAP) addendum. The results of this exploratory analysis may be presented in an addendum to the CSR.

9.6 Data Quality Assurance

The trial site was subject to quality assurance audits by the sponsor or designees. The sponsor-designated auditor contacted the site in advance to arrange an auditing visit to access the facilities where laboratory samples were collected, where the vaccine was stored and prepared, and any other facility used during the trial.

Three audits were performed during this study. Audit certificates are provided in **Appendix 16.1.8**. Documentation of inter-laboratory standardization methods and quality assurance procedures were not applicable for this study (**Appendix 16.1.10**).

9.6.1 Risk Management

The ICH E6 addendum (R2) guidance encourages a risk-based approach to the management of clinical studies and includes requirements for risk control and risk reporting. Before initiation of the study, Clover and the CRO agreed on the quality tolerance limits (QTL) taking into consideration the medical and statistical characteristics of the variables and the statistical design of the study.

9.7 Statistical Methods and Determination of Sample Size

The information provided in this section reflects the planned statistical methods used. A description of the planned statistical methods is presented in the latest version of the protocol (**Appendix 16.1.1**) and in the SAP (**Appendix 16.1.9)**. Changes to the planned statistical methods are described in Section 9.8.

9.7.1 Statistical and Analytical Plans

A SAP was prepared and finalized prior to the analysis. This document provides further details regarding the definition of analysis variables and analysis methodology to address all trial objectives. Unless otherwise stated, the statistical methods described in the following subsections apply to all groups.

The IA database snapshot was planned after 75 *any* RT-PCR confirmed COVID-19 events that met the primary endpoint definition within the PPS had been observed; the final analysis for the primary efficacy database snapshot was planned after 150 *any* RT-PCR confirmed COVID-19 events that met the primary endpoint definition within the PPS had been observed. The study was to be kept blinded until all subjects complete 1-year safety follow up after the last vaccination.

All analyses, descriptive summaries (mean, standard deviation, median, minimum, maximum, etc., for continuous variables, counts, percentages and associated Clopper-Pearson 95% CIs for categorical variables), and listings were performed using SAS® software (version 9.4 or higher).

The SAP is provided in **Appendix 16.1.9**.

9.7.1.1 Statistical Hypotheses

One primary efficacy endpoint was specified in this study. The primary endpoint was defined as first occurrence of RT-PCR-confirmed COVID-19 of *any* severity, with onset at least 14 days after the second vaccination.

The null ($H1_0$) and alternative ($H1_a$) hypotheses for the primary endpoint were:

$H1_0$: VE ≤30% vs $H1_a$: VE >30%.

VE was calculated as 100×[1 –incidence rate ratio (IRR)]. The incidence rate (IR) is the number of subjects with any RT-PCR-confirmed COVID-19 of *any* severity divided by cumulative follow-up person time among all subjects at risk. VE at the final analysis was demonstrated if the lower limit (LL) of adjusted confidence interval (CI) for VE against COVID-19 of *any* severity exceeded 30%.

The primary objective was evaluated based on exact binomial method and Type I-adjusted CIs.

9.7.1.2 Populations for Analyses

- **Enrolled Set:** All screened subjects who provided informed consent/assent, and received a subject ID, regardless of the subject's randomization and treatment status in the study.
- **Exposed Set**: All subjects who received at least one dose of the study vaccine/placebo.
- **Full Analysis Set (FAS)* – Efficacy** All subjects in the Enrolled Set who were randomized, received a study vaccination and provided efficacy data.
    - For VE evaluation 14 days post-Dose 2 (cases 14 days post Dose 2 were included in the analysis), FAS included all subjects who received both Dose 1 and Dose 2;
    - For VE evaluation 14 days post-Dose 1 in subjects who received 1 dose only, FAS included all subjects who received only one vaccine dose;
    - For VE evaluation 14 days post-Dose 1, FAS included all subjects who received at least one dose.

*Analyzed "as randomized" if vaccination error.

- **Per Protocol Set (PPS)* – Efficacy** For VE evaluation 14 days post-Dose 2, subjects in the FAS - Efficacy (Dose 2) who correctly received the full vaccination regimen and who had no other major protocol deviations that were judged to possibly impact the efficacy of the vaccine up to 14 days post Dose 2.

*Primary analysis population for the efficacy analysis.

- **Full Analysis Set (FAS) – Immunogenicity** All adult subjects in the immunogenicity/reactogenicity subset and adolescent who were randomized, received at least one dose of study vaccine, and provided immunogenicity data at Day 36 (Visit 3).
- **Per Protocol Set (PPS)* – Immunogenicity** Subjects in the FAS – Immunogenicity who correctly received the full vaccination regimen and who had no other major protocol deviations that were judged to possibly impact the immunogenicity of the vaccine.

*For laboratory-confirmed SARS-CoV-2 infection, samples taken after the event and samples taken outside protocol windows were not considered in the assessment of the immunogenicity. The PPS - immunogenicity population is the primary immunogenicity population.

- **Safety Set (SAF)** All subjects in the exposed set – For reactogenicity analysis after each dose, the safety set was to include all adult subjects in the immunogenicity/reactogenicity subset who received study vaccine and provided any solicited AE data after each dose. For unsolicited AE analysis, the SAF was to include all subjects who received at least one dose of study vaccine. (Note: for all adult subjects in the immunogenicity/reactogenicity subset were to record solicited AEs within 7 days after each vaccination and unsolicited AEs from Day 1 to Day 43; and a subject was to be analyzed as "treated" according to the study vaccine a subject received, rather than the study vaccine to which the subject may have been randomized).

9.7.1.3 Analysis of Demographics and Baseline Characteristics

Descriptive statistics (mean, standard deviation, median, minimum and maximum) for age, height, weight, and body mass index at enrollment, calculated overall and by study group.

Distributions of subjects by sex, age, ethnic origin (race, ethnicity), and risk of severe COVID-19, are summarized overall, and by study group.

9.7.1.4 Efficacy Analyses

The primary efficacy objective (Section 8.1) was to be evaluated based on exact binomial method. The VE estimate by (1 – IRR) and Type I error adjusted % CIs derived using Clopper-Pearson method were to be produced.

Success criteria:

At the interim analysis:

- Efficacy would be demonstrated if the LL of 98.66% CI for VE against COVID-19 of any severity exceeds 30%.

At the final analysis:

- Efficacy would be demonstrated if the LL of 95.72% CI for VE against COVID-19 of any severity exceeds 30%.

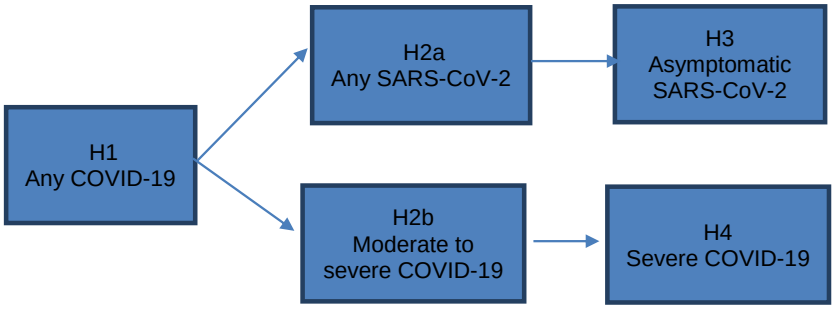
The events used in the analysis of the primary efficacy endpoint are events that occurred until the primary efficacy database snapshot occurred [the minimally required target number of events (TNEs) is reached].

The COVID-19 cases of any severity that occurred after the final database snapshot for primary efficacy analysis were to be presented in a descriptive manner.

Primary analysis was to be done in the PPS population without imputation of missing data. VE analysis based on the FAS (post Dose 2) was to be a supplement.VE analysis by subgroup (age, sex, baseline serostatus etc) was also to be performed. Furthermore, a sensitivity analysis with imputation of missing data, or logistic regression to evaluate the effect of the comorbidity, and some other factors (i.e., age, sex) as covariates may have been performed and was to be detailed in SAP.

If the primary objective was met, the key secondary efficacy objectives (Section 8.2) were to be evaluated in the order as shown in Figure 2.

Figure 2 Evaluation of the Key Secondary Objectives



The IA was to evaluate the primary objective only. The key secondary and other secondary efficacy endpoints (Section 8.2) were to be evaluated at the efficacy final analysis. If the primary objective was met, then the alpha level of 0.0107 (0.0214 divided by 2) (one-sided) was to be used for each of the key secondary endpoints of ($H2_a$), any SARS-CoV-2 infection, and ($H2_b$) any moderate-to-severe COVID-19.

- If the null hypothesis $H2_a$ was rejected, then the same alpha (0.0107) was to be re-allocated to (H3), asymptomatic infection of SARS-CoV-2;
- If the null hypothesis $H2_b$ was rejected, then the same alpha (0.0107) was to be re-allocated to (H4), any severe COVID-19;
- If the null hypotheses were not rejected for H1, then $H2_a$, $H2_b$, H3 and H4 were not to be tested and all the analyses were to be descriptive.

The key secondary VE analysis was to be done by PPS and FAS populations for efficacy without imputation of missing data.

Success criteria for key secondary points: efficacy would be demonstrated if the lower bound of the corresponding 97.86% CI for VE was greater than 0%.

All secondary efficacy endpoints were to be evaluated using the same method used for the primary VE endpoint 100× (1 – IRR), with 95% CI. By PPS and FAS for efficacy. Missing data was not to be imputed.

VE measured by BOD will be assessed by the following and 95% CI:

$100 \times (1- RR_{BOD})$

Where $1- RR_{BOD}$ is a RR in terms of BOD score weighted by number of diseases in vaccine and Placebo arm. Details are be presented in the SAP.

Sensitivity analyses were to be explored to assess the robustness of treatment effects for the primary efficacy objective, where different missing data mechanisms were to be explored using multiple imputation approaches.

Sensitivity analysis and analyses of exploratory endpoints were to be described in the SAP finalized before database lock.

9.7.1.5 Immunogenicity Analyses

Primary immunogenicity analyses were to be performed on the PPS - Immunogenicity.

For the secondary objectives, the geometric mean was to be calculated as the mean of the antibody results after the data were log-transformed and then exponentiating the log-mean to present the results on the original scale. Two-sided 95% CI were to be obtained by taking log transform of the antibody results and calculated based on t-distribution; then exponentiating the confidence limit.

GMFR analysis was to include subjects with antibody results available at both Baseline (prior to Dose 1) and post vaccination. It was to be calculated as the mean of the difference after log-transformed results (post baseline minus baseline) and exponentiating the mean. Two-sided 95% CI was to be obtained by taking log-transformed antibody results and calculating the 95% CI based on Student's t-distribution for the mean difference after the data were log-transformed, then exponentiating the confidence limit.

SCR was defined as: for seronegative subjects (baseline value < cutoff), the SCR = 4 × cutoff, for seropositive subjects (baseline value ≥ cutoff), SCR = 4-fold rise from Baseline.

Reverse cumulative distribution curves (RCDC) were to be generated for each assay result.

Phylogenetic analysis of full-length genome sequences was to be performed to characterize SARS-CoV-2 isolates by genetic sequencing in a subset of samples.

The Clopper-Pearson method was to be used to calculate the CIs for seroconversion.

Pre-specified threshold was to be defined before SAP finalization/database lock for serology analysis.

The serology data listing by subjects/site was to be produced at the final analysis.

All immunogenicity analyses were to be performed on the PPS – Immunogenicity. If more than 5% subjects were excluded from the PPS – immunogenicity, the immunogenicity by the FAS-immunogenicity was also to be produced.

Missing data were not to be imputed.

For the exploratory objectives, the numbers and frequency of CMI (lymphocyte and intracellular cytokine staining of PBMCs) specific to proteins related to SCB-2019 (including but not limited to SARS-CoV-2 S protein) and Trimer-Tag were to be summarized and comparisons of CMI based on cytokine expression including but not limited to Th1 (interferon γ, IL-2), Th2 (IL-4, IL-5), and Th17 (IL 17).

In addition, various exploratory analyses of humoral and cell-mediated immunities may have been performed, which may have included but not been limited to antibody titers to various proteins of interest, cross-reactivity of antibodies to other coronaviruses, inflammatory markers in serum, and potential analysis of antibody characteristics.

Evaluation of a Serological Predictor of Protection Against COVID-19 and/or SARS-CoV-2:

- The immunogenicity data of the blood draw 14 days after the second vaccination from all subjects reporting a RT-PCR-confirmed COVID-19 and subjects randomized from the population without a SARS-CoV-2 infection serving as the control group were to be used to evaluate the relationship between antibody levels tested with the ELISA binding assay

or alternative assays (e.g. VNA, ACE2 competitive) and clinical protection from COVID-19.

- The Prentice[5] criteria were to be used to assessed, to establish whether an immunologic correlate of protection could be determined.
- To accommodate the criterion, a linear logistic regression model was to be fitted with vaccine group included as the independent predictor and incidence of COVID-19 (or SARS CoV-2 infection) as the dependent variable to show that the observed vaccine effect could be explained in a statistical model using immunologic data.

The statistical and modelling considerations of estimating correlates of protection were to be further described in the SAP addendum.

9.7.1.6 Safety Analyses

All safety analyses were to be performed on the Safety Set where subjects were in the group according to the vaccine/placebo they actually received at the first dose.

- For Reactogenicity (solicited local and systemic AEs) in Phase 2 adult subjects and adolescents:
  - Frequencies and percentages of subjects experiencing each solicited AE were to be summarized along with 95% CIs for each symptom by any (severity), maximum severity (mild, moderate or severe, except fever) during 7 days after each dose and after any dose by vaccine group.
  - Duration and onset of events were also to be summarized by vaccine group descriptively by mean, standard deviation etc.
- Injection-site erythema and swelling were to be summarized according to categories based on linear measurements.
- Use of antipyretics and analgesics were to be summarized by frequency and percentage of subjects reporting use.
- Body temperature was summarized by 0.5°C increments from 38.0°C up to ≥40°C. In addition, fever was to be summarized according to "mild", "moderate" or "severe" categorization.
- For unsolicited AEs in Phase 2 adult subjects and adolescents:
  - Frequencies and percentages of subjects who reported at least one AE, related AE, SAE, MAAE, AESI from Day 1 through safety call (Day 43) were to be summarized by vaccine group along with 95% CIs.
  - Frequencies and percentages of subject withdrawal/early termination from Day 1 through Safety Call (Day 43) were to be summarized by vaccine along with 95% CIs.
- For AEs in all subjects:
  - Frequencies and percentages of subjects who reported at least one SAE, MAAE, AESI during the entire study period were to be summarized by vaccine group along with 95% CIs.

- Frequencies and percentages of subject withdrawal/early termination from the study were to be summarized by vaccine group along with 95% CIs.
- Frequencies and percentages of subjects who reported any AEs within 30 minutes after any study vaccination were to be summarized by vaccine group along with 95% CIs.
- Frequencies and percentages of deaths were to be summarized by vaccine group along with 95% CIs.

AEs were to be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). AEs were to be presented by system organ class (SOC) and preferred term (PT) by vaccine group.

The Clopper-Pearson method were to be used to calculate the CIs.

Data listings of all AEs were to be provided by subject. In addition, AEs in the categories above were to be provided as listed data.

All safety analyses were to be performed on the Safety Set. Missing data were not to be imputed.

9.7.2 Determination of Sample Size

The study sample size was driven by the primary efficacy objective. The final target of 150 any RT-PCR-confirmed COVID-19 events would provide approximately 90% power to reject the null hypothesis (VE ≤30% for any COVID-19), assuming the true VE is at least 60%, considering one IA (Table 10). An attack rate for any COVID-19 is 0.60% per month (in the Placebo arm), with approximately 2.04 months follow-up for the primary efficacy endpoint, a total of approximately 22 000 subjects, with randomization ratio 1:1, would have been enrolled assuming the non-evaluability is 20% or less.

Attack rate estimations may have been performed in a blinded manner under the efficacy assumptions used for planning the study. An average underlying attack rate substantially lower than 0.60% for any COVID-19, or baseline SARS-CoV-2 seropositivity rate higher than anticipated, the sample size would have been reassessed or the duration of follow-up for the primary endpoint adjusted; the maximum number of study subjects could have been increased up to 30 000.

Table 10 Sample Size Determination

Primary Endpoint	Assumed True VE	Number of Events[a]	Attack Rate	Number of Evaluable Subjects	Non-evaluable Rate	Total Enrollment
Any COVID-19	60.7%	150	0.60%/month	8798	20%	21996
	60.7%	150	0.60%/month	8798	30%	25136
	60.7%	150	0.60%/month	8798	35%	27070
	60.7%	150	0.60%/month	8798	40%	29326

[a] Gamma (-2) spending function is used so that Type I error=0.0067 use for the interim analysis (at 50% cases available), and 0.0214 for final analysis (one-sided).

The vaccine efficacy (VE) estimate has been reduced from 70% to 60% to account for the emergence of the SARS-COV-2 variants and the reduced efficacy observed with the current authorized COVID-19 vaccines against these variants.

9.8 Changes in the Conduct of the Study or Planned Analyses

Changes in the conduct of the study or planned analyses were as follows:

9.8.1 Changes to the Study Conduct

- Approximately 25% of enrolled participants were planned to be either ≥65 years of age or <65 years of age and at high risk of severe COVID-19. At time of recruitment, authorized COVID-19 vaccines were available and recommended for elderly individuals in all participating countries, as such the proportion of subjects ≥65 years of age recruited in the study was low (<1.5%). Overall, <25% of study population were at high risk of severe COVID-19 due to co-morbidity or age.
- A higher number of co-morbidities associated with a high risk of COVID-19 was reported in the electronic data capture (EDC) system than the IWRS system (used for randomization and stratification of subjects). For the statistical analysis, EDC data was used to define the population at a high risk of severe COVID-19.
- At the time of primary efficacy analysis, approximately 15% of subjects requested unblinding to receive the authorized study vaccines. After unblinding the subjects were asked to continue follow-up for safety only. No immunogenicity and efficacy data were collected after unblinding.
- The list of AESI was revised several times during the study conduct as per Safety Platform for Emergency Vaccines (SPEAC) recommendations, and PIs were informed accordingly.
- A total of 100 CMI samples collected initially did not meet quality requirements, as such these subjects were replaced to reach 150 individuals with evaluable CMI samples.
- Antibodies against Trimer-Tag related proteins (e.g., collagen type I) were not tested as no antibodies against Trimer-Tag-specific antibodies were detected in study participants.

9.8.2 Changes in the Planned Analyses

- Analysis of secondary efficacy objective #3 (VE by evidence of prior SARS-CoV-2 infection) was performed on the Efficacy FAS (Dose 2) instead of the PPS, as the PPS includes only SARS-CoV-2-naïve subjects.
- Analysis of exploratory immunogenicity objective (analysis of neutralizing antibodies to new emergent mutants of SARS-CoV-2) was performed in a randomly-selected set of samples collected in subjects from Phase 2 without evidence of prior SARS-CoV-2 infection (PPS – Immunogenicity) and SARS-CoV-2 exposed subjects (FAS – Immunogenicity) instead of PPS – Immunogenicity only.
- Forty-six additional test results for SCB-2019 binding ELISA for 17 subjects (15 in the vaccine group and 2 in the placebo group) were identified after the laboratory data transfer and the completion of statistical analysis. Four out of 15 subjects were to be included in PPS, and 5 out of 15 subjects were to be included in FAS. Considering the size of the PPS (N=381) and FAS (N=636) for the vaccine group, excluding the data from 4 and 5 subjects, respectively, has minimal or no impact on the immunogenicity results (CSR V1.0 November 2021).

- No viral load was measured in subjects with RT-PCR positive SARS-CoV-2 infection; as such, exploratory objective 2 was not assessed.
- Exploratory analysis for correlate of protection (CoP) was not performed at the time of the current report finalization.
- Additional medical conditions were considered as high risk of severe COVID-19, as per U.S. CDC recommendations (asthma, interstitial lung disease, cystic fibrosis, pulmonary hypertension, diabetes type 1, HIV, liver disease, and substance use disorders).
- There were two adjustments for the type I error for this study. First, the type I error was adjusted for the interim and final analyses for the primary endpoint; the secondary adjustment was for the key secondary endpoints, which corresponded to 95.72% CI for the primary endpoint at the final analysis, and 97.86% CI for the key secondary endpoints at the final analysis. No multiplicity adjustments were made for the key secondary objectives #2 and #4 as the analysis was performed at a later stage, after the efficacy analysis at Month 6 completion. The 95% CI was used for these key secondary objectives and for all other analyses.
- To exclude impact of asymptomatic SARS-CoV-2 infection on persistence of SARS-CoV-2 specific antibodies, an additional criterion was applied for PPS Immunogenicity Persistence. Only subjects with negative results for anti-N antibody titer at Day 36 (Visit 3) and Day 205 (Visit 4) were included in the per-protocol analysis.
- *The censoring rule was applied for the efficacy analysis, but 12 subjects who received other COVID-19 vaccines after 14 days post-dose 2 were incorrectly included in the efficacy analysis due to inappropriate censoring. Sensitivity analyses were performed for the primary efficacy analysis (cut-off date = 10 August 2021), and *the 6-month follow-up analysis (cut-off date = 1 December 2021) with the correct application of the censoring rule for all subjects (section 11.1.1.7.3). The outcome of this analysis is consistent with the efficacy results for the primary endpoint.
- *A re-analysis (sensitivity analysis) was carried out to apply the correct censoring due to participants receiving other COVID-19 vaccines after 14 days post-dose 2 (as above), and to account for additional 21 cases determined to be inconsistent with the study protocol case definition (according to the intensity assessment: mild, moderate, severe; and cases with start date earlier than 14 days post second dose). The analysis were performed for the primary efficacy analysis (cut-off date = 10 August 2021), and the 6-month follow-up analysis (cut-off date = 1 December 2021) (section 11.1.1.7.3). The outcome of this re-analysis was consistent with the efficacy results for the primary endpoint.

  *post hoc analysis

9.8.3 Protocol Amendments

Amendment 1 (v2.0) – 30 December 2020

- Following Committee for Medicinal Products for Human Use (CHMP) scientific advice, the protocol was amended to include a single primary efficacy objective in the study: the assessment of VE against RT-PCR-confirmed COVID-19 of any severity. The second co-primary objective of efficacy against moderate-to-severe COVID-19 was retained as a key

secondary objective. Only RT-PCR-confirmed cases of COVID-19 were to be used for analysis of study endpoints.

- Due to changes in the study design (a single primary efficacy objective) and changes in study assumptions, true VE of 70% (from 60%), attack rate of any COVID-19 in the Placebo arm of 0.30% per month (from 0.15%), and a follow up of about 2 months (from 6 months), the study sample size and target number of COVID-19 cases for primary analysis were revised.
- The final target of 76 (from 184 initial target cases) of any RT-PCR-confirmed COVID-19 events would provide approximately 90% power to reject the null hypothesis (VE ≤30% for any COVID-19), assuming a true VE of at least 70% and considering one interim analysis (IA). An attack rate for any COVID-19 of 0.30% per month (in the Placebo arm) and a follow-up of approximately 2 months for the primary efficacy endpoints, a total of 22 000 subjects (from 34 000 initially to be enrolled), with randomization ratio 1:1, would need to be enrolled assuming the non-evaluability of 14% or less. The IA was planned to be conducted for the primary endpoint evaluation only when 60% of target events (46 cases of any COVID-19 events) for the primary analysis was reached.
- In addition, the text was revised to describe options to perform a sample size or duration of follow-up reassessment in case of the observed attack rate of COVID-19 was lower than anticipated.
- Recruitment in Phase 2 of the study was planned to be done in a staggered way, starting with enrollment of 200 healthy adults, 18 to 64 years of age, and extend to the overall population, including adults over 65 years old and with comorbidities based on DSMB review of available safety data. Study pause rules were defined.
- Also, with the COVID-19 vaccination campaigns being initiated in a few countries in which study is conducted, subjects were to be informed of availability of an authorized vaccine outside of the study in a timely manner. In case a subject preferred to leave the study and receive a licensed vaccine according to societal prioritization and local recommendation, the information about the study vaccine was to be provided after withdrawal from the study.

Amendment 2 (v3.0) – 21 January 2021

- The formulation of study vaccine was changed from AS03-adjuvanted SCB-2019 to CpG 1018/alum-adjuvanted SCB-2019 to reflect the sponsor's decision to bring this candidate vaccine to clinical development.
- Individuals with a known history of COVID-19 were allowed for inclusion into the study.
- Additional exploratory objectives were added, to explore neutralization of new emergent mutants of SARS-CoV-2 by SCB 2019 vaccine-elicited sera (e.g. N501K, E484K mutants), and to perform characterization of SARS-CoV-2 isolates by genetic sequencing.
- Subject enrollment began when V3.0 was effective.

Amendment 3 (v4.1) – 19 May 2021

- About 600 healthy adolescents aged 12 to less than 18 years were to be enrolled at selected sites following favorable benefit-risk profile of safety adult data reviewed by the DSMB, to assess the safety, immunogenicity and efficacy of the study vaccine in this age group.

- In the context of the evolving SARS-CoV-2 epidemiology, a new secondary VE objective was added, VE against emerging SARS-CoV-2 VOCs.
- While monitoring the epidemiology of the SARS-CoV-2 in the countries in which the study was enrolling/ongoing, a reassessment of the sample size and the target cases for final and interim analysis was performed based on updated observed attack rate of COVID-19 and SARS-CoV-2 seroprevalence which were higher than anticipated as new, more virulent strains of SARS-CoV-2 were emerging and spreading worldwide.
- The VE estimate was reduced from 70% to 60% to account for the emergence of the SARS-CoV-2 variants and the reduced efficacy observed with the authorized COVID-19 vaccines against these variants. The attack rate of COVID-19 was increased to 0.60% per month in the placebo arm, and the non-evaluability to 20% or less to account for higher baseline SARS-CoV-2 seropositivity. With these new assumptions a sample size of approximately 22 000 subjects, randomized 1:1, was needed to meet the primary objective, and the sample size was not changed. However, a final target of 150 any RT-PCR confirmed COVID-19 events were to provide approximately 90% power to reject the null hypothesis (VE ≤30% for any COVID-19), assuming the true VE of at least 60%, and considering one IA.
- One interim efficacy analysis was planned to be conducted only when 50% of target events were reported across the active and control groups (75 cases).
- Attack rate estimations were to be performed in a blinded manner under the efficacy assumptions used for planning the study. If the average underlying attack rate was substantially lower than the expected 0.60% for any COVID-19, or baseline SARS-CoV-2 seropositivity rate was higher than anticipated, the sample size or the duration of follow-up for the primary endpoint were to be adjusted and the maximum number of study participants increased up to 30 000.

Amendment 4.0 (v5.1) – 27 September 2021

- Amendment to administer a booster (full dose SCB-2019 vaccine or half dose SCB-2019 vaccine) to approximately 4000 SCB-2019 recipients from the Phase 3 part of the study, and assess the immunogenicity and safety of the booster compared to placebo.
- Additional primary immunogenicity objective to demonstrate non-inferiority of the immune response after a booster dose compared to a 2-dose primary vaccination series in subjects without evidence of prior SARS-CoV-2 infection.
- Two new secondary immunogenicity objectives added: noninferiority immunogenicity analysis of adolescents versus young adults and evaluation of immune response of SCB-2019 when given as a booster dose, to allow bridging of efficacy results from young adults to adolescents, and to evaluate the immune response of a booster dose of SCB-2019 vaccine in adults.
- Additional secondary safety objective, to evaluate the safety of a booster dose.
- Additional exploratory efficacy objective, to assess the efficacy of booster dose versus primary 2-dose series only.
- Additional exploratory immunogenicity objective, to assess CMI following booster dose.

- Increase in sample size of adolescents from 600 to 1200 in order to have a sufficient number of evaluable subjects (without evidence of prior SARS-CoV-2 infection) for the noninferiority analysis.

These changes to the protocol had no impact on data integrity and subject safety.

All protocol and SAP versions are provided in **Appendix 16.1.1** and **Appendix 16.1.9**.

10.0 STUDY SUBJECTS

This trial was conducted at 31 sites, in 5 countries (3 sites in Belgium, 5 sites in Brazil, 9 sites in Colombia, 10 sites in the Philippines, and 4 sites in South Africa). Initially, and for the Phase 2 part, subjects were recruited from the Philippines, Colombia, and Belgium. The Phase 3 part of the study was launched on 12 April 2021, from when the recommendation to proceed to that stage of protocol was received from the DSMB's review of the safety and reactogenicity data of the first 400 study participants. For the Phase 3 part, subjects were also recruited from Brazil and South Africa.

In the body of this section, the "round half to the nearest even" rounding convention has been applied to the demographic and disposition data in certain cases to aid clarity. In this convention, a value exactly halfway between two digits is rounded to the nearest even digit (e.g., 1.5 and 2.5 are rounded to 2); and all other values are rounded to the nearest digit.

10.1 Disposition of Subjects

The primary efficacy, immunogenicity and safety analyses include data obtained between 24 March 2021 (study start) and 11 September 2024 (data lock point). The cutoff date for the efficacy analysis was 10 August 2021, and for safety was 20 August 2021.

The second efficacy, immunogenicity and safety analyses include data obtained between 24 March 2021 (study start) and 1 December 2021 (cutoff date for the 6-month follow up).

The disposition of the subjects in CLO-SCB-2019-003 is described in the following sections.

10.1.1 All Subjects

At the time of the primary analysis, 31201 individuals were screened, and 30174 subjects were included in the Randomized set of the study, initially for the Phase 2 and then as part of the Phase 3 (Figure 3). Hence the Phase-3 Randomized set included the Phase-2 Randomized set (see Section 10.1.1). After random allocation the SCB-2019 arm included 15092 subjects and the Placebo arm included 15082 subjects.

In each arm, 15064 subjects received at least 1 dose of SCB-2019 or Placebo and were included in the Exposed set and SAF. In the Efficacy (Dose 1) FAS, the SCB-2019 arm included 14684 subjects, and the Placebo arm included 14670 subjects. In the Efficacy (Dose 2) FAS, the SCB-2019 arm included 12989 subjects, and the Placebo arm included 12823 subjects.

The SCB-2019 arm and Placebo arm in the Efficacy (Dose 1) FAS and the Efficacy (Dose 2) FAS included similar sized subsets of baseline-SARS-CoV-2-naïve and baseline SARS-CoV-2-exposed subjects (i.e., those subjects without/with evidence of prior SARS-CoV-2 infection; Figure 3). In the Efficacy (Dose 1) FAS, the SCB-2019 arm was split 7331:7353, and the Placebo arm was split 7331:7339, respectively. In the Efficacy (Dose 2) FAS, the SCB-2019 arm was split 6283:6706, and the Placebo arm was split 6140:6683, respectively.

In the Efficacy PPS, the SCB-2019 arm included 6251 subjects, and the Placebo arm included 6104 subjects (Figure 3). Subjects were excluded from the Efficacy PPS with respect to the SAF, for one or more reasons. Most subjects were excluded because they were seropositive for SARS-CoV-2 at baseline (7315 subjects in the SCB-2019 arm and 7307 subjects in the Placebo arm) or had history of prior SARS-CoV-2 infection (802 and 800 subjects, respectively). The second most frequent reason for exclusion was the absence of a second dose, and covered 1386

subjects in the SCB-2019 arm and 1524 subjects in the Placebo arm. The third most frequent reason for exclusion was that the randomization code was broken, and covered 375 subjects in the SCB-2019 arm and 394 subjects in the Placebo arm.

In the Exposed set/SAF, the median duration of subjects in the study was 74 days (mean 82 days), and was similar between arms (75 days SCB2019 arm; 74 days Placebo arm; **Table 14.1.1.3**).

At the time of the 6-month follow-up analysis, 31483 individuals were screened, and 30338 subjects 12 years of age and above were included in the Randomized set. Overall, 30299 subjects received at least one dose of the study vaccine or placebo, including 30137 adult study participants and 162 adolescents (**Table 14.1.1.1_P6m**).

The safety set (SAF; adults) included 15070 recipients of at least 1 dose of SCB-2019, and 15067 recipients of at least 1 dose of placebo. By 1 December 2021, the SAF included nine more adult subjects than that reported in the primary analysis presented above, six more SCB-2019 recipients and three more placebo recipients. These 9 subjects were recruited prior to 20 August 2021 but data was not entered in the database before the data transfer for the analysis. As such these subjects were not included in the previous analysis.

By 1 December 2021, 162 adolescent subjects (82 SCB-2019 recipients and 80 placebo recipients; **Table 14.1.2.1.11_P6m**) were exposed and included in the FAS for efficacy analysis. Adolescent subjects were not included in the primary efficacy analysis. Immunogenicity and safety data for the adolescent cohort are presented in a separate report.

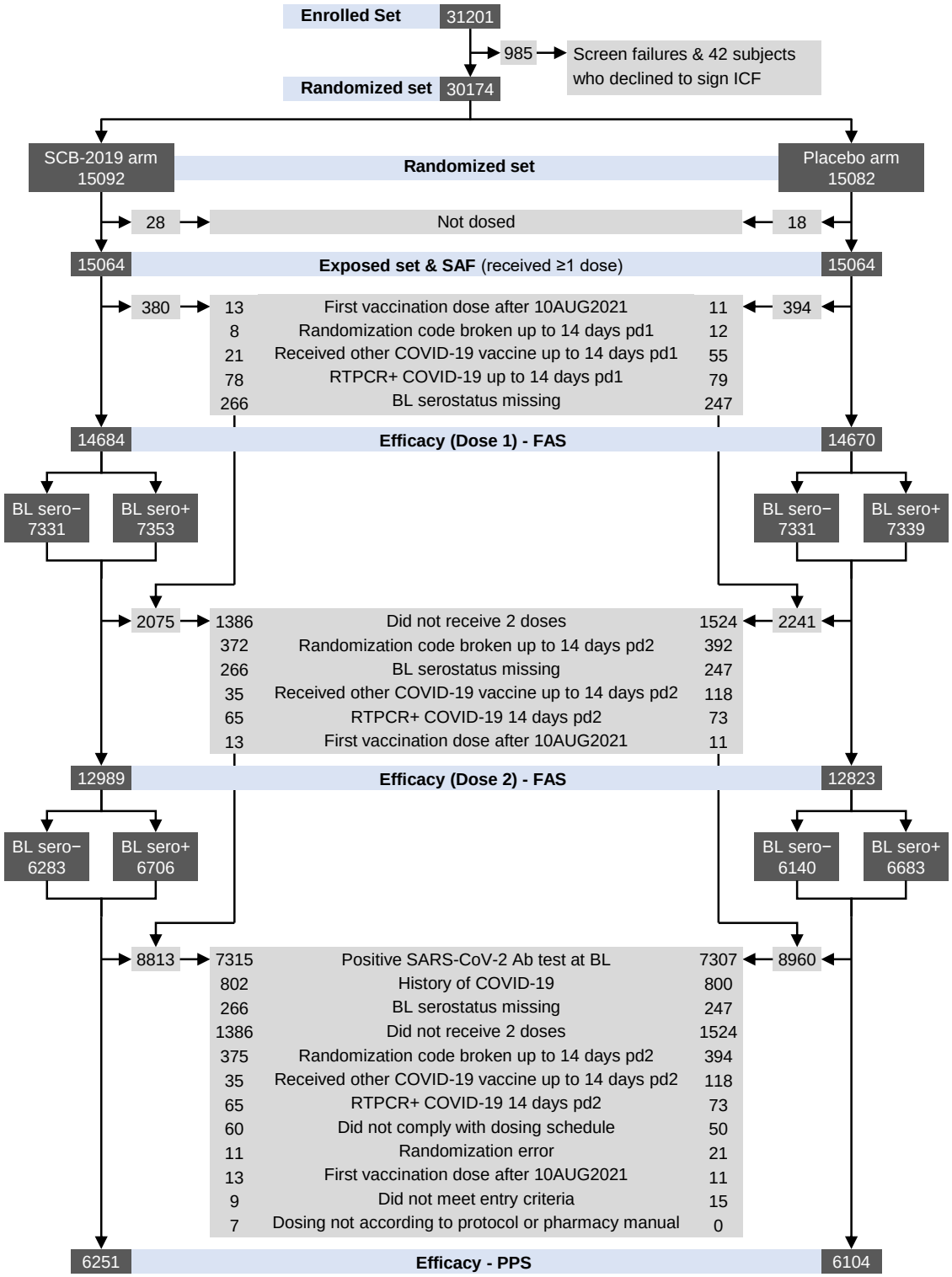
In the Efficacy PPS up to 1 December 2021, the SCB-2019 arm included 6336 subjects, and the Placebo arm included 6216 subjects (**Table 14.1.1.1_P6m**). Subjects were excluded from the Efficacy PPS with respect to the Exposed Set, for one or more reasons. Most subjects were excluded because they were seropositive for SARS-CoV-2 at baseline (7336 subjects in the SCB-2019 arm and 7318 subjects in the Placebo arm) or had history of prior SARS-CoV-2 infection (809 and 802 subjects, respectively). The second most frequent reason for exclusion was the absence of a second dose, and covered 1063 subjects in the SCB-2019 arm and 1213 subjects in the Placebo arm. The third most frequent reason for exclusion was that the randomization code was broken, and covered 414 subjects in the SCB-2019 arm and 427 subjects in the Placebo arm.

In the SAF up to 1 December 2021, the median duration of subject participation in the study was 177 days (mean 181 days; minimum 1 day; maximum 253 days), and was similar between arms (177 days SCB-2019 arm; 177 days Placebo arm; **Table 14.1.1.3.1_P6m**).

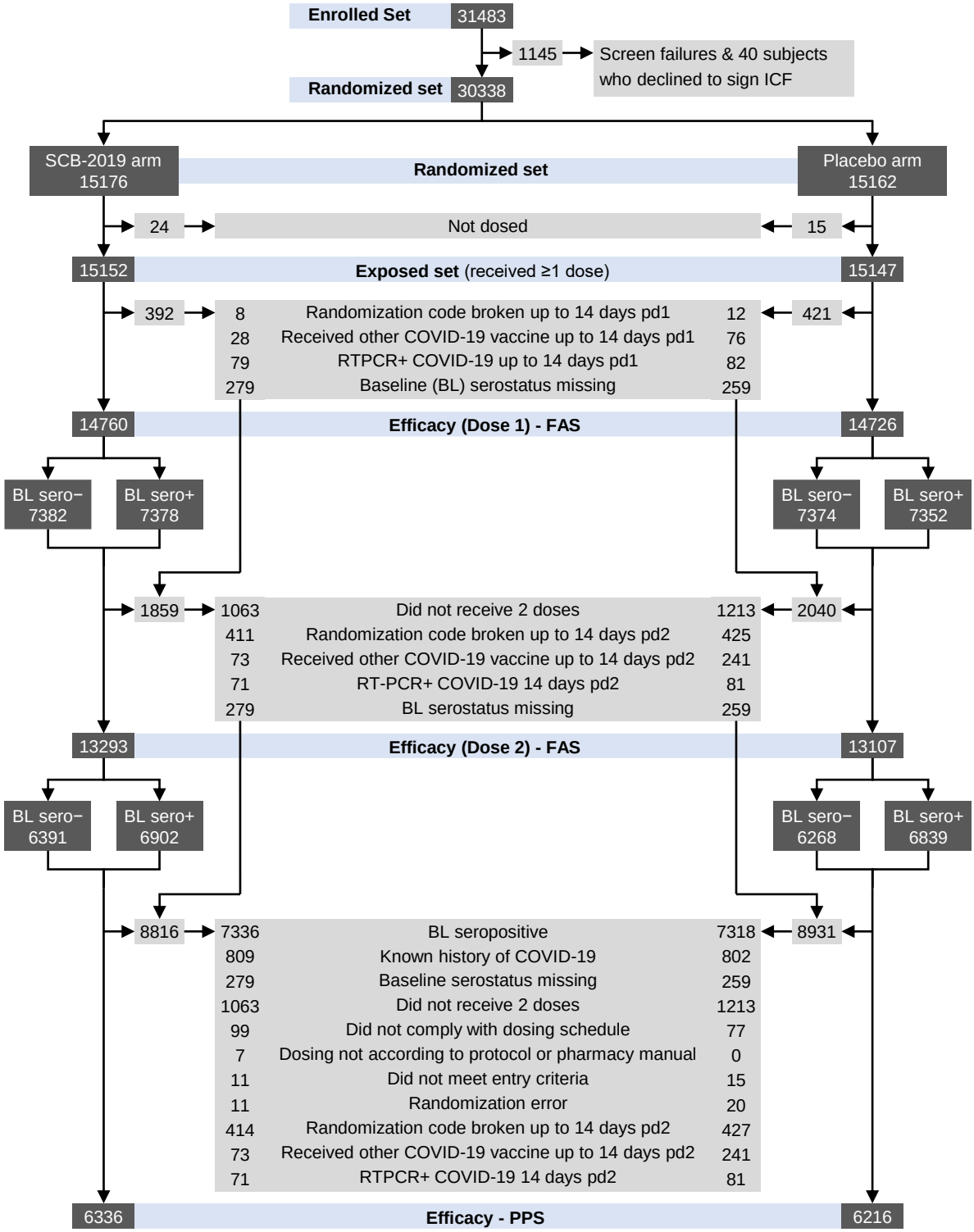
The disposition of subjects at the time of the primary efficacy analysis and at 6-month follow-up analysis is presented on Figure 3A and Figure 3B, respectively.

Figure 3 Disposition of all Study Subjects

A: At the time of the primary analysis



B: At the time of 6-month follow-up analysis:



Legend for Figure 3 on previous pages. Source: **Table 14.1.1.1_P6m** (as of 1 December 2021). Schematic description of subject disposition for all subjects and the association with the Exposed set, the Safety-Analysis set (SAF); Full-Analysis sets (FASs) for efficacy, and the Per-Protocol set (PPS) for efficacy. Also indicated are the subsets for whom there was no evidence (BL sero−) or evidence (BL sero+) of prior SARS-CoV-2 infection at baseline (BL) by positive antibody (Ab) test or medical history. The light grey boxes indicate excluded subjects, and the reasons for exclusion. Note that certain subjects were excluded for more than one reason. Also note that 5 subjects were unblinded for safety reasons before 14 days post-Dose 2; these subjects were excluded from the PPS only. Abbreviations: pd1 and pd2, post-dose 1 and post-dose 2, respectively.

At the time of the primary analysis, 1070 subjects discontinued from the vaccination schedule, 513/15064 (3.4%) of subjects in the SCB-2019 arm and 557/15064 (3.7%) of subjects in the Placebo arm (**Table 14.1.1.2**; Table 11). The most frequent reason for discontinuation was not specified (other) and was reported by a similar percentage of subjects in the SCB-2019 and Placebo arms (both 1.3%). The most frequent reason for discontinuation that was categorized, was an adverse event (AE), and was reported by a similar percentage of subjects in the SCB-2019 and Placebo arms (1.1% and 1.3%, respectively). Eight subjects in the SCB-2019 arm and six subjects in the Placebo arm discontinued based on the decision of the physician. One subject in the SCB-2019 arm and three subjects in the Placebo arm discontinued because of death; and eight subjects in the SCB-2019 arm and seven subjects in the Placebo arm discontinued because of pregnancy.

At the time of the primary analysis, 851 subjects discontinued from the study, 392/15064 (2.6%) of subjects in the SCB-2019 arm and 459/15064 (3.0%) of subjects in the Placebo arm (**Table 14.1.1.2**; Table 11). The most frequent reason for discontinuation was not specified (other) and was reported by a similar percentage of subjects in the SCB-2019 and Placebo arms (1.3% and 1.5%, respectively). The most frequent reason for discontinuation that was categorized was withdrawal-by-subject, and was reported by a similar percentage of subjects in the SCB-2019 and Placebo arms (0.9% and 1.0%, respectively). Three subjects in the SCB-2019 arm and four subjects in the Placebo arm discontinued based on the decision of the physician. Three subjects in the SCB-2019 arm and seven subjects in the Placebo arm discontinued because of death; and two subjects in the Placebo arm discontinued because of pregnancy.

Table 11 Reasons for Treatment Discontinuation and Early Study Termination (SAF) at the Time of the Primary Analysis

	SCB-2019 (N=15064)	Placebo (N=15064)
	n (%)	**n (%)**
Treatment discontinuation*	513 (3.4)	557 (3.7)
Primary reason for treatment discontinuation		
• Other	193 (1.3)	198 (1.3)
• Adverse event	162 (1.1)	189 (1.3)
• Withdrawal by subject	83 (0.6)	92 (0.6)
• Lost to follow up	36 (0.2)	40 (0.3)
• Protocol deviation	22 (0.1)	22 (0.1)
• Pregnancy	8 (0.1)	7 (0.0)
• Physician decision	8 (0.1)	6 (0.0)
• Death	1 (0.0)	3 (0.0)
Early discontinued from study**	392 (2.6)	459 (3.0)
Primary reason for early discontinuation from study		
• Other	200 (1.3)	233 (1.5)
• Withdrawal by subject	139 (0.9)	158 (1.0)
• Lost to follow up	41 (0.3)	49 (0.3)
• Protocol deviation	6 (0.0)	5 (0.0)
• Death	3 (0.0)	7 (0.0)
• Physician decision	3 (0.0)	4 (0.0)
• Pregnancy	0	2 (0.0)
• Adverse event	0	1 (0.0)

Source **Table 14.1.1.2**. *Subjects with missing reasons for treatment discontinuation are not included. **Subjects with missing reasons for study discontinuation are not included. Percentage of subjects was calculated as 100×n/N, where N=number of subjects.

At the time of the 6-month follow-up analysis, 2201 subjects discontinued from the vaccination schedule, 1018/15070 (6.8%) of subjects in the SCB-2019 arm and 1183/15067 (7.9%) of subjects in the Placebo arm (**Table 14.1.1.2.1_P6m**; Table 12). The most frequent reason for discontinuation was not specified (other) and was reported by a similar percentage of subjects in the SCB-2019 and Placebo arms (1.9% and 2.6%, respectively). The second most frequent reason for discontinuation that was categorized, was an adverse event (AE), and was reported by a similar percentage of subjects in the SCB-2019 and Placebo arms (1.8% and 2.0%, respectively). Eighteen subjects in the SCB-2019 arm and 25 subjects in the Placebo arm discontinued based on the decision of the physician. Two subjects in the Placebo arm discontinued because of death. 21 subjects in the SCB-2019 arm and 26 subjects in the Placebo arm discontinued because of pregnancy.

In the SAF up to 1 December 2021, 2149/30137 (7.1%) subjects discontinued from the study, 988/15070 (6.6%) of subjects in the SCB-2019 arm and 1161/15067 (7.7%) of subjects in the Placebo arm (**Table 14.1.1.2.1_P6m**; Table 12). The most frequent reason for discontinuation was withdrawal-by-subject, and was reported by a similar percentage of subjects in the SCB-2019 and Placebo arms (2.8% and 3.6%, respectively). Twenty-seven subjects in the SCB-2019 arm and 28 subjects in the Placebo arm discontinued based on the decision of the physician. 8 subjects in the SCB-2019 arm and 22 subjects in the Placebo arm discontinued because of death; and 1 subject in the SCB-2019 arm and 4 subjects in the Placebo arm discontinued because of pregnancy.

Table 12 Reasons for Treatment Discontinuation and Early Study Termination (SAF; adults) at the Time of the 6-month Follow-up Analysis

	SCB-2019 (N=15070)	Placebo (N=15067)
	n (%)	n (%)
Treatment discontinuation*	1018 (6.8)	1183 (7.9)
Primary reason for treatment discontinuation		
• Other	292 (1.9)	390 (2.6)
• Adverse event	274 (1.8)	298 (2.0)
• Withdrawal by subject	185 (1.2)	206 (1.4)
• Lost to follow up	194 (1.3)	189 (1.3)
• Protocol deviation	34 (0.2)	47 (0.3)
• Pregnancy	21 (0.1)	26 (0.2)
• Physician decision	18 (0.1)	25 (0.2)
• Death	0	2 (0.0)
Early discontinuation from study**	988 (6.6)	1161 (7.7)
Primary reason for early discontinuation from study		
• Withdrawal by subject	419 (2.8)	547 (3.6)
• Lost to follow up	307 (2.0)	327 (2.2)
• Other	220 (1.5)	224 (1.5)
• Physician decision	27 (0.2)	28 (0.2)
• Death	8 (0.1)	22 (0.1)
• Protocol deviation	6 (0.0)	8 (0.1)
• Pregnancy	1 (0.0)	4 (0.0)
• Adverse event	0	1 (0.0)

Source **Table 14.1.1.2.1_P6m**. *Subjects with missing reasons for treatment discontinuation are not included. **Subjects with missing reasons for study discontinuation are not included. Percentage of subjects was calculated as 100×n/N, where N=number of subjects.

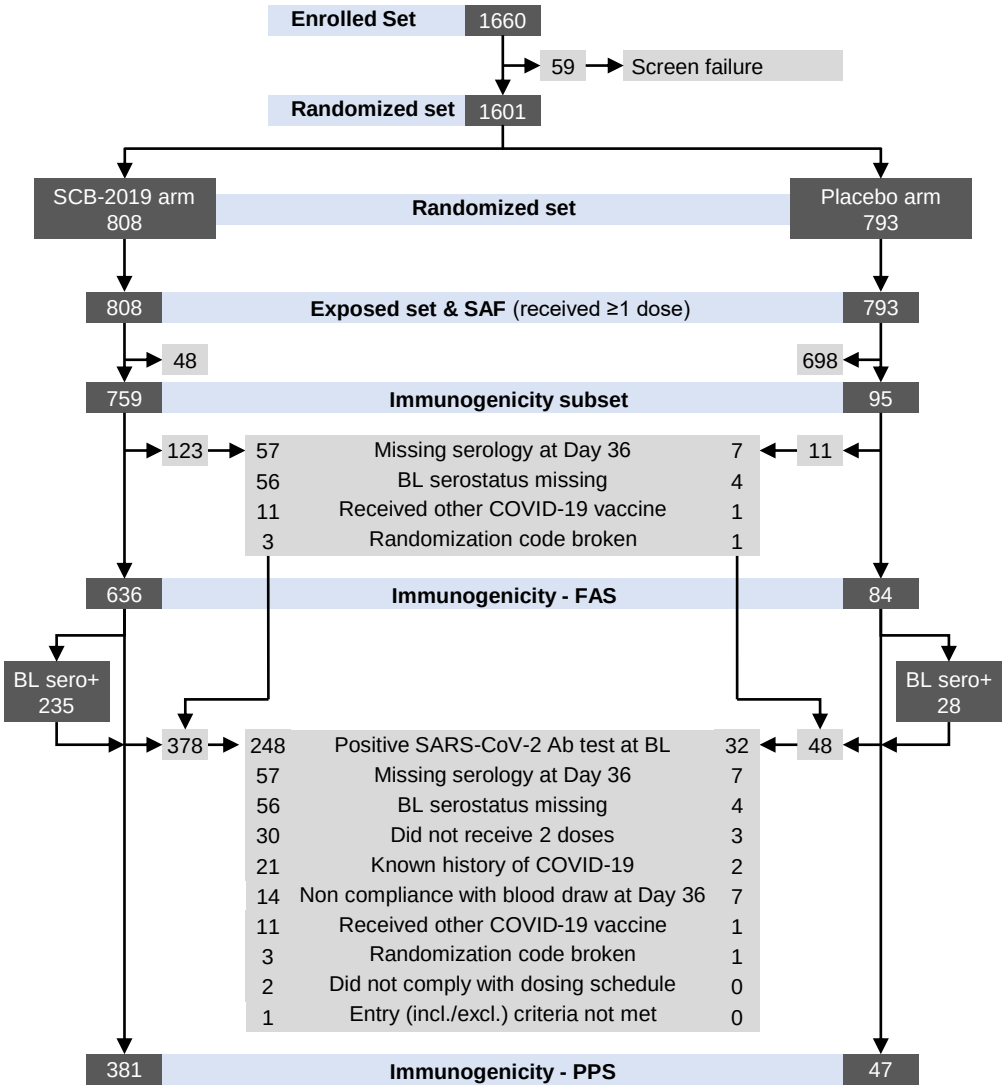
10.1.2 Phase 2 Cohort

In total, 1660 individuals were screened, and 1601 subjects were included in the Phase-2 Randomized set of the study (Figure 4). After random allocation, the SCB-2019 arm included 808 subjects and the Placebo arm included 793 subjects. All subjects received at least 1 dose and were included in the Phase-2 Exposed set and Phase 2 SAF. In the Immunogenicity subset, the SCB-2019 arm included 759 subjects, and the Placebo arm included 95 subjects (randomly selected from Phase 2 SAF). In the Immunogenicity FAS, the SCB-2019 arm included 636 subjects, and the Placebo arm included 84 subjects. In the Immunogenicity PPS, the SCB-2019 arm included 381 subjects, and the Placebo arm included 47 subjects.

Subjects were excluded from the Immunogenicity PPS with respect to the Phase 2 SAF, for one or more reasons. Most subjects were excluded because they had evidence of prior SARS-CoV-2 infection, and covered 248 subjects in the SCB-2019 arm and 32 subjects in the Placebo arm.

The second most frequent reason for exclusion was missing serology at Day 36, and covered 57 subjects in the SCB-2019 arm and 7 subjects in the Placebo arm. The third most frequent reason for exclusion was that the absence of a second dose, and covered 30 subjects in the SCB-2019 arm and 3 subjects in the Placebo arm.

Figure 4 Disposition of Phase-2 Subjects



Source: **Table 14.1.1.1.1.** Schematic description of subject disposition in the Phase 2 subjects and the association with the Exposed set, the Safety-Analysis set (SAF); and the Immunogenicity subset of the Full-Analysis set (FAS), and the Per-Protocol set (PPS). Baseline sero+ indicates subjects for whom there was evidence of prior SARS-CoV-2 infection at baseline by positive antibody (Ab) test or medical history. The light grey boxes indicate excluded subjects, and the reasons for exclusion. Note that certain subjects were excluded for more than one reason.

10.1.3 Subjects included in the Analysis of Efficacy against SARS-CoV-2 Infection

To assess efficacy of SCB-2019 against any laboratory-confirmed SARS-CoV-2 infection, any asymptomatic SARS-CoV-2 infection and burden of disease, associated with COVID-19, the proportion of subjects seroconverted with anti-N antibodies between Visit 3 (Day 36, 2 weeks post-Dose 2) and Visit 4 (Day 205) was assessed in both groups at the time of the 6-month follow-up analysis.

In total, 12552 subjects were included in the Efficacy PPS analysis up to 1 December 2021, 6336 from the SCB-2019 group and 6216 from the placebo group (Figure 3B).

Of 12552 subjects included in the PPS and seronegative for N (nucleocapsid) antigen at baseline, 1420 were tested at Visit 4: 692 in the SCB-2019 arm and 728 in the placebo arm. A total of 886 subjects were found to be anti-N seropositive (seroconverted): 400 in the SCB-2019 arm and 486 in the placebo arm. To assess the time of seroconversion, all anti-N positive subjects were tested at Visit 3 (Day 36). Overall, 788 subjects (356 in the SCB-2019 arm and 432 in the placebo arm) were seroconverted between Visit 3 and Visit 4, and 531 subjects (290 in the SCB-2019 arm and 241 in the placebo arm) remained anti-N negative at baseline (Visit 1) and Visit 4 (Table 13).

Table 13 Disposition of Subjects included in the efficacy analysis against SARS-CoV-2 infection - Per Protocol Set – Efficacy (All Subjects)

	SCB-2019 (N=6336)	**Placebo (N=6216)**
Number of subjects with anti-N antibodies tested at Visit 4, n (%)	692 (10.9)	728 (11.7)
Number of subjects with positive anti-N result at Visit 4, n (%)	400 (6.3)	486 (7.8)
Number of subjects who seroconverted with anti-N antibodies (from Visit 3 to Visit 4), excluding subjects with RT-PCR confirmed SARS-CoV-2 Infection, n*	356	432
Number of subjects with negative anti-N result at Visit 1 and Visit 4, n	290	241

Source: **Table 14.2.2.6_P6m**.
SCB-2019 = CpG 1018/Alum-adjuvanted SCB-2019 vaccine, RT-PCR = Reverse transcription-polymerase chain reaction, SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2.
N = Number of subjects without evidence of prior SARS-CoV-2 infection in treatment group in the analysis population, used as denominator for percentage calculation, n = Number of subjects with available data.
*: Seroconversion is defined as a subject with negative anti-N result at visit 3 and positive anti-N result at visit 4.

10.1.4 Subjects included in SARS-CoV-2 Cross-neutralization Analysis

In total, 99 randomly-selected subjects from both, SCB-2019 vaccine (90) and Placebo (9) groups had sample tested for cross neutralization. Of these, 78/90 subjects in the SCB-2019 group were included in the analysis; 49 subjects without evidence of prior SARS-CoV-2 infection and 29 subjects with evidence of prior SARS-CoV-2 infection. Subjects were excluded from analysis because they have received a commercial COVID-19 vaccine before Day 36 (1 subject); did not comply with the study vaccination schedule (1 subject); did not comply with the blood draw schedule at Day 36 (3 subjects); and were part of Phase 3 of the study (7 subjects).

All nine subjects in the Placebo group were included in the analysis: 6 subjects without evidence of prior SARS-CoV-2 infection and 3 subjects with evidence of prior SARS-CoV-2 infection.

10.1.5 Subjects included in Analysis of Cell-mediated Immune Response

In total, 137 subjects were recruited in pre-specified clinical sites and provided additional blood samples for assessment of cell-mediated immune response. Those subjects were included in the CMI analysis, 70 from the SCB-2019 arm and 67 from the placebo arm.

10.1.6 Selection of Subjects for other Exploratory Analyses

10.1.6.1 Immunogenicity and Safety in Elderly Subjects

Due to limited number of elderly subjects enrolled in the study, all the elderly subjects 60 years of age and above, who received SCB-2019 vaccine, with blood sample available at Visit 1 (baseline) and Visit 3 were included for the immunogenicity testing. In total, 215 elderly subjects met the selection criteria and were included in the full analysis set (FAS) population for immunogenicity analysis, including 129 subjects with evidence of previous SARS-CoV-2 infection (111 from the SCB-2019 arm and 18 from the placebo arm) and 86 SARS-CoV-2-naïve individuals (74 from the SCB-2019 arm and 12 from the placebo arm).

10.1.6.2 Immunogenicity and Safety in Subjects with HIV Infection

HIV positive individuals participated in the study if they:

- were in medically stable condition at screening (as determined by the investigator) and free of opportunistic infections in the year prior to first study vaccination;
- had an HIV-1 viral load < 1000 copies/mL within 45 days of randomization in the study;
- were receiving highly active antiretroviral therapy (HAART) for at least 3 months before screening. Changes in antiretroviral dosage within 3 months of entering the study were allowed, as were exchanges in pharmacological formulations.

In total, 62 HIV infected subjects (enrolled in South Africa, Brazil, and Colombia) who received at least one dose of the study vaccine were identified based on their medical history and included in the analysis: 33 subjects in the SCB-2019 group and 29 subjects in the Placebo group. Of these, all subjects in the SCB-2019 group and 15 subjects in the Placebo group were selected for immunogenicity testing; 31 subjects in the SCB-2019 group and 13 subjects in the placebo group had blood sample available, however, 1 subject in the SCB-2019 group had confirmed COVID-19 before 14 days post dose 2 and was excluded from immunogenicity analysis.

10.1.6.3 Immunogenicity and Safety in Subjects of Chinese Origin

In total, 81 oversea Chinese subjects were identified. Among these subjects, 67 subjects were included in the full analysis set (FAS) population for immunogenicity analysis as they had blood samples available at Visit 1 and Visit 3 (39 from the SCB-2019 arm and 28 from the placebo arm).

10.1.6.4 Immunogenicity and Safety of SCB-2019 Manufactured at Different Scales

The manufacturing scale comparison (200L vs. 2000L SCB-2019 batches) includes data obtained from seven clinical sites in Colombia (sites 301, 302, 303, 304, 305, 307, and 310) contributing to this analysis.

Subjects were to be included in the comparability assessment of the SCB-2019 vaccine produced at two manufacturing scales if meeting the following criteria: seronegative at baseline as measured by "Roche Elecsys anti-SARS-CoV-2 S" test, 18 through 55 years of age, have not received commercial COVID-19 vaccines or have not had their randomization code broken

prior to Day 36, and have blood sample available at Day 36. Subjects who did not receive a 2nd dose of the investigational vaccine or early terminated the study prior to Day 36, and subjects with mixed dosing schedule receiving both, 200L and 2000L vaccine, were excluded from selection.

A total of 316 SARS-CoV-2 seronegative subjects, who met selection criteria described above, were included in the safety analysis set (SAF): 136 and 180 subjects received SCB-2019 DS from 2000L (SCB-2019 2000L group) and 200L (SCB-2019 200L group) fermenter, respectively.

Among these subjects, 283 subjects were included in the per protocol set (PPS) population for immunogenicity analysis: 109 subjects in the SCB-2019 2000L group and 174 subjects in the SCB-2019 200L group. A total of 33 subjects were excluded from PPS: 27 of them had the 2nd dose of vaccine after the cutoff date, 3 subjects had RT-PCR confirmed COVID-19 from Day 1 to before 14 days post dose 2, 2 subjects had a known history of COVID-19, and one subject had randomization error.

10.2 Protocol Deviations

The protocol deviations for the subjects enrolled in CLO-SCB-2019-003 is described in the following sections.

10.2.1 Summary of Protocol Deviations at the Time of the Primary Analysis

The summary of major protocol deviations (PD) at the time of the primary analysis is presented in Table 14.

The proportions of subjects for each major PD were generally comparable across the study. The most commonly reported major PDs were within the category ‘Did not receive full vaccine regimen’ reported for 2910 (9.7%) subjects, and ‘Randomization code broken prior 14 days post-Dose 2’ reported for 769 (2.6%) subjects. After unblinding, a higher number of subjects in the Placebo arm decided to receive an authorized COVID-19 vaccine than in the SCB-2019 arm (118 [0.8%] versus 35 [0.2%], respectively).

Individual subjects with major PDs in the Enrolled Set (All adults), sorted by subject, are presented in **Listing 16.2.2**.

Table 14 Protocol Deviations at the Time of the Primary Analysis - Enrolled Set (All adults)

Protocol Deviations	SCB-2019 N=15064 n (%)	Placebo N=15064 n (%)	Total N=30128 n (%)
Subject did not meet entry criteria	9 (0.1)	15 (0.1)	24 (0.1)
Did not receive full vaccine regimen	1386 (9.2)	1524 (10.1)	2910 (9.7)
Other COVID-19 vaccines given prior 14 days post-Dose 2	35 (0.2)	118 (0.8)	153 (0.5)
Randomization error	11 (0.1)	21 (0.1)	32 (0.1)
Randomization code broken prior 14 days post-Dose 2	375 (2.5)	394 (2.6)	769 (2.6)
Vaccination not according to protocol or pharmacy manual	7 (0.0)	0	7 (0.0)

Note 1: As Randomized: according to the vaccine a subject was designated to receive, which may have been different from the vaccine the subject actually received.
Note 2: Percentages are based on the number of subjects in each vaccine group.
Note 3: Subjects with at least one PD were excluded from PPS-analysis.
Source: **Table 14.1.1.1**.

The summary of major protocol deviations for Phase 2 Immunogenicity Set is presented in Table 15. The most common major PDs were 'Serological results no available at Day 36 visit' reported for 64 (7.5%) subjects, 'Did not receive full vaccine regimen' reported for 33 (3.9%) subjects, and 'Did not comply with blood draw schedule at Day 36' reported for 21 (2.5%) subjects. The proportions of subjects for each major PD were generally comparable generally comparable across the study arms.

Individual subjects with major PDs in the Immunogenicity Set (Phase 2), sorted by subject, are presented in **Listing 16.2.2**.

Table 15 Protocol Deviations at the Time of the Primary Analysis – Immunogenicity Set

Protocol Deviations	SCB-2019 N=759 n (%)	Placebo N=95 n (%)	Total N=854 n (%)
Subject did not meet entry criteria	1 (0.1)	0	1 (0.1)
Did not receive full vaccine regimen	30 (4.0)	3 (3.2)	33 (3.9)
Second dose outside visit window	2 (0.3)	0	2 (0.2)
Serological results no available at Day 36 visit	57 (7.5)	7 (7.4)	64 (7.5)
Did not comply with blood draw schedule (Day 36)	14 (1.8)	7 (7.4)	21 (2.5)
Other COVID-19 vaccines given prior 14 days post-Dose 2	11 (1.4)	1 (1.1)	12 (1.4)
Randomization error	0	0	0
Randomization code broken prior 14 days post-Dose 2	3 (0.4)	1 (1.1)	4 (0.5)

Note 1: As Randomized: according to the vaccine a subject was designated to receive, which may have been different from the vaccine the subject actually received.
Note 2: Percentages are based on the number of subjects in each vaccine group.
Source: **Table 14.1.1.1.1**.

10.2.2 Summary of Protocol Deviations at the Time of the 6-month Follow-up Analysis

The summary of major protocol deviations (PD) at the time of the 6-month follow-up analysis is presented in Table 16.

The proportions of subjects for each major PD were generally comparable across the study. The most commonly reported major PDs were within the category 'Did not receive full vaccine regimen' reported for 2276 (7.5%) subjects, and 'Randomization code broken prior 14 days post-Dose 2' reported for 841 (2.8%) subjects. After unblinding, a higher number of subjects in the Placebo arm decided to receive an authorized COVID-19 vaccine than in the SCB-2019 arm (241 [1.6%] versus 73 [0.5%], respectively).

Individual subjects with major PDs in the Exposed Set (All subjects) sorted by subject, are presented in **Listing 16.2.2**.

Table 16 Protocol Deviations at the Time of the 6-month Follow-up Analysis - Exposed Set (All subjects)

Protocol Deviations	SCB-2019 N=15152 n (%)	Placebo N=15147 n (%)	Total N=30299 n (%)
Subject did not meet entry criteria	11 (0.1)	15 (0.1)	26 (0.1)
Did not receive full vaccine regimen	1063 (7.0)	1213 (8.0)	2276 (7.5)
Other COVID-19 vaccines given prior 14 days post-Dose 2	73 (0.5)	241 (1.6)	314 (1.0)
Randomization error	11 (0.1)	20 (0.1)	31 (0.1)
Randomization code broken prior 14 days post-Dose 2	414 (2.7)	427 (2.8)	841 (2.8)
Vaccination not according to protocol or pharmacy manual	7 (0.0)	0	7 (0.0)

Note 1: Exposed set: all subjects who received at least one dose of the study vaccine by 01Dec2021, including adults and adolescents.
Note 2: As Randomized: according to the vaccine a subject was designated to receive, which may have been different from the vaccine the subject actually received.
Note 3: Percentages are based on the number of subjects in each vaccine group.
Note 4: Subjects with at least one PD were excluded from PPS-analysis.
Source: **Table 14.1.1.1_P6m**

The summary of major protocol deviations for Phase 2 Immunogenicity Set is presented in Table 17. The most common major PDs were ‘Serological results not available at Day 36 visit’ reported for 65 (7.5%) subjects, ‘Did not receive full vaccine regimen’ reported for 34 (3.9%) subjects, and ‘Did not comply with blood draw schedule at Day 36’ reported for 30 (3.5%) subjects, with the additional PD of ‘Serological results not available at Day 205 visit’ reported for 397 (45.9%) subjects. A higher proportion of subjects in the Placebo arm had no serological results available at Day 205 than in the SCB-2019 arm (52 [54.2%] versus 345 [44.9%], respectively).

Individual subjects with major PDs in the Immunogenicity Set (Phase 2), sorted by subject, are presented in **Listing 16.2.2**.

Overall, the most common major protocol deviations reported were similar to the ones reported for the primary analysis.

Table 17 Protocol Deviations at the Time of the 6-month Follow-up Analysis – Immunogenicity Set

Protocol Deviations	SCB-2019 N=769 n (%)	Placebo N=96 n (%)	Total N=865 n (%)
Subject did not meet entry criteria	1 (0.1)	0	1 (0.1)
Did not receive full vaccine regimen	31 (4.0)	3 (3.1)	34 (3.9)
Second dose outside visit window	9 (1.2)	0	9 (1.0)
Serological results not available at Day 36 visit	58 (7.5)	7 (7.3)	65 (7.5)
Serological results not available at Day 205 visit	345 (44.9)	52 (54.2)	397 (45.9)
Did not comply with blood draw schedule (Day 36)	23 (3.0)	7 (7.3)	30 (3.5)
Other COVID-19 vaccines given from dose 1 to Day 205	14 (1.8)	2 (2.1)	16 (1.8)
Vaccination not according to protocol or pharmacy manual	7 (0.9)	0	7 (0.8)
Randomization error	0	0	0
Randomization code broken prior to Day 205	24 (3.1)	4 (4.2)	28 (3.2)

Note 1: As Randomized: according to the vaccine a subject was designated to receive, which may have been different from the vaccine the subject actually received.
Note 2: Percentages are based on the number of subjects in each vaccine group.
Source: **Table 14.1.1.1.1_P6m**

10.3 Data Sets Analyzed

The data sets analyzed are described in Section 9.7.1.2.

10.4 Demographic and Baseline Characteristics

The demographic and baseline characteristics of the subjects enrolled in CLO-SCB-2019-003 is described in the following sections.

10.4.1 Primary Analysis

10.4.1.1 SAF, Efficacy FAS (Dose 1), Efficacy FAS (Dose 2), and Efficacy PPS (Phase 3)

In the SAF, the demographic and baseline characteristics were generally balanced between arms (Table 18). In the SCB-2019 and Placebo arms, 47% of subjects were female (7086/15064 and 7033/15064, respectively). The mean age was 32 years in both arms, with most subjects (99%) being between the ages of 18 to 64. Mean height and mean weights were 164 cm and 68 kg, respectively, in both arms. Most subjects in both arms were from the Philippines (45%), followed by Brazil (26%), Colombia (22%), South Africa (4%) and Belgium (2%). Most subjects in both arms identified as Asian (46%).

In both the SCB-2019 and Placebo arms (Table 18), the percentage of subjects with high risk of severe COVID-19 was 18% (Table 18). The most prevalent of those risks were obesity, hypertension and asthma, being reported by 13%, 4.5% and 1.3% respectively, in both the SCB-2019 arm and the Placebo arm.

In both the SCB-2019 and Placebo arms, 49 to 50% of subjects had no evidence of prior SARS-CoV-2 infection and/or were SARS-CoV-2 seronegative at baseline (baseline seronegative) (Table 18).

In the Efficacy-FAS (Dose 1; **Tables 14.1.2.1.10** and **14.1.3.1.10**), and Efficacy FAS (Dose 2; **Table 14.1.2.1.7** and **14.1.3.1.7**), the demographic and baseline characteristics were generally

balanced between arms. The demographic and baseline characteristics were also similar to those in the SAF.

In the Efficacy-PPS, the demographic and baseline characteristics were generally balanced between arms (Table 19). The demographic and baseline characteristics were also similar to those in the SAF, except that all subjects in the Efficacy-PPS had no evidence of prior SARS-CoV-2–infection at baseline.

Table 18 Demographic and Baseline Characteristics overall (SAF)

Characteristic	SCB-2019 (N=15064)	Placebo (N=15064)
Age [years], mean (standard deviation, SD)	32.1 (11.2)	32 (11.2)
Age group [years], n (%)		
• 18 to 64	14863 (98.7)	14849 (98.6)
• 65 to 74	176 (1.2)	190 (1.3)
• ≥75	25 (0.2)	25 (0.2)
• 18 to 59	14672 (97.4)	14673 (97.4)
• ≥60	392 (2.6)	391 (2.6)
Female, n (%)	7086 (47)	7033 (46.7)
Height [cm], mean (SD)	164 (10)	164 (10)
Weight [kg], mean (SD)	68 (15.9)	68 (15.8)
Body mass index [BMI; kg/m^2], mean (SD)	25 (5)	25 (4.9)
BMI ≥30 kg/m^2, n (%)	2367 (15.7)	2277 (15.1)
Known history of COVID-19 at baseline, n (%)	802 (5.3)	800 (5.3)
Baseline SARS-CoV-2 Serostatus, n (%)**		
• Negative	7483 (49.7)	7510 (49.9)
• Positive	7315 (48.6)	7307 (48.5)
• Missing	266 (1.8)	247 (1.6)
Baseline evidence of prior SARS-CoV-2 infection, n (%)*		
• No	7426 (49.3)	7445 (49.4)
• Yes	7378 (49)	7379 (49)
• Missing	260 (1.7)	240 (1.6)
High risk of severe COVID-19, n (%)	2771 (18.4)	2698 (17.9)
n(%) subjects with risk factors associated with severe COVID-19 (>1%)***		
• Obesity	2002 (13.3)	1936 (12.9)
• Hypertension or high blood pressure	673 (4.5)	672 (4.5)
• Asthma	201 (1.3)	194 (1.3)
Country, n (%)		
• Philippines	6834 (45.4)	6842 (45.4)
• Brazil	3973 (26.4)	3974 (26.4)
• Colombia****	3348 (22.2)	3348 (22.2)
• South Africa	555 (3.7)	545 (3.6)
• Belgium	354 (2.3)	355 (2.4)
Race, n (%)		
• Asian	6852 (45.5)	6868 (45.6)
• American Indian or Alaska Native****	3274 (21.7)	3270 (21.7)
• White	3022 (20.1)	3076 (20.4)
• Black or African American	1519 (10.1)	1460 (9.7)
• Other	91 (0.6)	85 (0.6)
• Not Reported	175 (1.2)	184 (1.2)
• Unknown	127 (0.8)	118 (0.8)
Ethnic group, n (%)		
• Hispanic or Latino	6857 (45.5)	6869 (45.6)
• Not Hispanic or Latino	7950 (52.8)	7925 (52.6)
• Not Reported	212 (1.4)	226 (1.5)

Source **Tables 14.1.2.1** and **14.1.3.1**. Percentage of subjects was calculated as 100×n/N, where N=number of subjects. *Note: Baseline evidence of prior SARS-Cov-2 infection included subjects who are positive for anti-S at baseline (seropositive at baseline) and/or with a known history of COVID infection at baseline (as per medical history). **Note: baseline serostatus is determined using anti-SARS-CoV-2 ELISA IgG test kit in all subjects at baseline (Day 1). ***Refer to **Table 14.1.3.1**, for other medical conditions associated with high risk of COVID-19. ****Note: The majority of subjects in Colombia were coded as Hispanic/Latino - American Indian or Alaska Native instead of Hispanic/Latino – White.

Table 19 Demographic and Baseline Characteristics (Efficacy-PPS)

Characteristic	SCB-2019 (N=6251)	Placebo (N=6104)
Age [years], mean (standard deviation, SD)	31.2 (10.5)	31 (10.7)
Age group [years], n (%)		
• 18 to 64	6197 (99.1)	6040 (99.0)
• 65 to 74	49 (0.8)	55 (0.9)
• ≥75	5 (0.1)	9 (0.1)
• 18 to 59	6126 (98.0)	5972 (97.8)
• ≥60	125 (2.0)	132 (2.2)
Female, n (%)	2859 (45.7)	2713 (44.4)
Height [cm], mean (SD)	166 (10.0)	165 (9.8)
Weight [kg], mean (SD)	69 (15.9)	69 (15.6)
Body mass index [BMI; kg/m^2], mean (SD)	25 (4.8)	25 (4.8)
BMI ≥30 kg/m^2, n (%)	921 (14.7)	855 (14)
High risk of severe COVID-19, n (%)	1068 (17.1)	992 (16.3)
n(%) subjects with risk factors associated with severe COVID-19 (>1%)*		
• Obesity	767 (12.3)	726 (11.9)
• Hypertension or high blood pressure	224 (3.6)	212 (3.5)
• Asthma	100 (1.6)	92 (1.5)
Country, n (%)		
• Philippines	2218 (35.5)	2177 (35.7)
• Brazil	2258 (36.1)	2153 (35.3)
• Colombia**	1330 (21.3)	1294 (21.2)
• South Africa	190 (3.0)	203 (3.3)
• Belgium	255 (4.1)	277 (4.5)
Race, n (%)		
• Asian	2230 (35.7)	2200 (36)
• American Indian or Alaska Native**	1294 (20.7)	1252 (20.5)
• White	1829 (29.3)	1759 (28.8)
• Black or African American	716 (11.5)	705 (11.5)
• Other	46 (0.7)	47 (0.8)
• Not Reported	85 (1.4)	91 (1.5)
• Unknown	49 (0.8)	48 (0.8)
Ethnic group, n (%)		
• Hispanic or Latino	3356 (53.7)	3224 (52.8)
• Not Hispanic or Latino	2767 (44.3)	2759 (45.2)
• Not Reported	112 (1.8)	108 (1.8)

Source **Tables 14.1.2.1.1** and **14.1.3.1.1**. Percentage of subjects was calculated as 100×n/N, where N=number of subjects. *Refer to **Table 14.1.3.1.1**, for other medical conditions associated with high risk of COVID-19. **Note: The majority of subjects in Colombia were coded as Hispanic/Latino - American Indian or Alaska Native instead of Hispanic/Latino – White.

10.4.1.2 Phase 2 SAF (Reactogenicity Subset) and Immunogenicity PPS

In the Phase-2 SAF, the demographic and baseline characteristics were generally balanced between arms (Table 20). In the SCB-2019 and Placebo arms, 46% (373/808) and 43% (342/793) of subjects were female, respectively. The mean age was 37 years in both arms, with most subjects (97%) being between the ages of 18 to 64. Mean height and mean weights were 165 cm and 70 kg, respectively, in both arms. Most subjects in both arms were from the Philippines (57% in the SCB-2019 arm and 56% in the Placebo arm), followed by Belgium (24% in the SCB-2019 arm and 25% in the Placebo arm) and Colombia (19%). Most subjects

in both arms identified as Asian (57%). No subjects were from Brazil or South Africa [unlike in the remainder of the Phase 3 SAF (see Section 10.4.1.1)].

In both the SCB-2019 and Placebo arms, the percentage of subjects with high risk of severe COVID-19 was 21%. The most prevalent of those risks were obesity and hypertension, being reported by 13% and 8% of subjects, respectively, in the SCB-2019 arm, and both by 10% of subjects in the Placebo arm.

In both the SCB-2019 and Placebo arms, 60 to 65% of subjects had no evidence of prior SARS-CoV-2 infection or were SARS-CoV-2 seronegative at baseline (Table 20).

In the Immunogenicity FAS, the demographic and baseline characteristics were generally balanced between arms (**Table 14.1.2.1.3** and **Table 14.1.3.1.3**). The demographic and baseline characteristics were also similar to those in the Phase 2 SAF.

In the Immunogenicity PPS, the demographic and baseline characteristics were generally balanced between arms (Table 21). The demographic and baseline characteristics were also similar to those in the Phase 2 SAF, except that all subjects in the Immunogenicity PPS had no evidence of prior SARS-CoV-2–infection at baseline. Also, in the Immunogenicity PPS SCB-2019 or Placebo arms, there were proportionally more subjects from Belgium (34% or 49%) and subjects who identified as White (32% or 49%) than in the Phase-2 FAS (24 or 25%, and 23% or 24%, respectively).

Table 20 Demographic and Baseline Characteristics (Phase-2 SAF)

Characteristic	SCB-2019 (N=808)	Placebo (N=793)
Age [years], mean (standard deviation, SD)	36.6 (12.9)	37.3 (13.1)
Age group [years], n (%)		
• 18 to 64	783 (96.9)	771 (97.2)
• 65 to 74	23 (2.8)	19 (2.4)
• ≥75	2 (0.2)	3 (0.4)
• 18 to 59	753 (93.2)	741 (93.4)
• ≥60	55 (6.8)	52 (6.6)
Female, n (%)	373 (46.2)	342 (43.1)
Height [cm], mean (SD)	165 (10.6)	165 (10.6)
Weight [kg], mean (SD)	70 (17)	70 (15.4)
Body mass index [BMI; kg/m^2], mean (SD)	26 (4.8)	25 (4.9)
BMI ≥30 kg/m^2, n (%)	134 (16.6)	112 (14.1)
Known history of COVID-19 at baseline, n (%)	23 (2.8)	21 (2.6)
Baseline SARS-CoV-2 Serostatus, n (%)		
• Negative	489 (60.5)	513 (64.7)
• Positive	262 (32.4)	238 (30.0)
• Missing	57 (7.1)	42 (5.3)
Baseline evidence of prior SARS-CoV-2 infection, n (%)		
• No	488 (60.4)	512 (64.6)
• Yes	264 (32.7)	241 (30.4)
• Missing	56 (6.9)	40 (5.0)
High risk of severe COVID-19, n (%)	170 (21.0)	164 (20.7)
% subjects with risk factors associated with severe COVID-19 (>1%)*		
• Obesity	101 (12.5)	80 (10.1)
• Hypertension or high blood pressure	69 (8.5)	80 (10.1)
• Type 2 diabetes mellitus	15 (1.9)	10 (1.3)
• Asthma	14 (1.7)	11 (1.4)
Country, n (%)		
• Philippines	458 (56.7)	443 (55.9)
• Colombia	154 (19.1)	150 (18.9)
• Belgium	196 (24.3)	200 (25.2)
Race, n (%)		
• Asian	460 (56.9)	451 (56.9)
• American Indian or Alaska Native	90 (11.1)	87 (11.0)
• White	188 (23.3)	191 (24.1)
• Black or African American	4 (0.5)	0
• Other*	66 (8.2)	63 (7.9)
• Unknown	0	1 (0.1)
Ethnic group, n (%)		
• Hispanic or Latino	187 (23.1)	185 (23.3)
• Not Hispanic or Latino	621 (76.9)	608 (76.7)

Source **Tables 14.1.2.1.4** and **14.1.3.1.4**. Percentage of subjects was calculated as 100×n/N, where N=number of subjects. *Refer to **Table 14.1.3.1.4,** for other medical conditions associated with high risk of COVID-19. **Note: The majority of subjects in Colombia were coded as Hispanic/Latino - American Indian or Alaska Native instead of Hispanic/Latino – White.

Table 21 Demographic and Baseline Characteristics (Immunogenicity PPS)

Characteristic	SCB-2019 (N=381)	Placebo (N=47)
Age [years], mean (standard deviation, SD)	36 (12.5)	38.5 (13.8)
Age group [years], n (%)		
• 18 to 64	374 (98.2)	45 (95.7)
• 65 to 74	6 (1.6)	2 (4.3)
• ≥75	1 (0.3)	0 (0)
• 18 to 59	357 (93.7)	43 (91.5)
• ≥60	24 (6.3)	4 (8.5)
Female, n (%)	160 (42)	19 (40.4)
Height [cm], mean (SD)	167 (10.3)	167 (8.2)
Weight [kg], mean (SD)	72 (16.5)	70 (12.4)
Body mass index [BMI; kg/m^2], mean (SD)	26 (4.7)	25 (3.4)
BMI ≥30 kg/m^2, n (%)	63 (16.5)	4 (8.5)
High risk of severe COVID-19, n (%)	74 (19.4)	11 (23.4)
n(%) subjects with risk factors associated with severe COVID-19 (>1%)*		
• Obesity	46 (12.1)	2 (4.3)
• Hypertension or high blood pressure	24 (6.3)	6 (12.8)
• Asthma	7 (1.8)	2 (4.3)
• Type 2 diabetes mellitus	7 (1.8)	1 (2.1)
Country, n (%)		
• Philippines	198 (52)	20 (42.6)
• Colombia**	52 (13.6)	4 (8.5)
• Belgium	131 (34.4)	23 (48.9)
Race, n (%)		
• Asian	199 (52.2)	20 (42.6)
• American Indian or Alaska Native	30 (7.9)	2 (4.3)
• White	124 (32.5)	23 (48.9)
• Black or African American	4 (1.0)	0 (0.0)
• Other*	24 (6.3)	2 (4.3)
Ethnic group, n (%)		
• Hispanic or Latino	64 (16.8)	9 (19.1)
• Not Hispanic or Latino	317 (83.2)	38 (80.9)

Source **Tables 14.1.2.1.2** and **14.1.3.1.2**. Percentage of subjects was calculated as 100×n/N, where N=number of subjects. *Refer to **Table 14.1.3.1.2**, for other medical conditions associated with high risk of COVID-19. **Note: The majority of subjects in Colombia were coded as Hispanic/Latino - American Indian or Alaska Native instead of Hispanic/Latino – White.

Demographic and baseline characteristics data are summarized in **Table 14.1.2.1** and **Table 14.1.3.1**, and in **Listing 16.2.4**.

10.4.1.3 Medical History (SAF and Phase-2 SAF)

In the SAF, the medical histories of study participants were generally similar between arms in (Table 22). In both the SCB-2019 (N=15064) and Placebo (N=15064) arms, 40% of subjects reported at least one medical event. The most frequent medical event by SOC was Metabolism and Nutrition Disorders, being reported by 15% of subjects in the SCB-2019 and Placebo arms. Among those disorders, the most prevalent PT was obesity, reported by 14% and 13% of subjects in the SCB-2019 and Placebo arms, respectively.

The proportion of study participants who reported having had COVID-19 (PT) were generally similar between arms, being reported by 5.3% of subjects in the SCB-2019 and Placebo arms.

Table 22 Summary of Medical History (SAF)

	SCB-2019 N=15064 n (%)	**Placebo N=15064 n (%)**
Any Medical History	5972 (39.6)	6008 (39.9)
Conditions with overall frequency ≥1% by system organ class and (preferred term)		
Metabolism and nutrition disorders	2301 (15.3)	2240 (14.9)
• (Obesity)	2027 (13.5)	1959 (13.0)
Surgical and medical procedures	1225 (8.1)	1232 (8.2)
• (Female sterilization)	333 (2.2)	322 (2.1)
• (Intrauterine contraception)	200 (1.3)	201 (1.3)
Infections and infestations	1213 (8.1)	1208 (8.0)
• (COVID-19)	794 (5.3)	796 (5.3)
Vascular disorders	696 (4.6)	697 (4.6)
• (Hypertension)	659 (4.4)	664 (4.4)
Psychiatric disorders	619 (4.1)	669 (4.4)
• (Depression)	194 (1.3)	222 (1.5)
• (Anxiety)	196 (1.3)	195 (1.3)
Respiratory, thoracic and mediastinal disorders	581 (3.9)	595 (3.9)
• (Rhinitis allergic)	295 (2.0)	293 (1.9)
• (Asthma)	199 (1.3)	192 (1.3)
Gastrointestinal disorders	272 (1.8)	318 (2.1)
Skin and subcutaneous tissue disorders	203 (1.3)	251 (1.7)
Injury, poisoning and procedural complications	230 (1.5)	209 (1.4)
Immune system disorders	216 (1.4)	211 (1.4)
Endocrine disorders	211 (1.4)	195 (1.3)
• (Hypothyroidism)	170 (1.1)	162 (1.1)
Nervous system disorders	180 (1.2)	193 (1.3)
Reproductive system and breast disorders	166 (1.1)	170 (1.1)
Musculoskeletal and connective tissue disorders	161 (1.1)	154 (1.0)

Source: **Table 14.1.4.1**. Percentage of subjects was calculated as 100×n/N, where N=number of subjects in the SAF by group. The source table also includes SOC and PT frequencies <1% subjects.

In the Phase-2 SAF, the medical histories of study participants were generally similar between arms (Table 23). In both the SCB-2019 (N=808) and Placebo (N=793) arms, 41% of subjects reported at least one medical event. The most frequent medical event by SOC was Metabolism and Nutrition Disorders, being reported by 16% of subjects in the SCB-2019 arm and 14% of subjects in the Placebo arm. Among those disorders, the most prevalent PT was obesity, and was reported by 13% and 11% of subjects in the SCB-2019 and Placebo arms, respectively.

The proportion of study participants who reported having had COVID-19 (PT) were generally similar between arms, being reported by 2.5% of subjects in the SCB-2019 arm and 2.6% of subjects in the Placebo arm.

Table 23 Summary of Medical History (Phase-2 SAF)

	SCB-2019 N=808 n (%)	Placebo N=793 n (%)
Any Medical History	332 (41.1)	327 (41.2)
Conditions with overall frequency ≥1% by system organ class and (preferred term)		
Metabolism and nutrition disorders	129 (16.0)	109 (13.7)
• (Obesity)	105 (13.0)	84 (10.6)
• (Hypercholesterolaemia)	17 (2.1)	18 (2.3)
• (Type 2 diabetes mellitus)	11 (1.4)	5 (0.6)
Surgical and medical procedures	86 (10.6)	98 (12.4)
• (Intrauterine contraception)	13 (0.6)	14 (1.8)
• (Female sterilization)	10 (1.2)	9 (1.1)
Vascular disorders	69 (8.5)	83 (10.5)
• (Hypertension)	66 (8.2)	78 (9.8)
Infections and infestations	43 (5.3)	50 (6.3)
(COVID-19)	20 (2.5)	21 (2.6)
• (Appendicitis)	7 (0.9)	11 (1.4)
Immune system disorders	42 (5.2)	26 (3.3)
• (Seasonal allergy)	20 (2.5)	10 (1.3)
• (Drug hypersensitivity)	16 (2.0)	12 (1.5)
Respiratory, thoracic and mediastinal disorders	32 (4.0)	29 (3.7)
• (Asthma)	14 (1.7)	10 (1.3)
• (Rhinitis allergic)	7 (0.9)	9 (1.1)
Psychiatric disorders	21 (2.6)	29 (3.7)
• (Depression)	12 (1.5)	19 (2.4)
• (Insomnia)	6 (0.7)	11 (1.4)
Musculoskeletal and connective tissue disorders	28 (3.5)	20 (2.5)
Gastrointestinal disorders	21 (2.6)	23 (2.9)
Nervous system disorders	16 (2)	21 (2.6)
Reproductive system and breast disorders	12 (1.5)	15 (0.9)
Injury, poisoning and procedural complications	14 (1.7)	13 (1.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (0.9)	16 (2.0)
Endocrine disorders	12 (1.5)	8 (1.0)
Skin and subcutaneous tissue disorders	5 (0.6)	14 (1.8)
Cardiac disorders	8 (1.0)	8 (1.0)

Source: **Table 14.1.4.1.1**. Percentage of subjects was calculated as 100×n/N, where N=number of subjects in the SAF by group. The source table also includes SOC and PT frequencies <1% subjects.

Medical history data are summarized in **Table 14.1.4.1** and in **Listing 16.2.4.3**.

10.4.1.4 Prior Medications and Concomitant Medications (SAF and Phase-2 SAF)

In the SAF, 65 subjects in the SCB-2019 arm (0.4%; N=15064) and 69 subjects in the Placebo arm (0.5%; N=15064) reported prior medication (**Table 14.1.5.1**). The three most prevalent classifications of medications were under Sex Hormones and Modulators of the Genital System (12 and 13 subjects, respectively); Antibacterials for Systemic Use (5 and 6 subjects, respectively); and Analgesics (2 and 7 subjects, respectively).

During the study, 5577 subjects in the SCB-2019 arm (37.0%; N=15064) and 5990 subjects in the Placebo arm (39.8%; N=15064) reported the use of concomitant medications (**Table 14.1.5.2**). The three most prevalent classifications of medications were under Sex Hormones and Modulators of the Genital System (14.5% and 14.6% of subjects, respectively);

Analgesics (8.0% and 9.4% subjects, respectively); and Vaccines (4.3% and 7.5% subjects, respectively), the majority of which were other COVID-19 vaccines.

In the Phase-2 SAF, 2 subjects (0.1%; N=1601) in the SAF reported prior medication; one placebo recipient and one SCB-2019 recipient (**Table 14.1.5.1.1**). These medications were classified under Antimycotics for Systemic Use, and Nasal Preparations.

Within 7 days after either dose, a small but similar percentage of placebo recipients and SCB-2019 recipients reported using anti-pyretic medications (9.8% [78/793] and 10% [82/808], respectively; **Table 14.3.1.7**).

Prior and concomitant medications data are summarized in **Tables 14.1.5.1, 14.1.5.2** and **14.3.1.7**, and in **Listing 16.2.4.4**. Coded concomitant medications were summarized using WHO Drug Dictionary Version WHOGLOBAL_202103_B3 March 01, 2021.

10.4.1.5 Measurements of Compliance to Administration Schedule

In the SAF, 92.2% of subjects in the SCB-2019 arm (N=15064) and 91.4% of subjects in the Placebo arm (N=15064) received 2 doses; whereas 7.8% of subjects in the SCB-2019 arm and 8.6% of subjects in the Placebo arm received only 1 dose (Table 24). However, 74 subjects in the SCB-2019 arm (0.5%) and 65 of subjects in the Placebo arm (0.4%) received the 2nd dose outside the visit window, meaning that 91.7% of subjects in the SCB-2019 arm and 91.0% of subjects in the Placebo arm (N=15064) received the 2nd dose in the protocol-specific time window.

Table 24 Compliance to dosing Schedule (SAF)

	SCB-2019 (N=15064)	**Placebo (N=15064)**
	n (%)	**n (%)**
Received only one dose*	1173 (7.8)	1298 (8.6)
Received two doses	13891 (92.2)	13766 (91.4)
• 2nd dose within visit window**	13817 (91.7)	13701 (91.0)
• 2nd dose outside visit window**	74 (0.5)	65 (0.4)
Interval (Day) between Dose 1 and Dose 2	**Mean (SD)**	**Mean SD**
• 2nd dose within visit window**	31.0 (10.4)	31.1 (10.5)
• 2nd dose outside visit window**	67.0 (16.5)	65.7 (19.0)

Source **Table 14.1.1.7**. Percentage of subjects was calculated as 100×n/N, where N=number of subjects. *Two subjects had the entry of the 2nd dose, but without the entry of the 1st dose.
** The visit window is 19 to 62 days.

The number of subjects randomized by site and arm is shown in **Listing 16.2.5**.

10.4.2 6-month Follow-up Analysis

The demographic and baseline characteristics of the populations included in the 6-month follow-up analysis were similar to those in the primary analysis.

The demographic and baseline characteristics were generally balanced between arms (SAF: **Table 14.1.2.1_P6m** and **Table 14.1.3.1_P6m**; Efficacy PPS: **Table 14.1.2.1.1_P6m** and **Table 14.1.3.1.1_P6m**; Efficacy FAS (Dose 2): **Table 14.1.2.1.7_P6m** and **Table 14.1.3.1.7_P6m**); Immunogenicity PPS: **Table 14.1.2.1.2_P6m** and **Table 14.1.3.1.2_P6m**.

In the 6-month follow-up analysis, 162 adolescent subjects (82 SCB-2019 recipients and 80 placebo recipients were included in the FAS for efficacy analysis. The demographics and baseline characteristics for adolescents (Exposed set) are presented in **Table 14.1.2.1.11_P6m** and **Table 14.1.3.1.11_P6m**. Immunogenicity and safety data for the adolescent cohort will be presented in a separate report.

10.4.3 Additional Analyses

10.4.3.1 Analysis of SARS-CoV-2 Cross-neutralizing Antibodies

The demographic and baseline characteristics of subjects, included in the SARS-CoV-2 cross-neutralization analysis, are presented in **Tables 14.1.2.1.11 - 14.1.2.1.12** and **14.1.3.1.11 - 14.1.3.1.12**.

10.4.3.2 Analysis of cell-mediated immune response

The demographic and baseline characteristics of subjects, included in the CMI subset, are presented in **Table 14.1.2.1.13** and **Table 14.1.3.1.13**.

In the CMI subset, the demographic and baseline characteristics were generally balanced between arms. Approximately half of the subjects were female (42.9% and 50.7% of subjects in the SCB-2019 and Placebo groups, respectively). The mean age was 33.0 years in the SCB-2019 group and 30.0 years in the Placebo group, with most subjects (95.7% and 98.5%) being between the ages of 18 to 59. Mean height was 169.6 cm in the SCB-2019 group and 168.8 cm in the Placebo group. The mean weight was 73.4 kg in the SCB-2019 group and 71.2 kg in the Placebo group. All subjects in both arms were from Colombia (58.6% and 59.7%) and Belgium (41.4% and 40.3%). Approximately half of the subjects did not have evidence of prior SARS-CoV-2 infection (54.3% and 49.3% of subjects in the SCB-2019 and Placebo groups, respectively).

The percentage of subjects at high risk of severe COVID-19 was 20.0% and 28.4% in the SCB-2019 group and the Placebo group, respectively. The most prevalent of those risks was obesity with body mass index ≥30 kg/m^2, being reported by 14.3% and 17.9% of the subjects, respectively.

10.4.3.3 Immunogenicity and Safety Analysis in Elderly Subjects

The demographic and baseline characteristics of elderly subjects, included in immunogenicity and safety analysis, are presented in **Tables 14.1.2.10.3, 14.1.2.10.4, 14.1.3.10.3** and **14.1.3.10.4**.

In the elderly FAS population, the demographic and baseline characteristics were generally balanced between arms. Among subjects with evidence of prior SARS-CoV-2 infection, 58.6% and 50.0% of subjects were female in the SCB-2019 and Placebo arms, respectively. Among subjects without evidence of prior SARS-CoV-2 infection, 48.6% and 50.0% of subjects were female in the SCB-2019 and Placebo arms, respectively. The mean age ranged from 64.2 to 66.1 years. Mean height ranged from 156.8 to 161.7 cm and mean weight ranged from 59.4 to 69.2 kg. Most subjects in both arms were from the Philippines (66.2 to 94.4%). Most subjects identified as Asian (66.2 to 94.4%).

In the SCB-2019 groups, the percentage of subjects with high risk of severe COVID-19 was 45.0% and 48.6% in subjects with and without evidence of prior SARS-CoV-2 infection, respectively. The most prevalent of those risks was hypertension or high blood pressure, being reported by 39.6% and 39.2%, respectively. In the Placebo groups, the percentage of subjects with high risk of severe COVID-19 was 38.9% and 66.7% in subjects with and without evidence of prior SARS-CoV-2 infection, respectively. The most prevalent of those risks was hypertension or high blood pressure, being reported by 33.3% and 66.7%, respectively.

10.4.3.4 Immunogenicity and Safety Analysis in Subjects with HIV Infection

The demographic and baseline characteristics in subjects with HIV infection are presented in **Tables 14.1.2.1_HIV** and **14.1.3.1_HIV**.

In the HIV infected population, the demographic and baseline characteristics were generally balanced between arms. Most of the subjects were female, with 60.6% and 72.4% of subjects in the SCB-2019 and Placebo groups, respectively. The mean age was 35.2 years in the SCB-2019 group and 38.2 years in the Placebo group, with all subjects (100%) being between the ages of 18 to 59. Mean height was 163.2 cm in the SCB-2019 group and 160.2 cm in the Placebo group. The mean weight was 72.2 kg in the SCB-2019 group and 74.4 kg in the Placebo group. Most of the subjects in both arms were from South Africa (84.8% and 96.6%). All but one subject in each group identified as Black or African American (97.0% and 96.6%).

All subjects were with high risk of severe COVID-19 due to their HIV infection. Other risks reported were immunocompromised (87.9% and 96.6%), obesity with body mass index (BMI) $\geq$30 kg/m^2 (18.2% and 34.5%), and hypertension or high blood pressure (3.0% and 3.4%).

10.4.3.5 Immunogenicity and Safety Analysis in Subjects of Chinese Origin

The demographic and baseline characteristics of subjects of Chinese Origin are presented in **Tables 14.1.2.10.1, 14.1.2.10.2, 14.1.3.10.1** and **14.1.3.10.2**.

In the Chinese origin FAS population, the demographic and baseline characteristics were generally balanced between arms. Among subjects with evidence of prior SARS-CoV-2 infection, 36% and 33.3% of subjects were female in the SCB-2019 and Placebo arms, respectively. Among subjects without evidence of prior SARS-CoV-2 infection, 21.4% and 20.0% of subjects were female in the SCB-2019 and Placebo arms, respectively. The mean age ranged from 30.3 to 37.0 years, with all subjects (100%) being between the ages of 18 to 64. Mean height ranged from 159.2 to 165.9 cm and mean weight ranged from 64.6 to 72.6 kg. All subjects in both arms were from the Philippines (100%). All subjects identified as Asian (100%).

In the SCB-2019 groups, the percentage of subjects with high risk of severe COVID-19 was 16% and 21.4% in subjects with and without evidence of prior SARS-CoV-2 infection, respectively. The most prevalent of those risks was hypertension or high blood pressure, being reported by 8.0% and 21.4%, respectively. No subjects with high risk of severe COVID-19 were reported in Placebo groups.

10.4.3.6 Immunogenicity and Safety Analysis of SCB-2019 Manufactured at Different Scales

The demographic and baseline characteristics in subjects, included in the immunogenicity and safety analysis of SCB-2019 manufactured at different scales, are presented in **Table 14.1.2.10.5** and **Table 14.1.3.10.5**.

In the PPS population, the demographic and baseline characteristics were generally balanced between groups. A total of 50.5% and 52.3% of subjects were female in the SCB-2019 2000L and SCB-2019 200L groups, respectively. The mean age was 30.8 years in the SCB-2019 2000L group and 31.4 years in the SCB-2019 200L group with all subjects (100%) being between the ages of 18 to 55. Mean height was 161.6 cm in the SCB-2019 2000L group and 164.1 cm in the SCB-2019 200L group. Mean weight was 67.1 kg in the SCB-2019 2000L group and 70.9 kg in the SCB-2019 200L group. All subjects in both groups were from Colombia (100%). All subjects (100%) identified as American Indian or Alaska native and were of Hispanic or Latino ethnicity.

The percentage of subjects with high risk of severe COVID-19 was 19.3% in the SCB-2019 2000L group and 23.0% in the SCB-2019 200L group. The most prevalent of those risks was obesity with body mass index ≥30 kg/m^2, being reported by 18.3% and 21.3%, respectively.

11.0 EFFICACY AND IMMUNOGENICITY EVALUATIONS

In the body of this section, the "round half to the nearest even" rounding convention has been applied to the efficacy and immunogenicity data in certain cases to aid clarity. In this convention, a value exactly halfway between two digits is rounded to the nearest even digit (e.g., 1.5 is halfway between 1 and 2 and is rounded to 2); and all other values are rounded to the nearest digit.

11.1 Efficacy and Immunogenicity Results and Tabulations of Individual Subject Data

Efficacy data is described in Section 11.1.1. Immunogenicity data is described in Section 11.1.2.

11.1.1 Analysis of Efficacy Results

11.1.1.1 Characterization of COVID-19 and Asymptomatic SARS-CoV-2–infection Cases

11.1.1.1.1 *Primary Efficacy Analysis*

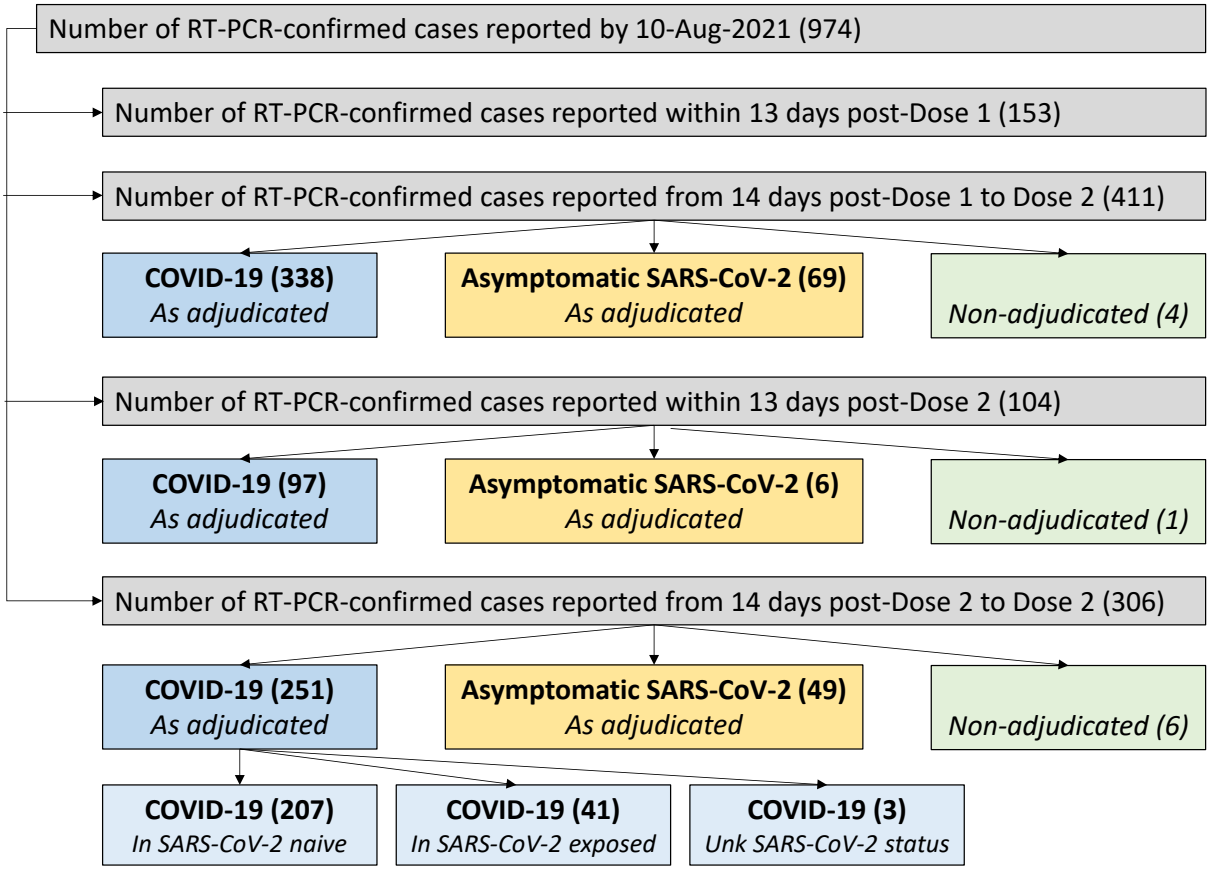
The surveillance for COVID-19 cases and asymptomatic SARS-CoV-2–infection cases was initiated after the first dose. Within 2 days after the onset of suspected COVID-19 symptoms or positive results of RAT, 2162/2268 (95.3%) subjects in the SAF provided nasopharyngeal swabs (**Table 14.1.1.8**). From 3 to 5 days, 87 subjects (3.8%) provided swabs, and after 5 days 19 subjects (0.8%) provided swabs.

Overall, 974 RT-PCR-confirmed cases of SARS-CoV-2 infection were reported in the study by the cut-off date of 10 August 2021. One hundred and fifty-three cases (15.7%) were reported within 13 days after the first dose, 411 cases (42.2%) were reported from 14 days after the first dose up to the second dose; 104 cases (10.7%) were reported within 13 days after the second dose; and 306 (31.4%) cases were reported 14 days after the second dose (**Table 14.1.1.9**).

Of the 820 SARS-CoV-2–infection cases reported from 14 days after the first dose, 810 cases (98.8%) were adjudicated by the EAC into pre-defined categories (see Section 9.5.5.4): 686 cases were categorized as COVID-19 of any severity and 124 cases were categorized as asymptomatic SARS-CoV-2 infection.

Eleven SARS-CoV-2–infection cases were not included in the efficacy analyses because they were not adjudicated by the EAC (Figure 5). All of these 11 cases occurred before the cut-off date for efficacy analysis (10 August 2021). One case was adjudicated but erroneously missed during data entry. For the remaining 10 cases, the information was provided by the investigators with a substantial delay. Four cases were reported from 14 days after the first dose up to the second dose; 1 case was reported within 13 days after the second dose; and 6 cases were reported 14 days after the second dose. Five were from subjects in the Efficacy PPS, 2 in the SCB-2019 arm and 3 in the Placebo arm.

Figure 5 Disposition of SARS-CoV-2 RT-PCR–confirmed Cases Reported in the Study by the Cut-off Date for the Efficacy Analysis



Source: **Table 14.1.1.9.**

Of the 306 SARS-CoV-2–infection cases reported from 14 days after the 2nd dose, 251 cases were categorized as COVID-19 of any severity. Of those 251 cases, 207 cases were reported by baseline-SARS-CoV-2-naïve subjects (**Table 14.2.1.1**), 41 cases were reported by baseline-SARS-CoV-2-exposed subjects (i.e., with evidence of past SARS-CoV-2 infection **Table 14.2.3.7.2**), and 3 cases had missing baseline seropositivity status or other protocol deviations.

In the Efficacy PPS, 207 SARS-CoV-2–infection cases were reported, of which 8 cases were categorized as severe COVID-19, and 34 cases were categorized as moderate COVID-19 (**Table 14.2.1.1, Table 14.2.2.1**).

Severe COVID-19 cases were presented by severe systemic illness or pneumonia associated with reduction of oxygen saturation (SpO_2 ≤93%) requiring supplemental oxygen and hospitalization, some associated with acute respiratory distress/failure requiring mechanical ventilation, by sepsis and acute renal injury. Seven subjects were hospitalized (on regular ward or ICU), and 3 subjects died. One subject recovered at home. Clinical summaries of the severe cases are presented in **Listing 16.2.7.6**.

Moderate COVID-19 cases were presented by new onset of shortness of breath (with exertion), associated with a reduction in oxygen saturation, increase of heart rate or respiratory rate but not requiring oxygen, significant diarrhea (>3 episodes a day, for at least 2 consecutive days),

severe fever (≥39.0°C for at least 2 consecutive days), or radiologically confirmed pneumonia not requiring oxygen.

Other cases represented symptomatic COVID-19 that did not meet definition of severe and moderate COVID-19. These cases include a broad spectrum of disease presentation - from a single day of mild cough and/or loss of taste and smell, up to three-week illness with multiple symptoms that prevent normal daily activities.

The genetic characterization of SARS-CoV-2 was performed for 179 of 207 (86.5%) COVID-19 cases included in the PPS-Efficacy (**Table 14.2.3.6.1**), and for 34 of 41 COVID-19 cases (83%) included in the Efficacy FAS (Dose 2) for SARS-CoV-2-exposed subjects (**Table 14.2.3.7.2**). The remaining samples [28 samples for PPS and 7 samples for Efficacy FAS (Dose 2)] were not available for sequence analysis and categorized as 'missing'.

For 146 of 207 and 23 of 41 COVID-19 cases, the data about lineage of SARS-CoV-2 was obtained.

Total number of SARS-CoV-2 lineages detected in nasopharyngeal samples of subjects with RT-PCR-confirmed COVID-19, with episode onset 14 days after the second vaccination and up to the cut-off date (10 Aug 2021) in PPS Efficacy and Efficacy FAS (Dose 2) SARS-CoV-2 exposed subjects is presented in Table 25.

Table 25 Sequence Analysis

Variant	Total	SARS-CoV-2 Naïve subjects (PPS - Efficacy)			SARS-CoV-2 Exposed subjects (FAS – Dose 2)		
	N (%)	SCB-2019	Placebo	Total	SCB-2019	Placebo	Total
Alpha	6 (2.8)	1	5	6	0	0	0
B.1.623	2 (0.9)	0	2	2	0	0	0
Beta	15 (7.0)	7	4	11	0	4	4
Delta	73 (34.3)	10	46	56	3	14	17
Gamma	13 (6.1)	1	12	13	0	0	0
Lambda	3 (1.4)	0	3	3	0	0	0
Mu	38 (17.8)	11	26	37	0	1	1
Theta	6 (2.8)	2	4	6	0	0	0
Others	13 (6.1)	3	9	12	0	1	1
None*	44 (20.7)	10	23	33	6	5	11
Total	213 (100)	45	134	179	9	25	34

Source: **Table 14.2.3.6.1** and **14.2.3.7.2**. *None: sample was sequenced but no information about SARS-CoV-2 lineage was obtained.

The cut-off date for the primary efficacy analysis was defined as the first day when 150 RT-PCR-confirmed cases of COVID-19 were reported that met the following criteria:

- A COVID-19 case was confirmed by RT-PCR test and verified by investigators;
- The case was reported starting from 14 days after the second vaccination;
- The case was associated with suspected COVID-19 symptoms;
- The case was observed in individuals without evidence of prior SARS-CoV-2 infection.

The required number of cases for the final efficacy analysis (150) was reached by 10 August 2021. However, a substantial number of suspected COVID-19 cases were in the assessment

process pending RT-PCR results, baseline seropositivity data, and/or under the monitoring of clinical symptoms. Overall, 207 cases were included in the per-protocol efficacy analysis prior to the database lock date (13 September 2021). The cumulative number of COVID-19 cases, according to the primary endpoint definition, with dates of onset is presented in **Table 14.1.1.10**.

11.1.1.1.2 *Six-month Follow-up Efficacy Analysis*

Overall, 5700 nasopharyngeal swabs were collected in 30299 study participants during the study period up to 1 December 2021. Within 2 days after the onset of suspected COVID-19 symptoms or positive results of rapid antigen tests (RAT), 5431/5700 (95.3%) subjects in the SAF provided nasopharyngeal swabs (**Table 14.1.1.8_P6m**). From 3 to 5 days, 229 subjects (4.0%) provided swabs, and after 5 days, 40 subjects (0.7%) provided swabs. In 909 cases of suspected COVID-19 symptoms or positive results of RAT, nasopharyngeal swab was not collected.

Overall, 1816 RT-PCR-confirmed cases of SARS-CoV-2 infection were reported by all study participants by the cutoff date of 1 December 2021 (**Table 14.1.1.9_P6m**), including 1137 cases reported from 14 days after the second vaccination by the cutoff date.

Of the 1137 SARS-CoV-2–infection cases reported from 14 days after the second dose, 1122 cases (98.7%) were adjudicated by the EAC into pre-defined categories (**Table 14.1.1.9_P6m**): 960 cases were categorized as COVID-19 of any severity and 162 cases were categorized as asymptomatic SARS-CoV-2 infection (Table 26).

Fifteen SARS-CoV-2–infection cases (1.3%) were not included in the efficacy analyses because they were not adjudicated by the EAC. For these cases, the available information was insufficient for adjudication or provided with a substantial delay.

Of the 960 cases of COVID-19 of any severity 14 days post dose 2, 747 cases were reported by subjects without evidence of SARS-CoV-2 infection prior to recruitment, 198 cases were reported by previously SARS-CoV-2 infected individuals, and 15 cases were reported by subjects with missed baseline serological status (13 subjects) or other data deficiencies (**Table 14.1.1.9_6m**).

In the Efficacy PPS, 742 of 747 COVID-19 cases were included, of which 20 cases were categorized as severe COVID-19, and 110 cases were categorized as moderate COVID-19 (**Table 14.2.1.1_P6m** and **Table 14.2.2.1_P6m**). Five cases were excluded from the PPS Efficacy due to randomization code broken (4 cases) and insufficient data to conclude on case severity (1 case).

Table 26 SARS-CoV-2 RT-PCR–confirmed Cases Reported from 14 Days Post Dose 2 by the Cutoff Date for the Efficacy Analysis (1 December 2021)

RT-PCR Confirmed cases		Number of cases
COVID-19 as adjudicated	Without evidence of prior SARS-CoV-2 infection	747
	With evidence of prior SARS-CoV-2 infection	198
	Unknown SARS-CoV-2 status	15
Asymptomatic SARS-CoV-2 infection as adjudicated		162
Non-adjudicated		15
Total		**1137**

Source: **Table 14.1.1.9_P6m**

Out of the 20 subjects with severe COVID-19, 17 subjects were hospitalized, and 10 subjects died. Clinical summaries of the severe cases are presented in **Listing 16.2.7.6**.

In total, 20 subjects were hospitalized, 17 subjects with severe COVID-19 (all from placebo arm), 2 subjects with moderate COVID-19 (both from placebo arm) and 1 subject with COVID-19 that did not meet the definition of severe and moderate COVID-19 (subject from SBC-2019 arm).

The genetic characterization of SARS-CoV-2 isolates was performed for 618 of 742 (83.3%) COVID-19 cases included in the PPS-Efficacy (**Table 14.2.3.6.1_P6m**), and for 165 of 198 COVID-19 cases (83.3%) included in the Efficacy FAS (Dose 2) for SARS-CoV-2-exposed subjects (**Table 14.2.3.6.3_P6m**). The remaining samples (124 samples for PPS and 33 samples for Efficacy FAS [Dose 2]) were not available for sequence analysis and categorized as ‘missing’. For 494 of 742 (66.6%) and 120 of 198 (60.6%) COVID-19 cases, the data about lineage of SARS-CoV-2 was obtained. Table 27 includes the distribution of SARS-CoV-2 variants by study arm.

From 14 days after Dose 2 to 1 December 2021, COVID-19 cases with any severity were reported by 256 SCB-2019 recipients and 486 Placebo recipients in the PPS Efficacy and by 45 SCB-2019 recipients and 153 Placebo recipients in the FAS Efficacy (Dose 2) for SARS-CoV-2-exposed subjects (Table 27). Approximately 50% of the subjects in each cohort reported cases associated with the Delta variant (384/742 cases in the PPS and 113/198 cases in the FAS (Dose 2) for SARS-CoV-2-Exposed individuals. In PPS, other most common variants of SARS-CoV-2 included Mu (51/742 cases) and Gamma (19/742 cases).

Table 27 Subjects Reporting COVID-19 Cases Classified by SARS-CoV-2 Variant (Efficacy-PPS) and FAS (Dose 2) for Subjects with Evidence of Prior SARS-CoV-2 Infection

SARS-CoV-2 Variant	Number (%) of subjects [n] with case			
	PPS		FAS (Dose 2) With Evidence of Prior SARS-CoV-2 Infection	
	SCB-2019 (N=6336)	Placebo (N=6216)	SCB-2019 (N=6902)	Placebo (N=6839)
	N_E=256	N_E=486	N_E=45	N_E=153
Alpha (B.1.1.7 and Q)	1 (0.4)	5 (1)	0 (0)	0 (0)
B.1.623	0 (0)	2 (0.4)	0 (0)	0 (0)
Beta (B.1.351, B.1.351.2, B.1.351.3)	7 (2.7)	5 (1)	0 (0)	4 (2.6)
Delta (B.1.617.2, AY series)	133 (52)	251 (51.6)	22 (48.9)	91 (59.5)
Gamma (P.1, P.1.1, P.1.2, P.1.3, P.1.7, P.1.8, P.1.10)	2 (0.8)	17 (3.5)	0 (0)	0 (0)
Lambda (C.37)	0 (0)	3 (0.6)	0 (0)	0 (0)
Mu (B.1.621, B.1.621.1)	15 (5.9)	36 (7.4)	0 (0)	2 (1.3)
Theta (P.3)	2 (0.8)	4 (0.8)	0 (0)	1 (0.7)
All others	3 (1.2)	8 (1.6)	0 (0)	0 (0)
None*	48 (18.8)	76 (15.6)	14 (31.1)	31 (20.3)
Missing**	45 (17.6)	79 (16.3)	9 (20.0)	24 (15.7)

Source: **Table 14.2.3.6.1_P6m** and **Table 14.2.3.6.3_P6m**. Percentage of subjects was calculated as $100 \times n/N_E$. N_E = number of subjects with RT-PCR confirmed COVID-19. *None: sample was sequenced but no information about SARS-CoV-2 lineage was obtained. **Missing: sample was lost or not sent for sequencing.

11.1.1.2 Identification of Subjects with Laboratory-confirmed SARS-CoV-2 Infection and Asymptomatic SARS-CoV-2 Infection

The disposition of subjects with any laboratory-confirmed SARS-CoV-2 infection and laboratory confirmed asymptomatic SARS-CoV-2 infection from 14 days after dose 2 to the 1 December cut-off date in subjects without evidence of prior SARS-CoV-2 infection is presented in Table 28.

Overall, 742 cases of RT-PCR-confirmed COVID-19 of any severity were adjudicated and included in the 6-month follow-up Efficacy PPS analysis (256 cases in the SCB-2019 group and 486 cases in placebo group).

In the SCB-2019 group, among the 256 subjects with RT-PCR confirmed COVID-19, the severity was adjudicated as mild, moderate and severe for 223, 33 and 0 subjects, respectively.

In the placebo group, among the 486 subjects with RT-PCR confirmed COVID-19, the severity was adjudicated as mild, moderate and severe for 389, 77 and 20 subjects, respectively.

Seven additional RT-PCR-confirmed COVID-19 cases (4 in the SCB-2019 group and 3 in the placebo group) were reported by subjects without evidence of prior SARS-CoV-2 infection and were not adjudicated.

In total, 110 cases (59 in the SCB-2019 group and 51 in the placebo group) of asymptomatic RT-PCR-confirmed SARS-CoV-2 infection (as adjudicated) were reported by subjects without evidence of prior-SARS-CoV-2 infection.

In total, 319 (4%) subjects in the SCB-2019 group and 543 (7.8%) subjects in the placebo group reported RT-PCR-confirmed COVID-19 of any severity (adjudicated or non-adjudicated) or RT-PCR-confirmed asymptomatic SARS-CoV-2 infection.

Overall, the number of subjects who seroconverted between Visit 3 and Visit 4, was 356 (5.6%) in SCB-2019 group and 432 (6.9%) in placebo group.

The number of subjects who seroconverted between Visit 3 and Visit 4, excluding subjects with RT-PCR confirmed SARS-CoV-2 Infection, was 274 (4.3%) in SCB-2019 group and 308 (5.0%) in placebo group.

The number of subjects with any laboratory-confirmed SARS-CoV-2 infection was 593 (9.4%) in the SCB-2019 group and 851 (13.7%) in the placebo group.

The number of subjects with laboratory-confirmed asymptomatic SARS-CoV-2 infection (defined as asymptomatic RT-PCR-confirmed infection or seroconversion for anti-N protein) was 333 (5.3%) and 360 (5.8%), respectively.

Table 28 Disposition of Subjects with any Laboratory-Confirmed SARS-CoV-2 Infection and Laboratory-Confirmed Asymptomatic SARS-CoV-2 Infection from 14 Days after Dose 2 to the Cutoff Date (1 December 2021) in Subjects Without Evidence of Prior SARS-CoV-2 Infection (Efficacy PPS)

	SCB-2019 (N=6336)¥	Placebo (N=6216) ¥
[1] Number of subjects with RT-PCR confirmed COVID-19 of any severity (excluding asymptomatic SARS-CoV-2 infection) - as adjudicated, n (%)		
Any	256 (4.0)	486 (7.8)
Mild	223 (3.5)	389 (6.3)
Moderate	33 (0.5)	77 (1.2)
Severe	0 (0.0)	20 (0.3)
[2] Number of subjects with asymptomatic RT-PCR confirmed SARS-CoV-2 infection – as adjudicated, n (%)	59 (0.9)	51 (0.8)
[3] Number of subjects with RT-PCR confirmed COVID-19 of any severity) - as non-adjudicated, n (%)	4 (0.1)	3 (<0.1)
[4 = 1+2+3] Number of subjects with RT-PCR confirmed SARS-CoV-2 infection (COVID-19 of any severity (adjudicated and non-adjudicated) and asymptomatic SARS-CoV-2 infection), n (%)	319 (5.0)	543 (8.7)*
[5] Number of subjects who seroconverted with anti-N antibodies (from Visit 3 to Visit 4), n (%) **	356 (5.6)	432 (6.9)
[6] Number of subjects who seroconverted with anti-N antibodies (from Visit 3 to Visit 4), excluding subjects with RT-PCR confirmed SARS-CoV-2 Infection, n (%)	274 (4.3)	308 (5.0)
[7=4+6] Number of subjects with any laboratory-confirmed SARS-CoV-2 infection, n (%)	593 (9.4)	851 (13.7)
[8=6+2] Number of subjects with laboratory-confirmed asymptomatic SARS-CoV-2 infection, n (%)	333 (5.3)	360 (5.8)***

Source: **Table 14.2.2.2_P6m**, **Table 14.2.2.4_P6m**, **Table 14.2.2.5_P6m**.
SCB-2019 = CpG 1018/Alum-adjuvanted SCB-2019 vaccine, RT-PCR = Reverse transcription-polymerase chain reaction, SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2.
N = Number of subjects without evidence of prior SARS-CoV-2 infection in the treatment group in the analysis population, used as a denominator for percentage calculation, n = Number of subjects with available data.
¥ number used as denominator for the % calculation.
*: included three additional subjects with RT-PCR confirmed SARS-CoV-2 infection: 2 subjects with insufficient data to complete adjudication, and one subject with asymptomatic RT-PCR confirmed SARS-CoV-2 infection as non-adjudicated.
**: Seroconversion is defined as a subject with a negative anti-N result at visit 3 and a positive anti-N result at visit 4.
***: included one subject with asymptomatic RT-PCR confirmed SARS-CoV-2 infection as non-adjudicated.

11.1.1.3 Primary Efficacy Analysis

The analyses of the primary objective, the key secondary objectives, and the Secondary Objectives #1 (VE against BOD), #2 (VE against any RT-PCR-confirmed COVID-19 of any severity, associated with hospitalization), #3 (VE by risk of severe COVID-19) and #5 (VE against SARS-CoV-2 VOCs) were performed on the Efficacy PPS. These analyses considered COVID-19 cases with onset at least 14 days after the second dose. To complement the Efficacy-PPS analyses, secondary analyses were performed on the subgroup of the Efficacy FAS (Dose 2) that only included baseline-SARS-CoV-2-naïve subjects.

The analysis of the Secondary Objective #3 (VE by evidence of prior SARS-CoV-2 infection) was performed on the subgroup of the Efficacy FAS (Dose 2) that only included baseline-SARS-CoV-2-exposed subjects. This analysis considered COVID-19 cases with onset at least 14 days after the second dose.

The analysis of Secondary Objective #4 (VE after the first dose) was performed on two subgroups of the Efficacy FAS (Dose 1):

1. The subgroup that only included baseline-SARS-CoV-2-naïve subjects; and
2. The subgroup that only included baseline-SARS-CoV-2-exposed subjects.

This analysis considered COVID-19 cases with onset at least 14 days after first dose up to the second dose.

See Section 10.4.1.1 for details on the analysis sets for the efficacy analyses.

11.1.1.3.1 *Primary Efficacy Objective (H1) - VE against COVID-19 of any severity*

Vaccine efficacy against COVID-19 of any severity in the Efficacy PPS was 67.2% (95.72% CI: 54.3–76.8), and the lower limit of the CI was above the pre-specified success threshold of 30% (Table 29). In the SCB-2019 arm, 52 endpoint cases were reported among the 5935 subjects at risk; whereas in the Placebo arm, 155 endpoint cases were reported among 5806 subjects at risk.

Table 29 Vaccine Efficacy against COVID-19 of any Severity (Efficacy PPS)

	No. of subjects at risk of endpoint	Cumulative follow up period (person.years)	No. of subjects with endpoint case	% VE (95.72% CI)
SCB-2019 (N=6251)	5935	517.3	52	67.2 (54.3–76.8)
Placebo (N=6104)	5806	506.1	155	

Source: **Table 14.2.1.1**. Follow-up period was from 14 days after Dose 2 to the end of the surveillance period. Vaccine efficacy (VE) = 100×(1 minus the ratio of incidence rates [IR] in the Vaccine and Placebo arms). IR = number (No.) of subjects with endpoint case per cumulative follow-up.

In SARS-CoV-2-naïve adults (i.e., adults without prior evidence of SARS-CoV-2 infection) in the Efficacy FAS (Dose 2), vaccine efficacy against COVID-19 of any severity was 67.2% (95.72% CI 54.3–76.8; **Table 14.2.1.1.1**), and was consistent with the Efficacy PPS.

11.1.1.3.2 *Key Secondary Efficacy Objectives #1 (H2b) and #3 (H4) - VE against moderate-to-severe COVID-19 and severe COVID-19*

Vaccine efficacy against moderate-to-severe COVID-19 in the Efficacy PPS was 83.7% (97.86% CI 55.9–95.4), and the lower limit of the CI was above the pre-specified success threshold of 0% (Table 30). In the SCB-2019 arm, 6 endpoint cases were reported among the 5935 subjects at risk, whereas in the Placebo arm, 36 endpoint cases were reported among 5806 subjects at risk.

Vaccine efficacy against severe COVID-19 was 100% (97.86% CI 25.3–100.0), and the lower bound of the CI was above the pre-specified success threshold of 0% (Table 30). In the SCB-2019 arm, no endpoint case was reported among the 5935 subjects at risk, whereas in the Placebo arm, 8 endpoint cases were reported among 5806 subjects at risk.

Therefore SCB-2019 had statistically significant efficacy against moderate-to-severe COVID-19 and had statistically-significant efficacy against severe-COVID-19 in the Efficacy PPS.

Table 30 Vaccine Efficacy against Moderate-to-severe COVID-19 and Severe COVID-19 (Efficacy-PPS)

	No. of subjects at risk of endpoint	Cumulative follow up period (person.years)	No. of subjects with endpoint case	% VE (97.86% CI)
	Endpoint: moderate-to-severe COVID-19			
SCB-2019 (N=6251)	5935	517.3	6	83.7 (55.9–95.4)
Placebo (N=6104)	5806	506.1	36	
	Endpoint: severe COVID-19			
SCB-2019 (N=6251)	5935	517.3	0	100 (25.3–100.0)
Placebo (N=6104)	5806	506.1	8	

Source: **Table 14.2.2.1**. Follow-up period was from 14 days after Dose 2 to the end of the surveillance period. Vaccine efficacy (VE) = 100×(1 minus the ratio of incidence rates [IR] in the Vaccine and Placebo arms). IR = number (No.) of subjects with endpoint case per cumulative follow-up.

In SARS-CoV-2-naïve subjects in the Efficacy FAS (Dose 2), the vaccine efficacy against moderate-to-severe COVID-19 was 83.7% (97.86% CI 55.9–95.4; **Table 14.2.2.1.1**), and the vaccine efficacy against severe COVID-19 was 100% (97.86% CI 25.3–100.0; **Table 14.2.2.1.1**). Results of the Efficacy FAS (Dose 2) in SARS-CoV-2 naïve subjects were consistent with the results of the Efficacy PPS.

11.1.1.3.3 *Key Secondary Efficacy Objectives #2 (H2a) and #4 (H3) – VE against any laboratory-confirmed SARS-CoV-2 infection and any laboratory-confirmed asymptomatic SARS-CoV-2 infection*

Vaccine efficacy against any laboratory-confirmed SARS-CoV-2 infection from 14 days after Dose 2 to the cutoff date (1 December 2021) in subjects without evidence of prior SARS-CoV-2 infection is presented in Table 31.

From 14 days after Dose 2 to the cutoff date of 1 December 2021, vaccine efficacy against any laboratory-confirmed SARS-CoV-2 infection was 34.4% (95% CI: 27.1–41.0), with endpoint cases reported by 593 SCB-2019 recipients and 851 placebo recipients. The lower limit (LL) of 95% CI for vaccine efficacy (27.1%) is above 0.

Vaccine efficacy against any laboratory-confirmed asymptomatic SARS-CoV-2 infection was 12.9% (95% CI: -1.4–25.2), with endpoint cases reported by 333 SCB-2019 recipients and 360 placebo recipients. The LL of 95% CI for vaccine efficacy (-1.4%) is below 0.

Table 31 Vaccine Efficacy Against any Laboratory-Confirmed SARS-CoV-2 Infection and Laboratory-Confirmed Asymptomatic SARS-CoV-2 Infection from 14 Days after Dose 2 to the Cutoff Date (1 December 2021) in Subjects Without Evidence of Prior SARS-CoV-2 Infection (Efficacy PPS)

SCB-2019 (N=6336)			Placebo (N=6216)				
No. of subject at risk [1]	Cumulative FU PY[2]	No. of subjects with observed event [3]	No. of subject at risk [1]	Cumulative FU PY[2]	No. of subjects with observed event [3]	VE [4]	95% CI [5]
Laboratory-Confirmed SARS-CoV-2 Infection							
6331	1889.5	593	6212	1778.7	851	34.4%	27.1%, 41.0%
Laboratory-Confirmed Asymptomatic SARS-CoV-2 Infection							
6331	1889.5	333	6212	1778.7	360	12.9%	-1.4%, 25.2%

Source: **Table 14.2.2.2_P6m**.

SCB-2019 = CpG 1018/Alum-adjuvanted SCB-2019 vaccine, RT-PCR = Reverse transcription-polymerase chain reaction, COVID-19 = Coronavirus disease 2019, SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2, FU = Follow-up, PY = Person-year, VE = Vaccine efficacy, CI = Confidence interval. N = Number of subjects without evidence of prior SARS-CoV-2 infection in treatment group in the analysis population.

[1] Number of subjects at risk for the endpoint.

[2] Cumulative follow-up person-year is calculated among all subjects at risk within each treatment group. Time period for observed event accrual is from 14 days after dose 2 to the end of the surveillance period.

[3] Observed event = first occurrence of the endpoint with onset at least 14 days after dose 2 in subjects at risk.

[4] Vaccine Efficacy = 1 - incidence rate ratio of the vaccine to placebo in subjects with the endpoint per cumulative follow-up person-year.

[5] Confidence interval (CI) for vaccine efficacy is derived using the Clopper-Pearson method based on conditional binomial distribution.

11.1.1.3.3.1 Post-hoc analysis – VE against any RT-PCR-confirmed asymptomatic SARS-CoV-2 infection

To get more insight in the VE efficacy against asymptomatic SARS-CoV-2 infection, a post-hoc analysis was conducted to assess the VE against any RT-PCR-confirmed asymptomatic SARS-CoV-2 infection from 14 days after Dose 2 to the cutoff date (1 December 2021) in SARS-CoV-2-naïve and SARS-CoV-2-exposed adults (Table 32).

In SARS-CoV-2-naïve recipients, from 14 days after Dose 2 to the cutoff date of 1 December 2021, vaccine efficacy against any RT-PCR-confirmed asymptomatic SARS-CoV-2 infection was -9.0% (95% CI: -61.8–26.3), with endpoint cases reported by 59 SCB-2019 recipients and 51 placebo recipients.

In SARS-CoV-2-exposed recipients, from 14 days after Dose 2 to the cutoff date of 1 December 2021, vaccine efficacy against any RT-PCR-confirmed asymptomatic SARS-CoV-2 infection was 63.5% (95% CI: 30.8–81.8), with endpoint cases reported by 14 SCB-2019 recipients and 37 placebo recipients.

Table 32 Vaccine Efficacy Against Asymptomatic RT-PCR-Confirmed SARS-CoV-2 Infection From 14 Days After Dose 2 in Subjects With and Without Evidence of Prior SARS-CoV-2 Infection - (Efficacy PPS, Efficacy FAS)

SCB-2019 (N=6336)			Placebo (N=6216)				
No. of subject at risk [1]	Cumulative FU PY[2]	No. of subjects with observed event [3]	No. of subject at risk [1]	Cumulative FU PY[2]	No. of subjects with observed event [3]	VE [4]	95% CI [5]
Subjects Without Evidence of Prior SARS-CoV-2 Infection							
6331	1902.8	59	6212	1793.0	51	-9.0%	-61.8%, 26.3%
Subjects With Evidence of Prior SARS-CoV-2 Infection							
6896	2464.8	14	6834	2380.0	37	63.5%	30.8%, 81.8%

Source: **Table 14.2.2.4_P6m** and **Table 14.2.2.4.1_P6m**.
SCB-2019 = CpG 1018/Alum-adjuvanted SCB-2019 vaccine, RT-PCR = Reverse transcription-polymerase chain reaction, SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2, FU = Follow-up, PY = Person-year, VE = Vaccine efficacy, CI = Confidence interval.
N = Number of subjects without evidence of prior SARS-CoV-2 infection in treatment group in the analysis population.
[1] Number of subjects at risk for the endpoint.
[2] Cumulative follow-up person-year is calculated among all subjects at risk within each treatment group. Time period for observed event accrual is from 14 days after dose 2 to the end of the surveillance period.
[3] Observed event = first occurrence of any RT-PCR-confirmed asymptomatic SARS-CoV-2 infection with onset at least 14 days after dose 2 in subjects at risk.
[4] Vaccine Efficacy = 1 - incidence rate ratio of the vaccine to placebo in subjects with any RT-PCR confirmed asymptomatic SARS-CoV-2 infection per cumulative follow-up person-year.
[5] Confidence interval (CI) for vaccine efficacy is derived using the Clopper-Pearson method based on conditional binomial distribution.

11.1.1.3.4 *Secondary Efficacy Objective #1 - Vaccine efficacy against BOD*

Vaccine efficacy against BOD from 14 days after Dose 2 in subjects without evidence of prior SARS-CoV-2 infection is presented in Table 33. From 14 days after Dose 2 to the cutoff date of 1 December 2021, the number of subjects with RT-PCR-confirmed COVID-19 of any severity was 260 for SCB-2019 recipients and 489 for placebo recipients. None of the subjects presented RT-PCR-confirmed severe COVID-19 in SCB-2019 group. Twenty subjects presented RT-PCR-confirmed severe COVID-19 in placebo group. During this period, vaccine efficacy against BOD was 48.9% (95% CI: 40.5–56.0), with a BOD score of 260 for SCB-2019 recipients and 509 for placebo recipients.

Vaccine efficacy against BOD using the alternative definition from 14 days after Dose 2 in subjects without evidence of prior SARS-CoV-2 infection is presented in Table 34. From 14 days after Dose 2 to the cutoff date of 1 December 2021, the number of subjects with RT-PCR-confirmed COVID-19 of mild severity was 224 for SCB-2019 recipients and 390 for placebo recipients. The number of subjects with RT-PCR-confirmed COVID-19 of moderate severity was 36 for SCB-2019 recipients and 79 for placebo recipients. None of the subjects had RT-PCR-confirmed severe COVID-19 in SCB-2019 group. Twenty subjects had RT-PCR-confirmed severe COVID-19 in placebo group. During this period, vaccine efficacy against BOD (alternative definition) was 51.3% (95% CI: 42.8–58.4), with a BOD score of 296 for SCB-2019 recipients and 608 for placebo recipients.

Table 33 Vaccine Efficacy Against Burden of Disease from 14 Days after Dose 2 to the Cutoff Date (1 December 2021) in Subjects without Evidence of Prior SARS-CoV-2 Infection (Efficacy PPS)

	SCB-2019 (N=6336)	Placebo (N=6216)
Number of subjects with RT-PCR-confirmed COVID-19 of any severity from 14 days after dose 2	260	489
Number of subjects with RT-PCR-confirmed Severe COVID-19 from 14 days after dose 2	0	20
Burden of disease (BOD) score [1]	260	509
Vaccine Efficacy against BOD (%) [2]	48.9	
(95% CI) for Vaccine Efficacy against BOD	(40.5, 56.0)	

Source: **Table 14.2.3.1_P6m**.
SCB-2019 = CpG 1018/Alum-adjuvanted SCB-2019 vaccine, RT-PCR = Reverse transcription-polymerase chain reaction, COVID-19 = Coronavirus disease 2019, SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2, BOD = Burden of Disease, CI = Confidence Interval.
N = Number of subjects without evidence of prior SARS-CoV-2 infection in treatment group in the analysis population.
[1] Burden of disease (BOD) score = Number of subjects with RT-PCR-confirmed COVID-19 of any severity + number of subjects with RT-PCR-confirmed Severe COVID-19.
[2] Vaccine Efficacy against BOD = 1 – BOD score ratio of the vaccine to placebo in subjects with any RT-PCR confirmed COVID 19 of any severity.

Table 34 Vaccine Efficacy Against Burden of Disease (Alternative Definition) from 14 Days after Dose 2 to the Cutoff Date (1 December 2021) in Subjects without Evidence of Prior SARS-CoV-2 Infection (Efficacy PPS)

	SCB-2019 (N=6336)	Placebo (N=6216)
Number of subjects with RT-PCR-confirmed Mild COVID-19 from 14 days after dose 2	224	390
Number of subjects with RT-PCR-confirmed Moderate COVID-19 from 14 days after dose 2	36	79
Number of subjects with RT-PCR-confirmed Severe COVID-19 from 14 days after dose 2	0	20
Burden of disease (BOD) score [1]	296	608
Vaccine Efficacy against BOD (%) [2]	51.3	
(95% CI) for Vaccine Efficacy against BOD	(42.8, 58.4)	

Source: **Table 14.2.3.1.2_P6m**.
SCB-2019 = CpG 1018/Alum-adjuvanted SCB-2019 vaccine, RT-PCR = Reverse transcription-polymerase chain reaction, COVID-19 = Coronavirus disease 2019, SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2, BOD = Burden of Disease, CI = Confidence Interval.
N = Number of subjects without evidence of prior SARS-CoV-2 infection in treatment group in the analysis population.
[1] Burden of disease (BOD) score = Number of subjects with RT-PCR-confirmed Mild COVID-19 + 2* Number of subjects with RT-PCR-confirmed Moderate COVID-19 + 3* number of subjects with RT-PCR-confirmed Severe COVID-19.
[2] Vaccine Efficacy against BOD = 1 – BOD score ratio of the vaccine to placebo in subjects with any RT-PCR confirmed COVID 19 of any severity.

11.1.1.3.5 *Secondary Efficacy Objective #2 – VE against any COVID-19 of any severity, associated with hospitalization*

In the Efficacy PPS, vaccine efficacy against COVID-19 leading to hospitalization was 100% (95% CI 42.7–100; **Table 14.2.3.2**). In the SCB-2019 arm, no endpoint case was reported among the 5935 subjects at risk; whereas in the Placebo arm, 8 endpoint cases were reported among 5806 subjects at risk. In SARS-CoV-2-naïve subjects in the Efficacy FAS (Dose 2), vaccine efficacy against COVID-19 leading to hospitalization was 100% (95% CI 42.7–100; **Table 14.2.3.2.1**), and was consistent with the Efficacy PPS.

11.1.1.3.6 *Secondary Efficacy Objective #3 – VE by evidence of prior SARS-CoV-2 infection and by risk of severe COVID-19*

11.1.1.3.6.1 Vaccine Efficacy in SARS-CoV-2-exposed Subjects

In SARS-CoV-2-exposed subjects in the Efficacy-FAS (Dose 2), and from 14 days after the 2nd dose, vaccine efficacy against COVID-19 of any severity was 64.2% (95% CI 26.5–83.8; Table 35; **Table 14.2.3.7.2**). In the SCB-2019 arm, 11 endpoint cases were reported among the 6195 subjects at risk; whereas in the Placebo arm, 30 endpoint cases were reported among 6147 subjects at risk.

In SARS-CoV-2-exposed subjects in the Efficacy-FAS (Dose 2), and from 14 days after the 2nd dose, vaccine efficacy against moderate-to severe COVID-19 was 67.5% (95% CI −305.2 to 99.4; Table 35; **Table 14.2.3.7.2**). In the SCB-2019 arm, 1 endpoint case was reported among the 6195 subjects at risk; whereas in the Placebo arm, 3 endpoint cases were reported among 6147 subjects at risk.

In SARS-CoV-2-exposed subjects in the Efficacy-FAS (Dose 2), and from 14 days after the 2nd dose, no severe COVID-19 case, or a COVID-19 case leading to hospitalization was reported (**Table 14.2.3.7.2**).

Table 35 Vaccine Efficacy in SARS-CoV-2-exposed Subjects [Efficacy-FAS (Dose 2) Including only Subjects with Evidence of Prior SARS-CoV-2 Infection]

	No. of subjects at risk of endpoint	Cumulative follow up period (person.years)	No. of subjects with endpoint case	% VE (95% CI)
	Endpoint: any severity			
SCB-2019 (N=6706)	6195	551.0	11	64.2 (26.5-83.8)
Placebo (N=6683)	6147	537.8	30	
	Endpoint: moderate-to-severe COVID-19			
SCB-2019 (N=6706)	6195	551.0	1	67.5 (-305.2-99.4)
Placebo (N=6683)	6147	537.8	3	
	Endpoint: severe COVID-19			
SCB-2019 (N=6706)	6195	551.0	0	-
Placebo (N=6683)	6147	537.8	0	
	Endpoint: COVID-19 of any severity leading to hospitalization			
SCB-2019 (N=6706)	6195	551.0	0	-
Placebo (N=6683)	6147	537.8	0	

Source: **Table 14.2.3.7.2**. Follow-up period was from 14 days after Dose 2 to the end of the surveillance period. Vaccine efficacy (VE) = 100×(1 minus the ratio of incidence rates [IR] in the Vaccine and Placebo arms). IR = number (No.) of subjects with endpoint case per cumulative follow-up.

11.1.1.3.6.2 Vaccine Efficacy by risk of severe COVID-19

In the Efficacy PPS, in adults at high risk of severe COVID-19, vaccine efficacy against COVID-19 of any severity was 65.9% (95% CI 35.7–82.9; Table 36; **Table 14.2.3.4.4**). In the SCB-2019 arm, 14 endpoint cases were reported among the 1027 subjects at risk; whereas in the Placebo arm, 38 endpoint cases were reported among 949 subjects at risk. In adults at low risk of severe COVID-19, vaccine efficacy against COVID-19 of any severity was 67.9% (95% CI 53.3–78.3; **Table 14.2.3.4.4**). In the SCB-2019 arm, 38 endpoint cases were reported among the 4908 subjects at risk; whereas in the Placebo arm, 117 endpoint cases were reported among 4857 subjects at risk.

Table 36 Vaccine Efficacy by Risk of Severe COVID-19 (Efficacy-PPS)

	No. of subjects at risk of endpoint	Cumulative follow up period (person.years)	No. of subjects with endpoint case	% VE (95% CI)
	Endpoint: any severity			
Low risk				
SCB-2019	4908	427.8	38	67.9 (53.3-78.3)
Placebo	4857	423.3	117	
High risk				
SCB-2019	1027	89.5	14	65.9 (35.7-82.9)
Placebo	949	82.8	38	
	Endpoint: moderate-to-severe COVID-19			
Low risk				
SCB-2019	4908	427.8	3	87.1 (57.3–97.5)
Placebo	4857	423.3	23	
High risk				
SCB-2019	1027	89.5	3	78.7 (22.3–96.1)
Placebo	949	82.8	13	
	Endpoint: severe COVID-19			
Low risk				
SCB-2019	4908	427.8	0	100 (−3759.3 to 100.0)
Placebo	4857	423.3	1	
High risk				
SCB-2019	1027	89.5	0	100 (35.8–100.0)
Placebo	949	82.8	7	
	Endpoint: COVID-19 of any severity leading to hospitalization			
Low risk				
SCB-2019	4908	427.8	0	100 (−426.9 to 100.0)
Placebo	4857	423.3	2	
High risk				
SCB-2019	1027	89.5	0	100 (21.5–100.0)
Placebo	949	82.8	6	

Source: **Table 14.2.3.4.4**. Follow-up period was from 14 days after Dose 2 to the end of the surveillance period. Vaccine efficacy (VE) = 100×(1 minus the ratio of incidence rates [IR] in the Vaccine and Placebo arms). IR = number (No.) of subjects with endpoint case per cumulative follow-up.

11.1.1.3.7 *Secondary Efficacy Objective #4 – VE against COVID-19 cases with onset after the 1st dose*

In SARS-CoV-2–naïve subjects in the Efficacy-FAS (Dose 1), vaccine efficacy against COVID-19 of any severity was 7.8% (95% CI −16.7 to 27.3) from 14 days after Dose 1 through to Dose 2 (Table 37). In the SCB-2019 arm, 140 endpoint cases were reported among the 7311

subjects at risk, whereas in the Placebo arm, 152 endpoint cases were reported among 7312 subjects at risk.

In SARS-CoV-2–naïve subjects in the Efficacy-FAS (Dose 1), vaccine efficacy against moderate-to-severe COVID-19 was 16.1% (95% CI −46.1 to 52.1) (Table 37). In the SCB-2019 arm, 26 endpoint cases were reported among the 7311 subjects at risk, whereas in the Placebo arm, 31 endpoint cases were reported among 7312 subjects at risk. Regarding severe COVID-19, one endpoint case was reported in the SCB-2019 arm and one endpoint case in the Placebo arm.

In SARS-CoV-2–exposed subjects in the Efficacy-FAS (Dose 1), vaccine efficacy against COVID-19 of any severity was 49.9% (95% CI 1.5–75.6; Table 37). In the SCB-2019 arm, 14 endpoint cases were reported among the 7325 subjects at risk; whereas in the Placebo arm, 28 endpoint cases were reported among 7305 subjects at risk. Regarding moderate-to-severe COVID-19, three endpoint cases were reported in each arm. No severe endpoint cases were reported in SARS-CoV-2-exposed adults in the interval from 14 days after Dose 1 to Dose 2.

Table 37 Vaccine Efficacy after First Dose from 14 Days after Dose 1 through to Dose 2 [Efficacy-FAS (Dose 1)]

	No. of subjects at risk of endpoint	Cumulative follow up period (person.years)	No. of subjects with endpoint case	% VE (95% CI)
	Endpoint: any severity			
Subjects without evidence of prior SARS-CoV-2 infection				
SCB-2019	7311	356.9	140	7.8 (−16.7 to 27.3)
Placebo	7312	357.2	152	
Subjects with evidence of prior SARS-CoV-2 infection				
SCB-2019	7325	419.9	14	49.9 (1.5–75.6)
Placebo	7305	421.1	28	
	Endpoint: moderate-to-severe COVID-19			
Subjects without evidence of prior SARS-CoV-2 infection				
SCB-2019	7311	356.9	26	16.1 (−46.1 to 52.1)
Placebo	7312	357.2	31	
Subjects with evidence of prior SARS-CoV-2 infection				
SCB-2019	7325	419.9	3	−0.3% (−648.8 to 86.6)
Placebo	7305	421.1	3	
	Endpoint: severe COVID-19			
Subjects without evidence of prior SARS-CoV-2 infection				
SCB-2019	7311	356.9	1	−0.1% (−7755.8 to 98.7)
Placebo	7312	357.2	1	
Subjects with evidence of prior SARS-CoV-2 infection				
SCB-2019	7325	419.9	0	-
Placebo	7305	421.1	0	

Source: **Tables 14.2.3.7.7** and **14.2.3.7.8**. Follow-up period was from 14 days after Dose 1 to Dose 2.
Vaccine efficacy (VE) = 100×(1 minus the ratio of incidence rates [IR] in the Vaccine and Placebo arms). IR = number (No.) of subjects with endpoint case per cumulative follow-up.

11.1.1.3.8 *Secondary Efficacy Objective #5 – VE against SARS-CoV-2 VOCs (Efficacy PPS)*

In the Efficacy PPS, the three most frequent lineages of SARS-CoV-2 detected in the COVID-19 cases of any severity were the Delta, Mu and Gamma lineages (Table 38 and **Table 14.2.3.6.1**). The Delta and Gamma lineages represent VOCs, whereas the Mu lineage represents variants of interest (VOIs).

Vaccine efficacy against COVID-19 of any severity associated with Delta lineage was 78.7% (95% CI 57.3–90.4; Table 38). In the SCB-2019 arm, 10 endpoint cases were reported among the 5935 subjects at risk; whereas in the Placebo arm, 46 endpoint cases were reported among 5806 subjects at risk.

Vaccine efficacy against COVID-19 of any severity associated with Mu lineage was 58.6% (95% CI 13.3–81.5; Table 38). In the SCB-2019 arm, 11 endpoint cases were reported among the 5935 subjects at risk; whereas in the Placebo arm, 26 endpoint cases were reported among 5806 subjects at risk.

Vaccine efficacy against COVID-19 of any severity associated with Gamma lineage was 91.8% (95% CI 44.9–99.8; Table 38). In the SCB-2019 arm, 1 endpoint case was reported among the 5935 subjects at risk; whereas in the Placebo arm, 12 endpoint cases were reported among 5806 subjects at risk.

For all other lineages, except the Beta lineage, there were more cases in the placebo arm than in the SCB-2019 group. For the Beta lineage, 7 endpoint cases were reported among the 5935 subjects at risk in the SCB-2019 arm; whereas in the Placebo arm, 4 endpoint cases were reported among 5806 subjects at risk. Regarding the vaccine efficacy in the cases for which no lineage could be defined or for cases where results biological samples were not available for sequencing (missing), a similar vaccine efficacy as in the primary endpoint was observed (57.5 and 67.4%, respectively; **Table 14.2.3.7**).

Table 38 Vaccine Efficacy against COVID-19 of any Severity by the three most Frequent SARS-CoV-2 Variants (Efficacy-PPS)

Endpoint: any severity COVID-19	No. of subjects at risk of endpoint	Cumulative follow up period (person.years)	No. of subjects with endpoint case	% VE (95% CI)
	Delta (B.1.617.2, AY.1–12)[a]			
SCB-2019 (N=6251)	5935	517.3	10	78.7 (57.3–90.4)
Placebo (N=6104)	5806	506.1	46	
	Mu (B.1.621)			
SCB-2019 (N=6251)	5935	517.3	11	58.6 (13.3–81.5)
Placebo (N=6104)	5806	506.1	26	
	Gamma (P.1, P.1.1, P.1.2)			
SCB-2019 (N=6251)	5935	517.3	1	91.8 (44.9–99.8)
Placebo (N=6104)	5806	506.1	12	

Source: **Table 14.2.3.7**. Follow-up period was from 14 days after Dose 2 to the end of the surveillance period. Vaccine efficacy (VE) = 100×(1 minus the ratio of incidence rates [IR] in the Vaccine and Placebo arms). IR = number (No.) of subjects with endpoint case per cumulative follow-up. [a]Note: the Delta and Gamma lineages represent VOCs, whereas the Mu lineage represents VOIs.

Results of the Efficacy FAS (Dose 2) in SARS-CoV-2–naïve subjects were consistent with the results of the Efficacy PPS. Vaccine efficacy against any severity with Delta lineage was 78.7% (95% CI 57.3–90.4; **Table 14.2.3.7.1**), against Mu lineage was 58.6% (95% CI 13.3–81.5;

Table 14.2.3.7.1) and against Gamma lineage was 91.8% (95% CI 44.9-99.8; **Table 14.2.3.7.1**).

11.1.1.3.8.1 Supplementary Analysis – VE against SARS-CoV-2 VOCs in subjects with prior evidence of SARS-CoV-2 infection

In SARS-CoV-2-exposed subjects in the Efficacy FAS (Dose 2), the most frequent lineage of SARS-CoV-2 detected in the COVID-19 cases of any severity was the Delta lineage (**Table 14.2.3.7.2**).

Vaccine efficacy against COVID-19 of any severity associated with Delta lineage was 79.1% (95% CI 25.1–96.1; **Table 14.2.3.7.2**). In the SCB-2019 arm, 3 endpoint cases were reported among the 6195 subjects at risk; whereas in the Placebo arm, 14 endpoint cases were reported among 6147 subjects at risk.

11.1.1.3.9 *Exploratory Efficacy Objective #1 – To explore the effect of SCB-2019 on the severity of COVID-19 using the National Early Warning Scoring 2 (NEWS2) score in subjects with COVID-19-associated hospitalization*

For subjects with COVID-19–associated hospitalization from 14 days after Dose 2, the NEWS2 score was calculated during hospitalization. The maximum value of NEWS2 score was used for analysis.

In total, 7 subjects from the Placebo arm in the Efficacy FAS [Dose2]) had NEWS2 data available at the cutoff date for the primary efficacy analysis. Five out of the seven subjects (71.4%) had a total NEWS2 score of ≥ 5 (**Table 14.2.5.1**). A score of 5 or more represents the key threshold for urgent response for COVID-19 patients. No subjects from the SCB-2019 arm were hospitalized.

11.1.1.3.10 *Exploratory Efficacy Objective #3 –To explore the effect of SCB-2019 on the prevention of COVID-19 long-term sequelae*

No long-term sequelae of COVID-19 were observed up to the cutoff date for the primary efficacy analysis.

11.1.1.3.11 *Exploratory Efficacy Objective #4 – To explore the effect of SCB-2019 on the risk of disease enhancement, including but not limited to enhanced respiratory disease*

Results of the exploratory analysis of the effect of the SCB-2019 on the risk of disease enhancement at the cutoff date for the primary efficacy analysis are presented in Table 39.

The ratio of severe COVID-19 to COVID-19 of any severity was 0 for the SCB-2019 arm and 5.2 for the Placebo arm.

Table 39 Risk of Disease Enhancement in Subjects With RT-PCR-confirmed COVID-19 of any Severity From 14 Days after Dose 2 (Efficacy PPS)

	SCB-2019 (N=6251)	**Placebo (N=6104)**
Number of subjects with RT-PCR-confirmed COVID-19 of any severity from 14 days after Dose 2	52	155
Number of subjects with RT-PCR-confirmed severe COVID-19 from 14 days after Dose 2	0	8
Ratio of severe COVID-19 to COVID-19 of any severity	0.0	5.2

Source: **Table 14.2.5.4.1**. Follow-up period was from 14 days after Dose 2 to the end of the surveillance period.

11.1.1.3.12 *Exploratory Efficacy Objective #5 – To perform characterization of SARS-CoV-2 isolates by genetic sequencing (in a subset of samples)*

SARS-CoV-2 lineage distribution of RT-PCR-confirmed COVID-19 of any severity from 14 days after Dose 2 in the Efficacy PPS (SARS-CoV-2-naïve subjects) is presented in **Table 14.2.3.6.1**. Similar data for period from 14 Days after Dose 1 is presented in **Table 14.2.3.6.2**.

11.1.1.4 Six-month Follow-up Efficacy Analysis

The section below represents the results of the second efficacy analysis with mean duration of follow-up period of 154.2 days after completion of the primary immunization series (**Table 14.1.1.3.2_6Pm**).

11.1.1.4.1 *Vaccine efficacy in SARS-CoV-2 naïve subjects (6-month follow up)*

From 14 days after Dose 2 to the cutoff date of 1 December 2021, vaccine efficacy against COVID-19 of any severity was 50.4% (95% CI: 42.1–57.5), with endpoint cases reported by 256 SCB-2019 recipients and 486 placebo recipients (Table 40). Vaccine efficacy against moderate-to-severe COVID-19 was 67.9% (95% CI: 52.0–79.1), with endpoint cases reported by 33 SCB-2019 recipients and 97 placebo recipients. Vaccine efficacy against severe COVID-19 was 100.0% (95% CI: 80.9–100.0), with endpoint cases reported by 20 placebo recipients and no SCB-2019 recipients (Table 40). Vaccine efficacy against COVID-19–related hospitalization was 95% (95% CI: 68.8–99.9).

The most frequently reported variant of SARS-CoV-2 was Delta, which was detected in approximately 50% of COVID-19 cases (Table 27). Vaccine efficacy against COVID-19 of any severity associated with the Delta variant was 50.1% (95% CI: 38.1–59.8), with endpoint cases reported by 133 SCB-2019 recipients and 251 placebo recipients (Table 40). Vaccine efficacy against Mu variant was 60.7% (95% CI: 26.5–80.0), with endpoint cases reported by 15 SCB-2019 recipients and 36 placebo recipients (Table 40). Vaccine efficacy against Gamma variant was 88.9% (95% CI: 53.3–98.8), with endpoint cases reported by 2 SCB-2019 recipients and 17 placebo recipients (Table 40).

Table 40 Vaccine Efficacy against RT-PCR-confirmed COVID-19 from 14 Days after Dose 2 in Subjects without Evidence of Prior SARS-CoV-2 Infection (Efficacy PPS – 6-month follow-up analysis)

	SCB-2019 (N=6336)	Placebo (N=6216)	% VE (95% CI)
No. of subjects at risk of endpoint:	6331	6212	
Cumulative follow up period (person.years):	1902.8	1793.0	
Endpoint	**No. of subjects with endpoint case**		
Any severity	256	486	50.4 (42.1–57.5)
Moderate-to-severe	33	97	67.9 (52.0–79.1)
Severe	0	20	100.0 (80.9–100.0)
Hospitalization due to COVID-19	1*	19	95.0 (68.8–99.9)
Any COVID-19 associated with:			
VOC Delta	133	251	50.1 (38.1–59.8)
VOC Mu	15	36	60.7 (26.5–80.0)
VOC Gamma	2	17	88.9 (53.3–98.8)

Source: **Tables 14.2.1.1_P6m**, **14.2.2.1_P6m**, **14.2.3.2_P6m** and **14.2.3.7_P6m**. Follow-up period was from 14 days after Dose 2 to the end of the surveillance period. Vaccine efficacy (VE) = 100×(1 minus the ratio of incidence rates [IR] in the Vaccine and Placebo arms). IR = number (No.) of subjects with endpoint case per cumulative follow-up. VOC=variant of concern, of which the VE for the three most frequent SARS-CoV-2–types are shown. * Subject 6060075 in the SCB-2019 group with positive SARS-CoV-2 RT-PCR test reported loss of taste and cough and was diagnosed with mild COVID-19. Subject was hospitalized for 3 days for monitoring of symptoms.

In SARS-CoV-2-naïve subjects in the Efficacy FAS (Dose 2), the vaccine efficacy against COVID-19 of any severity from 14 days after Dose 2 to the cutoff date was 50.5% (95% CI 42.3–57.6; **Table 14.2.1.1.1_P6m**), against moderate-to-severe COVID-19 was 68.0% (95% CI 52.0–79.1; **Table 14.2.2.1.1_P6m**), and against severe COVID-19 was 100% (95% CI 80.9–100.0; **Table 14.2.2.1.1_P6m**). Vaccine efficacy for RT-PCR-confirmed COVID-19 of any severity associated with hospitalization was 95.0% (95% CI 68.8–99.9; **Table 14.2.3.2.1_P6m**). Results of the Efficacy FAS (Dose 2) in SARS-CoV-2 naïve subjects were consistent with the results of the Efficacy PPS.

11.1.1.4.2 *Vaccine Efficacy in SARS-CoV-2 naïve subjects by risk of severe COVID-19 (6-month follow-up)*

A presence of medical conditions associated with high risk of severe COVID-19 appeared not to affect VE against COVID-19 of any severity. Vaccine efficacy was 57.5% (95% CI: 40.2–70.1) for subjects with high risk of severe COVID-19 whereas for subjects at low risk of severe COVID-19, it was 48.5% (95% CI: 38.8–56.8). Similarly, VE against moderate to severe COVID-19 was 72.1% (95% CI: 39.2–88.4) and 66.7% (95% CI: 46.3–80.0), in subjects at high and low risk of severe COVID-19, respectively. Vaccine efficacy against severe COVID-19 was 100% in both cohorts (Table 41 and Table 42).

Table 41 Vaccine Efficacy against RT-PCR-confirmed COVID-19 in SARS-CoV-2-naïve Subjects with High Risk of Severe COVID-19 (Efficacy PPS – 6-month follow-up)

	SCB-2019 (N=1080)	Placebo (N=1004)	% VE (95% CI)
No. of subjects at risk of endpoint:	1080	1004	
Cumulative follow up period (person.years):	339.1	294.0	
Endpoints related to Secondary Objective#3	**No. of subjects with endpoint case**		
Any severity	52	106	57.5 (40.2–70.1)
Moderate-to-severe	9	28	72.1 (39.2–88.4)
Severe	0	10	100.0 (61.3–100.0)
Hospitalization due to COVID-19	0	8	100.0 (49.2–100.0)

Source: **Table 14.2.3.4.4_P6m**. Follow-up period was from 14 days after Dose 2 to the end of the surveillance period. Vaccine efficacy (VE) = 100×(1 minus the ratio of incidence rates [IR] in the Vaccine and Placebo arms). IR = number (No.) of subjects with endpoint case per cumulative follow-up.

Table 42 Vaccine Efficacy against RT-PCR-confirmed COVID-19 in SARS-CoV-2-Naïve Subjects with Low Risk of Severe COVID-19 (Efficacy PPS – 6-month follow-up)

	SCB-2019 (N=5256)	Placebo (N=5212)	% VE (95% CI)
No. of subjects at risk of endpoint	5251	5208	
Cumulative follow up period (person.years):	1563.7	1499.0	
Endpoints related to Secondary Objective#3	**No. of subjects with endpoint case**		
Any severity	204	380	48.5 (38.8–56.8)
Moderate-to-severe	24	69	66.7 (46.3–80.0)
Severe	0	10	100.0 (57.2–100.0)
Hospitalization due to COVID-19	1	11	91.3 (40.0–99.8)

Source: **Table 14.2.3.4.4_P6m**. Follow-up period was from 14 days after Dose 2 to the end of the surveillance period. Vaccine efficacy (VE) = 100×(1 minus the ratio of incidence rates [IR] in the Vaccine and Placebo arms). IR = number (No.) of subjects with endpoint case per cumulative follow-up.

11.1.1.4.3 *Vaccine Efficacy in SARS-CoV-2-exposed Subjects (6-month follow-up)*

In SARS-CoV-2-exposed subjects in the Efficacy-FAS (Dose 2), and from 14 days after Dose 2 to the cutoff date, vaccine efficacy against COVID-19 of any severity was 71.6% (95%CI 60.2–80.1; Table 43). Vaccine efficacy against moderate-to-severe COVID-19 was similar - 74.3% (95% CI: 19.2–93.8). No cases of severe COVID-19 and COVID-19 cases leading to hospitalization, were reported in SARS-CoV-2-exposed subjects.

In SARS-CoV-2-exposed subjects in the Efficacy FAS (Dose 2), the most frequent lineage of SARS-CoV-2 detected in the COVID-19 cases of any severity was the Delta lineage (Table 27). Vaccine efficacy against COVID-19 of any severity associated with the Delta lineage was 76.7% (95% CI 62.5–86.1; Table 43).

Table 43 Vaccine Efficacy against RT-PCR-confirmed COVID-19 in SARS-CoV-2-Exposed Subjects (Efficacy FAS [Dose 2] – 6-month follow-up analysis)

	SCB-2019 (N=6902)	Placebo (N=6839)	% VE (95% CI)
No. of subjects at risk of endpoint	6896	6834	
Cumulative follow up period (person.years):	2464.8	2380.0	
Endpoints related to Secondary Objective#3	**No. of subjects with endpoint case**		
Any severity	45	153	71.6 (60.2–80.1)
Moderate-to-severe	4	15	74.3 (19.2–93.8)
Severe	0	0	-
Hospitalization due to COVID-19	0	0	-
Any severity due to Delta VoC	22	91	76.7 (62.5, 86.1)

Source: **Table 14.2.3.7.2_P6m**. Follow-up period was from 14 days after Dose 2 to the end of the surveillance period. Vaccine efficacy (VE) = 100×(1 minus the ratio of incidence rates [IR] in the Vaccine and Placebo arms). IR = number (No.) of subjects with endpoint case per cumulative follow-up.

11.1.1.4.4 *Exploratory Efficacy Objective #1 – To explore the effect of SCB-2019 on the severity of COVID-19 using the National Early Warning Scoring 2 (NEWS2) score in subjects with COVID-19-associated hospitalization (6-month follow-up)*

For subjects with COVID-19–associated hospitalization from 14 days after Dose 2, the NEWS2 score was calculated during hospitalization. The maximum value of NEWS2 score was used for analysis.

In total, 12 subjects from the Placebo arm and 1 subject in the SCB-2019 arm in the Efficacy FAS [Dose 2]) had NEWS2 data available at the 1 December cutoff date. Mean NEWS2 score was 8.2 in the placebo group and 0 in the SCB-2019 group (**Table 14.2.5.1_P6m**).

Seven out of the twelve Placebo subjects (58.3%) had a total NEWS2 score of ≥5 (**Table 14.2.5.1_P6m**). A score of 5 or more represents the key threshold for urgent response for COVID-19 patients. No subjects from the SCB-2019 arm had a NEWS2 score of ≥5.

11.1.1.4.5 *Exploratory Efficacy Objective #3 –To explore the effect of SCB-2019 on the prevention of COVID-19 long-term sequelae (6-month follow up)*

No remarkable difference was observed between SCB-2019 and placebo recipients in the frequency of MAAEs and SAEs reported after a COVID-19 episode up to the cutoff date of 1 December 2021 (**Table 14.3.2.6c_P6m** and **Table 14.3.2.8c_P6m**). No long-term sequelae of COVID-19 were observed up to the cutoff date.

11.1.1.4.6 *Exploratory Efficacy Objective #4 – To explore the effect of SCB-2019 on the risk of disease enhancement, including but not limited to enhanced respiratory disease (6-month follow up)*

Results of the exploratory analysis of the effect of the SCB-2019 on the risk of disease enhancement in subjects without evidence of prior SARS-CoV-2 infection, and with RT-PCR-confirmed COVID-19 of any severity from 14 days after Dose 2 (Efficacy PPS) at the cutoff date of the 1 December 2021 are presented in Table 44.

The ratio of severe COVID-19 to COVID-19 of any severity was 0 for the SCB-2019 arm and 4.1 for the Placebo arm.

Table 44 Risk of Disease Enhancement in Subjects with RT-PCR-confirmed COVID-19 of any Severity from 14 Days after Dose 2 (Efficacy PPS – 6-month follow-up analysis)

	SCB-2019 (N=6336)	Placebo (N=6216)
Number of subjects with RT-PCR-confirmed COVID-19 of any severity from 14 days after dose 2	256	486
Number of subjects with RT-PCR-confirmed severe COVID-19 from 14 days after dose 2	0	20
Ratio of severe COVID-19 to COVID-19 of any severity (%)	0.0	4.1

Source: **Table 14.2.5.4.1_P6m**. Follow-up period was from 14 days after Dose 2 to the end of the surveillance period.

The total number of fatal cases reported in the study is 32 [9/ 15152 (0.1%) in the SCB-2019 group and 23/15147 (0.2%) in the placebo group] (**Table 14.2.5.4.2_P6m**).

Eleven fatal cases were associated with COVID-19: one case (0.0%) in the SCB-2019 group and 10 cases (0.1%) in the placebo group.

11.1.1.5 Subgroup Efficacy Analyses

11.1.1.5.1 *Primary Efficacy Analysis (cut-off date of 10 August 2021)*

11.1.1.5.1.1 Subgroup Analysis – VE against COVID-19 by Age (Efficacy PPS)

In subjects aged 60 years or over in the Efficacy PPS, vaccine efficacy against COVID-19 of any severity was 58.4% (95% CI −73.4 to 92.9; Table 45; **Table 14.2.4.1**). In the SCB-2019 arm, 3 endpoint cases were reported among the 121 subjects at risk; whereas in the Placebo arm, 8 endpoint cases were reported among 127 subjects at risk.

In subjects aged 18 to 59 years in the Efficacy PPS, vaccine efficacy against COVID-19 of any severity was 67.5% (95% CI 54.8 to 77.0; Table 45; **Table 14.2.4.1**). In the SCB-2019 arm, 49 endpoint cases were reported among the 5814 subjects at risk; whereas in the Placebo arm, 147 endpoint cases were reported among 5679 subjects at risk.

In subjects aged 65 years or over in the Efficacy PPS, no endpoint case was reported among the 53 subjects at risk in the SCB-2019 arm; whereas in the Placebo arm, 5 endpoint cases were reported among 61 subjects at risk (Table 45; **Table 14.2.4.1**).

In subjects aged 18 to 64 years in the Efficacy PPS, vaccine efficacy against COVID-19 of any severity was 66.2% (95% CI 53.4 to 75.8; Table 45; **Table 14.2.4.1**). In the SCB-2019 arm, 52 endpoint cases were reported among the 5882 subjects at risk; whereas in the Placebo arm, 150 endpoint cases were reported among 5745 subjects at risk.

Vaccine efficacy against moderate -to-severe or severe COVID-19 by age is presented in **Table 14.2.4.2** and **Table 14.2.4.3**, respectively.

The number of subjects in the older adult age groups (≥60 years or ≥65 years) was insufficient to draw statistical conclusions, but the efficacy estimate was in the same range as for the overall Efficacy PPS.

11.1.1.5.1.2 Subgroup Analysis – VE against COVID-19 by sex (Efficacy PPS)

In female subjects in the Efficacy PPS, vaccine efficacy against COVID-19 of any severity was 67.1% (95% CI 47.5 to 80.0; Table 45; **Table 14.2.4.1**). In the SCB-2019 arm, 25 endpoint

cases were reported among the 2703 subjects at risk; whereas in the Placebo arm, 72 endpoint cases were reported among 2569 subjects at risk.

In male subjects in the Efficacy PPS, vaccine efficacy against COVID-19 of any severity was 67.4% (95% CI 49.1 to 79.7; Table 45; **Table 14.2.4.1**). In the SCB-2019 arm, 27 endpoint cases were reported among the 3232 subjects at risk; whereas in the Placebo arm, 83 endpoint cases were reported among 3237 subjects at risk.

Vaccine efficacy against moderate -to-severe or severe COVID-19 by sex is presented in **Table 14.2.4.2** and **Table 14.2.4.3**, respectively. Overall results were consistent across the sexes.

11.1.1.5.1.3 Subgroup Analysis – VE against COVID-19 by Race (Efficacy PPS)

In Asian subjects in the Efficacy PPS, vaccine efficacy against COVID-19 of any severity was 69.1% (95% CI 50.6 to 81.3; Table 45; **Table 14.2.4.1**). In the SCB-2019 arm, 24 endpoint cases were reported among the 2154 subjects at risk; whereas in the Placebo arm, 78 endpoint cases were reported among 2145 subjects at risk.

In Black or African American subjects in the Efficacy PPS, vaccine efficacy against COVID-19 of any severity was 76.9% (95% CI -15.8 to 97.6; Table 45; **Table 14.2.4.1**). In the SCB-2019 arm, 2 endpoint cases were reported among the 702 subjects at risk; whereas in the Placebo arm, 8 endpoint cases were reported among 681 subjects at risk.

In White subjects in the Efficacy PPS, vaccine efficacy against COVID-19 of any severity was 54.1% (95% CI -12.3 to 82.8; Table 45; **Table 14.2.4.1**). In the SCB-2019 arm, 8 endpoint cases were reported among the 1737 subjects at risk; whereas in the Placebo arm, 17 endpoint cases were reported among 1660 subjects at risk.

In American Indian or Alaska Native subjects in the Efficacy PPS, vaccine efficacy against COVID-19 of any severity was 66.5% (95% CI 41.5 to 81.6; Table 45; **Table 14.2.4.1**). In the SCB-2019 arm, 18 endpoint cases were reported among the 1186 subjects at risk; whereas in the Placebo arm, 50 endpoint cases were reported among 1157 subjects at risk.

Vaccine efficacy against moderate-to-severe or severe COVID-19 by race is presented in **Table 14.2.4.2** and **Table 14.2.4.3**, respectively. Overall, efficacy results were consistent across races.

11.1.1.5.1.4 Subgroup Analysis – VE against COVID-19 by Country (Efficacy PPS)

In subjects from Brazil in the Efficacy PPS, vaccine efficacy against COVID-19 of any severity was 64.8% (95% CI −5.2 to 90.2; Table 45; **Table 14.2.4.1**). In the SCB-2019 arm, 5 endpoint cases were reported among the 2126 subjects at risk; whereas in the Placebo arm, 13 endpoint cases were reported among 2007 subjects at risk.

In subjects from Colombia in the Efficacy PPS, vaccine efficacy against COVID-19 of any severity was 65.1% (95% CI 39.8–80.5; Table 45; **Table 14.2.4.1**). In the SCB-2019 arm, 19 endpoint cases were reported among the 1224 subjects at risk; whereas in the Placebo arm, 51 endpoint cases were reported among 1200 subjects at risk.

In subjects from Philippines in the Efficacy PPS, vaccine efficacy against COVID-19 of any severity was 69.3% (95% CI 51.0–81.4; Table 45; **Table 14.2.4.1**). In the SCB-2019 arm, 24 endpoint cases were reported among the 2142 subjects at risk; whereas in the Placebo arm, 78 endpoint cases were reported among 2122 subjects at risk.

In subjects from South Africa in the Efficacy PPS, vaccine efficacy against COVID-19 of any severity was 59.0% (95% CI −38.4 to 90.5; Table 45; **Table 14.2.4.1**). In the SCB-2019 arm, 4 endpoint cases were reported among the 188 subjects at risk; whereas in the Placebo arm, 11 endpoint cases were reported among 200 subjects at risk.

In subjects from Belgium in the Efficacy PPS, no endpoint case was reported in 255 subjects at risk in the SCB-2019 arm; whereas in the placebo arm, 2 endpoint cases were reported in 277 subjects at risk.

Vaccine efficacy against moderate -to-severe or severe COVID-19 by country is presented in **Table 14.2.4.2** and **Table 14.2.4.3**, respectively. Overall, efficacy results were consistent across countries.

11.1.1.5.1.5 Subgroup Analysis – VE against COVID-19 by BMI (Efficacy PPS)

In subjects with BMI <30 in the Efficacy PPS, vaccine efficacy against COVID-19 of any severity was 67.6% (95% CI 53.7–77.7; Table 45; **Table 14.2.4.1**). In the SCB-2019 arm, 42 endpoint cases were reported among the 5054 subjects at risk; whereas in the Placebo arm, 128 endpoint cases were reported among 4987 subjects at risk.

In subjects with BMI ≥30 in the Efficacy PPS, vaccine efficacy against COVID-19 of any severity was 66.0% (95% CI 27.6–85.3; Table 45; **Table 14.2.4.1**). In the SCB-2019 arm, 10 endpoint cases were reported among the 880 subjects at risk; whereas in the Placebo arm, 27 endpoint cases were reported among 817 subjects at risk. Overall, efficacy results were consistent between subjects with BMI <30 and BMI ≥30.

Table 45 Vaccine Efficacy of RT-PCR-confirmed COVID-19 of any Severity – Subgroup Analyses (Efficacy PPS)

		No. of subjects at risk of endpoint	Cumulative follow up period (person.years)	No. of subjects with endpoint case	% VE (95% CI)
Age group					
≥18 to ≤64 years	**SCB-2019**	5882	511.0	52	66.2 (53.4-75.8)
	Placebo	5745	498.5	150	
≥65 years	**SCB-2019**	53	6.3	0	-
	Placebo	61	7.6	5	
≥18 to ≤59 years	**SCB-2019**	5814	502.3	49	67.5 (54.8-77.0)
	Placebo	5679	489.5	147	
≥60 years	**SCB-2019**	121	15.0	3	58.4 (-73.4-92.9)
	Placebo	127	16.7	8	
Sex					
Female	**SCB-2019**	2703	229.2	25	67.1 (47.5-80.0)
	Placebo	2569	217.0	72	
Male	**SCB-2019**	3232	288.1	27	67.4 (49.1-79.7)
	Placebo	3237	289.1	83	
Race					
American Indian/ Alaska Native	**SCB-2019**	1186	93.4	18	66.5 (41.5-81.6)
	Placebo	1157	86.9	50	
Asian	**SCB-2019**	2154	259.1	24	69.1 (50.6-81.3)
	Placebo	2145	260.3	78	
Black or African American	**SCB-2019**	702	39.1	2	76.9 (-15.8-97.6)
	Placebo	681	36.1	8	
White	**SCB-2019**	1737	114.0	8	54.1 (-12.3-82.8)
	Placebo	1660	111.3	17	
Country					
Belgium	**SCB-2019**	255	44.2	0	-
	Placebo	277	47.6	2	
Brazil	**SCB-2019**	2126	105.1	5	64.8 (-5.2-90.2)
	Placebo	2007	96.2	13	
Colombia	**SCB-2019**	1224	99.7	19	65.1 (39.8-80.5)
	Placebo	1200	93.5	51	
Philippines	**SCB-2019**	2142	257.9	24	69.3 (51.0-81.4)
	Placebo	2122	257.1	78	
South Africa	**SCB-2019**	188	10.4	4	59.0 (-38.4-90.5)
	Placebo	200	11.7	11	

Source: **Table 14.2.4.1**. Follow-up period was from 14 days after Dose 2 to the end of the surveillance period. Vaccine efficacy (VE) = 100×(1 minus the ratio of incidence rates [IR] in the Vaccine and Placebo arms). IR = number (No.) of subjects with endpoint case per cumulative follow-up.

11.1.1.5.2 *Six-month Follow-up Efficacy Analysis (cut-off date of 1 December 2021)*

Vaccine Efficacy against RT-PCR-confirmed COVID-19 by Age Group in the Efficacy PPS is presented in Table 46.

In subjects aged 60 years or over in the Efficacy PPS, vaccine efficacy against COVID-19 of any severity was 54.5% (95% CI: 18.2-75.5; **Table 14.2.4.1_P6m**).

In subjects aged 18 to 59 years in the Efficacy PPS, vaccine efficacy against COVID-19 of any severity was 50.1% (95% CI 41.5 to 57.6; **Table 14.2.4.1_P6m**).

In subjects aged 60 years or over in the Efficacy PPS, vaccine efficacy against moderate-to-severe COVID-19 was 88.0% (95% CI: 48.9-98.7; **Table 14.2.4.2_P6m**).

In subjects aged 18 to 59 years in the Efficacy PPS, vaccine efficacy against moderate-to-severe COVID-19 was 65.2% (95% CI 46.5 to 77.9; **Table 14.2.4.2_P6m**).

In subjects aged 60 years or over in the Efficacy PPS, vaccine efficacy against severe COVID-19 was 100.0% (95% CI: 33.3-100.0; **Table 14.2.4.3_P6m**).

In subjects aged 18 to 59 years in the Efficacy PPS, vaccine efficacy against severe COVID-19 was 100.0% (95% CI 69.1 to 100.0; **Table 14.2.4.3_P6m**).

Vaccine efficacy against COVID-19 of any severity, moderate -to-severe COVID-19, and severe COVID-19 by other age categories, sex, race, country, and BMI is presented in **Table 14.2.4.1_P6m**, **Table 14.2.4.2_P6m** and **Table 14.2.4.3_P6m**.

Overall, efficacy results were consistent across age groups, sexes, races, countries, and between subjects with BMI <30 and BMI ≥30.

Table 46 Vaccine Efficacy against RT-PCR-confirmed COVID-19 in SARS-CoV-2-Naïve Subjects by Age Group– (Efficacy PPS)

		No. of subjects at risk of endpoint	Cumulative follow up period (person.years)	No. of subjects with endpoint case	% VE (95% CI)
COVID-19 of any severity					
≥18 to ≤59 years	**SCB-2019**	6163	1843.1	236	50.1 (41.5-57.6)
	Placebo	6026	1733.1	445	
≥60 years	**SCB-2019**	123	47.0	18	54.5 (18.2-75.5)
	Placebo	132	45.2	38	
Moderate-to-severe COVID-19					
≥18 to ≤59 years	**SCB-2019**	6163	1843.1	30	65.2 (46.5-77.9)
	Placebo	6026	1733.1	81	
≥60 years	**SCB-2019**	123	47.0	2	88.0 (48.9-98.7)
	Placebo	132	45.2	16	
Severe COVID-19					
≥18 to ≤59 years	**SCB-2019**	6163	1843.1	0	100 (69.1-100.0)
	Placebo	6026	1733.1	13	
≥60 years	**SCB-2019**	123	47.0	0	100 (33.3-100.0)
	Placebo	132	45.2	7	

Source: **Table 14.2.4.1_P6m**, **Table 14.2.4.2_P6m**, **Table 14.2.4.3_P6m**. Follow-up period was from 14 days after Dose 2 to the end of the surveillance period.
Vaccine efficacy (VE) = 100×(1 minus the ratio of incidence rates [IR] in the Vaccine and Placebo arms). IR = number (No.) of subjects with endpoint case per cumulative follow-up.

11.1.1.6 Efficacy – Supplementary Analyses

11.1.1.7 Efficacy – Supplementary Analyses – Cutoff Date of 10 August 2021

As about half of the enrolled study population had evidence of prior SARS-CoV-2 infection and were excluded from the primary efficacy, key secondary and most of the secondary

analyses, supplementary analyses were conducted using Efficacy FAS (Dose 2) or Efficacy FAS (Dose 1) which includes both subjects with and without evidence of prior SARS-CoV-2 infection. In addition, efficacy analyses using the WHO classification of disease severity in Efficacy PPS was conducted as supplementary analysis.

11.1.1.7.1.1 Supplementary Analysis – VE against COVID-19 of any severity, moderate-to-severe COVID-19, severe COVID-19 and COVID-19 leading to hospitalization in Subjects With and Without Evidence of Prior SARS-CoV-2 Infection [Efficacy FAS (Dose 2)]

In the Efficacy FAS (Dose 2) at the cutoff date of the 10 August 2021, vaccine efficacy against COVID-19 of any severity was 66.7% (95% CI 55.5–75.4; **Table 14.2.3.7.3**). In the SCB-2019 arm, 63 endpoint cases were reported among the 12153 subjects at risk; whereas in the Placebo arm, 185 endpoint cases were reported among 11983 subjects at risk. Vaccine efficacy against moderate-to-severe COVID-19 disease was 82.5% (95% CI 60.3-93.4), against severe COVID-19 disease was 100.0% (95% CI 42.7-100.0) and against COVID-19 leading to hospitalization was 100.0% (95% CI 42.7-100.0) (**Table 14.2.3.7.3**). Results were consistent with the efficacy results in the Efficacy PPS.

11.1.1.7.1.2 Supplementary Analysis - VE after first dose in Subjects With and Without Evidence of Prior SARS-CoV-2 Infection [Efficacy FAS (Dose 1)]

In the Efficacy FAS [Dose 1], vaccine efficacy against COVID-19 of any severity with onset at least 14 days after first vaccination to second vaccination was 14.3% (95 CI −6.9 to 31.3), against moderate-to-severe COVID-19 was 14.5% (−44.5 to 49.8) and against severe COVID-19 was −0.2% (−7764.7 to 98.7) (**Table 14.2.3.7.9**).

11.1.1.7.1.3 Supplementary Analysis – VE against SARS-CoV-2 VOCs in Subjects With and Without Evidence of Prior SARS-CoV-2 Infection [Efficacy FAS (Dose2)]

In the Efficacy FAS (Dose 2) at the cutoff date of the 10 August 2021, vaccine efficacy against COVID-19 of any severity associated with the Delta lineage was 78.8% (95% CI 61.0–89.3; **Table 14.2.3.7.3**). In the SCB-2019 arm, 13 endpoint cases were reported among the 12153 subjects at risk; whereas in the Placebo arm, 60 endpoint cases were reported among 11983 subjects at risk.

In the Efficacy FAS (Dose 2), vaccine efficacy against COVID-19 of any severity associated with the Mu lineage was 60.2% (95% CI 17.1–82.2; **Table 14.2.3.7.3**). In the SCB-2019 arm, 11 endpoint cases were reported among the 12153 subjects at risk; whereas in the Placebo arm, 27 endpoint cases were reported among 11983 subjects at risk.

In the Efficacy FAS (Dose 2), vaccine efficacy against COVID-19 of any severity associated with the Gamma lineage was 91.9% (95% CI 45.0–99.8; **Table 14.2.3.7.3**). In the SCB-2019 arm, 1 endpoint case was reported among the 12153 subjects at risk; whereas in the Placebo arm, 12 endpoint cases were reported among 11983 subjects at risk.

Vaccine efficacy against moderate-to-severe COVID-19 associated with the Delta lineage was 83.7% (95% CI 44.2–96.9) and against the Mu lineage was 100% (17.0–100.0) (**Table 14.2.3.7.3**).

For moderate-to-severe COVID-19 associated with the Gamma lineage, no case of was reported among the 12153 subjects at risk in the SCB-2019 arm; and 1 case was reported among 11983 subjects at risk in the Placebo arm (**Table 14.2.3.7.3**).

11.1.1.7.1.1 Supplementary Analysis – VE by severity using WHO classification of disease severity

Using the WHO classification of disease severity in Efficacy PPS, the vaccine efficacy against RT-PCR-confirmed severe COVID-19 disease was 100.0% (95% CI 42.7–100.0), against moderate COVID-19 disease was 70.6% (95% CI 24.2–90.4) and against mild COVID-19 disease was 64.6 (95% CI 50.0–75.3) (**Table 14.2.5.6**). Results were consistent with the primary and key secondary efficacy analysis using protocol-specific categorization of COVID-19 severity.

11.1.1.7.2 *Efficacy – Supplementary Analyses – Cutoff Date of 1 December 2021 (6-month follow up)*

11.1.1.7.2.1 Supplementary Analysis - VE against COVID-19 of any severity, moderate-to-severe COVID-19, severe COVID-19 and COVID-19 leading to hospitalization in Subjects With and Without Evidence of Prior SARS-CoV-2 Infection (Efficacy FAS [Dose 2]).

In the Efficacy FAS (Dose 2) at the cutoff date of the 1 December 2021, vaccine efficacy against COVID-19 of any severity was 55.1% (95% CI 48.4–61.0; **Table 14.2.3.7.3_P6m**). Vaccine efficacy against moderate-to-severe COVID-19 was 68.4% (95% CI 53.9-78.9), against severe COVID-19 was 100.0% (95% CI 80.7-100.0) and against COVID-19 leading to hospitalization was 95.0% (95% CI 68.4-99.9) (**Table 14.2.3.7.3_P6m**). Results were consistent with the efficacy results in the Efficacy PPS.

11.1.1.7.2.2 Supplementary Analysis - VE against SARS-CoV-2 VOCs in Subjects With and Without Evidence of Prior SARS-CoV-2 Infection [Efficacy FAS (Dose2)].

In the Efficacy FAS (Dose 2) at the data cut off of the 1 December 2021, vaccine efficacy against COVID-19 of any severity associated with the Delta lineage was 56.7% (95% CI 47.5–64.4; **Table 14.2.3.7.3_P6m**).

In the Efficacy FAS (Dose 2), vaccine efficacy against COVID-19 of any severity associated with the Mu lineage was 62.3% (95% CI 29.8–80.7; **Table 14.2.3.7.3_P6m**).

In the Efficacy FAS (Dose 2), vaccine efficacy against COVID-19 of any severity associated with the Gamma lineage was 88.8% (95% CI 52.7–98.7; **Table 14.2.3.7.3_P6m**).

Vaccine efficacy against moderate-to-severe COVID-19 associated with the Delta lineage was 66.0% (95% CI 43.2–80.4) and against the Mu lineage was 100% (18.9–100.0) (**Table 14.2.3.7.3_P6m**).

For moderate-to-severe COVID-19 associated with the Gamma lineage, no case of was reported among the 13293 subjects at risk in the SCB-2019 arm; and 3 cases was reported among 13107 subjects at risk in the Placebo arm (**Table 14.2.3.7.3_P6m**).

Results were consistent with the efficacy results in the Efficacy PPS.

11.1.1.7.2.3 Supplementary Analysis – VE by severity using WHO classification of disease severity

Using the WHO classification of disease severity in Efficacy PPS, the vaccine efficacy against RT-PCR-confirmed severe COVID-19 was 100.0% (95% CI 80.9–100.0), against moderate COVID-19 was 54.4% (95% CI 28.9–71.3) and against mild COVID-19 was 47.3% (95% CI 37.8–55.4) (**Table 14.2.5.6_P6m**). Results were consistent with the results of efficacy analysis using protocol-specific categorization of COVID-19 severity.

11.1.1.7.3 *Efficacy – Sensitivity Analysis*

Five sensitivity analyses were performed for the study.

A first sensitivity analysis was conducted for the primary efficacy endpoint. Overall, 207 cases were included in the per-protocol primary efficacy analysis with the cutoff date of 10 August 2021, whereas the cut-off date for the efficacy was defined as the date when 150 RT-PCR confirmed cases were reported. A sensitivity analysis for primary efficacy endpoint was conducted for the first 150 reported cases and results (VE=67.7%, 95.72% CI=52.2-78.6%) were consistent (**Table 14.2.1.1.2** and **Table 14.2.1.1**).

The second sensitivity analysis was performed by applying a Cox proportional hazard model, including treatment group as a fixed variable, age and risk of severe COVID-19 as covariates and country as a stratification factor, to estimate the impact of covariates to vaccine efficacy.

Based on the Efficacy PPS by Cox proportional hazard model by PPS-Efficacy (6-month follow-up analysis), vaccine efficacy against COVID-19 of any severity was 50.7% (95%CI 42.7, 57.7; **Table 14.2.5.7.1_P6m**); vaccine efficacy against moderate-to-severe COVID-19 was 68.1% (95%CI 53.2, 78.8, **Table 14.2.5.7.2_P6m**), vaccine efficacy against COVID-19 of any severity due to Delta was 50.8% (95%CI 39.4, 60.2, **Table 14.2.5.7.3_P6m**); which were all consistent with the results produced previously (**Table14.2.1.1_P6m**, **Table 14.2.2.1_P6m**, **Table 14.2.3.7_P6m**).

The third sensitivity analysis was missing data imputation. 129 subjects (in the PPS, 72 from SCB-2019 group, 57 from placebo group) who reported suspected COVID-19 symptoms with onset 14 days post dose 2 but not RT-PCR confirmed, were considered missing data. A multiple imputation with assumption of missing at random (MAR) and a fully conditional specification (FCS) logistic model (treatment group as a fixed variable, country as a covariate) was used to impute the RT-PCR results.

With the imputation 1000 time run, the average efficacy against COVID-19 of any severity was 50.3% (100% of LL of 95%CI >30%, **Table 14.2.5.8_P6m**). This analysis shows the conclusion of vaccine efficacy against COVID-19 of any severity remains the same.

A fourth sensitivity analysis was performed for the primary efficacy analysis (cut-off date of 10 August 2021), and the 6-month follow-up analysis (cut-off date of 1 Dec 2021) with the correct application of the censoring rule (using unblinding report and other authorized COVID-19 vaccines administration as recorded on concomitant medication eCRF page) for all subjects (see details in Section 9.8). Refer to **Table 14.2.1.1_Sen4, Table 14.2.2.1_Sen4, Table 14.2.3.2_Sen4, Table 14.2.3.7_Sen4** for the Primary analysis – Efficacy PPS (cut-off date 10 August 2021); **Table 14.2.1.1_P6m_Sen4, Table 14.2.2.1_P6m_Sen4, Table 14.2.3.2_P6m_Sen4, Table 14.2.3.7_P6m_Sen4** for the Six month follow up – Efficacy PPS (cut-off date 1 December 2021); **Table 14.2.3.7.2_Sen4** for the Primary analysis – Efficacy FAS with evidence of prior SARS-CoV-2 infection (Dose 2) (cut-off date 10 August 2021); **Table 14.2.3.7.2_P6m_Sen4** for the Six month follow up – Efficacy FAS with evidence of prior SARS-CoV-2 infection (Dose 2) (cut-off date 1 Dec 2021). Efficacy results for the PPS - Efficacy and the FAS-Efficacy populations for both the primary analysis and the 6-month follow-up analysis are similar to the original results for the primary endpoint.

A fifth sensitivity analysis (re-analysis) was performed for the primary efficacy analysis (cut-off date of 10 August 2021), and the 6-month follow-up analysis (cut-off date of 1 Dec 2021) with the correct application of the censoring rule (as per fourth sensitivity analysis) and accounting for cases determined to be inconsistent with the study protocol case definition (according to the intensity assessment: mild, moderate, severe; and cases with start date earlier than 14 days post second dose). The re-analyzed efficacy results by Efficacy PPS and the Efficacy FAS populations for both the primary analysis and the 6-month follow-up analysis were similar to the original results for the primary endpoint. For the primary analysis, vaccine efficacy against COVID-19 of any severity in the Efficacy PPS was 64.4% (95.72% CI: 50.3–74.9); and, for the 6-month follow-up analysis, vaccine efficacy was 50.4% (95.72% CI: 42.0–57.6).

Refer to **Table 14.2.1.1_S, Table 14.2.2.1_S, Table 14.2.3.2_S, Table 14.2.3.7_S,** and **Table 14.2.4.1_S** for the Primary analysis – Efficacy PPS (cut-off date 10 August 2021); **Table 14.2.1.1_P6m_S, Table 14.2.2.1_P6m_S, Table 14.2.3.2_P6m_S, Table 14.2.3.7_P6m_S,** and **Table 14.2.4.1_P6m_S** for the Six month follow up – Efficacy PPS (cut-off date 1 December 2021); **Table 14.2.3.7.2_S** for the Primary analysis – Efficacy FAS with evidence of prior SARS-CoV-2 infection (Dose 2) (cut-off date 10 August 2021); **Table 14.2.3.7.2_P6m_S** for the Six month follow up – Efficacy FAS with evidence of prior SARS-CoV-2 infection (Dose 2) (cut-off date 1 Dec 2021). Efficacy results for the PPS - Efficacy and the FAS-Efficacy populations for both the primary analysis and the 6-month follow-up analysis are consistent with the original results for the primary endpoint.

11.1.2 Analysis of Immunogenicity Results

11.1.2.1 Immunogenicity results – primary vaccination series

The immunogenicity of SCB-2019 was evaluated in the Immunogenicity PPS for the secondary objective. As about half of the enrolled study population had evidence of prior SARS-CoV-2 infection and were excluded from the Immunogenicity PPS analysis, a supplementary analysis was also performed in the Immunogenicity FAS, in the subgroups defined by prior evidence of SARS-CoV-2 infection. The Immunogenicity PPS and Immunogenicity FAS were both subsets of the Phase-2 cohort (see Section 10.1.2).

Immunogenicity data are presented in **Table 14.3.3.1.1** to **14.3.4.8.**

11.1.2.1.1 *Secondary Immunogenicity Objective –the immunogenicity of SCB-2019 in adult by prototype SARS-CoV-2 neutralization assay*

Table 47 presents the immunogenicity results as measured by prototype SARS-CoV-2 neutralization assay (expressed as IU/ml) at 21 days post Dose 1 (Day 22) and 14 days-post Dose 2 (Day 36) in subjects without and with evidence of prior SARS-CoV-2 infection.

In SARS-CoV-2–naïve subjects (Immunogenicity PPS), at Day 22, the GMT was 16 (N=215), the GMFR was 1.2 (N=212) and the SCR was 4% (9/212) in the SCB-2019 recipients. At Day 36, the GMT was 224 (N=220) and the corresponding GMFR at Day 36 was 17.5 (N=217), and the percentage of SCB-2019 recipients who seroconverted (i.e., the SCR) was 82% (179/217). At Day 36, 97% (213/220) of SCB-2019 recipients had titers ≥LLoQ. By contrast, in the placebo recipients, the GMTs at Days 1, 22 and 36 were 12 (N=27), 13 (N=28) and 13

(N=28), respectively; and were similar to the baseline titer in the SCB-2019 recipients (13, N=219).

In baseline SARS-CoV-2-exposed subjects (Immunogenicity FAS), in the SCB-2019 recipients at Day 22, the GMT was 1276 (N=118) and higher than a GMT of 26 (N=118) at baseline (Day 1). The corresponding GMFR at Day 22 was 48.3 (N=118), and the SCR was 92% (109/118). At Day 36, 2 weeks after the 2nd dose, the GMT was 1831 (N=118), the GMFR was 69.3 (N=118) and the SCR was 98% (116/118). At Day 36, 100% (118/118) of SCB-2019 recipients had titers ≥LLoQ.

In baseline SARS-CoV-2–naïve subjects, 2 doses of SCB-2019 were immunogenic, whereas in baseline SARS-CoV-2-exposed subjects, a single dose of SCB-2019 showed significant boosting effect, in terms of the neutralizing antibodies.

11.1.2.1.2 *Secondary Immunogenicity Objective –the immunogenicity of SCB-2019 in adults by pseudovirus SARS-CoV-2 neutralization assay*

Table 48 presents the immunogenicity results as measured by pseudovirus SARS-CoV-2 neutralization assay (expressed as IU/ml) at 21 days post Dose 1 (Day 22) and 14 days-post Dose 2 in subjects without and with evidence of prior SARS-CoV-2 infection.

In SARS-CoV-2 naïve subjects (Immunogenicity PPS), at Day 22 the GMT was 23 (N=214), the GMFR was 1.5 (N=212) and the SCR was 8% (16/212). At Day 36, the GMT was 540 (N=220) and the corresponding GMFR at Day 36 was 34.1 (N=218), and the SCR was 94% (204/218). At Day 36, 98% (216/220) of SCB-2019 recipients had titers ≥LLoQ. By contrast, in the placebo recipients, the GMTs at Days 1, 22 and 36 were 16 (N=27), 16 (N=28) and 20 (N=28), respectively; were similar to each other, and were similar to the baseline titer in the SCB-2019 recipients (16, N=219).

In SARS-CoV-2-exposed subjects (Immunogenicity FAS), at Day 22, the GMT of SCB-2019 recipients was 1560 (N=118) and higher than a GMT of 48 (N=119) at baseline (Day 1). The corresponding GMFR at Day 22 was 32.4 (N=118), and the SCR was 91% (107/118). At Day 36, 2 weeks after the 2nd dose, the GMT was 2192 (N=119), the GMFR was 46.0 (N=119) and the SCR was 96% (114/119). At Day 36, 100% (119/119) of SCB-2019 recipients had titers ≥LLoQ.

Results as measured by pseudovirus SARS-CoV-2 neutralization assay were consistent with the prototype neutralization assay (Section 11.1.2.1.1); in SARS-CoV-2–naïve subjects, 2 doses of SCB-2019 were immunogenic, whereas in SARS-CoV-2-exposed adults, a single dose of SCB-2019 showed significant boosting effect.

Table 47 Study CLO-SCB-2019-003: Immunogenicity of SCB-2019 as Measured by VNA with Prototype Virus (MN50, expressed as IU/ml) per PPS and FAS Populations

Time point	Endpoint	No Evidence of Prior SARS-CoV-2 Infection (Immunogenicity-PPS)				Evidence of Prior SARS-CoV-2 Infection (Immunogenicity-FAS)			
		SCB-2019 (N=381)		Placebo (N=47)		SCB-2019 (N=235)		Placebo (N=28)	
		N_e	Value (95% CI)	N_e	Value (95% CI)	N_e	Value (95% CI)	N_e	Value (95% CI)
Day 1	Mean GMT, IU/ml	219	12.7 (12.6-12.9)	27	12.5 (-)	118	26.4 (22.3-31.3)	18	32.7 (16.3-65.8)
	≥LLoQ, %	219	0.9 (0.1-3.3)	27	0.0 (0.0-12.8)	118	44.1 (34.9-53.5)	18	38.9 (17.3-64.3)
Day 22	Mean GMT, IU/ml	215	15.7 (14.1-17.5)	28	12.8 (12.4-13.3)	118	1276.1 (999.3-1629.7)	18	42.1 (20.6-86.0)
	GMFR	212	1.2 (1.1-1.4)	27	1.0 (1.0-1.1)	118	48.3 (36.9-63.2)	18	1.3 (0.7-2.3)
	SCR, %	212	4.2 (2.0-7.9)	27	0.0 (0.0-12.8)	118	92.4 (86.0-96.5)	18	5.6 (0.1-27.3)
	≥LLoQ, %	215	9.3 (5.8-14.0)	28	0.0 (0.0-12.3)	118	97.5 (92.7-99.5)	18	61.1 (35.7-82.7)
Day 36	Mean GMT, IU/ml	220	224 (194.0-258.7)	28	12.8 (12.4-13.3)	118	1831.4 (1545.9-2169.8)	18	58.3 (26.6- 128.1)
	GMFR	217	17.5 (15.1-20.2)	27	1.0 (1.0-1.1)	118	69.3 (55.9-85.8)	18	1.8 (0.8-3.8)
	SCR, %	217	82.5 (76.8-87.3)	27	0.0 (0.0-12.8)	118	98.3 (94.0-99.8)	18	16.7 (3.6-41.4)
	≥LLoQ, %	220	96.8 (93.6-98.7)	28	0.0 (0-12.3)	118	100.0 (96.9-100.0)	18	61.1 (35.7-82.7)

Source: **Table 14.3.3.1.1**, **Table 14.3.3.2.1**, **Table 14.3.3.3.1**, **Table 14.3.3.4.4**, **Table 14.3.3.4.1**, **Table 14.3.3.4.2**, **Table 14.3.3.4.3** and **Table 14.3.3.4.6**.
CI = confidence interval; FAS = full analysis set; GMFR = geometric mean fold rise; GMT = geometric mean titer; LLoQ = lower limit of quantification; N = number of subjects in treatment group; N_e = Number of subjects with results available at the visit; PPS = Per protocol set; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SCB-2019 = CpG 1018/alum-adjuvanted SCB-2019 vaccine; SCR = seroconversion rate; VNA = virus neutralization assay.
Titer value measured as below lower limit of quantification (LLoQ) of the assay is set to LLoQ/2. Seroconversion was defined as ≥4-fold rise in the titer at the post-baseline time point from the baseline titer (Day 1) or from the lower limit of quantification (LLoQ) of the assay if that baseline titer was below the LLoQ.

Table 48 Study CLO-SCB-2019-003: Immunogenicity of SCB-2019 as Measured by VNA with Pseudovirus (NT50, expressed as IU/ml) per PPS and FAS Populations

Time point	Endpoint	No Evidence of Prior SARS-CoV-2 Infection (Immunogenicity-PPS)				Evidence of Prior SARS-CoV-2 Infection (Immunogenicity-FAS)			
		SCB-2019 (N=381)		Placebo (N=47)		SCB-2019 (N=235)		Placebo (N=28)	
		N_e	Value (95% CI)	N_e	Value (95% CI)	N_e	Value (95% CI)	N_e	Value (95% CI)
Day 1	Mean GMT, IU/ml	219	15.8 (15.5-16.1)	27	15.5 (-)	119	47.6 (39.2-57.9)	18	56.7 (27.5-117.0)
	≥LLoQ, %	219	1.4 (0.3-4.0)	27	0.0 (0.0-12.8)	119	63.9 (54.6-72.5)	18	61.1 (35.7-82.7)
Day 22	Mean GMT, IU/ml	214	22.9 (20.1-26.1)	28	15.9 (15.0-16.9)	118	1559.9 (1266.3-1921.5)	18	70.8 (32.5-154.3)
	GMFR	212	1.5 (1.3-1.6)	27	1.0 (1.0-1.1)	118	32.4 (25.0-42.2)	18	1.2 (0.6-2.4)
	SCR, %	212	7.5 (4.4-12.0)	27	0.0 (0.0-12.8)	118	90.7 (83.9-95.3)	18	5.6 (0.1-27.3)
	≥LLoQ, %	214	19.6 (14.5-25.6)	28	3.6 (0.1-18.3)	118	97.5 (92.7-99.5)	18	66.7 (41.0-86.7)
Day 36	Mean GMT, IU/ml	220	540.3 (472.8-617.5)	28	20.3 (14.8-27.8)	119	2192.1 (1931.7-2487.6)	18	74.0 (35.3-155.0)
	GMFR	218	34.1 (29.8-39.0)	27	1.3 (1.0-1.8)	119	46.0 (37.1-57.0)	18	1.3 (0.7-2.5)
	SCR, %	218	93.6 (89.5-96.4)	27	3.7 (0.1-19.0)	119	95.8 (90.5-98.6)	18	11.1 (1.4-34.7)
	≥LLoQ, %	220	98.2 (95.4-99.5)	28	14.3 (4.0-32.7)	119	100.0 (96.9-100.0)	18	66.7 (41.0-86.7)

Source: **Table 14.3.3.1.1**, **Table 14.3.3.2.1**, **Table 14.3.3.3.1**, **Table 14.3.3.4.4**, **Table 14.3.3.4.1**, **Table 14.3.3.4.2**, **Table 14.3.3.4.3** and **Table 14.3.3.4.6**.
CI = confidence interval; FAS = full analysis set; GMFR = geometric mean fold rise; GMT = geometric mean titer; LLoQ = lower limit of quantification; N = number of subjects in treatment group; N_e = Number of subjects with results available at the visit; PPS = Per protocol set; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SCB-2019 = CpG 1018/alum-adjuvanted SCB-2019 vaccine; SCR = seroconversion rate; VNA = virus neutralization assay.
Titer value measured as below lower limit of quantification (LLoQ) of the assay is set to LLoQ/2. Seroconversion was defined as ≥4-fold rise in the titer at the post-baseline time point from the baseline titer (Day 1) or from the lower limit of quantification (LLoQ) of the assay if that baseline titer was below the LLoQ.

11.1.2.1.3 *Secondary Immunogenicity Objective –the immunogenicity of SCB-2019 vaccine in adults by SCB-2019 binding ELISA*

Table 49 presents the immunogenicity results as measured by SCB-2019 binding ELISA (expressed as IU/ml) at 21 days post-Dose 1 (Day 22) and 14 days post-Dose 2 (Day 36) in subjects without and with evidence of prior SARS-CoV-2 infection.

In SARS-CoV-2 naïve subjects (Immunogenicity PPS), at Day 22 the GMT was 0.7 (N=367), the GMFR was 1.4 (N=364) and the SCR was 4% (15/364). At Day 36, the GMT was 8.4 (N=378) and the corresponding GMFR at Day 36 was 16.6 (N=375), and the SCR was 78% (291/375). At Day 36, 94% (356/378) of SCB-2019 recipients had titers ≥LLoQ.

In SARS-CoV-2-exposed subjects (Immunogenicity FAS), at Day 22, the GMT of SCB-2019 recipients was 31.3 (N=233) and higher than a GMT of 0.9 (N=233) at baseline (Day 1). The corresponding GMFR at Day 22 was 34.5 (N=231), and the SCR was 90% (207/231). At Day 36, the GMT was 34.5 (N=235), the GMFR was 37.9 (N=233) and the SCR was 94% (218/233). At Day 36, 99% (233/235) of SCB-2019 recipients had titers ≥LLoQ.

Results as measured by SCB-2019 binding ELISA were consistent with the prototype SARS-CoV-2 neutralization assay; in SARS-CoV-2–naïve subjects, 2 doses of SCB-2019 were immunogenic, whereas in SARS-CoV-2-exposed adult, a clear booster effect was observed with a single dose of SCB-2019 immunization.

11.1.2.1.4 *Secondary Immunogenicity Objective –the immunogenicity of SCB-2019 vaccine in adults by ACE2 competitive ELISA*

Table 50 presents the immunogenicity results as measured by ACE2 competitive ELISA (expressed as CP50) at 21 days post Dose 1 (Day 22) and 14 days post-Dose 2 in subjects without and with evidence of prior SARS-CoV-2 infection.

In SARS-CoV-2 naïve subjects (Immunogenicity PPS), at Day 22, the GMT was 17.3 (N=213), the GMFR was 1.4 (N=212) and the SCR was 6% (13/212). At Day 36, the GMT was 258 (N=183) and the corresponding GMFR at Day 36 was 20.1 (N=182), and the SCR was 63% (115/182). At Day 36, 65% (119/183) of SCB-2019 recipients had titers ≥LLoQ.

In SARS-CoV-2-exposed subjects (Immunogenicity FAS), at Day 22, the GMT of SCB-2019 recipient was 1261.9 (N=109) and higher than a GMT of 27.5 (N=113) at baseline (Day 1). The corresponding GMFR at Day 22 was 45.5 (N=105), and the SCR was 76% (80/105). At Day 36, 2 weeks after the 2nd dose, the GMT was 992.5 (N=109), the GMFR was 33.8 (N=106) and the SCR was 76% (81/106). At Day 36, 86% (94/109) of SCB-2019 recipients had titers ≥LLoQ.

Results as measured by ACE2-competitive ELISA were consistent with the prototype SARS-CoV-2 neutralization assay; in-SARS-CoV-2–naïve subjects, 2 doses of SCB-2019 were immunogenic, whereas in SARS-CoV-2-exposed adults, a single dose of SCB-2019 showed a clear booster effect.

Table 49 Study CLO-SCB-2019-003: Immunogenicity of SCB-2019 as Measured by SCB-2019– Antibody Binding Assay (EC50, expressed as IU/ml) per PPS and FAS Populations

Time point	Endpoint	No Evidence of Prior SARS-CoV-2 Infection (Immunogenicity-PPS)				Evidence of Prior SARS-CoV-2 Infection (Immunogenicity-FAS)			
		SCB-2019 (N=381)		Placebo (N=47)		SCB-2019 (N=235)		Placebo (N=28)	
		N_e	Value (95% CI)	N_e	Value (95% CI)	N_e	Value (95% CI)	N_e	Value (95% CI)
Day 1	Mean GMT, IU/ml	375	0.5 (0.5-0.5)	46	0.5 (0.5-0.5)	233	0.9 (0.8-1.0)	27	1.0 (0.7-1.6)
	≥LLoQ, %	375	1.3 (0.4-3.1)	46	4.3 (0.5-14.8)	233	36.5 (30.3-43.0)	27	40.7 (22.4-61.2)
Day 22	Mean GMT, IU/ml	367	0.7 (0.6-0.8)	46	0.6 (0.5-0.6)	233	31.3 (26.6-36.9)	27	1.1 (0.7-1.8)
	GMFR	364	1.4 (1.2-1.5)	45	1.1 (1.0-1.2)	231	34.5 (28.5-41.7)	27	1.1 (0.8-1.6)
	SCR, %	364	4.1 (2.3-6.7)	45	2.2 (0.1-11.8)	231	89.6 (84.9-93.2)	27	3.7 (0.1-19.0)
	≥LLoQ, %	367	19.3 (15.4-23.8)	46	6.5 (1.4-17.9)	233	98.3 (95.7-99.5)	27	44.4 (25.5-64.7)
Day 36	Mean GMT, IU/ml	378	8.4 (7.5-9.5)	47	0.5 (0.5-0.6)	235	34.5 (30.3-39.3)	27	1.2 (0.7-1.9)
	GMFR	375	16.6 (14.6-18.8)	46	1.0 (1.0-1.1)	233	37.9 (32.1-44.9)	27	1.2 (0.8-1.7)
	SCR, %	375	77.6 (73.0-81.7)	46	0 (0-7.7)	233	93.6 (89.6-96.4)	27	3.7 (0.1-19.0)
	≥LLoQ, %	378	94.2 (91.3-96.3)	47	4.3 (0.5-14.5)	235	99.1 (97.0-99.9)	27	44.4 (25.5-64.7)

Source: **Table 14.3.3.1.1**, **Table 14.3.3.2.1**, **Table 14.3.3.3.1**, **Table 14.3.3.4.4**, **Table 14.3.3.4.1**, **Table 14.3.3.4.2**, **Table 14.3.3.4.3** and **Table 14.3.3.4.6** (≥LLoQ, FAS - S+).

CI = confidence interval; FAS = full analysis set; GMFR = geometric mean fold rise; GMT = geometric mean titer; LLoQ = lower limit of quantification; N = number of subjects in treatment group; N_e = Number of subjects with results available at the visit; PPS = Per protocol set; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SCB-2019 = CpG 1018/alum-adjuvanted SCB-2019 vaccine; SCR = seroconversion rate.

Titer value measured as below lower limit of quantification (LLOQ) of the assay is set to LLOQ/2. Seroconversion was defined as ≥4-fold rise in the titer at the post-baseline time point from the baseline titer (Day 1) or from the lower limit of quantification (LLoQ) of the assay if that baseline titer was below the LLoQ.

Table 50 Study CLO-SCB-2019-003: Immunogenicity of SCB-2019 as Measured by ACE2-receptor-binding Abs Assay (CP50, expressed as 1/dilution) per PPS and FAS Populations

Time point	Endpoint	No Evidence of Prior SARS-CoV-2 Infection (Immunogenicity-PPS)				Evidence of Prior SARS-CoV-2 Infection (Immunogenicity-FAS)			
		SCB-2019 (N=381)		Placebo (N=47)		SCB-2019 (N=235)		Placebo (N=28)	
		N_e	Value (95% CI)	N_e	Value (95% CI)	N_e	Value (95% CI)	N_e	Value (95% CI)
Day 1	Mean GMT, CP50	213	12.6 (12.4-12.8)	27	12.5 (-)	113	27.5 (20.1-37.7)	18	47.9 (17.6-130.3)
	≥LLoQ, %	213	0.5 (0.0-2.6)	27	0.0 (0.0-12.8)	113	23.0 (15.6-31.9)	18	33.3 (13.3-59.0)
Day 22	Mean GMT, CP50	213	17.3 (14.7-20.5)	27	12.9 (12.1-13.7)	109	1261.9 (801.1-1987.7)	17	30.1 (9.6-94.1)
	GMFR	212	1.4 (1.2-1.6)	27	1.0 (1.0-1.1)	105	45.5 (27.8-74.6)	17	0.7 (0.2-2.8)
	SCR, %	212	6.1 (3.3-10.3)	27	0.0 (0.0-12.8)	105	76.2 (66.9-84.0)	17	11.8 (1.5-36.4)
	≥LLoQ, %	213	8.0 (4.7-12.5)	27	3.7 (0.1-19.0)	109	84.4 (76.2-90.6)	17	17.6 (3.8-43.4)
Day 36	Mean GMT, CP50	183	258.0 (178.5-372.8)	27	12.5 (-)	109	992.5 (681.6-1445.4)	18	41.3 (13.7-124.5)
	GMFR	182	20.1 (13.9-29.0)	27	1.0 (-)	106	33.8 (19.7-58.0)	18	0.9 (0.3-2.8)
	SCR, %	182	63.2 (55.7-70.2)	27	0.0 (0.0-12.8)	106	76.4 (67.2-84.1)	18	11.1 (1.4-34.7)
	≥LLoQ, %	183	65.0 (57.6-71.9)	27	0.0 (0.0-12.8)	109	86.2 (78.3-92.1)	18	27.8 (9.7-53.5)

Source: **Table 14.3.3.1.1**, **Table 14.3.3.2.1**, **Table 14.3.3.3.1**, **Table 14.3.3.4.4**, **Table 14.3.3.4.1**, **Table 14.3.3.4.2**, **Table 14.3.3.4.3** and **Table 14.3.3.4.6** (≥LLoQ, FAS - S+).

ACE2, angiotensin-converting enzyme 2; CI = confidence interval; FAS = full analysis set; GMFR = geometric mean fold rise; GMT = geometric mean titer; LLoQ = lower limit of quantification; N = number of subjects in treatment group; N_e = Number of subjects with results available at the visit; PPS = Per protocol set; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SCB-2019 = CpG 1018/alum-adjuvanted SCB-2019 vaccine; SCR = seroconversion rate.

Titer value measured as below lower limit of quantification (LLoQ) of the assay is set to LLoQ/2. Seroconversion was defined as ≥4-fold rise in the titer at the post-baseline time point from the baseline titer (Day 1) or from the lower limit of quantification (LLoQ) of the assay if that baseline titer was below the LLoQ.

11.1.2.1.5 *Immunogenicity Subgroup Analysis by Age, Sex, Race, Country, and risk of severe COVID-19*

Subgroup Analysis by Age, Sex, Race, Country, and risk of severe COVID-19 are presented in **Table 14.3.4.1** (GMT), **Table 14.3.4.2** (Geometric Mean Fold Rise), **Table 14.3.4.3** (SCR) and **Table 14.3.4.4** (subjects with antibody response ≥LLoQ).

It appeared that:

- A lower immunogenicity in subjects 60 years of age and above as compared to 18 to 59 age group
- No consistent difference in immunogenicity between male and female subjects
- A trend to higher immunogenicity in Asian subjects compared to other
- A trend to higher immunogenicity in subjects recruited in the Philippines, compared to other countries
- A trend to a lower immune response in subjects with comorbidities associated with a high risk of severe COVID-19 as compared to healthy subjects

11.1.2.1.6 *Exploratory immunogenicity objective #1 –To assess the CMI of SCB-2019 vaccine in a subset of Phase 2 adult subjects*

CMI data corresponds to different conditions (S1 subunit peptide pool and S2 subunit peptide pool from the SARS-CoV-2 spike protein, Trimer Tag, Gly repeats, CICP domain peptide pools, negative control and positive control) by visit in the FAS. The peptide pool of each stimulant is composed of a multimer (formed by 15 monomers) with 11 overlapping amino acids, expanding through the entire length of the stimulant.

11.1.2.1.6.1 S1 and S2 subunit peptide pools

An overview of the CMI response following *in vitro* stimulation with SARS-CoV-2 S1 and S2 subunit peptide pools is presented in Table 51 and Figure 6.

The percentage of CD4+ T cells expressing for IL-2, IFNγ and TNFα was increased from baseline (Day 1, pre-vaccination) to 2 weeks post dose 2 (Day 36, post-vaccination) when stimulated with both S1 and S2 subunit peptide pools for subjects who received 2 doses of SCB-2019. This Th1 response against S1 subunit tended to be higher than that against S2 subunit of the SARS-CoV-2 spike protein.

No changes in the expression of IL-2, IFNγ and TNFα were observed between Day 1 and Day 36 in the Placebo group after *in vitro* stimulation with S1 or S2 subunit peptide pools.

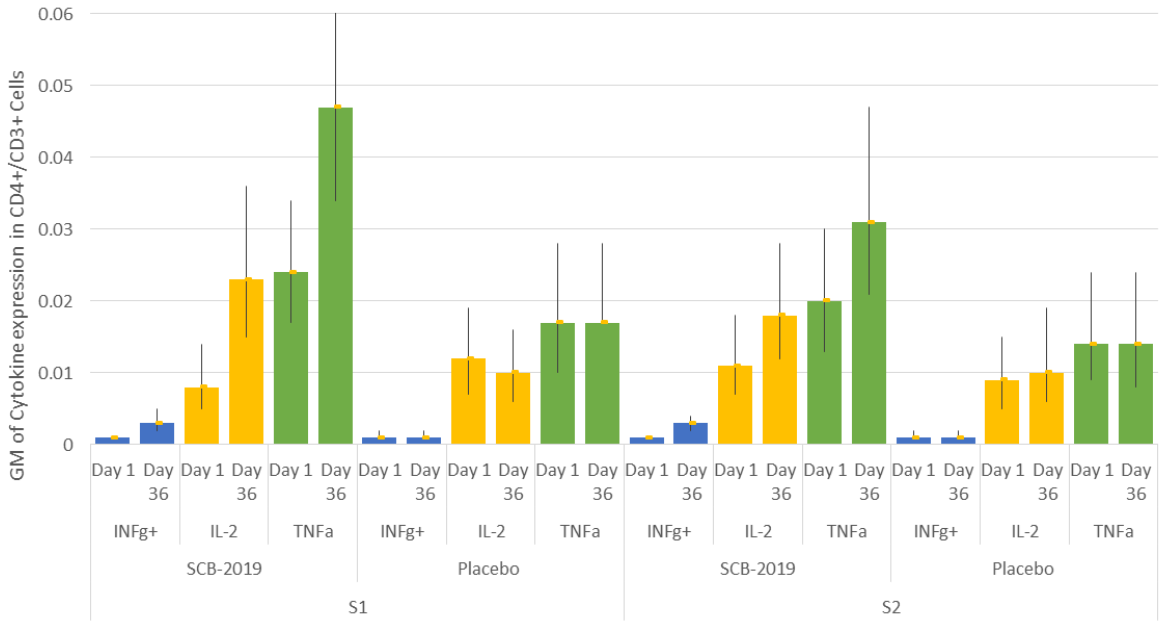
No changes in the expression of IL-4, IL-5, IL-17 and CD154 were observed between Day 1 and Day 36 in both SCB-2019 and Placebo groups after *in vitro* stimulation of PBMCs with S1 or S2 subunit peptides.

Table 51 CMI Response to SCB-2019 After *in Vitro* Stimulation with SARS-CoV-2 S1 and S2 Peptide Pools as Measured by Geometric Means of Cytokine Expression in CD4+/CD3+ Cells - FAS Population

		SCB2019 (N = 70)				Placebo (N = 67)			
Cytokine	**Visit**	**n**	**median**	**GMT**	**95% CI**	**n**	**median**	**GMT**	**95% CI**
S1									
INFγ+	V1	67	0.001	0.001	(0.001-0.001)	64	0.002	0.001	(0.001-0.002)
	V3	66	0.005	0.003	(0.002-0.005)	60	0.002	0.001	(0.001-0.002)
IL-2+	V1	67	0.015	0.008	(0.005-0.014)	64	0.017	0.012	(0.007-0.019)
	V3	66	0.030	0.023	(0.015-0.036)	60	0.014	0.010	(0.006-0.016)
TNFα+	V1	67	0.036	0.024	(0.017-0.034)	64	0.029	0.017	(0.010-0.028)
	V3	66	0.053	0.047	(0.034-0.064)	60	0.022	0.017	(0.017-0.028)
IL-4+	V1	67	0.018	0.016	(0.011-0.024)	64	0.024	0.020	(0.014-0.030)
	V3	66	0.022	0.023	(0.017-0.031)	60	0.022	0.026	(0.018-0.036)
IL-5+	V1	67	0.015	0.012	(0.009-0.017)	64	0.017	0.011	(0.007-0.018)
	V3	66	0.014	0.011	(0.008-0.016)	60	0.019	0.017	(0.012-0.025)
IL-17+	V1	67	0.021	0.018	(0.013-0.025)	64	0.023	0.024	(0.018-0.031)
	V3	66	0.025	0.021	(0.016-0.028)	60	0.024	0.022	(0.015-0.033)
CD154+	V1	67	4.350	4.201	(3.762-4.691)	64	4.206	4.236	(3.779-4.748)
	V3	66	4.158	4.239	(3.821-4.702)	60	4.365	4.241	(3.728-4.824)
S2									
INFγ+	V1	65	0.002	0.001	(0.001-0.002)	64	0.001	0.001	(0.000-0.001)
	V3	65	0.004	0.003	(0.002-0.004)	59	0.001	0.001	(0.001-0.002)
IL-2+	V1	65	0.021	0.011	(0.007-0.018)	64	0.015	0.009	(0.005-0.015)
	V3	65	0.029	0.018	(0.012-0.028)	59	0.016	0.010	(0.006-0.019)
TNFα+	V1	65	0.026	0.020	(0.013-0.030)	64	0.023	0.014	(0.009-0.024)
	V3	65	0.041	0.031	(0.021-0.047)	59	0.020	0.014	(0.008-0.024)
IL-4+	V1	65	0.022	0.015	(0.010-0.024)	64	0.018	0.010	(0.006-0.017)
	V3	65	0.023	0.022	(0.016-0.031)	59	0.021	0.025	(0.017-0.037)
IL-5+	V1	65	0.013	0.012	(0.008-0.017)	64	0.017	0.010	(0.006-0.016)
	V3	65	0.012	0.011	(0.008-0.016)	59	0.018	0.018	(0.013-0.026)
IL-17+	V1	65	0.023	0.024	(0.017-0.033)	64	0.030	0.025	(0.018-0.034)
	V3	65	0.024	0.027	(0.022-0.033)	59	0.020	0.017	(0.011-0.025)
CD154+	V1	65	3.993	3.950	(3.535-4.414)	64	4.527	4.356	(3.856-4.921)
	V3	65	4.167	4.293	(3.791-4.860)	59	4.236	4.052	(3.573-4.595)

Source: **Table 14.3.3.8**.
CI = Confidence Interval; CMI = cell-mediated immunity; FAS = full analysis set; GMT = geometric mean titer; IL-2, -4, -5, -17 = interleukin-2, -4, -5, -17; INFγ = interferon gamma; N = number of subjects in treatment group; n = number of subjects with results available at the visit; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SCB-2019 = CpG 1018/Alum-adjuvanted SCB-2019 vaccine, TNFα = tumor necrosis factor alpha.

Figure 6 CMI Response to SCB-2019 After *in Vitro* Stimulation with SARS-CoV-2 S1 and S2 Peptide Pools as Measured by Geometric Means of Cytokine Expression in CD4+/CD3+ Cells - FAS Population



Source: **Table 14.3.3.8**.
CMI = cell-mediated immunity; FAS = full analysis set; GM = geometric mean; IL-2, = interleukin-2; INFγ = interferon gamma; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SCB-2019 = CpG 1018/Alum-adjuvanted SCB-2019 vaccine, TNFa = tumor necrosis factor alpha.

11.1.2.1.6.2 Trimer Tag, Gly repeats and CICP domain peptide pools

An overview of the CMI response following *in vitro* stimulation with Trimer Tag, Gly repeats and CICP domain peptides is presented in Table 52.

No changes in the expression of IL-2, IFNγ, TNFα, IL-4, IL-5, IL-17 and CD154 were observed between Day 1 and Day 36 in either the SCB-2019 or the Placebo group after *in vitro* stimulation with Trimer Tag, Gly repeats and CICP domain peptide pools.

Table 52 CMI Response to SCB-2019 After *in Vitro* stimulation with Trimer Tag, Gly Repeat, and CICP Peptide Pools as Measured by Geometric Means of Cytokine Expression in CD4+/CD3+ Cells - FAS population

		SCB2019 (N = 70)				Placebo (N = 67)			
Cytokine	**Visit**	**n**	**median**	**GMT**	**95% CI**	**n**	**median**	**GMT**	**95% CI**
Trimer Tag									
INFγ+	V1	63	0.000	0.000	(0.000-0.001)	63	0.001	0.001	(0.000-0.001)
	V3	65	0.002	0.001	(0.001-0.001)	59	0.002	0.002	(0.001-0.001)
IL-2+	V1	63	0.016	0.010	(0.006-0.017)	63	0.013	0.008	(0.005-0.014)
	V3	65	0.014	0.010	(0.007-0.016)	59	0.010	0.007	(0.004-0.011)
TNFα+	V1	63	0.019	0.015	(0.010-0.022)	63	0.016	0.009	(0.005-0.016)
	V3	65	0.022	0.018	(0.012-0.027)	59	0.014	0.009	(0.005-0.016)
IL-4+	V1	63	0.026	0.023	(0.017-0.031)	63	0.028	0.029	(0.022-0.039)
	V3	65	0.025	0.028	(0.022-0.038)	59	0.028	0.024	(0.016-0.037)
IL-5+	V1	63	0.015	0.012	(0.008-0.016)	63	0.019	0.014	(0.009-0.021)
	V3	65	0.013	0.010	(0.007-0.015)	59	0.015	0.011	(0.008-0.017)
IL-17+	V1	63	0.020	0.019	(0.013-0.028)	63	0.026	0.020	(0.014-0.029)
	V3	65	0.021	0.023	(0.018-0.029)	59	0.017	0.012	(0.007-0.020)
CD154+	V1	63	3.944	3.972	(3.470-4.547)	63	4.304	4.278	(3.775-4.848)
	V3	65	4.681	4.166	(3.646-4.761)	59	4.076	3.51	(2.388-5.158)
Gly repeats									
INFγ+	V1	61	0.001	0.001	(0.000-0.001)	59	0.001	0.001	(0.000-0.001)
	V3	63	0.001	0.001	(0.000-0.001)	57	0.001	0.001	(0.000-0.001)
IL-2+	V1	61	0.015	0.012	(0.008-0.019)	59	0.012	0.009	(0.005-0.015)
	V3	63	0.015	0.011	(0.007-0.017)	57	0.013	0.007	(0.004-0.012)
TNFα+	V1	61	0.022	0.015	(0.010-0.023)	59	0.018	0.011	(0.006-0.018)
	V3	63	0.024	0.017	(0.011-0.026)	57	0.015	0.008	(0.005-0.015)
IL-4+	V1	61	0.023	0.019	(0.013-0.028)	59	0.026	0.026	(0.018-0.037)
	V3	63	0.023	0.025	(0.019-0.033)	57	0.029	0.025	(0.016-0.040)
IL-5+	V1	61	0.014	0.012	(0.008-0.018)	59	0.019	0.015	(0.011-0.022)
	V3	63	0.014	0.014	(0.010-0.019)	57	0.016	0.011	(0.007-0.018)
IL-17+	V1	61	0.021	0.025	(0.021-0.031)	59	0.025	0.021	(0.014-0.031)
	V3	63	0.018	0.015	(0.010-0.022)	57	0.022	0.016	(0.010-0.026)
CD154+	V1	61	4.169	3.773	(3.254-4.373)	59	4.085	3.965	(3.486-4.511)
	V3	63	4.170	4.136	(3.618-4.729)	57	4.395	3.993	(3.491-4.567)

Table 52 CMI Response to SCB-2019 After *in Vitro* stimulation with Trimer Tag, Gly Repeat, and CICP Peptide Pools as Measured by Geometric Means of Cytokine Expression in CD4+/CD3+ Cells - FAS population (continued)

		SCB2019 (N = 70)				Placebo (N = 67)			
Cytokine	**Visit**	**n**	**median**	**GMT**	**95% CI**	**n**	**median**	**GMT**	**95% CI**
CICP									
INFγ+	V1	62	0.001	0.001	(0.000-0.001)	60	0.001	0.001	(0.000-0.001)
	V3	64	0.002	0.001	(0.001-0.001)	59	0.000	0.001	(0.000-0.001)
IL-2+	V1	62	0.014	0.008	(0.005-0.014)	60	0.015	0.009	(0.006-0.015)
	V3	64	0.014	0.010	(0.006-0.016)	59	0.011	0.006	(0.003-0.011)
TNFα+	V1	62	0.021	0.018	(0.012-0.027)	60	0.018	0.010	(0.006-0.018)
	V3	64	0.024	0.021	(0.014-0.029)	59	0.016	0.009	(0.006-0.016)
IL-4+	V1	62	0.019	0.014	(0.009-0.021)	60	0.025	0.020	(0.012-0.032)
	V3	64	0.025	0.024	(0.018-0.033)	59	0.026	0.026	(0.017-0.038)
IL-5+	V1	62	0.015	0.011	(0.007-0.016)	60	0.017	0.011	(0.007-0.019)
	V3	64	0.015	0.015	(0.011-0.019)	59	0.017	0.014	(0.009-0.021)
IL-17+	V1	62	0.020	0.017	(0.012-0.024)	60	0.019	0.014	(0.008-0.022)
	V3	64	0.020	0.019	(0.014-0.025)	59	0.020	0.012	(0.007-0.022)
CD154+	V1	62	4.255	4.237	(3.668-4.893)	60	4.433	4.296	(3.835-4.813)
	V3	64	4.630	4.429	(3.882-5.053)	59	4.594	4.348	(3.879-4.874)

Source: **Table 14.3.3.8**.
CI = Confidence Interval; CICP = C-propeptide domain of pro-collagen; CMI = cell-mediated immunity; FAS = full analysis set; Gly = Glycine; GMT = geometric mean titer; IL-2, -4, -5, -17 = interleukin-2, -4, -5, -17; INFγ = interferon gamma; N = number of subjects in treatment group; n = number of subjects with results available at the visit; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SCB-2019 = CpG 1018/Alum-adjuvanted SCB-2019 vaccine, TNFα = tumour necrosis factor alpha.

11.1.2.1.7 *Exploratory immunogenicity objective #2 – To explore neutralization of new emergent mutants of SARS-CoV-2 by SCB-2019 vaccine-elicited sera*

Immunogenicity data for cross neutralization using a virus-neutralizing assay (VNA) by visit in the per-protocol set (PPS) and full analysis set (FAS) for subjects with evidence of prior SARS-CoV-2 infection are presented in **Table 14.3.3.1.1.1a** and **Table 14.3.3.1.1.2a**, respectively. The Immunogenicity PPS and Immunogenicity FAS were both subsets of the Phase 2 cohort. Details on the overall population are provided in Section 10.1.2.

Neutralizing immune responses, as expressed in MN_{50} (1/dilution), against nine SARS-CoV-2 variants, Alpha, Beta, Gamma, Delta, Mu and Omicron (BA.1, BA.2, BA.4 and BA.5) in serum

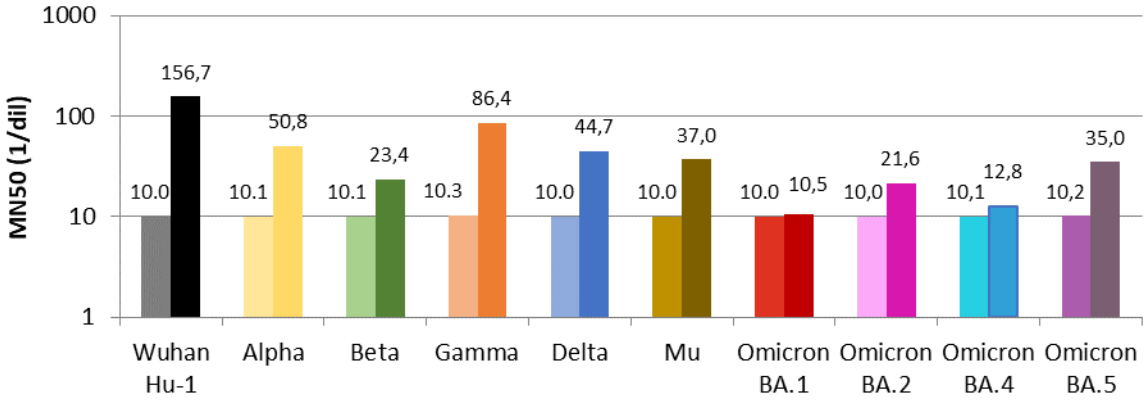
samples collected at Baseline and Day 36 (14 days post-Dose 2), are presented in Figure 7 and Figure 8.

For subjects without evidence of prior SARS-CoV-2 infection, a neutralizing response was observed against all variants except for Omicron BA.1 and BA.4. At Baseline, the geometric mean titers (GMTs) against Alpha, Beta, Gamma, Delta, Mu and Omicron ranged from 10.0 to 10.3 as compared to the Wuhan-Hu-1 prototype for which the GMT was 10.0. On Day 36, the GMTs against Alpha, Beta, Gamma, Delta, Mu, Omicron BA.1, Omicron BA.2, Omicron BA.4 and Omicron BA.5 were 50.8, 23.4, 86.4, 44.7, 37.0, 10.5, 21.6, 12.8 and 35.0, respectively as compared to the Wuhan-Hu-1 prototype for which GMT was 156.7.

For subjects with evidence of prior SARS-CoV-2 infection, a neutralizing response was observed against all variants. At Baseline, the GMTs against Alpha, Beta, Gamma, Delta, Mu, Omicron ranged from 10.0 to 20.4 as compared to the Wuhan-Hu-1 prototype for which GMT was 22.5. On Day 36, the GMTs against Alpha, Beta, Gamma, Delta, Mu, Omicron BA.1, Omicron BA.2, Omicron BA.4 and Omicron BA.5 were 602.9, 760.8, 1442.6, 1069.9, 1220.2, 208.1, 441.9, 152.5 and 984.1, respectively as compared to the Wuhan-Hu-1 prototype for which the GMT was 1705.1.

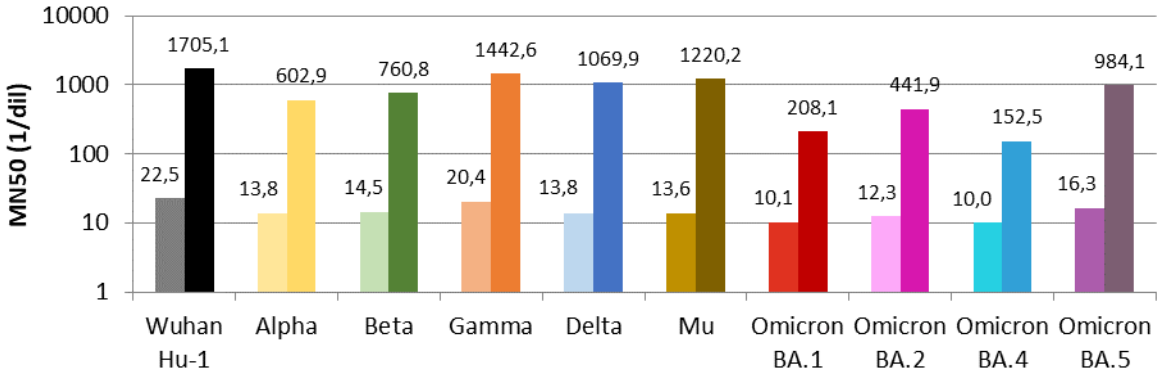
For subjects with and without evidence of prior SARS-CoV-2 infection, cross-reactivity with the Omicron BA.1 and BA.4 variants was lower as compared with the other variants.

Figure 7 **Neutralizing antibody titers against SARS-CoV-2 variants as measured by virus neutralization assay at Baseline and Day 36 (2 weeks post-Dose 2) in SARS-CoV-2 Naïve (PPS) individuals (N=49) after primary vaccination**



Source: **Table 14.3.3.1.1.1a**.
Note: Baseline data are presented in the left-hand column whereas Day 36 data are presented in the right-hand column. "Omicron BA.1" is labelled as "Omicron" in the source tables. PPS = per-protocol set; FAS = full analysis set; GMT = geometric mean titer; VNA = virus-neutralizing assay.

Figure 8 Neutralizing antibody titers against SARS-CoV-2 variants as measured by virus neutralization assay at Baseline and Day 36 (2 weeks post-Dose 2) in SARS-CoV-2 Exposed (FAS) individuals (N=29) after primary vaccination



Source: **Table 14.3.3.1.1.2a**.
Note: Baseline data are presented in the left-hand column whereas Day 36 data are presented in the right-hand column. "Omicron BA.1" is labelled as "Omicron" in the source tables. PPS = per-protocol set; FAS = full analysis set; GMT = geometric mean titer; VNA = virus-neutralizing assay.

11.1.2.1.8 *Exploratory immunogenicity objective #3 – To explore potential immune correlates of protection based on binding antibody ELISA and/or other immunological assays*
The data are not yet available at the time of this CSR writing.

11.1.2.2 Immunogenicity results – 6-month persistence data

Antibody persistence following SCB-2019 vaccination was evaluated in the PPS-Immunogenicity Persistence which includes baseline SARS-CoV-2-naïve subjects who received study vaccination according to the protocol, did not received other COVID-19 vaccines, did no report RT-PCR-positive SARS-CoV-2 infection and did not have major protocol deviations during the study period. In total, 189 subjects were included in the PPS Immunogenicity Persistence.

To eliminate impact of asymptomatic SARS-CoV-2 infection on antibody titers, all subjects in the PPS – Immunogenicity Persistence were tested for presence of anti-N antibodies at Visit 3 (Day 36) and Visit 4 (Day 205).

Based on this we have defined three different analysis sets for PPP-Immunogenicity Persistence:

- PPS immunogenicity Persistence (anti-N negative at both Visits 3 and 4). In total, 33 subjects were included in this population;
- PPS Immunogenicity Persistence (regardless of anti-N results);
- PPS Immunogenicity Persistence (anti-N negative at Visit 3 and anti-N positive at Visit 4).

Immunogenicity results for PPS Immunogenicity Persistence (anti-N negative) are presented in **Table 14.3.3.1.1a_P6m**, **Table 14.3.3.2.1a_P6m**, **Table 14.3.3.3.1a_P6m**, **Table 14.3.3.4.4a_P6m**.

Immunogenicity results for the overall PPS Immunogenicity Persistence population (regardless of anti-N results) are presented in **Table 14.3.3.1.1_P6m**, **Table 14.3.3.2.1_P6m**, **Table 14.3.3.3.1_P6m**, **Table 14.3.3.4.4_P6m**.

Immunogenicity results for PPS Immunogenicity Persistence population with evidence of asymptomatic SARS-CoV-2 infection during the study period (anti-N negative at Visit 3 and anti-N positive at Visit 4) are presented in **Table 14.3.3.1.1b_P6m**, **Table 14.3.3.2.1b_P6m**, **Table 14.3.3.3.1b_P6m**, **Table 14.3.3.4.4b_P6m**.

The analysis of antibody persistence was also performed in the Immunogenicity FAS, in the subgroups defined by prior evidence of SARS-CoV-2 infection at baseline. As these subjects were exposed to SARS-CoV-2 prior to the enrollment, anti-N test was not used to control asymptomatic SARS-CoV-2 infection during the study period.

Immunogenicity results for FAS Immunogenicity Persistence (with Evidence of Prior SARS-CoV-2 Infection) are presented in **Table 14.3.3.4.1_P6m**, **Table 14.3.3.4.2_P6m**, **Table 14.3.3.4.3_P6m** and **Table 14.3.3.4.6_P6m**.

Immunogenicity results with an alternative definition for seroconversion rate (SCR defined as ≥4-fold rise in titer from baseline) are presented in **Table 14.3.3.6.1_P6m** for PPS Immunogenicity Persistence (regardless of anti-N results), **Table 14.3.3.6.1a_P6m** for PPS Immunogenicity Persistence (anti-N negative) and **Table 14.3.3.6.2.1_P6m** for FAS Immunogenicity Persistence (with Evidence of Prior SARS-CoV-2 Infection).

11.1.2.2.1 *Antibody persistence following SCB-2019 vaccination in adult subjects as measured by prototype SARS-CoV-2 neutralization assay*

Table 53 presents the immunogenicity results as measured by prototype SARS-CoV-2 neutralization assay (expressed as IU/ml) at baseline (Day 1), 21 days post Dose 1 (Day 22), 14 days-post Dose 2 (Day 36), and 183 days post-Dose 2 (Day 205) in subjects without and with evidence of prior SARS-CoV-2 infection.

In SARS-CoV-2–naïve subjects (PPS – Immunogenicity Persistence [anti-N negative at both V3 and V4]) in the SCB-2019 recipients at Day 22, the GMT was 14.3 (N=33), the GMFR was 1.1 and the SCR was 3% (1/33) in the SCB-2019 recipients. At Day 36, the GMT was 279.9 (N=33) and the corresponding GMFR at Day 36 was 22.4, and the percentage of SCB-2019 recipients who seroconverted (i.e., the SCR) was 87.9% (29/33). At Day 36, 97% (32/33) of SCB-2019 recipients had titers ≥LLoQ. At Day 205, the GMT was 111.1 (N=33) and the corresponding GMFR at Day 205 was 8.9, and the percentage of SCB-2019 recipients who seroconverted (i.e., the SCR) was 45.5% (15/33). At Day 205, 90.9% (30/33) of SCB-2019 recipients had titers ≥LLoQ.

Only one subject from the Placebo arm was included in the PPS – Immunogenicity Persistence (anti-N negative) and remained seronegative during the study period up to Day 205.

In baseline SARS-CoV-2-exposed subjects (FAS Immunogenicity Persistence), in the SCB-2019 recipients at Day 22, the GMT was 1316.3 (N=87) and higher than a GMT of 25.6 (N=87) at baseline (Day 1). The corresponding GMFR at Day 22 was 51.4, and the SCR was 94.3% (82/87). At Day 36, 2 weeks after the 2nd dose, the GMT was 1803.1 (N=87), the GMFR was 70.4 and the SCR was 97.7% (85/87). At Day 36, 100% (87/87) of SCB-2019 recipients had titers ≥LLoQ.

At Day 205, 183 days after the 2nd dose, the GMT was 803.4 (N=82), the GMFR was 32.3 and the SCR was 93.9% (77/82). At Day 205, 100% (82/82) of SCB-2019 recipients still had titers ≥LLoQ.

In SARS-CoV-2-exposed placebo recipients, GMT were consistent at Day 1, Day 22 and Day 36 (37.5, 35.4 and 39.7, respectively) and increased up to 200.0 at Day 205, likely due to asymptomatic SARS-CoV-2 infection in a subset of participants.

In baseline SARS-CoV-2–naïve subjects without evidence of asymptomatic SARS-CoV-2 infection (anti-N negative), antibody decay was observed at 6 months after the primary vaccination to 40% of the peak level. In baseline SARS-CoV-2-exposed subjects, at 6 months post-vaccination the GMTs were lower as compared to Day 36 (45 % of the peak level) but the antibody level remained very high (GMT was 803.4). Nevertheless, the neutralizing antibodies remained high at 6 months post second dose of SCB-2019 vaccination for both baseline SARS-CoV-2-naïve or exposed subjects.

11.1.2.2.2 *Antibody persistence following SCB-2019 vaccination in adult subjects as measured by pseudovirus SARS-CoV-2 neutralization assay*

Table 54 presents the immunogenicity results as measured by pseudovirus SARS-CoV-2 neutralization assay (expressed as IU/ml) at Baseline (Day1), 21 days post Dose 1 (Day 22) and 14 days-post Dose 2 (Day 36), and 183 days post-Dose 2 (Day 205) in subjects without and with evidence of prior SARS-CoV-2 infection.

In SARS-CoV-2–naïve subjects (PPS – Immunogenicity Persistence [anti-N negative at both V3 and V4]) in the SCB-2019 recipients at Day 22 the GMT was 20.7 (N=33), the GMFR was 1.3 and the SCR was 3% (1/33). At Day 36, the GMT was 736.5 (N=33) and the corresponding GMFR at Day 36 was 47.5, and the SCR was 93.9% (31/33). At Day 36, 97% (32/33) of SCB-2019 recipients had titers ≥LLoQ.

At Day 205, the GMT was 105.5 (N=32) and the corresponding GMFR at Day 205 was 6.8, and the percentage of SCB-2019 recipients who seroconverted (i.e., the SCR) was 34.4% (11/32). At Day 205, 81.3% (26/32) of SCB-2019 recipients had titers ≥LLoQ.

Only one subject from the Placebo arm was included in PPS – Immunogenicity Persistence (anti-N negative) and remained seronegative during the study period up to Day 205.

In SARS-CoV-2-exposed subjects (Immunogenicity FAS), at Day 22, the GMT of SCB-2019 recipients was 1509.7 (N=88) and higher than a GMT of 45.5 (N=88) at baseline (Day 1). The corresponding GMFR at Day 22 was 33.2, and the SCR was 92% (81/88). At Day 36, 2 weeks after the 2nd dose, the GMT was 2087 (N=88), the GMFR was 45.8 and the SCR was 96.6% (85/88). At Day 36, 100% (88/88) of SCB-2019 recipients had titers ≥LLoQ.

At Day 205, the GMT was 752.2 (N=88) and the corresponding GMFR at Day 205 was 16.5, and the percentage of SCB-2019 recipients who seroconverted (i.e., the SCR) was 87.5% (77/88). At Day 205, 100% (88/88) of SCB-2019 recipients had titers ≥LLoQ.

In baseline SARS-CoV-2–naïve subjects without evidence of asymptomatic SARS-CoV-2 infection (anti-N negative), antibody decay was observed at 6 months after the primary vaccination to 14% of peak level. In baseline SARS-CoV-2-exposed subjects, at 6 months post-vaccination level of antibodies was 36% of peak level. Nevertheless, the neutralizing antibodies

remained high at 6 months post second dose of SCB-2019 vaccination for both baseline SARS-CoV-2-naïve or exposed subjects.

Results as measured by pseudovirus SARS-CoV-2 neutralization assay were consistent with the wild-type live SARS-CoV-2 neutralization assay in both SARS-CoV-2–naïve and SARS-CoV-2-exposed subjects.

Table 53 Study CLO-SCB-2019-003: Antibody Persistence after Vaccination as Measured by VNA with Prototype Virus (MN50, expressed as IU/ml) per PPS (anti-N negative) and FAS Populations

Time point	Endpoint	No Evidence of Prior SARS-CoV-2 Infection (PPS – Immunogenicity Persistence and anti-N negative at Visit 3 and Visit 4)				Evidence of Prior SARS-CoV-2 Infection (FAS – Immunogenicity Persistence)			
		SCB-2019 (N=33)		Placebo (N=1)		SCB-2019 (N=171)		Placebo (N=19)	
		N_e	Value (95% CI)	N_e	Value (95% CI)	N_e	Value (95% CI)	N_e	Value (95% CI)
Day 1	Mean GMT, IU/ml	33	12.5 (.-.)	1	12.5 (-)	87	25.6 (21.1-31.1)	12	37.5 (14.1-99.8)
	≥LLoQ, %	33	0.0 (0.0-10.6)	1	0.0 (0.0-97.5)	87	41.4 (30.9-52.4)	12	41.7 (15.2-72.3)
Day 22	Mean GMT, IU/ml	33	14.3 (12.2-16.8)	1	12.5 (-)	87	1316.3 (1009.5-1716.2)	12	35.4 (14.4-86.6)
	GMFR	33	1.1 (1.0-1.3)	1	1.0 (.-.)	87	51.4 (39.0-67.7)	12	0.9 (0.8-1.1)
	SCR, %	33	3.0 (0.1-15.8)	1	0.0 (0.0-97.5)	87	94.3 (87.1-98.1)	12	0.0 (0.0-26.5)
	≥LLoQ, %	33	9.1 (1.9-24.3)	1	0.0 (0.0-97.5)	87	98.9 (93.8-100.0)	12	50.0 (21.1-78.9)
Day 36	Mean GMT, IU/ml	33	279.9 (188.5-415.5)	1	12.5 (-)	87	1803.1 (1454.9-2234.6)	12	39.7 (16.0- 98.3)
	GMFR	33	22.4 (15.1-33.2)	1	1.0 (.-.)	87	70.4 (54.3-91.3)	12	1.1 (0.8-1.4)
	SCR, %	33	87.9 (71.8-96.6)	1	0.0 (0.0-97.5)	87	97.7 (91.9-99.7)	12	0.0 (0.0-26.5)
	≥LLoQ, %	33	97.0 (84.2-99.9)	1	0.0 (0.0-97.5)	87	100.0 (95.8-100.0)	12	50.0 (21.1-78.9)
Day 205	Mean GMT, IU/ml	33	111.1 (63.2-195.1)	1	12.5 (-)	82	803.4 (642.1-1005.1)	12	200.0 (60.8- 658.3)
	GMFR	33	8.9 (5.1-15.6)	1	1.0 (.-.)	82	32.3 (24.5-42.5)	12	5.3 (1.4-21.0)
	SCR, %	33	45.5 (28.1-63.6)	1	0.0 (0.0-97.5)	82	93.9 (86.3-98.0)	12	41.7 (15.2-72.3)
	≥LLoQ, %	33	90.9 (75.7-98.1)	1	0.0 (0.0-97.5)	82	100.0 (95.6-100.0)	12	75.0 (42.8-94.5)

Source: **Table 14.3.3.1.1a_P6m**, **Table 14.3.3.2.1a_P6m**, **Table 14.3.3.3.1a_P6m**, **Table 14.3.3.4.4a_P6m**, **Table 14.3.3.4.1_P6m**, **Table 14.3.3.4.2_P6m**, **Table 14.3.3.4.3_P6m** and **Table 14.3.3.4.6_P6m**.

CI= confidence interval; FAS= full analysis set; GMFR= geometric mean fold rise; GMT= geometric mean titer; LLoQ= lower limit of quantification; N= number of subjects in treatment group; N_e= Number of subjects with results available at the visit; PPS= Per protocol set; SARS-CoV-2= severe acute respiratory syndrome coronavirus 2; SCB-2019= CpG 1018/alum-adjuvanted SCB-2019 vaccine; SCR= seroconversion rate; VNA= virus neutralization assay.

Titer value measured as below lower limit of quantification (LLoQ) of the assay is set to LLoQ/2. Seroconversion was defined as ≥4-fold rise in the titer at the post-baseline time point from the baseline titer (Day 1) or from the lower limit of quantification (LLoQ) of the assay if that baseline titer was below the LLoQ.

Table 54 Study CLO-SCB-2019-003: Antibody Persistence after Vaccination as Measured by VNA with Pseudovirus (NT50, expressed as IU/ml) per PPS (anti-N negative) and FAS Populations

Time point	Endpoint	No Evidence of Prior SARS-CoV-2 Infection (PPS – Immunogenicity Persistence and anti-N negative at Visit 3 and Visit 4)				Evidence of Prior SARS-CoV-2 Infection (FAS – Immunogenicity Persistence)			
		SCB-2019 (N=33)		Placebo (N=1)		SCB-2019 (N=171)		Placebo (N=19)	
		N_e	Value (95% CI)	N_e	Value (95% CI)	N_e	Value (95% CI)	N_e	Value (95% CI)
Day 1	Mean GMT, IU/ml	33	15.5 (.-.)	1	15.5 (-)	88	45.5 (37.0-56.1)	12	67.4 (23.9-190.1)
	≥LLoQ, %	33	0.0 (0.0-10.6)	1	0.0 (0.0-97.5)	88	65.9 (55.0-75.7)	12	66.7 (34.9-90.1)
Day 22	Mean GMT, IU/ml	33	20.7 (15.8-27.1)	1	15.5 (-)	88	1509.7 (1192.6-1911.0)	12	56.0 (21.9-143.0)
	GMFR	33	1.3 (1.0-1.7)	1	1.0 (.-.)	88	33.2 (24.7-44.5)	12	0.8 (0.6-1.1)
	SCR, %	33	3.0 (0.1-15.8)	1	0.0 (0.0-97.5)	88	92.0 (84.3-96.7)	12	0.0 (0.0-26.5)
	≥LLoQ, %	33	18.2 (7.0-35.5)	1	0.0 (0.0-97.5)	88	97.7 (92.0-99.7)	12	58.3 (27.7-84.8)
Day 36	Mean GMT, IU/ml	33	736.5 (488.8-1109.6)	1	15.5 (-)	88	2087.0 (1787.1-2437.3)	12	54.4 (21.2-139.8)
	GMFR	33	47.5 (31.5-71.6)	1	1.0 (.-.)	88	45.8 (36.0-58.4)	12	0.8 (0.6-1.1)
	SCR, %	33	93.9 (79.8-99.3)	1	0.0 (0.0-97.5)	88	96.6 (90.4-99.3)	12	0.0 (0.0-26.5)
	≥LLoQ, %	33	97.0 (84.2-99.9)	1	0.0 (0.0-97.5)	88	100.0 (95.9-100.0)	12	58.3 (27.7-84.8)
Day 205	Mean GMT, IU/ml	32	105.5 (58.3-190.9)	1	15.5 (-)	88	752.2 (623.8-907.0)	12	212.3 (66.4-679.0)
	GMFR	32	6.8 (3.8-12.3)	1	1.0 (.-.)	88	16.5 (12.6-21.7)	12	3.1 (0.9-11.4)
	SCR, %	32	34.4 (18.6-53.2)	1	0.0 (0.0-97.5)	88	87.5 (78.7-93.6)	12	33.3 (9.9-65.1)
	≥LLoQ, %	32	81.3 (63.6-92.8)	1	0.0 (0.0-97.5)	88	100.0 (95.9-100.0)	12	83.3 (51.6-97.9)

Source: **Table 14.3.3.1.1a_P6m**, **Table 14.3.3.2.1a_P6m**, **Table 14.3.3.3.1a_P6m**, **Table 14.3.3.4.4a_P6m**, **Table 14.3.3.4.1_P6m**, **Table 14.3.3.4.2_P6m**, **Table 14.3.3.4.3_P6m** and **Table 14.3.3.4.6_P6m**.

CI= confidence interval; FAS= full analysis set; GMFR= geometric mean fold rise; GMT= geometric mean titer; LLoQ= lower limit of quantification; N= number of subjects in treatment group; N_e=Number of subjects with results available at the visit; PPS= Per protocol set; SARS-CoV-2= severe acute respiratory syndrome coronavirus 2; SCB-2019= CpG 1018/alum-adjuvanted SCB-2019 vaccine; SCR= seroconversion rate; VNA= virus neutralization assay.

Titer value measured as below lower limit of quantification (LLoQ) of the assay is set to LLoQ/2. Seroconversion was defined as ≥4-fold rise in the titer at the post-baseline time point from the baseline titer (Day 1) or from the lower limit of quantification (LLoQ) of the assay if that baseline titer was below the LLoQ.

11.1.2.2.3 *Antibody persistence following SCB-2019 vaccination in adult subjects as measured by SCB-2019 binding ELISA*

Table 55 presents the immunogenicity results as measured by SCB-2019 binding ELISA (expressed as IU/ml) at 21 days post-Dose 1 (Day 22) and 14 days post-Dose 2 (Day 36), and 183 days post-Dose 2 (Day 205) in subjects without and with evidence of prior SARS-CoV-2 infection.

In SARS-CoV-2–naïve subjects (PPS – Immunogenicity Persistence [anti-N negative at both V3 and V4]) in the SCB-2019 recipients at Day 22 the GMT was 0.8 (N=33), the GMFR was 1.7 and the seroconversion rate (SCR) was 3% (1/33). At Day 36, the GMT was 14.8 (N=33) and the corresponding GMFR at Day 36 was 29.9, and the SCR was 87.9% (29/33). At Day 36, 100% (33/33) of SCB-2019 recipients had titers ≥LLoQ.

At Day 205, the GMT was 2.1 (N=32) and the corresponding GMFR at Day 205 was 4.3, and the percentage of SCB-2019 recipients who seroconverted (i.e., the SCR) was 21.9% (7/32). At Day 205, 62.5% (20/32) of SCB-2019 recipients had titers ≥LLoQ.

Only one subject from the Placebo arm was included in PPS – Immunogenicity Persistence (anti-N negative) and remained seronegative during the study period up to Day 205.

In SARS-CoV-2-exposed subjects (Immunogenicity FAS), at Day 22, the GMT of SCB-2019 recipients was 32.9 (N=170) and higher than a GMT of 0.9 (N=170) at baseline (Day 1). The corresponding GMFR at Day 22 was 37.8, and the SCR was 91.1% (154/169). At Day 36, the GMT was 37.8 (N=171), the GMFR was 43.6 and the SCR was 95.9% (163/170). At Day 36, 100% (171/171) of SCB-2019 recipients had titers ≥LLoQ.

At Day 205, the GMT was 5.5 (N=166) and the corresponding GMFR at Day 205 was 6.3, and the percentage of SCB-2019 recipients who seroconverted (i.e., the SCR) was 55.2% (91/165). At Day 205, 99.4% (165/166) of SCB-2019 recipients had titers ≥LLoQ.

In baseline SARS-CoV-2–naïve subjects without evidence of asymptomatic SARS-CoV-2 infection (anti-N negative), antibody decay was observed at 6 months after the primary vaccination to 14% of peak level. In baseline SARS-CoV-2-exposed subjects, at 6 months post-vaccination level of antibodies was 15% of peak level. Nevertheless, the SCB-2019 binding antibodies remained high at 6 months post second dose of SCB-2019 vaccination for both baseline SARS-CoV-2 naive or exposed subjects.

11.1.2.2.4 *Antibody persistence following SCB-2019 vaccination in adult subjects as measured by ACE2 competitive ELISA*

Table 56 presents the immunogenicity results as measured by ACE2 competitive ELISA (expressed as CP50) at 21 days post Dose 1 (Day 22) and 14 days post-Dose 2, and 183 days post-Dose 2 (Day 205) in subjects without and with evidence of prior SARS-CoV-2 infection.

In SARS-CoV-2–naïve subjects (PPS – Immunogenicity Persistence (anti-N negative), at Day 22 the GMT was 22.7 (N=33), the GMFR was 1.8 and the SCR was 12.1% (4/33). At Day 36, the GMT was 364.1 (N=33) and the corresponding GMFR at Day 36 was 29.1, and the SCR was 71.4% (20/28). At Day 36, 71.4% (20/28) of SCB-2019 recipients had titers ≥LLoQ.

At Day 205, the GMT was 77.6 (N=33) and the corresponding GMFR at Day 205 was 6.2, and the percentage of SCB-2019 recipients who seroconverted (i.e., the SCR) was 36.4% (12/33). At Day 205, 42.4% (14/33) of SCB-2019 recipients had titers ≥LLoQ.

Only one subject in the Placebo arm was included in the PPS – Immunogenicity Persistence (anti-N negative) and remained seronegative during the study period up to Day 205.

At Day 205, the GMT was 385.2 (N=76) and the corresponding GMFR at Day 205 was 12.4, and the percentage of SCB-2019 recipients who seroconverted (i.e., the SCR) was 64.5% (49/76). At Day 205, 82.9% (63/76) of SCB-2019 recipients had titers ≥LLoQ.

In baseline SARS-CoV-2–naïve subjects without evidence of asymptomatic SARS-CoV-2 infection (anti-N negative), antibody decay was observed at 6 months after the primary vaccination to 21% of peak level. In baseline SARS-CoV-2-exposed subjects, at 6 months post-vaccination level of antibodies was 28% of peak level. Nevertheless, the ACE2 receptor binding antibodies remained high at 6 months post second dose of SCB-2019 vaccination for both baseline SARS-CoV-2 naive or exposed subjects.

11.1.2.2.5 *Immunogenicity Subgroup Analysis by Age, Sex, Race, Country, and risk of severe COVID-19*

Subgroup analysis by age, sex, race, country, and risk of severe COVID-19 are presented in **Table 14.3.4.1_P6m** (GMT), **Table 14.3.4.2_P6m** (GMFR), **Table 14.3.4.3_P6m** (SCR) and **Table 14.3.4.4_P6m** (subjects with antibody response ≥LLoQ). Subgroup analyses were performed for the PPS – Immunogenicity Persistence (regardless of anti-N results).

Table 55 Study CLO-SCB-2019-003: Antibody Persistence after Vaccination as Measured by SCB-2019– Antibody Binding Assay (EC50, expressed as IU/ml) per PPS (anti-N negative) and FAS Populations

Time point	Endpoint	No Evidence of Prior SARS-CoV-2 Infection (PPS – Immunogenicity Persistence and anti-N negative at Visit 3 and Visit 4)				Evidence of Prior SARS-CoV-2 Infection (FAS – Immunogenicity Persistence)			
		SCB-2019 (N=33)		Placebo (N=1)		SCB-2019 (N=171)		Placebo (N=19)	
		N_e	Value (95% CI)	N_e	Value (95% CI)	N_e	Value (95% CI)	N_e	Value (95% CI)
Day 1	Mean GMT, IU/ml	33	0.5 (.-.)	1	0.5 (.-.)	170	0.9 (0.8-1.0)	19	1.0 (0.6-1.9)
	≥LLoQ, %	33	0.0 (0.0-10.6)	1	0.0 (0.0-97.5)	170	35.3 (28.1-43.0)	19	36.8 (16.3-61.6)
Day 22	Mean GMT, IU/ml	33	0.8 (0.6-1.1)	1	0.5 (.-.)	170	32.9 (27.5-39.4)	19	1.1 (0.6-1.8)
	GMFR	33	1.7 (1.2-2.3)	1	1.0 (.-.)	169	37.8 (30.4-47.0)	19	1.0 (0.8-1.3)
	SCR, %	33	3.0 (0.1-15.8)	1	0.0 (0.0-97.5)	169	91.1 (85.8-94.9)	19	0.0 (0.0-17.6)
	≥LLoQ, %	33	30.3 (15.6-48.7)	1	0.0 (0.0-97.5)	170	99.4 (96.8-100.0)	19	47.4 (24.4-71.1)
Day 36	Mean GMT, IU/ml	33	14.8 (10.2-21.4)	1	0.5 (.-.)	171	37.8 (33.3-42.9)	19	1.0 (0.6-1.7)
	GMFR	33	29.9 (20.6-43.3)	1	1.0 (.-.)	170	43.6 (36.4-52.1)	19	1.0 (0.7-1.3)
	SCR, %	33	87.9 (71.8-96.6)	1	0.0 (0.0-97.5)	170	95.9 (91.7-98.3)	19	0.0 (0.0-17.6)
	≥LLoQ, %	33	100.0 (89.4-100.0)	1	0.0 (0.0-97.5)	171	100.0 (97.0-100.0)	19	36.8 (16.3-61.6)
Day 205	Mean GMT, IU/ml	32	2.1 (1.1-4.0)	1	0.5 (.-.)	166	5.5 (4.9-6.3)	19	2.3 (1.1-4.7)
	GMFR	32	4.3 (2.3-8.1)	1	1.0 (.-.)	165	6.3 (5.2-7.6)	19	2.2 (1.0-5.1)
	SCR, %	32	21.9 (9.3-40.0)	1	0.0 (0.0-97.5)	165	55.2 (47.2-62.9)	19	31.6 (12.6-56.6)
	≥LLoQ, %	32	62.5 (43.7-78.9)	1	0.0 (0.0-97.5)	166	99.4 (96.7-100.0)	19	63.2 (38.4-83.7)

Source: **Table 14.3.3.1.1a_P6m**, **Table 14.3.3.2.1a_P6m**, **Table 14.3.3.3.1a_P6m**, **Table 14.3.3.4.4a_P6m**, **Table 14.3.3.4.1_P6m**, **Table 14.3.3.4.2_P6m**, **Table 14.3.3.4.3_P6m** and **Table 14.3.3.4.6_P6m**.

CI = confidence interval; FAS = full analysis set; GMFR = geometric mean fold rise; GMT = geometric mean titer; LLoQ = lower limit of quantification; N = number of subjects in treatment group; N_e = Number of subjects with results available at the visit; PPS = Per protocol set; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SCB-2019 = CpG 1018/alum-adjuvanted SCB-2019 vaccine; SCR = seroconversion rate.

Titer value measured as below lower limit of quantification (LLOQ) of the assay is set to LLOQ/2. Seroconversion was defined as ≥4-fold rise in the titer at the post-baseline time point from the baseline titer (Day 1) or from the lower limit of quantification (LLoQ) of the assay if that baseline titer was below the LLoQ.

Table 56 Study CLO-SCB-2019-003: Antibody Persistence after Vaccination as Measured by ACE2-receptor-binding Abs Assay (CP50, expressed as 1/dilution) per PPS (anti-N negative) and FAS Populations

Time point	Endpoint	No Evidence of Prior SARS-CoV-2 Infection (PPS – Immunogenicity Persistence and anti-N negative at Visit 3 and Visit 4)				Evidence of Prior SARS-CoV-2 Infection (FAS – Immunogenicity Persistence)			
		SCB-2019 (N=33)		Placebo (N=1)		SCB-2019 (N=171)		Placebo (N=19)	
		N_e	Value (95% CI)	N_e	Value (95% CI)	N_e	Value (95% CI)	N_e	Value (95% CI)
Day 1	Mean GMT, CP50	33	12.5 (.-.)	1	12.5 (.-.)	86	33.3 (22.5-49.4)	12	76.8 (18.3-322.5)
	≥LLoQ, %	33	0.0 (0.0-10.6)	1	0.0 (0.0-97.5)	86	29.1 (19.8-39.9)	12	41.7 (15.2-72.3)
Day 22	Mean GMT, CP50	33	22.7 (13.5-38.2)	1	12.5 (.-.)	81	1396.2 (838.9-2323.6)	11	27.2 (6.6-112.4)
	GMFR	33	1.8 (1.1-3.1)	1	1.0 (.-.)	80	40.8 (23.4-71.0)	11	0.4 (0.1-2.2)
	SCR, %	33	12.1 (3.4-28.2)	1	0.0 (0.0-97.5)	80	77.5 (66.8-86.1)	11	9.1 (0.2-41.3)
	≥LLoQ, %	33	18.2 (7.0-35.5)	1	0.0 (0.0-97.5)	81	86.4 (77.0-93.0)	11	18.2 (2.3-51.8)
Day 36	Mean GMT, CP50	28	364.1 (148.1-894.8)	1	12.5 (.-.)	81	796.6 (503.4-1259.2)	12	30.4 (7.7-120.2)
	GMFR	28	29.1 (11.9-71.6)	1	1.0 (.-.)	81	22.8 (12.0-43.6)	12	0.4 (0.1-1.5)
	SCR, %	28	71.4 (51.3-86.8)	1	0.0 (0.0-97.5)	81	72.8 (61.8-82.1)	12	8.3 (0.2-38.5)
	≥LLoQ, %	28	71.4 (51.3-86.8)	1	0.0 (0.0-97.5)	81	84.0 (74.1-91.2)	12	16.7 (2.1-48.4)
Day 205	Mean GMT, CP50	33	77.6 (32.5-185.3)	1	12.5 (.-.)	76	385.2 (250.4-592.5)	11	147.1 (29.5-734.3)
	GMFR	33	6.2 (2.6-14.8)	1	1.0 (.-.)	76	12.4 (7.2-21.3)	11	2.5 (0.7-8.3)
	SCR, %	33	36.4 (20.4-54.9)	1	0.0 (0.0-97.5)	76	64.5 (52.7-75.1)	11	18.2 (2.3-51.8)
	≥LLoQ, %	33	42.4 (25.5-60.8)	1	0.0 (0.0-97.5)	76	82.9 (72.5-90.6)	11	54.5 (23.4-83.3)

Source: **Table 14.3.3.1.1a_P6m**, **Table 14.3.3.2.1a_P6m**, **Table 14.3.3.3.1a_P6m**, **Table 14.3.3.4.4a_P6m**, **Table 14.3.3.4.1_P6m**, **Table 14.3.3.4.2_P6m**, **Table 14.3.3.4.3_P6m** and **Table 14.3.3.4.6_P6m**.

ACE2, angiotensin-converting enzyme 2; CI = confidence interval; FAS = full analysis set; GMFR = geometric mean fold rise; GMT = geometric mean titer; LLoQ = lower limit of quantification; N = number of subjects in treatment group; N_e = Number of subjects with results available at the visit; PPS = Per protocol set; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SCB-2019 = CpG 1018/alum-adjuvanted SCB-2019 vaccine; SCR = seroconversion rate.

Titer value measured as below lower limit of quantification (LLoQ) of the assay is set to LLoQ/2. Seroconversion was defined as ≥4-fold rise in the titer at the post-baseline time point from the baseline titer (Day 1) or from the lower limit of quantification (LLoQ) of the assay if that baseline titer was below the LLoQ.

11.1.2.3 Exploratory Immunogenicity Analyses

11.1.2.3.1 *Immunogenicity of SCB-2019 in elderly subjects*

Table 57 and Table 58 present the immunogenicity results in elderly study participants (60 years of age and above) as measured by prototype SARS-CoV-2 neutralization assay (expressed as IU/ml) at Day 1 and Day 36 (14 days-post Dose 2) in subjects without and with evidence of prior SARS-CoV-2 infection, respectively.

In elderly SARS-CoV-2–naïve subjects (Immunogenicity FAS), at Day 36, the GMT was 75.5 (N=74) and the corresponding GMFR at Day 36 was 5.9 (N=74), and the percentage of SCB-2019 recipients who seroconverted (i.e., the SCR) was 44.6% (33/74). At Day 36, 78.4% (58/74) of SCB-2019 recipients had titers ≥LLoQ. By contrast, in the placebo recipients, the GMTs at Days 1 and 36 were 12.5 (N=12) and 12.5 (N=12), respectively; and were similar to the baseline titer in the SCB-2019 recipients (12.9, N=74).

In the overall population of SARS-CoV-2–naïve subjects (Immunogenicity FAS), at Day 36, the geometric mean titer (GMT) was 211.3 (N=233) and the corresponding geometric mean fold rise (GMFR) at Day 36 was 16.5 (N=231), and the percentage of SCB-2019 recipients who seroconverted (i.e., the SCR) was 80.1% (185/231). At Day 36, 96.2% (225/234) of SCB-2019 recipients had titers ≥LLoQ. By contrast, in the placebo recipients, the GMTs at Days 1 and 36 were 12.5 (N=30) and 12.8 (N=31), respectively; and were similar to the baseline titer in the SCB-2019 recipients (12.7, N=233) (Section 11.1.2.1.1).

In elderly baseline SARS-CoV-2-exposed subjects (Immunogenicity FAS), in the SCB-2019 recipients at Day 36, 2 weeks after the 2nd dose, the GMT was 1285.9 (N=111) and higher than a GMT of 50.6 (N=111) at baseline (Day 1). The corresponding GMFR at Day 36 was 25.4 (N=111), and the SCR was 86.5% (96/111). At Day 36, 98.2% (109/111) of SCB-2019 recipients had titers ≥LLoQ.

In the overall population of baseline SARS-CoV-2-exposed subjects (Immunogenicity FAS), in the SCB-2019 recipients at Day 36, 2 weeks after the 2nd dose, the GMT was 1831 (N=118), the GMFR was 69.3 (N=118) and the SCR was 98% (116/118). At Day 36, 100% (118/118) of SCB-2019 recipients had titers ≥LLoQ (Section 11.1.2.1.1).

Two doses of SCB-2019 vaccine were immunogenic in SARS-CoV-2 naïve individuals 60 years of age and above. Antibody titers in elderly subjects appeared to be lower compared to younger general study population. In SARS-CoV-2 exposed elderly subjects, immune response was significantly higher than in SARS-CoV-2 naïve subjects, the observation was consistent with the overall study population.

Table 57 Immunogenicity of SCB-2019 in Subjects Without Evidence of Prior SARS-CoV-2 Infection as Measured by VNA with Prototype Virus (MN_{50}, expressed as IU/ml) per Immunogenicity FAS Population

Time point	Endpoint	Overall population (Immunogenicity-FAS)				Elderly population (Immunogenicity-FAS)			
		SCB-2019 (N=401)		Placebo (N=56)		SCB-2019 (N=74)		Placebo (N=12)	
		N_e	Value (95% CI)	N_e	Value (95% CI)	N_e	Value (95% CI)	N_e	Value (95% CI)
Day 1	Mean GMT, IU/ml	233	12.7 (12.5-12.9)	30	12.5 (-)	74	12.9 (12.2-13.6)	12	12.5 (-)
	≥LLoQ, %	233	0.9 (0.1-3.1)	30	0.0 (0.0-11.6)	74	1.4 (0.0-7.3)	12	0.0 (0.0-26.5)
Day 36	Mean GMT, IU/ml	234	211.3 (183.0-243.9)	31	12.8 (12.4-13.2)	74	75.5 (56.0-101.8)	12	12.5 (-)
	GMFR	231	16.5 (14.3-19.0)	30	1.0 (1.0-1.1)	74	5.9 (4.4-7.9)	12	1.0 (-)
	SCR, %	231	80.1 (74.3-85.0)	30	0.0 (0.0-11.6)	74	44.6 (33.0-56.6)	12	0.0 (0.0-26.5)
	≥LLoQ, %	234	96.2 (92.8-98.2)	31	0.0 (0-11.2)	74	78.4 (67.3-87.1)	12	0.0 (0.0-26.5)

Source: **Table 14.3.3.4.7** to **14.3.3.4.10** and **Table 14.3.5.2.5**, **Table 14.3.5.2.6**, **Table 14.3.5.2.7** and **Table 14.3.5.2.8**.
CI = confidence interval; FAS = full analysis set; GMFR = geometric mean fold rise; GMT = geometric mean titer; LLoQ = lower limit of quantification; N = number of subjects in treatment group; Ne = Number of subjects with results available at the visit; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SCB-2019 = CpG 1018/alum-adjuvanted SCB-2019 vaccine; SCR = seroconversion rate.
Titer value measured as below lower limit of quantification (LLOQ) of the assay is set to LLOQ/2. Seroconversion was defined as ≥4-fold rise in the titer at the post-baseline time point from the baseline titer (Day 1) or from the lower limit of quantification (LLoQ) of the assay if that baseline titer was below the LLoQ. Baseline evidence of prior SARS-CoV-2 infection includes subjects with seropositivity at baseline and/or with a known history of COVID-19 at baseline.

Table 58 Immunogenicity of SCB-2019 in Subjects with Evidence of Prior SARS-CoV-2 Infection as Measured by VNA with Prototype Virus (MN_{50}, expressed as IU/ml) per Immunogenicity FAS Population

Time point	Endpoint	Overall population (Immunogenicity-FAS)				Elderly population (Immunogenicity-FAS)			
		SCB-2019 (N=235)		Placebo (N=28)		SCB-2019 (N=111)		Placebo (N=18)	
		N_e	Value (95% CI)	N_e	Value (95% CI)	N_e	Value (95% CI)	N_e	Value (95% CI)
Day 1	Mean GMT, IU/ml	118	26.4 (22.3-31.3)	18	32.7 (16.3-65.8)	111	50.6 (38.8-66.1)	18	57.2 (26.4-124.0)
	≥LLoQ, %	118	44.1 (34.9-53.5)	18	38.9 (17.3-64.3)	111	67.6 (58.0-76.1)	18	72.2 (46.5-90.3)
Day 36	Mean GMT, IU/ml	118	1831.4 (1545.9-2169.8)	18	58.3 (26.6- 128.1)	111	1285.9 (1046.9-1579.4)	18	55.1 (27.3-111.0)
	GMFR	118	69.3 (55.9-85.8)	18	1.8 (0.8-3.8)	111	25.4 (18.9-34.1)	18	1.0 (0.7-1.2)
	SCR, %	118	98.3 (94.0-99.8)	18	16.7 (3.6-41.4)	111	86.5 (78.7-92.2)	18	0 (0.0-18.5)
	≥LLoQ, %	118	100.0 (96.9-100.0)	18	61.1 (35.7-82.7)	111	98.2 (93.6-99.8)	18	72.2 (46.5-90.3)

Source: **Table 14.3.3.4.1, Table 14.3.3.4.2, Table 14.3.3.4.3**, **Table 14.3.3.4.6**, **Table 14.3.5.2.1**, **Table 14.3.5.2.2**, **Table 14.3.5.2.3** and **Table 14.3.5.2.4**.
CI = confidence interval; FAS = full analysis set; GMFR = geometric mean fold rise; GMT = geometric mean titer; LLoQ = lower limit of quantification; N = number of subjects in treatment group; Ne = Number of subjects with results available at the visit; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SCB-2019 = CpG 1018/alum-adjuvanted SCB-2019 vaccine; SCR = seroconversion rate.
Titer value measured as below lower limit of quantification (LLOQ) of the assay is set to LLOQ/2. Seroconversion was defined as ≥4-fold rise in the titer at the post-baseline time point from the baseline titer (Day 1) or from the lower limit of quantification (LLoQ) of the assay if that baseline titer was below the LLoQ. Baseline evidence of prior SARS-CoV-2 infection includes subjects with seropositivity at baseline and/or with a known history of COVID-19 at baseline.

Table 59 and Table 60 present the cross-neutralizing activity against the Delta (B.1.617) variant as measured by SARS-CoV-2 neutralization assay (MN50 expressed as 1/dilution) at Day 1 and Day 36 (14 days-post Dose 2) in subjects without and with evidence of prior SARS-CoV-2 infection, respectively.

In the overall population of SARS-CoV-2–naïve subjects (Immunogenicity PPS), the GMT in the SCB-2019 recipients against the Delta variant was 44.7 (N=49) at Day 36. By contrast, in the placebo recipients, the GMTs at Days 1 and 36 were 10.0 (N=6) and 10.0 (N=6), respectively, and were similar to the baseline titer in the SCB-2019 recipients (10.0, N=49).

In elderly SARS-CoV-2–naïve subjects (Immunogenicity FAS), the GMT in the SCB-2019 recipients against the Delta variant was 25.3 (N=74) at Day 36. By contrast, in the placebo recipients, the GMTs at Days 1 and 36 were 10.0 (N=12) and 10.0 (N=12), respectively, and were similar to the baseline titer in the SCB-2019 recipients (10.3, N=74).

In the overall population of baseline SARS-CoV-2-exposed subjects (Immunogenicity FAS), the GMT in the SCB-2019 recipients against the Delta variant was 1069.9 (N=29) at Day 36. By contrast, in the placebo recipients, the GMTs at Days 1 and 36 were 10.0 (N=3) and 10.0 (N=3), respectively, and were similar to the baseline titer in the SCB-2019 recipients (13.8, N=29).

In elderly baseline SARS-CoV-2-exposed subjects (Immunogenicity FAS), the GMT in the SCB-2019 recipients against the Delta variant was 709.5 (N=111) at Day 36. By contrast, in the placebo recipients, the GMTs at Days 1 and 36 were 31.1 (N=18) and 27.2 (N=18), respectively, and were similar to the baseline titer in the SCB-2019 recipients (33.0, N=111).

Two doses of SCB-2019 vaccine induce cross-neutralization antibodies against the Delta variant in SARS-CoV-2 naïve subjects 60 years and above. In elderly subjects with history of previous SARS-CoV-2 infection, SCB-2019 induced high titers of cross-neutralizing antibodies against Delta variant. Overall, GMT in elderly subjects appeared to be lower compared to younger general study population.

Immunogenicity results as measured by SCB-2019 binding ELISA (expressed as IU/ml) at Day 1 and Day 36 (14 days post-Dose 2) in elderly subjects without evidence of prior SARS-CoV-2 infection and in general population are presented in **Tables 14.3.5.2.5** to **14.3.5.2.8** and **Tables 14.3.3.4.7** to **14.3.3.4.10**, respectively.

Similar results for elderly subjects with evidence of prior SARS-CoV-2 infection and for general population are presented in **Tables 14.3.5.2.1** to **14.3.5.2.4** and **Tables 14.3.3.4.1** to **14.3.3.4.3**, and **Table 14.3.3.4.6**, respectively.

In both overall and elderly populations, results as measured by SCB-2019 binding ELISA were consistent with the prototype SARS-CoV-2 neutralization assay.

Table 59 Immunogenicity of SCB-2019: Delta Variant Cross-Neutralizing Data GMT Results by Visit in Subjects Without Evidence of Prior SARS-CoV-2 Infection as Measured by VNA with Prototype Virus (MN_{50}, expressed as 1/dilution) per Immunogenicity PPS and FAS Populations

Time point	Endpoint	Overall population (Immunogenicity-PPS*)				Elderly population (Immunogenicity-FAS)			
		SCB-2019 (N=381)		Placebo (N=47)		SCB-2019 (N=74)		Placebo (N=12)	
		N_e	Value (95% CI)	N_e	Value (95% CI)	N_e	Value (95% CI)	N_e	Value (95% CI)
Day 1	Mean GMT (MN50)	49	10.0 (-)	6	10.0 (-)	74	10.3 (9.7-11.0)	12	10.0 (-)
Day 36	Mean GMT (MN50)	49	44.7 (31.5-63.3)	6	10.0 (-)	74	25.3 (19.2-33.3)	12	10.0 (-)

Source: **Table 14.3.3.1.1.1a** and **Table 14.3.5.2.5**.
CI = confidence interval; FAS = full analysis set; GMT = geometric mean titer; N = number of subjects in treatment group; Ne = Number of subjects with results available at the visit; PPS = per protocol set; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SCB-2019 = CpG 1018/alum-adjuvanted SCB-2019 vaccine.
Titer value measured as below lower limit of quantification (LLOQ) of the assay is set to LLOQ/2. Baseline evidence of prior SARS-CoV-2 infection includes subjects with seropositivity at baseline and/or with a known history of COVID-19 at baseline.
* Per-Protocol Set used for assessment of cross-neutralization activity against Delta variant in SARS-CoV-2 naïve population in the main clinical study report.

Table 60 Immunogenicity of SCB-2019: Delta Variant Cross-Neutralizing Data GMT Results by Visit in Subjects With Evidence of Prior SARS-CoV-2 Infection as Measured by VNA with Prototype Virus (MN_{50}, expressed as I1/dilution) per Immunogenicity FAS Population

Time point	Endpoint	Overall population (Immunogenicity-FAS)				Elderly population (Immunogenicity-FAS)			
		SCB-2019 (N=235)		Placebo (N=28)		SCB-2019 (N=111)		Placebo (N=18)	
		N_e	Value (95% CI)	N_e	Value (95% CI)	N_e	Value (95% CI)	N_e	Value (95% CI)
Day 1	Mean GMT (MN50)	29	13.8 (11.5-16.6)	3	10.0 (-)	111	33.0 (24.9-43.6)	18	31.1 (14.1-68.8)
Day 36	Mean GMT (MN50)	29	1069.9 (841.2-1360.9)	3	10.0 (-)	111	709.5 (575.3-875.0)	18	27.2 (13.7-53.9)

Source: **Table 14.3.3.1.1.2a** and **Table 14.3.5.2.1**.
CI = confidence interval; FAS = full analysis set; GMT = geometric mean titer; N = number of subjects in treatment group; Ne = Number of subjects with results available at the visit; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SCB-2019 = CpG 1018/alum-adjuvanted SCB-2019 vaccine.
Titer value measured as below lower limit of quantification (LLOQ) of the assay is set to LLOQ/2. Baseline evidence of prior SARS-CoV-2 infection includes subjects with seropositivity at baseline and/or with a known history of COVID-19 at baseline.

11.1.2.3.2 *Immunogenicity of SCB-2019 in individuals with HIV infection*

Immunogenicity data for HIV infected subjects are presented in **Table 14.3.3.1.1_HIV** to **14.3.3.6.2.1_HIV.**

Table 61 and Table 62 present the immunogenicity results as measured by prototype SARS-CoV-2 neutralization assay (MN_{50}, expressed as IU/ml) at Day 1 and Day 36 (14 days-post Dose 2) in HIV-infected subjects and the general population without and with evidence of prior SARS-CoV-2 infection, respectively.

In the overall population of SARS-CoV-2–naïve subjects (Immunogenicity FAS), at Day 36, 2 weeks after the 2nd dose, the geometric mean titer (GMT) was 211.3 (N=234) and the corresponding geometric mean fold rise (GMFR) at Day 36 was 16.5 (N=231), and the percentage of SCB-2019 recipients who seroconverted (i.e., the seroconversion rate [SCR]) was 80.1% (185/231). At Day 36, 96.2% (225/234) of SCB-2019 recipients had titers ≥ lower limit of quantification (LLoQ). By contrast, in the placebo recipients, the GMTs at Days 1 and 36 were 12.5 (N=30) and 12.8 (N=31), respectively; and were similar to the baseline titer in the SCB-2019 recipients (12.7, N=233).

In HIV infected SARS-CoV-2–naïve subjects (Immunogenicity FAS), at Day 36, the GMT was 388.6 (N=12) and the corresponding GMFR at Day 36 was 30.2 (N=12), and the percentage of SCB-2019 recipients who seroconverted (i.e., the SCR) was 100.0% (12/12). At Day 36, 100.0% (12/12) of SCB-2019 recipients had titers ≥LLoQ. By contrast, in the placebo recipients, the GMTs at Days 1 and 36 were 12.5 (N=9) and 17.7 (N=9), respectively; and were similar to the baseline titer in the SCB-2019 recipients (12.9, N=12).

In the overall population of baseline SARS-CoV-2-exposed subjects (Immunogenicity FAS), in the SCB-2019 recipients at Day 36, 2 weeks after the 2nd dose, the GMT was 1831.4 (N=118), the GMFR was 69.3 (N=118) and the SCR was 98.3% (116/118). At Day 36, 100% (118/118) of SCB-2019 recipients had titers ≥LLoQ.

In HIV infected baseline SARS-CoV-2-exposed subjects (Immunogenicity FAS), in the SCB-2019 recipients at Day 36, 2 weeks after the 2nd dose, the GMT was 1939.7 (N=18) and higher than a GMT of 57.2 (N=18) at baseline (Day 1). The corresponding GMFR at Day 36 was 33.9 (N=18), and the SCR was 94.4% (17/18). At Day 36, 100.0% (18/18) of SCB-2019 recipients had titers ≥LLoQ.

Immunogenicity results as measured by SCB-2019 binding enzyme-linked immunosorbent assay (ELISA; expressed as IU/ml) at Day 1 and Day 36 (14 days post-Dose 2) in HIV-infected subjects and in the general population without and with evidence of prior SARS-CoV-2 infection are presented in **Tables 14.3.3.1.1_HIV, 14.3.3.2.1_HIV, 14.3.3.3.1_HIV, 14.3.3.4.4_HIV**, and **Tables 14.3.3.4.7** to **14.3.3.4.10**, respectively.

Similar results for HIV-infected subjects with evidence of prior SARS-CoV-2 infection and for general population are presented in **Tables 14.3.3.4.1_HIV, 14.3.3.4.2_HIV, 14.3.3.4.3_HIV, 14.3.3.4.6_HIV**, and **Tables 14.3.3.4.1, 14.3.3.4.2, 14.3.3.4.3, 14.3.3.4.6**, respectively.

In both overall and HIV infected populations, results as measured by SCB-2019 binding ELISA were consistent with the prototype SARS-CoV-2 neutralization assay.

Table 61 Immunogenicity of SCB-2019 in Subjects Without Evidence of Prior SARS-CoV-2 Infection as Measured by VNA with Prototype Virus (MN_{50}, expressed as IU/ml) per Immunogenicity FAS Population

Time point	Endpoint	Overall population (Immunogenicity-FAS)				HIV infected population (Immunogenicity-FAS)			
		SCB-2019 (N=401)		Placebo (N=56)		SCB-2019 (N=12)		Placebo (N=9)	
		N_e	Value (95% CI)	N_e	Value (95% CI)	N_e	Value (95% CI)	N_e	Value (95% CI)
Day 1	Mean GMT, IU/ml	233	12.7 (12.5-12.9)	30	12.5 (-)	12	12.9 (12.1- 13.7)	9	12.5 (-)
	≥LLoQ, %	233	0.9 (0.1-3.1)	30	0.0 (0.0-11.6)	12	0.0 (0.0-26.5)	9	0.0 (0.0-33.6)
Day 36	Mean GMT, IU/ml	234	211.3 (183.0-243.9)	31	12.8 (12.4-13.2)	12	388.6 (235.5-641.3)	9	17.7 (10.0-31.1)
	GMFR	231	16.5 (14.3-19.0)	30	1.0 (1.0-1.1)	12	30.2 (19.1-47.8)	9	1.4 (0.8-2.5)
	SCR, %	231	80.1 (74.3-85.0)	30	0.0 (0.0-11.6)	12	100.0 (73.5-100.0)	9	11.1 (0.3-48.2)
	≥LLoQ, %	234	96.2 (92.8-98.2)	31	0.0 (0-11.2)	12	100.0 (73.5-100.0)	9	22.2 (2.8-60.0)

Source: **Table 14.3.3.4.7** to **14.3.3.4.10** and **Table 14.3.3.1.1_HIV**, **Table 14.3.3.2.1_HIV**, **Table 14.3.3.3.1_HIV** and **Table 14.3.3.4.4_HIV**.
CI = confidence interval; FAS = full analysis set; GMFR = geometric mean fold rise; GMT = geometric mean titer; LLoQ = lower limit of quantification; N = number of subjects in treatment group; Ne = Number of subjects with results available at the visit; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SCB-2019 = CpG 1018/alum-adjuvanted SCB-2019 vaccine; SCR = seroconversion rate.
Titer value measured as below lower limit of quantification (LLOQ) of the assay is set to LLOQ/2. Seroconversion was defined as ≥4-fold rise in the titer at the post-baseline time point from the baseline titer (Day 1) or from the lower limit of quantification (LLoQ) of the assay if that baseline titer was below the LLoQ. Baseline evidence of prior SARS-CoV-2 infection includes subjects with seropositivity at baseline and/or with a known history of COVID-19 at baseline.

Table 62 Immunogenicity of SCB-2019 in Subjects with Evidence of Prior SARS-CoV-2 Infection as Measured by VNA with Prototype Virus (MN_{50}, expressed as IU/ml) per Immunogenicity FAS Population

Time point	Endpoint	Overall population (Immunogenicity-FAS)				HIV infected population (Immunogenicity-FAS)			
		SCB-2019 (N=235)		Placebo (N=28)		SCB-2019 (N=18)		Placebo (N=4)	
		N_e	Value (95% CI)	N_e	Value (95% CI)	N_e	Value (95% CI)	N_e	Value (95% CI)
Day 1	Mean GMT, IU/ml	118	26.4 (22.3-31.3)	18	32.7 (16.3-65.8)	18	57.2 (25.7-127.3)	4	118.9 (7.5-1874.0)
	≥LLoQ, %	118	44.1 (34.9-53.5)	18	38.9 (17.3-64.3)	18	61.1 (35.7-82.7)	4	75.0 (19.4-99.4)
Day 36	Mean GMT, IU/ml	118	1831.4 (1545.9-2169.8)	18	58.3 (26.6- 128.1)	18	1939.7 (1138.6-3304.6)	4	336.4 (6.4-17714.9)
	GMFR	118	69.3 (55.9-85.8)	18	1.8 (0.8-3.8)	18	33.9 (15.3-75.0)	4	2.8 (0.2-39.1)
	SCR, %	118	98.3 (94.0-99.8)	18	16.7 (3.6-41.4)	18	94.4 (72.7-99.9)	4	25.0 (0.6-80.6)
	≥LLoQ, %	118	100.0 (96.9-100.0)	18	61.1 (35.7-82.7)	18	100.0 (81.5-100.0)	4	75.0 (19.4-99.4)

Source: **Table 14.3.3.4.1**, **Table 14.3.3.4.2**, **Table 14.3.3.4.3** and **Table 14.3.3.4.6** and **Table 14.3.3.4.1_HIV**, **Table 14.3.3.4.2_HIV**, **Table 14.3.3.4.3_HIV** and **Table 14.3.3.4.6_HIV**.

CI = confidence interval; FAS = full analysis set; GMFR = geometric mean fold rise; GMT = geometric mean titer; LLoQ = lower limit of quantification; N = number of subjects in treatment group; Ne = Number of subjects with results available at the visit; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SCB-2019 = CpG 1018/alum-adjuvanted SCB-2019 vaccine; SCR = seroconversion rate.

Titer value measured as below lower limit of quantification (LLOQ) of the assay is set to LLOQ/2. Seroconversion was defined as ≥4-fold rise in the titer at the post-baseline time point from the baseline titer (Day 1) or from the lower limit of quantification (LLoQ) of the assay if that baseline titer was below the LLoQ. Baseline evidence of prior SARS-CoV-2 infection includes subjects with seropositivity at baseline and/or with a known history of COVID-19 at baseline.

11.1.2.4 Immunogenicity of CLO-SCB-2019 in Subjects of Chinese Origin

Immunogenicity data for Chinese origin subjects are presented in **Table 14.3.5.1.1** to **14.3.5.1.8.**

Table 63 and Table 64 present the immunogenicity results as measured by prototype SARS-CoV-2 neutralization assay (expressed as IU/ml) at Day 1 and Day 36 (14 days-post Dose 2) in Chinese origin subjects without and with evidence of prior SARS-CoV-2 infection, respectively.

In the overall population of SARS-CoV-2–naïve subjects (Immunogenicity FAS), at Day 36, the geometric mean titer (GMT) was 211.3 (N=233) and the corresponding geometric mean fold rise (GMFR) at Day 36 was 16.5 (N=231), and the percentage of SCB-2019 recipients who seroconverted (i.e., the SCR) was 80.1% (185/231). At Day 36, 96.2% (225/234) of SCB-2019 recipients had titers ≥LLoQ. By contrast, in the placebo recipients, the GMTs at Days 1 and 36 were 12.5 (N=30) and 12.8 (N=31), respectively; and were similar to the baseline titer in the SCB-2019 recipients (12.7, N=233).

In Chinese origin SARS-CoV-2–naïve subjects (Immunogenicity FAS), at Day 36, the GMT was 237.8 (N=14) and the corresponding GMFR at Day 36 was 19.0 (N=14), and the percentage of SCB-2019 recipients who seroconverted (i.e., the SCR) was 85.7% (12/14). At Day 36, 100.0% (14/14) of SCB-2019 recipients had titers ≥LLoQ. By contrast, in the placebo recipients, the GMTs at Days 1 and 36 were 12.5 (N=10) and 12.5 (N=10), respectively; and were similar to the baseline titer in the SCB-2019 recipients (12.5, N=14).

In the overall population of baseline SARS-CoV-2-exposed subjects (Immunogenicity FAS), in the SCB-2019 recipients at Day 36, 2 weeks after the 2nd dose, the GMT was 1831.4 (N=118), the GMFR was 69.3 (N=118) and the SCR was 98% (116/118). At Day 36, 100% (118/118) of SCB-2019 recipients had titers ≥LLoQ.

In Chinese origin baseline SARS-CoV-2-exposed subjects (Immunogenicity FAS), in the SCB-2019 recipients at Day 36, 2 weeks after the 2nd dose, the GMT was 1026.7 (N=25) and higher than a GMT of 29.1 (N=25) at baseline (Day 1). The corresponding GMFR at Day 36 was 35.3 (N=25), and the SCR was 96.0% (24/25). At Day 36, 100% (25/25) of SCB-2019 recipients had titers ≥LLoQ.

Immunogenicity results as measured by SCB-2019 binding ELISA (expressed as IU/ml) at Day 1 and Day 36 (14 days post-Dose 2) in subjects of Chinese origin without evidence of prior SARS-CoV-2 infection are presented in **Tables 14.3.5.1.5** to **14.3.5.1.8**. The results obtained in general population are presented in **Tables 14.3.3.4.7** to **14.3.3.4.10**.

Similar results for subjects of Chinese origin with evidence of prior SARS-CoV-2 infection are presented in **Tables 14.3.5.1.1** to **14.3.5.1.4**. The results obtained in general population are presented in **Tables 14.3.3.4.1** to **14.3.3.4.3** and **Table 14.3.3.4.6**.

In both overall and Chinese origin populations, results as measured by SCB-2019 binding ELISA were consistent with the prototype SARS-CoV-2 neutralization assay.

Table 63 Immunogenicity of SCB-2019 in Subjects Without Evidence of Prior SARS-CoV-2 Infection as Measured by VNA with Prototype Virus (MN_{50}, expressed as IU/ml) per Immunogenicity FAS Population

Time point	Endpoint	Overall population (Immunogenicity-FAS)				Chinese origin population (Immunogenicity-FAS)			
		SCB-2019 (N=401)		Placebo (N=56)		SCB-2019 (N=14)		Placebo (N=10)	
		N_e	Value (95% CI)	N_e	Value (95% CI)	N_e	Value (95% CI)	N_e	Value (95% CI)
Day 1	Mean GMT, IU/ml	233	12.7 (12.5-12.9)	30	12.5 (-)	14	12.5 (-)	10	12.5 (-)
	≥LLoQ, %	233	0.9 (0.1-3.1)	30	0.0 (0.0-11.6)	14	0.0 (0.0-23.2)	10	0.0 (0.0-30.8)
Day 36	Mean GMT, IU/ml	234	211.3 (183.0-243.9)	31	12.8 (12.4-13.2)	14	237.8 (118.5-477.3)	10	12.5 (-)
	GMFR	231	16.5 (14.3-19.0)	30	1.0 (1.0-1.1)	14	19.0 (9.5-38.2)	10	1.0 (-)
	SCR, %	231	80.1 (74.3-85.0)	30	0.0 (0.0-11.6)	14	85.7 (57.2-98.2)	10	0.0 (0.0-30.8)
	≥LLoQ, %	234	96.2 (92.8-98.2)	31	0.0 (0-11.2)	14	100.0 (76.8-100.0)	10	0.0 (0.0-30.8)

Source: **Tables 14.3.3.4.7** to **14.3.3.4.10** and **Table 14.3.5.1.5**, **Table 14.3.5.1.6**, **Table 14.3.5.1.7** and **Table 14.3.5.1.8**.
CI = confidence interval; FAS = full analysis set; GMFR = geometric mean fold rise; GMT = geometric mean titer; LLoQ = lower limit of quantification; N = number of subjects in treatment group; Ne = Number of subjects with results available at the visit; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SCB-2019 = CpG 1018/alum-adjuvanted SCB-2019 vaccine; SCR = seroconversion rate.
Titer value measured as below lower limit of quantification (LLOQ) of the assay is set to LLOQ/2. Seroconversion was defined as ≥4-fold rise in the titer at the post-baseline time point from the baseline titer (Day 1) or from the lower limit of quantification (LLoQ) of the assay if that baseline titer was below the LLoQ. Baseline evidence of prior SARS-CoV-2 infection includes subjects with seropositivity at baseline and/or with a known history of COVID-19 at baseline.

Table 64 Immunogenicity of SCB-2019 in Subjects with Evidence of Prior SARS-CoV-2 Infection as Measured by VNA with Prototype Virus (MN_{50}, expressed as IU/ml) per Immunogenicity FAS Population

Time point	Endpoint	Overall population (Immunogenicity-FAS)				Chinese origin population (Immunogenicity-FAS)			
		SCB-2019 (N=235)		Placebo (N=28)		SCB-2019 (N=25)		Placebo (N=18)	
		N_e	Value (95% CI)	N_e	Value (95% CI)	N_e	Value (95% CI)	N_e	Value (95% CI)
Day 1	Mean GMT, IU/ml	118	26.4 (22.3-31.3)	18	32.7 (16.3-65.8)	25	29.1 (18.3-46.4)	18	30.3 (15.9-58.0)
	≥LLoQ, %	118	44.1 (34.9-53.5)	18	38.9 (17.3-64.3)	25	48.0 (27.8-68.7)	18	44.4 (21.5-69.2)
Day 36	Mean GMT, IU/ml	118	1831.4 (1545.9-2169.8)	18	58.3 (26.6- 128.1)	25	1026.7 (690.2-1527.5)	18	29.7 (15.7-56.4)
	GMFR	118	69.3 (55.9-85.8)	18	1.8 (0.8-3.8)	25	35.3 (19.6-63.4)	18	1.0 (0.6-1.6)
	SCR, %	118	98.3 (94.0-99.8)	18	16.7 (3.6-41.4)	25	96.0 (79.6-99.9)	18	5.6 (0.1-27.3)
	≥LLoQ, %	118	100.0 (96.9-100.0)	18	61.1 (35.7-82.7)	25	100.0 (86.3-100.0)	18	44.4 (21.5-69.2)

Source: **Table 14.3.3.4.1, Table 14.3.3.4.2, Table 14.3.3.4.3** and **Table 14.3.3.4.6** and **Table 14.3.5.1.1**, **Table 14.3.5.1.2**, **Table 14.3.5.1.3** and **Table 14.3.5.1.4**.
CI = confidence interval; FAS = full analysis set; GMFR = geometric mean fold rise; GMT = geometric mean titer; LLoQ = lower limit of quantification; N = number of subjects in treatment group; Ne = Number of subjects with results available at the visit; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2, SCB-2019 = CpG 1018/alum-adjuvanted SCB-2019 vaccine; SCR = seroconversion rate.
Titer value measured as below lower limit of quantification (LLOQ) of the assay is set to LLOQ/2. Seroconversion was defined as ≥4-fold rise in the titer at the post-baseline time point from the baseline titer (Day 1) or from the lower limit of quantification (LLoQ) of the assay if that baseline titer was below the LLoQ. Baseline evidence of prior SARS-CoV-2 infection includes subjects with seropositivity at baseline and/or with a known history of COVID-19 at baseline.

11.1.2.5 Immunogenicity of SCB-2019 Manufactured at Different Scales (2000L and 200L)

The investigational SCB-2019 vaccine manufactured at 200 liter (L) scale was used in all sites and countries participating in the study. In addition, selected clinical sites in Colombia initiated recruitment using 200L scale materials and shifted to the administration of SCB-2019 vaccine manufactured at 2000L scale. This exploratory analysis was performed to assess the comparability of SCB-2019 drug substance manufactured at 2000L and 200L scales.

Two manufacturing scales were considered to be comparable if the lower limit (LL) of the 95% confidence interval (CI) for GMT ratio (2000L/200L) exceeded 0.67.

A total of 283 subjects with blood sample available at Visit 3 were included in PPS for immunogenicity testing including SCB-2019 binding antibody enzyme-linked immunosorbent assay (ELISA) and wild-type SARS-CoV-2 virus-neutralizing assay (VNA) for prototype (Wuhan) virus.

Table 65 presents the immunogenicity results as measured by prototype SARS-CoV-2 neutralization assay (expressed as IU/ml) and by SCB-2019 binding ELISA (expressed as IU/ml) at Day 36 (14 days-post Dose 2) in subjects who received SCB-2019 vaccines produced at two manufacturing scales (DS from 2000 or 200 liter fermenter).

At Day 36, the GMT as measured by prototype SARS-CoV-2 neutralization assay (expressed as IU/ml) was 109.3 (N=109) in the SCB-2019 2000L group and 101.6 (N=174) in the SCB-2019 200L group with a GMT2000L/GMT200L ratio of 1.1 (0.8,1.5).

At Day 36, the GMT as measured by SCB-2019 binding ELISA (expressed as IU/ml) was 6.6 (N=109) in the SCB-2019 2000L group and 5.2 (N=174) in the SCB-2019 200L group with a GMT2000L/GMT200L ratio of 1.3 (0.9,1.7).

The two manufacturing scales were considered to be comparable as the pre-specified non-inferiority criteria for immunogenicity of SCB-2019 vaccine manufactured at 2000L scale vs 200L scale were met for both assays.

Table 65 Immunogenicity of SCB-2019 at Visit 3 as Measured by VNA with Prototype Virus (MN_{50}, expressed as IU/ml) and by SCB-2019– Antibody Binding Assay (EC_{50}, expressed as IU/ml) per Immunogenicity PPS Population

MN_{50} (IU/ml)					**EC_{50} (IU/ml)**				
SCB-2019 2000L (N=109)		**SCB-2019 200L (N=174)**		**Ratio of GMT2000L /GMT200L**	**SCB-2019 2000L (N=109)**		**SCB-2019 200L (N=174)**		**Ratio of GMT2000L /GMT200L**
N_e	**Value (95% CI)**	**N_e**	**Value (95% CI)**	**Estimate (95% CI)**	**N_e**	**Value (95% CI)**	**N_e**	**Value (95% CI)**	**Estimate (95% CI)**
109	109.3 (85.1,140.4)	174	101.6 (84.5,122.1)	1.1 (0.8,1.5)	109	6.6 (5.2,8.4)	174	5.2 (4.2,6.3)	1.3 (0.9,1.7)

Source: **Table 14.3.5.3.1**.
CI = confidence interval; GMT = geometric mean titer; N = number of subjects in treatment group; Ne = Number of subjects with results available at the visit; SCB-2019 2000L= CpG 1018/Alum-adjuvanted SCB-2019 vaccine, DS from 2000 Liter fermenter, SCB-2019 200L= CpG 1018/Alum-adjuvanted SCB-2019 vaccine, DS from 200 Liter fermenter.
Titer value measured as below lower limit of quantification (LLOQ) of the assay is set to LLOQ/2.
Two manufacturing scales were considered to be comparable if the lower limit (LL) of the 95% confidence interval (CI) for GMT ratio (2000L/200L) exceeded 0.67.

11.1.3 Statistical and Analytical Issues

11.1.3.1 Adjustments for Covariates

Adjustments for covariates are described in the SAP.

11.1.3.2 Handling of Dropouts or Missing Data

There was no imputation of missing data for the safety and immunogenicity analyses. For the efficacy analysis, missing data imputation based on predicted probability using a fully conditional specification method has been performed for the primary endpoint by assuming missing at random. Please refer to Section 11.1.1.7.3 for the results of this sensitivity analysis.

11.1.3.3 Interim Analyses and Data Monitoring

One interim efficacy analysis was planned and conducted when 50% of number of target events (75) have been reported across the active and control groups. For the IA, the Gamma (2) spending function was to be used for efficacy boundary specification. The unblinded statistical team performed the IA (at 76 cases for the primary endpoint) to assess the VE and provide the results to DSMB for review. The DSMB declared that the success criterion for the primary objective was not met at the interim and the study was to continue. No modifications in the study conduct or statistical analysis plan have been made based on the outcome of the IA. The alpha spending for IA was adjusted according to the actual number of reported cases and associated information fraction available at IA.

11.1.3.4 Multicenter Studies

This was a multi-site trial conducted by 31 PIs at 31 trial sites, in 5 countries (Section 6.1).

11.1.3.5 Multiple Comparisons/Multiplicity

For this study, multiple hypothesis testing for key secondary endpoints were planned, and were evaluated after the primary objective was met. The type I error for the key secondary was split equally for each hypothesis evaluation ($H2_a$ and $H2_b$). The statistical testing for H4 followed the success of the key secondary objective $H2_b$, similarly, the statistical hypothesis testing for H3 will follow the success of the key secondary objective $H2_a$. In this way, the overall type I error for the study was controlled at 5% level.

11.1.4 Tabulation of Individual Response Data

Individual response data are not provided with this report.

11.1.5 Vaccine Dose, Dosage and Relationships to Response

The vaccine composition is presented in **Listing 16.2.5**.

11.1.6 Vaccine – Vaccine/ Vaccine – Disease Interactions

No vaccine-vaccine or vaccine-disease interactions were assessed in this study.

11.1.7 By-Subject Displays

No by-subject displays are provided.

11.2 Efficacy Conclusions

11.2.1 Conclusions Relating to the Primary Efficacy Objective

The primary objective of the study was met:

- Two doses of SCB-2019 induced protection against COVID-19 of any severity in SARS-CoV-2–naïve adults with an efficacy of 67.2% (95.72% CI: 54.3–76.8).
- A re-analysis (sensitivity analysis) performed for the primary and 6-month follow-up efficacy objectives has shown SCB-2019 vaccine efficacy to be consistent with the original efficacy analysis results.

11.2.2 Conclusions Relating to the Key Secondary Efficacy Objectives

The pre-specified success criteria were met for three of four key secondary efficacy objectives.

- The efficacy of 2 doses SCB-2019 against moderate-to-severe COVID-19 was 83.7% (97.86% CI 55.9–95.4) in SARS-CoV-2–naïve adults. The pre-specified success criterion (LL of multiplicity-adjusted CI above 0) was met.
- The efficacy of 2 doses SCB-2019 against severe COVID-19 was 100% (97.86% CI 25.3–100.0) in SARS-CoV-2–naïve adults. The pre-specified success criterion (LL of multiplicity-adjusted CI above 0) was met.
- The efficacy of 2 doses SCB-2019 against any laboratory-confirmed SARS-CoV-2 infection was 34.4% (95% CI: 27.1-41.0) in SARS-CoV-2-naïve adults. The pre-specified success criterion (LL of multiplicity-adjusted CI above 0) was met.
- The efficacy of 2 doses SCB-2019 against any laboratory-confirmed asymptomatic SARS-CoV-2 infection was 12.9% (95% CI: -1.4-25.2) in SARS-CoV-2-naïve adults. The pre-specified success criterion (LL of multiplicity-adjusted CI above 0) was not met.

11.2.3 Conclusions Relating to the Other Secondary Efficacy Objectives

Secondary Efficacy Objective #1 – VE against burden of disease (BOD):

- The efficacy of 2 doses SCB-2019 against BOD was 48.9% (95% CI: 40.5-56.0) in SARS-CoV-2-naïve adults, with a BOD score of 260 for SCB-2019 recipients and 509 for placebo recipients.
- The efficacy of 2 doses SCB-2019 against BOD using an alternative score was 51.3% (95% CI: 42.8-58.4) in SARS-CoV-2-naïve adults, with a BOD score of 296 for SCB 2019 recipients and 608 for placebo recipients.

Secondary Efficacy Objective #2 – VE against RT-PCR-confirmed COVID-19 of any severity, associated with hospitalization:

- In SARS-CoV-2–naïve subjects, vaccine efficacy against COVID-19 of any severity, associated with hospitalization was 100% (95% CI 42.7–100).

Secondary Efficacy Objective #3 – VE by evidence of prior SARS-CoV-2 infection and risk of severe COVID-19:

- In SARS-CoV-2–exposed subjects, vaccine efficacy against COVID-19 of any severity was 64.2% (95% CI 26.5–83.8).
- In SARS-CoV-2–naïve adults at high risk of severe COVID-19, vaccine efficacy against COVID-19 of any severity was 65.9% (95% CI 35.7–82.9).
- In SARS-CoV-2–naive adults at low risk of severe COVID-19, vaccine efficacy against COVID-19 of any severity was 67.9% (95% CI 53.3–78.3).

Secondary Efficacy Objective #4 – VE after the first dose:

- In SARS-CoV-2–naïve subjects, vaccine efficacy against COVID-19 of any severity was 7.8% (95% CI −16.7 to 27.3) from 14 days after Dose 1 through to Dose 2.
- In SARS-CoV-2–exposed subjects in the Efficacy-FAS (Dose 1), vaccine efficacy against COVID-19 of any severity was 49.9% (95% CI 1.5–75.6) from 14 days after Dose 1 through to Dose 2.

Secondary Efficacy Objective #5 – VE against SARS-CoV-2 variants of concern:

- In SARS-CoV-2–naive subjects, vaccine efficacy against COVID-19 of any severity caused by the most frequent lineages of SARS-CoV-2 was 78.7% (95% CI 57.3–90.4) for Delta lineage, 58.6% (95% CI 13.3–81.5) for Mu lineage, and 91.8% (95% CI 44.9–99.8) for Gamma lineage.

In summary, the study was conducted in multiple countries with dominant circulation of various SARS-CoV-2 variants of concerns and variants of interest. The pre-specified success criteria to demonstrate efficacy of SCB-2019 vaccine against RT-PCR confirmed COVID-19 of any severity (primary efficacy objective), moderate-to severe COVID-19 and severe COVID-19 (key secondary objectives) in SARS-CoV-2 naïve individuals were met. Vaccine induces protection against COVID-19 disease caused by dominant lineages of SARS-CoV-2 (Delta, Mu, and Gamma).

In addition, SCB-2019 vaccine induces protection against COVID-19 of any severity in individuals with evidence of prior exposure to SARS-CoV-2.

11.2.4 Other Efficacy Conclusions

- Among SARS-CoV-2-naïve subjects, VE against severe COVID-19 and COVID-19-associated hospitalizations remains high within approximately 6 months after the primary vaccination.
- Among SARS-CoV-2-naïve subjects, VE against any cases of COVID-19 tends to be reduced within 6 months after vaccination.
- In subjects previously infected with SARS-CoV-2, no reduction in the protective efficacy of the vaccine was observed 6 months after primary vaccination.
- SCB-2019 vaccine provides sustained protection against COVID-19 disease in young (18-59 years of age) and older (≥60 years of age) adult subjects.

11.3 Immunogenicity Conclusions

11.3.1 Immunogenicity Conclusions for the Primary Vaccination Series

11.3.1.1 Conclusion Relating to the Secondary Immunogenicity Objective

Immunogenicity was assessed using the panel of serological assays in a subset of Phase 2 study participants at baseline (Day 1), at 21 days after the first vaccination (Day 22), and 14 days after the second vaccination (Day 36).

- Two doses of SCB-2019 vaccine, administered 21 days apart, induced robust immune response in SARS-CoV-2-naïve individuals as measured by prototype SARS-CoV-2 neutralization assay, pseudovirus SARS-CoV-2 neutralization assay, SCB-2019 binding ELISA, and ACE2 competitive ELISA.

11.3.1.2 Conclusions Relating to the Other Immunogenicity Objectives

- In SARS-CoV-2 exposed subjects, a single dose of SCB-2019 vaccine induced a rapid, significant and specific humoral immune response at 21 days after vaccination. The second dose was associated with further increase of antibody titers.
- For subjects without evidence of prior SARS-CoV-2 infection, after 2-dose immunization with SCB-2019 vaccine a cross-neutralizing response was observed against Alpha, Beta, Gamma, Delta, Mu, and Omicron BA.2 and BA.5 variants, but not against Omicron BA.1 and BA.4.
- For subjects with evidence of prior SARS-CoV-2 infection, a cross neutralizing response was observed against all variants at antibody levels associated with clinical protection. The antibody levels observed against different variants in the exposed subjects were comparable or higher to the levels observed against Wuhan-Hu-1 strain (GMTs: 156.7) in naïve subjects for whom a clinical efficacy was demonstrated.
- For all SARS-CoV-2 variants, cross-neutralizing response was higher in SARS-CoV-2 exposed subjects than in SARS-CoV-2-naïve subjects.
- Two doses of SCB-2019 induced Th1 polarized CD4 T cells responses, as evidenced by increasing frequency of IL-2, IFNγ and TNFα secreting CD4+ T cells. The Th1 response against S1 subunit tended to be higher than that against S2 subunit of the SARS-CoV-2 spike protein.
- No significant increase in Th2 or Th17 response were detected when stimulating with overlapping peptide pools from either S1 or S2 subunits of SARS-CoV-2 i.e. no increase in IL-4 or IL-5 or IL-17 or CD154 secreting cells were found.
- No significant increase in CD4+ response was observed when stimulating PBMCs from SCB 2019 vaccinees with Trimer-tag peptide pools or peptide pools from Gly repeats or CICP (portion of the trimer-tag molecule).

11.3.2 Immunogenicity Conclusions for the 6-month Follow-up Analysis

- SARS-CoV-2–specific antibodies persist for at least 6 months after the primary immunization of SARS-CoV-2 naïve subjects. Higher titers of neutralizing antibodies were observed in SARS-CoV-2 exposed subjects at 6 months after the primary immunization.

11.3.3 Immunogenicity Conclusions for Exploratory Analyses

11.3.3.1 Immunogenicity Conclusions for Elderly Subjects

Two doses of SCB-2019 vaccine, administered 21 days apart, induced immune response in SARS-CoV-2-naïve and SARS-CoV-2 exposed individuals 60 years and above as measured by prototype SARS-CoV-2 neutralization assay, and SCB-2019 binding ELISA. A two-dose vaccination series also induces cross-neutralizing antibodies against the Delta variant of SARS-CoV-2. Consistent with observation in overall study population, SCB-2019 vaccine boosts the immune response in individuals with a history of COVID-19 disease or presence of anti-SARS-CoV-2 antibodies at baseline. The magnitude of immune response in elderly subjects appeared to be lower compared to younger population.

11.3.3.2 Immunogenicity Conclusions for Individuals with HIV Infection

Two doses of SCB-2019 vaccine, administered 21 days apart, induced a robust immune response in SARS-CoV-2-naïve and exposed individuals as measured by prototype SARS-CoV-2 neutralization assay, and SCB-2019 binding ELISA in both the overall and HIV infected populations. Consistent with observation in overall study population, SCB-2019 vaccine boosts the immune response in HIV infected individuals with a history of COVID-19 disease or presence of anti-SARS-CoV-2 antibodies at baseline. No difference in immunogenicity was observed in HIV infected subjects compared to the overall population.

11.3.3.3 Immunogenicity Conclusions for Subjects of Chinese Origin

Two doses of SCB-2019 vaccine, administered 21 days apart, induced a robust immune response in SARS-CoV-2-naïve and exposed individuals as measured by prototype SARS-CoV-2 neutralization assay, and SCB-2019 binding ELISA in both the overall and Chinese origin populations. No consistent difference in immunogenicity was observed in Chinese origin subjects compared to the overall population.

11.3.3.4 Immunological Comparability of SCB-2019 Drug Substance Manufactured at 2000L and 200L Scales

The two manufacturing scales evaluated were considered to be comparable as the pre-specified non-inferiority criteria for immunogenicity of SCB-2019 vaccine manufactured at 2000L scale vs 200L scale were met as measured by prototype SARS-CoV-2 neutralization assay and by SCB-2019 binding ELISA.

12.0 SAFETY EVALUATION

This section presents the safety data for all adults enrolled in the study from Dose 1 to 1 December 2021 (SAF).

All summaries and analyses of safety data were based on subjects in the Phase-2 SAF for reactogenicity and unsolicited AEs in the 6-week period after the first dose; in the SAF (including Phase 2 and Phase 3 subjects) for SAEs, MAAEs, AESIs, AE leading to study termination, and unsolicited AEs in the 6-week period after the first dose; and in the Immunogenicity PPS for the measurement of Trimer-Tag–specific serum antibodies. In both SAF and Phase-2 SAF, subjects were grouped according to the vaccine/placebo they received at least the first dose.

In addition, this section presents the safety data for specific adult populations, including elderly subjects, subjects with HIV infection, subjects who are of Chinese origin, and subjects who received SCB-2019 vaccine from two different manufacturing scales.

In the body of this section, the "round half to the nearest even" rounding convention has been applied to the safety data in certain cases to aid clarity. In this convention, a value exactly halfway between two digits is rounded to the nearest even digit (e.g., 1.5 is halfway between 1 and 2 and is rounded to 2); and all other values are rounded to the nearest digit.

12.1 Extent of Exposure

The SAF adults (including both, Phase 2 and Phase 3 subjects), from Dose 1 up to 1 December 2021 included 15070 adult recipients of at least 1 dose of SCB-2019, and 15067 adult recipients of at least 1 dose of placebo (**Table 14.1.1.1_P6m**). Of those, 14011 subjects (93.0%) received 2 doses of SCB-2019, and 13861 subjects (92.0%) received 2 doses of placebo (**Table 14.1.1.2.1_P6m**).

A total of 1601 subjects participated in Phase 2 part of the study and included in the Phase 2–SAF (Table 66). These subjects were requested to report unsolicited AEs from Day 1 to Day 43 and record solicited AEs within 7 days after each dose, using electronic diary cards. Overall, solicited safety data was available for 99.4% and 99.1% of subjects after the first dose, and 86.9% and 88.1% after the second dose, in SCB-2019 and Placebo arms, respectively. All Phase 2 subjects provided information about unsolicited AEs after the first dose. The proportion of subjects included in the safety analysis sets was similar between SCB-2019 and Placebo arms.

Table 66 Subject Exposure

	SCB-2019 n (%)	Placebo n (%)	Total n (%)
SAF	15070	15067	30137
Phase 2 – SAF	808 (100%)	793 (100%)	1601 (100%)
Solicited Safety Set			
Days 1-7 post-Dose 1	802 (99.2%)	784 (98.9%)	1586 (98.9%)
Days 1-7 post-Dose 2	701 (86.8%)	698 (88.0%)	1399 (87.4%)
Unsolicited Safety Set			
Day 1 – Day 43	808 (100%)	793 (100%)	1601 (100%)

Source **Table 14.1.1.1_P6m**, **Table 14.3.1.1** and **Table 14.3.2.2**. Percentage of subjects was calculated as $100 \times n_s/N$, where n_s=number of subjects provided safety information for respective safety endpoint, and N=number of subjects in the Phase 2 - SAF.

12.2 Adverse Events

Medical Dictionary for Regulatory Activities (MedDRA) terms presented in Sections 12.2 and 12.3 are MedDRA SOCs/HLTs/PTs.

Safety data are located in **Tables 14.3.1.1** to **14.3.2.14** and **Tables 14.3.2.1_P6m** to **14.3.2.14_P6m**. Individual subject data are in **Listing 16.2.7**.

12.2.1 Brief Summary of Adverse Events

In the Phase-2 SAF, and within the 7-day periods after either dose, solicited local AEs were reported by 44% (349/803) of SCB-2019 recipients and 15% (119/787) of placebo recipients (Table 67). Solicited systemic AEs were reported by 43% (347/803) of SCB-2019 recipients and 40% (312/787) of placebo recipients (Table 67).

In the Phase-2 SAF, and within the 6-week period after receiving the 1st dose, unsolicited AEs were reported by 12% (94/808) of SCB-2019 recipients and 14% (112/793) of placebo recipients (Table 67). Related unsolicited AEs (i.e., unsolicited AEs considered by the investigator as related to vaccination were reported by 3.1% (25/808) of SCB-2019 recipients and 3.3% (26/793) of placebo recipients (Table 67).

In the SAF, from Dose 1 to 3-weeks after Dose 2 (Day 43), unsolicited AEs were reported by 10.2% (1543/15070) of SCB-2019 recipients and 9.4% (1414/15067) of placebo recipients (Table 68). Related unsolicited AEs (i.e. unsolicited AEs considered by the investigator as related to vaccination) were reported by 4.6% (690/15070) of SCB-2019 recipients and 3.0% (459/15067) of placebo recipients.

From Dose 1 to 1 December 2021, 114 SAEs were reported by 0.6% (90/15070) of SCB-2019 recipients and 176 SAEs were reported by 0.8% (114/15067) of placebo recipients (Table 68). Nine deaths were reported among SCB-2019 recipients, and 23 deaths were reported among placebo recipients. Four related SAEs were reported by four SCB-2019 recipients, and four related SAEs were reported by two placebo recipients.

From Dose 1 to 1 December 2021, MAAEs were reported by 7.1% (1071/15070) of SCB-2019 recipients and 8.0% (1211/15067) of placebo recipients (Table 68). AESIs were reported by 2.1% (323/15070) of SCB-2019 recipients and 3.3% (496/15067) of placebo recipients. AEs leading to early study termination were reported by 0.1% (9/15070) of SCB-2019 recipients and 0.2% (23/15067) of placebo recipients.

Overall, a lower proportion of subjects experienced SAEs, MAAEs and AESIs with SCB-2019 than with placebo.

Table 67 Overall Summary of Solicited (Days 1-7) and Unsolicited AEs (Days 1-43) (Phase 2 - SAF)

Adverse event [AE]	SCB-2019 (N=803-808)		Placebo (N=786-793)	
	Number of subjects, n_s (number of events, n_e)	% subjects (95% CI)	Number of subjects, n_s (number of events, n_e)	% subjects (95% CI)
Any local solicited AE	349	44 (40-47)	119	15 (13-18)
Any systemic solicited AE	347	43 (40-47)	312	40 (36-43)
Any unsolicited AE	94 (123)	11.6 (9.5–14.0)	112 (140)	14.1 (11.8–16.7)
• Related	25 (31)	3.1 (2.0–4.5)	26 (33)	3.3 (2.2–4.8)
• Severe	1 (1)	0.1 (0.0-0.7)	2 (2)	0.3 (0.0-0.9)

Source **Table 14.3.1.1**, **Table 14.3.1.4**, **Table 14.3.2.2, Table 14.3.2.3, Table 14.3.2.4**. Percentage of subjects was calculated as $100 \times n_s/N$, where n_s=number of subjects reporting the AE, and N=number of subjects in the Phase 2 - SAF by arm. A related AE was an AE which the investigator considered to be probably or possibly caused by the study vaccine. CI, confidence interval. AE were excluded if occurring after the administration of another COVID-19 vaccine.

Table 68 Overall Summary of Unsolicited AEs, SAEs MAAEs, AESIs and AEs Leading to Study Termination (SAF)

Adverse event (AE) type	SCB-2019 (N=15070)		Placebo (N=15067)	
	Number of subjects, n_s (number of events, n_e)	% subjects (95% CI)	Number of subjects, n_s (number of events, n_e)	% subjects (95% CI)
Unsolicited AE*	1543 (2293)	10.2 (9.8–10.7)	1414 (2040)	9.4 (8.9–9.9)
• Related	690 (1024)	4.6 (4.3–4.9)	459 (616)	3.0 (2.8–3.3)
• Severe	33 (39)	0.2 (0.2-0.3)	33 (37)	0.2 (0.2-0.3)
Serious AE (SAE)	90 (114)	0.6 (0.5–0.7)	114 (176)	0.8 (0.6–0.9)
• Related	4 (4)	0 (0.0–0.1)	2 (4)	0 (0.0–0.0)
Medically attended AE (MAAE)	1071 (1697)	7.1 (6.7–7.5)	1211 (1910)	8.0 (7.6–8.5)
AE of special interest (AESI)	323 (509)	2.1 (1.9–2.4)	496 (791)	3.3 (3.0–3.6)
AE leading to early study termination	9 (10)	0.1 (0.0–0.1)	23 (29)	0.2 (0.1–0.2)
Death	9 (9)	0.1 (0.0–0.1)	23 (29)	0.2 (0.1–0.2)

Source **Tables 14.3.2.1_P6m**, **14.3.2.2_P6m** and **14.3.2.3_P6m** and **14.3.2.4_P6m**. Percentage of subjects was calculated as $100 \times n_s/N$, where n_s=number of subjects reporting the AE, and N=number of subjects in the SAF by arm. A related AE was an AE which the investigator considered to be probably or possibly caused by the study vaccine. CI, confidence interval. AEs were excluded if occurring after other COVID-19 vaccine. *Any unsolicited AEs were collected from Day 1 up to 3 weeks after Dose 2 (Day 43). Other AE types were collected from Day 1 up to 1 December 2021.

12.2.2 Display of Adverse Events

For the Phase-2 SAF, summaries of AEs (solicited local and systemic) within 7 days after each dose are presented in Figure 9, Figure 10, Table 69, Table 70, and **Table 14.3.1.1** to **Table 14.3.1.7**; and summaries of unsolicited AEs within 21 days after each dose are presented in Table 75, Table 76, and **Table 14.3.2.2** to **Table 14.3.2.4**. For SAF, summaries of unsolicited AEs within 21 days after each dose are presented in **Table 14.3.2.2_P6m** to **Table 14.3.2.4_P6m**; summaries of SAEs, AESIs, MAAEs, and AEs that led to early study

termination throughout the study are presented in Table 71 to Table 74, and **Table 14.3.2.6_P6m** to **Table 14.3.2.11_P6m**; summary of unsolicited AEs reported within 30 minutes after any vaccination are presented in Table 77 and **Table 14.3.2.5**.

12.2.3 Analysis of Adverse Events

12.2.3.1 Primary objective: the safety and reactogenicity of SCB-2019

12.2.3.1.1 *Solicited Local Reactions (Phase 2 SAF)*

Solicited local AEs were reported more frequently by SCB-2019 recipients than placebo recipients (Table 69 and Figure 9). Within the 7-day periods after either dose, these solicited AEs were reported by 44% (349/803) of SCB-2019 recipients and 15% (119/787) of placebo recipients. The majority of solicited local AEs reported were mild in intensity. Moderate intensity AEs were reported by 4.4% (35/803) SCB-2019 recipients and 0.1% (1/787) of placebo recipients; and severe intensity AEs (PTs: injection site pain, erythema and swelling) were reported by 0.9% (7/803) SCB-2019 recipients and 0.1% (1/787) of placebo recipients.

Injection-site pain was the most frequent local symptom, being reported by 42% (340/803) of SCB-2019 recipients and 14% (107/787) of placebo recipients (Table 69). Severe AEs of injection-site pain was experienced by 6 subjects (0.7%) after any injection in SCB-2019 recipients.

Frequencies of solicited local AEs were generally lower after the 2nd dose than after the 1st dose (Table 69). After the 2nd and 1st doses, solicited local AEs were reported by 28% (198/702) and 36% (290/803) of SCB-2019 recipients, respectively, and 8% (57/699) and 11% (89/786) of placebo recipients, respectively. A similar pattern was observed with severe solicited local AEs, even though very few subjects reported severe AEs. Notably, after the 2nd and 1st doses, severe solicited local AEs were reported by 0.4% (3/702) and 0.6% (5/803) of SCB-2019 recipients, respectively.

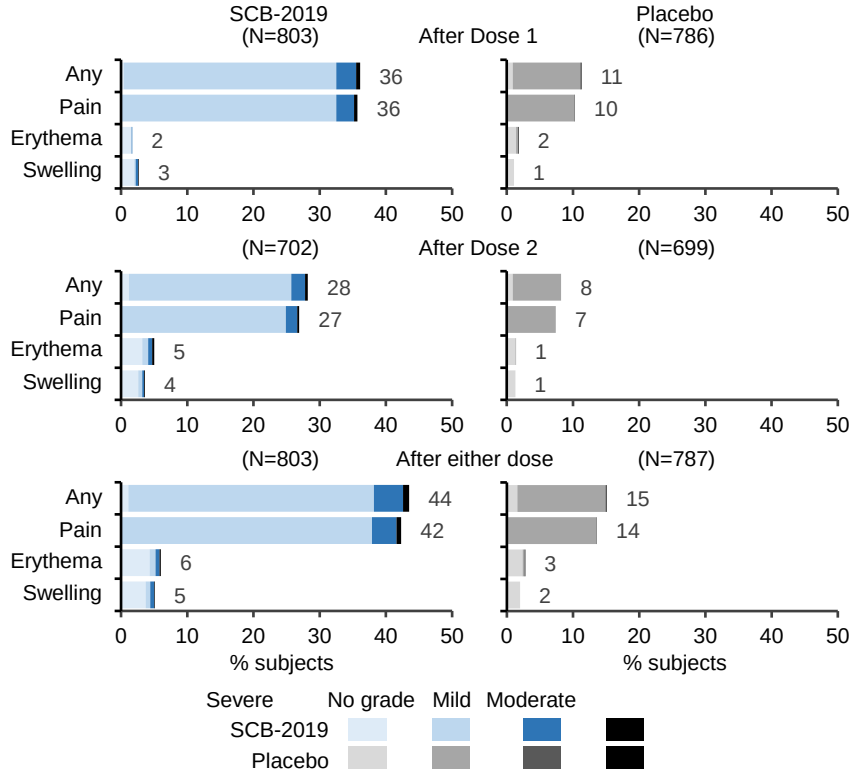
Solicited local AEs were transient, generally resolved in the 7-day period after dosing; and the duration of these AEs were similar between the SCB-2019 arm and the Placebo arm (**Table 14.3.1.2**). For SCB-2019 recipients, the mean duration of symptoms ranged from 1.5 days (erythema, N=14; Dose 1) to 2.0 days (injection-site pain, N=189; Dose 2). The mean duration of injection-site pain – the most frequent symptom – was 1.9 days after Dose 1 (N=287), and 2.0 days after Dose 2 (N=189). For Placebo recipients, the mean duration of symptoms ranged from 1.2 day (swelling, N=9, Dose 1) to 2.7 days (erythema, N=10; Dose 2). The mean duration of injection-site pain – the most frequent symptom – was 1.5 days after Dose 1 (N=81), and after Dose 2 (N=52).

Table 69: Solicited Local Adverse Events (Phase 2 SAF)

After Dose	Solicited Local Adverse Event (AE)	N_e	Any intensity		Moderate		Severe	
			n	% (95%CI)	n	% (95%CI)	n	% (95%CI)
SCB-2019 (N=808)								
1	**Any**	803	290	36 (33–40)	24	3.0 (1.9–4.4)	5	0.6 (0.2–1.4)
2	**Any**	702	198	28 (25–32)	15	2.1 (1.2–3.5)	3	0.4 (0.1–1.2)
1 or 2	**Any**	803	349	44 (40–47)	35	4.4 (3.1–6.0)	7	0.9 (0.4–1.8)
	• Injection-site pain		340	42 (39–46)	30	3.7 (2.5–5.3)	6	0.7 (0.3–1.6)
	• Erythema		48	6.0 (4.4–7.8)	5	0.6 (0.2–1.4)	2	0.2 (0.0–0.9)
	• Swelling		41	5.1 (3.7–6.9)	5	0.6 (0.2–1.4)	1	0.1 (0.0–0.7)
Placebo (N=793)								
1	**Any**	786	89	11 (9–14)	1	0.1 (0.0–0.7)	1	0.1 (0.0–0.7)
2	**Any**	699	57	8 (6–10)	0	0.0 (0.0–0.5)	0	0.0 (0.0–0.5)
1 or 2	**Any**	787	119	15 (13–18)	1	0.1 (0.0–0.7)	1	0.1 (0.0–0.7)
	• Injection-site pain		107	14 (11–16)	1	0.1 (0.0–0.7)	0	0.0 (0.0–0.5)
	• Erythema		22	2.8 (1.8–4.2)	0	0.0 (0.0–0.5)	1	0.1 (0.0–0.7)
	• Swelling		16	2.0 (1.2–3.3)	0	0.0 (0.0–0.5)	0	0.0 (0.0–0.5)

Source: **Table 14.3.1.1**. Solicited local AEs were recorded within 7 days after each dose. For a given subject and when more than one AE was reported for a given symptom within the 7-day period, the most severe AE in intensity grading was included in the calculations of percentages. Some values have been rounded to 2 significant figures or to the nearest integer to aid comprehension.

Figure 9 Solicited Local Adverse Events (Phase 2 SAF)



Legend to Figure 9 on previous page. Source: **Table 14.3.1.1**. Percentage of subjects with solicited local adverse events (AEs) after Dose 1 (upper graphs), Dose 2 (middle graphs) and either dose (lower graphs) overall, and by symptom and intensity. Solicited local AEs were recorded within 7 days after each dose. For a given subject and when more than one AE was reported for a given symptom within the 7-day period, the most severe AE in intensity grading was included in the calculations of percentages. The percentages annotated in the graphs have been rounded in accordance with the "round half to the nearest even integer" convention.

Subgroup Analysis for Solicited Local Adverse Events

No notable differences in frequency and severity of solicited local AEs were observed in the subgroup analysis. The results of the subgroup analyses were in line with the overall analysis (the results by age: **Table 14.3.1.1.1**, by sex: **Table 14.3.1.1.2**, by race: **Table 14.3.1.1.3**, by country: **Table 14.3.1.1.4**, by evidence of prior SARS-CoV-2 infection: **Table 14.3.1.1.5**, by baseline risk factors: **Table 14.3.1.1.6**).

12.2.3.1.2 *Solicited Systemic Adverse Events (Phase 2 SAF)*

Solicited systemic AEs were reported by SCB-2019 recipients at a similar frequency to that reported by placebo recipients (Table 70 and Figure 10). Within the 7-day periods after either dose, these solicited AEs were reported by 43% (347/803) of SCB-2019 recipients and 40% (312/787) of placebo recipients. The majority of solicited systemic AEs were mild in intensity. Solicited systemic AEs of moderate intensity were reported by 11% (89/803) of SCB-2019 recipients and 11% (89/787) of placebo recipients; and solicited systemic AEs of severe intensity were reported by 3.6% (29/803) SCB-2019 recipients and 2.3% (18/787) of placebo recipients.

Fatigue and headache were the most frequent systemic symptoms; fatigue being reported by 27% (219/803) of SCB-2019 recipients and 24% (189/787) of placebo recipients; and headache being reported by 27% (219/803) of SCB-2019 recipients and 26% (201/787) of placebo recipients (Table 70).

Frequencies of solicited systemic AEs were generally lower after the 2nd dose than after the 1st dose (Table 70). After the 2nd and 1st doses, solicited systemic AEs were reported by 23% (162/702) and 36% (288/803) of SCB-2019 recipients, respectively, and 21% (147/699) and 34% (268/786) of placebo recipients, respectively. A similar pattern was observed with severe solicited systemic AEs. Notably, after the 2nd and 1st doses, severe solicited systemic AEs were reported by 1.4% (10/702) and 2.4% (19/803) of SCB-2019 recipients, respectively.

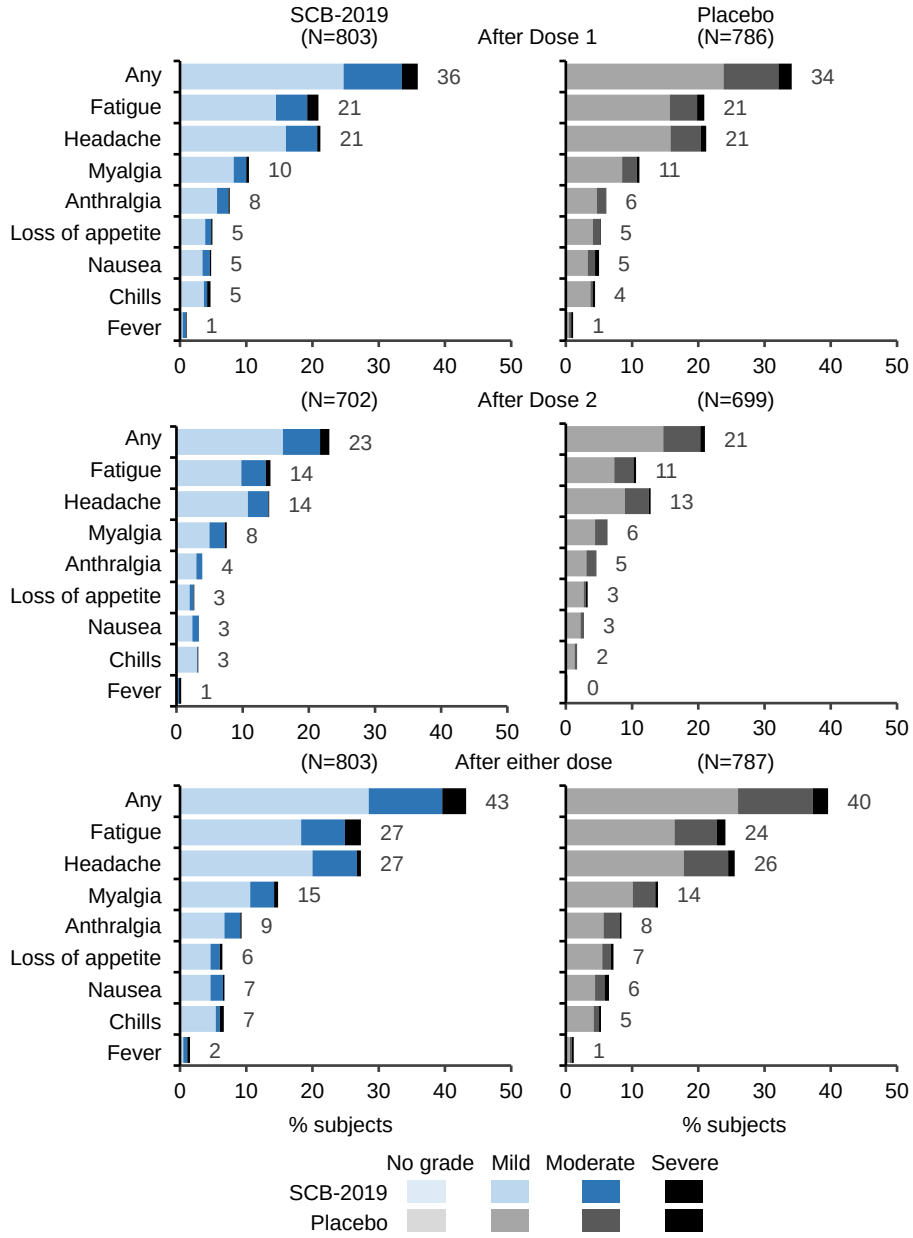
Solicited systemic AEs were transient, generally resolved in the 7-day period after dosing; and the duration of these AEs were similar between the SCB-2019 arm and the Placebo arm (**Table 14.3.1.5**). For SCB-2019 recipients, the mean duration of symptoms ranged from 1.3 days (loss of appetite, N=39; fever, N=8; Dose 1) to 2.4 days (loss of appetite, N=19; Dose 2). The mean duration of headache – the most frequent symptom – was 2.1 days after Dose 1 (N=170), and 2.0 days after Dose 2 (N=98). For placebo recipients, the mean duration of symptoms ranged from 1.0 day (fever, N=2, Dose 2) to 2.4 days (fatigue, N=74; Dose 2). The mean duration of headache – the most frequent symptom – was 2.1 days after Dose 1 (N=166), and 2.2 days after Dose 2 (N=89).

Table 70: Solicited Systemic Adverse Events (Phase 2 SAF)

After Dose	Solicited Systemic Adverse Event (AE)	N_e	Any intensity		Moderate		Severe	
			n	% (95%CI)	n	% (95%CI)	n	% (95%CI)
SCB-2019 (N=808)								
1	**Any**	803	288	36 (32–39)	71	8.8 (7.0–11.0)	19	2.4 (1.4–3.7)
2	**Any**	702	162	23 (20–26)	39	5.6 (4.0–7.5)	10	1.4 (0.7–2.6)
1 or 2	**Any**	803	347	43 (40–47)	89	11.1 (9.0–13.5)	29	3.6 (2.4–5.1)
	• Fatigue		219	27 (24–30)	53	6.6 (5.0–8.5)	19	2.4 (1.4–3.7)
	• Headache		219	27 (24–30)	54	6.7 (5.1–8.7)	5	0.6 (0.2–1.4)
	• Myalgia		119	15 (12–18)	29	3.6 (2.4–5.1)	5	0.6 (0.2–1.4)
	• Arthralgia		75	9.3 (7.4–11.6)	19	2.4 (1.4–3.7)	2	0.2 (0.0–0.9)
	• Loss of appetite		51	6.4 (4.8–8.3)	11	1.4 (0.7–2.4)	3	0.4 (0.1–1.1)
	• Nausea		54	6.7 (5.1–8.7)	15	1.9 (1.0–3.1)	2	0.2 (0.0–0.9)
	• Chills		53	6.6 (5.0–8.5)	5	0.6 (0.2–1.4)	5	0.6 (0.2–1.4)
	• Fever		12	1.5 (0.8–2.6)	5	0.6 (0.2–1.4)	3	0.4 (0.1–1.1)
Placebo (N=793)								
1	**Any**	786	268	34 (31–38)	65	8.3 (6.4–10.4)	16	2.0 (1.2–3.3)
2	**Any**	699	147	21 (18–24)	39	5.6 (4.0–7.5)	5	0.7 (0.2–1.7)
1 or 2	**Any**	787	312	40 (36–43)	89	11.3 (9.2–13.7)	18	2.3 (1.4–3.6)
	• Fatigue		189	24 (21–27)	50	6.4 (4.8–8.3)	10	1.3 (0.6–2.3)
	• Headache		201	26 (22–29)	53	6.7 (5.1–8.7)	8	1.0 (0.4–2.0)
	• Myalgia		109	14 (12–16)	27	3.4 (2.3–5.0)	3	0.4 (0.1–1.1)
	• Arthralgia		66	8.4 (6.5–10.5)	19	2.4 (1.5–3.7)	2	0.3 (0.0–0.9)
	• Loss of appetite		56	7.1 (5.4–9.1)	10	1.3 (0.6–2.3)	3	0.4 (0.1–1.1)
	• Nausea		51	6.5 (4.9–8.4)	12	1.5 (0.8–2.6)	5	0.6 (0.2–1.5)
	• Chills		41	5.2 (3.8–7.0)	6	0.8 (0.3–1.7)	2	0.3 (0.0–0.9)
	• Fever		9	1.1 (0.5–2.2)	2	0.3 (0.0–0.9)	2	0.3 (0.0–0.9)

Source: **Table 14.3.1.4**. Solicited systemic AEs were recorded within 7 days after each dose. For a given subject and when more than one AE was reported for a given symptom within the 7 day period, the most severe AE in intensity grading was included in the calculations of percentages. Percentages were calculated as 100×n/Ne. n_e= number of events. Some values have been rounded to 2 significant figures or to the nearest integer to aid comprehension.

Figure 10 Solicited Systemic Adverse Events (Phase 2 SAF)



Source: **Table 14.3.1.4**. Percentage of subjects with solicited systemic adverse events (AEs) after Dose 1 (upper graphs), Dose 2 (middle graphs) and either dose (lower graphs) overall, and by symptom and intensity. Solicited systemic AEs were recorded within 7 days after each dose. For a given subject and when more than one AE was reported for a given symptom within the 7-day period, the most severe AE in intensity grading was included in the calculations of percentages. The percentages annotated in the graphs have been rounded in accordance with the "round half to the nearest even integer" convention.

Subgroup Analyses for Solicited Systemic Adverse Events

No notable differences in frequency and severity of solicited systemic AEs were observed in the subgroup analysis. The results of the subgroup analyses were in line with the overall analysis (the results by age: **Table 14.3.1.4.1**, by sex: **Table 14.3.1.4.2**, by race: **Table 14.3.1.4.3**, by country: **Table 14.3.1.4.4**, by evidence of prior SARS-CoV-2 infection: **Table 14.3.1.4.5**, by baseline risk factors: **Table 14.3.1.4.6**).

Other Indicators of Reactogenicity

Overall, 82 of 808 (10%) and 78 of 793 (9.8%) subjects in the SCB-2019 and placebo arms, respectively, used antipyretics/analgesics for treatment or prophylaxis of injection site pain and/or other post-dosing reactions (**Table 14.3.1.7**).

12.2.3.1.3 *Serious Adverse Events From Day 1 to the Cutoff Date (1 December 2021) (SAF)*

From Dose 1 to 1 December 2021, overall, 90 (0.6%) subjects in the SCB-2019 arm and 114 (0.8%) subjects in the Placebo arm reported at least one SAE. The number of SAEs reported in subjects appeared to be lower in the SCB-2019 arm (114) than in the Placebo arm (176), possibly reflecting a lower frequency of AEs categorized under preferred terms related to COVID-19 (Table 71, **Table 14.3.2.6_P6m** and **Section 14.3.3**).

SAEs were most frequently reported in the SOCs Infections and infestations (reported by 23 [0.2%] of subjects in SCB-2019 arm and 46 [0.3%] in the Placebo arm), and Injury, poisoning and procedural complications (reported by 18 [0.1%] of subjects in SCB-2019 arm and 20 [0.1%] in the Placebo arm).

The most frequently reported SAEs by PTs were COVID-19 (reported by 2 [0.0%] of subjects in SCB-2019 arm and 19 [0.1%] in the Placebo arm), COVID-19 pneumonia (reported by 0 [0.0%] of subjects in SCB-2019 arm and 9 [0.1%] in the Placebo arm) and abortion spontaneous (reported by 4 [0.0%] of subjects in SCB-2019 arm and 8 [0.1%] in the Placebo arm).

Please refer to **Section 14.3.3** for full list of narratives.

Table 71 SAEs, Reported by ≥3 Subjects in any Group, by PTs up to the Cutoff Date for Safety Analysis (SAF)

Serious adverse event (SAE) by System organ class (SOC)/Preferred term (PT)	SCB-2019 (N=15070)		Placebo (N=15067)	
	Number of subjects, n_s (number of events, n_e)	% subjects (95% CI)	Number of subjects, n_s (number of events, n_e)	% subjects (95% CI)
Any SAE	90 (114)	0.6 (0.5–0.7)	114 (176)	0.8 (0.6–0.9)
Cardiac disorders	8 (8)	0.1 (0–0.1)	8 (11)	0.1 (0–0.1)
• Acute myocardial infarction	2 (2)	0.0 (0–0)	3 (3)	0.0 (0–0.1)
• Acute coronary syndrome	1 (1)	0.0 (0–0)	3 (3)	0.0 (0–0.1)
• Cardiogenic shock	0 (0)	0.0 (0–0)	3 (3)	0.0 (0–0.1)
General disorders and administration site conditions	3 (3)	0.0 (0–0.1)	2 (2)	0.0 (0–0)
Hepatobiliary disorders	2 (2)	0.0 (0–0)	6 (7)	0.0 (0–0.1)
• Cholelithiasis	0 (0)	0.0 (0–0)	4 (4)	0.0 (0–0.1)
Immune system disorders	3 (3)	0.0 (0–0.1)	1 (1)	0.0 (0–0)
• Hypersensitivity	3 (3)	0.0 (0–0.1)	0 (0)	0.0 (0–0)
Infections and infestations	23 (25)	0.2 (0.1–0.2)	46 (62)	0.3 (0.2-0.4)
• Urinary tract infection	4 (4)	0.0 (0–0.1)	4 (4)	0.0 (0–0.1)
• COVID-19	2 (2)	0.0 (0–0)	19 (19)	0.1 (0.1–0.2)
• Pneumonia	2 (2)	0.0 (0–0)	6 (6)	0.0 (0–0.1)
• Appendicitis	1 (1)	0.0 (0–0)	4 (4)	0 (0-0.1)
• COVID-19 pneumonia	0 (0)	0.0 (0–0)	9 (9)	0.1 (0–0.1)
Injury, poisoning and procedural complications	18 (24)	0.1 (0.1-0.2)	20 (24)	0.1 (0.1-0.2)
• Humerus fracture	3 (3)	0.0 (0–0.1)	1 (1)	0.0 (0–0)
• Animal bite	1 (2)	0.0 (0–0)	4 (4)	0.0 (0–0.1)
• Gunshot wound	0 (0)	0.0 (0–0)	3 (3)	0.0 (0–0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (3)	0.0 (0-0.1)	3 (3)	0.0 (0-0.1)
Nervous system disorders	7 (7)	0.0 (0-0.1)	12 (14)	0.1 (0-0.1)
Pregnancy, puerperium and perinatal conditions	9 (12)	0.1 (0-0.1)	12 (12)	0.1 (0-0.1)
• Abortion spontaneous	4 (4)	0.0 (0-0.1)	8 (8)	0.1 (0-0.1)
Psychiatric disorders	5 (5)	0.0 (0-0.1)	1 (2)	0.0 (0–0)
Renal and urinary disorders	3 (3)	0.0 (0–0.1)	6 (6)	0.0 (0-0.1)
Reproductive system and breast disorders	4 (4)	0.0 (0–0.1)	2 (2)	0.0 (0-0)
Respiratory, thoracic and mediastinal disorders	5 (6)	0.0 (0–0.1)	11 (14)	0.1 (0–0.1)
• Acute respiratory distress syndrome	1 (1)	0.0 (0–0)	3 (3)	0.0 (0–0.1)
• Acute respiratory failure	0 (0)	0.0 (0–0)	4 (4)	0.0 (0–0.1)

Source **Table 14.3.2.6_P6m.** Percentage of subjects was calculated as $100 \times n_s/N$, where n_s=number of subjects reporting the AE, and N=number of subjects in the SAF by arm. SAEs were collected from Day 1 cutoff date for safety analysis (1 December 2021). CI, confidence interval. AEs were excluded if occurring after the administration of another COVID-19 vaccine.

12.2.3.1.4 *Related Serious Adverse Events from Day 1 to the Cutoff Date (1 December 2021) (SAF)*

From Dose 1 to 1 December 2021, eight SAEs considered by the investigator as related to vaccination were reported by 4 SCB-2019 recipients (4 events) and 2 placebo recipients (4 events) (**Table 14.3.2.7_P6m** and **Section 14.3.3**).

The four related SAEs reported by the four SCB-2019 recipients were hypersensitivity (2 events), Bell's palsy, and spontaneous abortion (**Listing 14.3.2.2_P6m** and **Section 14.3.3**). Three related SAEs were reported by one placebo recipient and were (i) COVID-19 and (ii) pneumonia, and (iii) acute respiratory distress syndrome. A fourth related SAE was reported by one placebo recipient and was spontaneous abortion.

12.2.3.1.5 *Adverse Events of Special Interest From Day 1 to the Cutoff Date (1 December 2021) (SAF)*

Two categories of AEs of special interest were collected in the study: potential immune mediated diseases and AEs relevant to COVID-19 (according to Guidance document from Safety Platform for Emergency vACcines [SPEAC]. These categories of AESIs are summarized together.

Table 72 and **Table 14.3.2.9_P6m** provides overview of AESIs reported by ≥2 subjects in this study by arm, grouped by MedDRA SOC and PT:

- Overall, 323 (2.1%) subjects in the SCB-2019 arm and 496 (3.3%) subjects in the Placebo arm reported at least one AESI. The number of AESIs reported in subjects appeared to be lower in the SCB-2019 arm (509) than in the Placebo arm (791), reflecting a difference in the number of Anosmia (252 vs 386) and Ageusia (201 vs 327) AEs in the SCB-2019 and Placebo arms.
- AESIs were most frequently reported in the SOCs Nervous system disorders (reported by 288 [1.9%] subjects in the SCB-2019 arm and 463 [3.1%] subjects in the Placebo arm), Skin and subcutaneous tissue disorders (reported by 12 [0.1%] subjects in the SCB-2019 arm and 13 [0.1%] subjects in the Placebo arm), and Immune system disorders (reported by 6 [0.0%] subjects in the SCB-2019 arm and 6 [0.0%] subjects in the Placebo arm).
- The most frequently reported AESIs were Anosmia (reported by 251 [1.7%] subjects in the SCB-2019 arm and 384 [2.5%] subjects in the Placebo arm), and Ageusia (reported by 199 [1.3%] subjects in the SCB-2019 arm and 326 [2.3%] subjects in the Placebo arm).
- No notable differences in frequency of AESIs between the SCB-2019 and Placebo arms were observed for all SOCs and PTs, except Anosmia (252 vs 386 events), and Ageusia (201 vs 327 events). Two cases of Bell's palsy were reported in the SCB-2019 arm, with no cases in the Placebo arm (Section 12.3.2).
- AESIs assessed as related to study vaccination were reported by 12 (0.1%) subjects in the SCB-2019 arm and 13 (0.1%) subjects in Placebo arm (**Table 14.3.2.9c_P6m**).
- AESIs related to study vaccination were most frequently reported in the following SOCs: Skin and subcutaneous tissue disorders [reported by 5 (0.0%) subjects in the SCB 2019 arm and 8 (0.1%) subjects in the Placebo arm], and Immune system disorders [reported by 4 (0.0%) subjects in the SCB-2019 arm and 2 (0.0%) subjects in the Placebo arm].
- The two most frequently reported AESIs related to study vaccination by PT were Hypersensitivity [reported by 4 (0.0%) subjects in the SCB-2019 arm and 2 (0.0%) subjects in the Placebo arm], Urticaria [reported by 3 (0.0%) subjects in the SCB-2019 arm and 2 (0.0%) subjects in the Placebo arm], and Alopecia areata [reported by 1 (0.0%) subjects in the SCB-2019 arm and 2 (0.0%) subjects in the Placebo arm].

A brief narrative for the subjects who experienced hypersensitivity reactions and Bell's palsy, and for the subject with dermatitis herpetiformis is presented in Section 12.3.2.

Table 72 AESIs, Reported by ≥2 Subjects in any Group, by PT up to the Cutoff Date for Safety Analysis (SAF)

Adverse event of special interest (AESI) by System organ class (SOC)/Preferred term (PT)	SCB-2019 (N=15070)		Placebo (N=15067)	
	Number of subjects, n_s (number of events, n_e)	% subjects (95% CI)	Number of subjects, n_s (number of events, n_e)	% subjects (95% CI)
Any	323 (509)	2.1 (1.9–2.4)	496 (791)	3.3 (3.0-3.6)
Cardiac disorders	7 (7)	0.0 (0–0.1)	2 (2)	0.0 (0–0.0)
• Sinus tachycardia	2 (2)	0.0 (0–0)	0 (0)	0.0 (0–0)
• Tachycardia	2 (2)	0.0 (0–0)	0 (0)	0.0 (0–0)
Immune system disorders	6 (6)	0.0 (0–0.1)	6 (6)	0.0 (0–0.1)
• Hypersensitivity	6 (6)	0.0 (0–0.1)	4 (4)	0.0 (0–0.1)
• Anaphylactic reaction	0 (0)	0.0 (0–0)	2 (2)	0.0 (0–0)
Infections and infestations	1 (1)	0.0 (0–0)	3 (4)	0.0 (0–0.1)
• Sepsis	0 (0)	0.0 (0–0)	2 (2)	0.0 (0–0)
Metabolism and nutrition disorder	4 (4)	0.0 (0–0.1)	5 (5)	0.0 (0–0.1)
• Gout	3 (3)	0.0 (0–0.1)	4 (4)	0.0 (0–0.1)
Musculoskeletal and connective tissue disorder	2 (2)	0.0 (0–0)	3 (3)	0.0 (0–0.1)
• Gouty arthritis	2 (2)	0.0 (0–0)	2 (2)	0.0 (0–0)
Nervous system disorders	288 (473)	1.9 (1.7-2.1)	463 (745)	3.1 (2.8-3.4)
• Anosmia	251 (252)	1.7 (1.5-1.9)	384 (386)	2.5 (2.3-2.8)
• Ageusia	199 (201)	1.3 (1.1-1.5)	326 (327)	2.2 (1.9-2.4)
• Hyposmia	4 (4)	0.0 (0–0.1)	9 (9)	0.1 (0–0.1)
• Parosmia	4 (4)	0.0 (0–0.1)	7 (7)	0.0 (0–0.1)
• Hypogeusia	3 (3)	0.0 (0–0.1)	9 (9)	0.1 (0–0.1)
• Agnosia	2 (2)	0.0 (0–0)	2 (2)	0.0 (0–0)
• Taste disorder	2 (2)	0.0 (0–0)	2 (2)	0.0 (0–0)
• Bell's palsy	2 (2)	0.0 (0–0)	0 (0)	0.0 (0–0)
• Seizure	2 (2)	0.0 (0–0)	0 (0)	0.0 (0–0)
Renal and urinary disorders	0 (0)	0.0 (0–0)	3 (3)	0.0 (0–0.1)
• Acute kidney injury	0 (0)	0.0 (0–0)	3 (3)	0.0 (0–0.1)
Respiratory, thoracic and mediastinal disorders	2 (2)	0.0 (0–0)	6 (6)	0.0 (0–0.1)
• Acute respiratory distress syndrome	1 (1)	0.0 (0–0)	3 (3)	0.0 (0–0.1)
• Acute respiratory failure	0 (0)	0.0 (0–0)	2 (2)	0.0 (0–0)
Skin and subcutaneous tissue disorders	12 (13)	0.1 (0–0.1)	13 (14)	0.1 (0–0.1)
• Urticaria	9 (10)	0.1 (0–0.1)	6 (7)	0.0 (0–0.1)
• Alopecia	1 (1)	0.0 (0–0)	2 (2)	0.0 (0–0.1)

Source **Table 14.3.2.9_P6m**. Percentage of subjects was calculated as $100 \times n_s/N$, where n_s=number of subjects reporting the AE, and N=number of subjects in the SAF by arm. AESIs were collected from Day 1 up to the cutoff date for safety analysis (1 December 2021). AESIs were categorized by investigators or identified during the safety database review. CI, confidence interval. AEs were excluded if occurring after the administration of another COVID-19 vaccine.

12.2.3.1.6 *Medically-attended Adverse Event from Day 1 to the Cutoff Date (1 December 2021) (SAF)*

Table 73 and **Table 14.3.2.8_P6m** summarize the MAAEs, reported during the entire study period up to the cutoff date for safety analysis, grouped by MedDRA SOC and PT.

- At least one MAAE was reported by 7.1% (1071/15070) of SCB-2019 recipients and 8.0% (1211/15067) of placebo recipients.
- The most frequently reported MAAEs by SOC in the SCB-2019 and Placebo arms were Infections and infestations (5.0% and 5.9% of subjects, respectively), Nervous system disorders (0.7% and 0.9% of subjects, respectively), Respiratory, thoracic and mediastinal disorders (0.4% and 0.5% of subjects, respectively), and Vascular disorders (0.5% and 0.4% of subjects, respectively).
- The most frequently reported MAAEs by PT in the SCB-2019 and Placebo arms were upper respiratory tract infection (1.9% of subjects in both arms), COVID-19 (1.5% and 2.5% respectively), systemic viral infection (0.7% and 0.8% of subjects, respectively), and gastroenteritis (0.6% and 0.5% respectively), Vascular disorders (0.5% and 0.4% of subjects, respectively), and Hypertension (0.4% of subjects in both arms).

Table 73 MAAEs, Reported by ≥0.1% Subjects in any Group, by PT up to the Cutoff Date for Safety Analysis (SAF)

	SCB-2019 (N=15070)		Placebo (N=15067)	
Medically attended adverse event (MAAE) by System organ class (SOC)/Preferred term (PT)	**Number of subjects, n_s (number of events, n_e)**	**% subjects (95% CI)**	**Number of subjects, n_s (number of events, n_e)**	**% subjects (95% CI)**
Any MAAE	1071 (1697)	7.1 (6.7-7.5)	1211 (1910)	8.0 (7.6-8.5)
Gastrointestinal disorders	58 (59)	0.4 (0.3-0.5)	57 (63)	0.4 (0.3-0.5)
• Gastroesophageal reflux disease	17 (17)	0.1 (0.1-0.2)	14 (14)	0.1 (0.1-0.2)
• Diarrhoea	8 (8)	0.1 (0.0-0.1)	15 (15)	0.1 (0.1-0.2)
General disorders and administration site conditions	55 (69)	0.4 (0.3-0.5)	40 (45)	0.3 (0.2-0.4)
• Vaccination site pain	17 (18)	0.1 (0.1-0.2)	5 (5)	0.0 (0.0-0.1)
• Pyrexia	14 (14)	0.1 (0.1-0.2)	13 (13)	0.1 (0.0-0.1)
• Fatigue	13 (13)	0.1 (0.0-0.1)	6 (6)	0.0 (0.0-0.1)
Infections and infestations	747 (1050)	5.0 (4.6-5.3)	892 (1218)	5.9 (5.5-6.3)
• Upper respiratory tract infection	279 (349)	1.9 (1.6-2.1)	287 (359)	1.9 (1.7-2.1)
• COVID-19	228 (230)	1.5 (1.3-1.7)	382 (383)	2.5 (2.3-2.8)
• Systemic viral infection	102 (114)	0.7 (0.6-0.8)	119 (129)	0.8 (0.7-0.9)
• Gastroenteritis	86 (94)	0.6 (0.5-0.7)	71 (74)	0.5 (0.4-0.6)
• Pharyngotonsillitis	21 (21)	0.1 (0.1-0.2)	15 (15)	0.1 (0.1-0.2)
• Urinary tract infection	18 (18)	0.1 (0.1-0.2)	20 (21)	0.1 (0.1-0.2)
• Pneumonia	17 (18)	0.1 (0.1-0.2)	26 (26)	0.2 (0.1-0.3)
• Influenza	16 (16)	0.1 (0.1-0.2)	11 (13)	0.1 (0.0-0.1)
• Pulmonary tuberculosis	15 (15)	0.1 (0.1-0.2)	11 (12)	0.1 (0.0-0.1)
• Rhinitis	15 (16)	0.1 (0.1-0.2)	7 (7)	0.0 (0.0-0.1)
• Viral upper respiratory tract infection	12 (13)	0.1 (0.0-0.1)	19 (19)	0.1 (0.1-0.2)
• Asymptomatic COVID-19	11 (10)	0.1 (0.0-0.1)	7 (7)	0.0 (0.0-0.1)
• Pharyngitis	10 (10)	0.1 (0.0-0.1)	4 (4)	0.0 (0.0-0.1)
• Nasopharyngitis	9 (9)	0.1 (0.0-0.1)	14 (14)	0.1 (0.1-0.2)
• Acute sinusitis	9 (9)	0.1 (0.0-0.1)	5 (5)	0.0 (0.0-0.1)

Table 73 MAAEs, Reported by ≥0.1% Subjects in any Group, by PT up to the Cutoff Date for Safety Analysis (SAF) (continued)

Medically attended adverse event (MAAE) by System organ class (SOC)/Preferred term (PT)	SCB-2019 (N=15070)		Placebo (N=15067)	
	Number of subjects, n_s (number of events, n_e)	% subjects (95% CI)	Number of subjects, n_s (number of events, n_e)	% subjects (95% CI)
Suspected COVID-19	9 (9)	0.1 (0.0-0.1)	4 (4)	0.0 (0.0-0.1)
Bronchitis	5 (5)	0.0 (0.0-0.1)	8 (8)	0.1 (0.0-0.1)
Sinusitis	0 (0)	0.0 (0-0)	9 (9)	0.1 (0.0-0.1)
Injury, poisoning and procedural complications	54 (56)	0.4 (0.3-0.5)	66 (68)	0.4 (0.3-0.6)
• Muscle strain	8 (8)	0.1 (0.0-0.1)	7 (7)	0.0 (0.0-0.1)
• Animal bite	7 (8)	0.0 (0.0-0.1)	11 (11)	0.1 (0.0-0.1)
Metabolism and nutrition disorders	12 (15)	0.1 (0.0-0.1)	29 (36)	0.2 (0.1-0.3)
• Type 2 diabetes mellitus	1 (1)	0.0 (0-0)	8 (8)	0.1 (0.0-0.1)
Musculoskeletal and connective tissue disorders	33 (36)	0.2 (0.2-0.3)	36 (37)	0.2 (0.2-0.3)
• Myalgia	9 (9)	0.1 (0.0-0.1)	5 (5)	0.0 (0.0-0.1)
Nervous system disorders	104 (141)	0.7 (0.6-0.8)	139 (200)	0.9 (0.8-1.1)
• Anosmia	37 (37)	0.2 (0.2-0.3)	68 (68)	0.5 (0.4-0.6)
• Ageusia	33 (34)	0.2 (0.2-0.3)	60 (60)	0.4 (0.3-0.5)
• Headache	21 (23)	0.1 (0.1-0.2)	29 (30)	0.2 (0.1-0.3)
• Tension headache	14 (14)	0.1 (0.1-0.2)	16 (18)	0.1 (0.1-0.2)
• Migraine	11 (12)	0.1 (0.0-0.1)	5 (5)	0.0 (0.0-0.1)
Respiratory, thoracic and mediastinal disorders	63 (83)	0.4 (0.3-0.5)	69 (76)	0.5 (0.4-0.6)
• Cough	15 (15)	0.1 (0.1-0.2)	17 (17)	0.1 (0.1-0.2)
• Rhinitis allergic	13 (13)	0.1 (0.0-0.1)	17 (17)	0.1 (0.1-0.2)
• Oropharyngeal pain	11 (11)	0.1 (0.0-0.1)	6 (6)	0.0 (0.0-0.1)
• Allergic cough	9 (9)	0.1 (0.0-0.1)	7 (7)	0.0 (0.0-0.1)
Vascular disorders	68 (69)	0.5 (0.4-0.6)	62 (62)	0.4 (0.3-0.5)
• Hypertension	64 (64)	0.4 (0.3-0.5)	55 (55)	0.4 (0.3-0.5)

Source **Table 14.3.2.8_P6m**. Percentage of subjects was calculated as 100×ns/N, where ns=number of subjects reporting the AE, and N=number of subjects in the SAF by arm. MAAEs were collected from Day 1 up to the cutoff date for safety analysis (1 December 2021). CI, confidence interval. AEs were excluded if occurring after the administration of another COVID-19 vaccine.

Subgroup Analyses for Medically-Attended Adverse Events

No notable differences in frequency of MAAEs were observed in the subgroup analysis. The results of the subgroup analyses were in line with the overall analysis (the results by age: **Table 14.3.2.8.1_P6m**, by sex: **Table 14.3.2.8.2_P6m**, by race: **Table 14.3.2.8.3_P6m**, by country: **Table 14.3.2.8.4_P6m**, by evidence of prior SARS-CoV-2 infection: **Table 14.3.2.8.5_P6m**, by baseline risk factors: **Table 14.3.2.8.6_P6m**).

12.2.3.1.7 *AEs Leading to Early Termination from Day 1 to the Cutoff Date (1 December 2021) (SAF)*

Fewer SCB-2019 recipients than placebo recipients reported AEs that led to early termination from the study (Table 74). From Day 1 to the cutoff date for this report, 10 of these AEs were reported by 9/15070 SCB-2019 recipients, whereas 30 of these AEs were reported by 24/15067 placebo recipients (**Table 14.3.2.10_P6m**). The events reported in the SCB-2019 arm were not

considered related to SCB-2019 by the investigator and sponsor evaluations (**Listing 14.3.2.7_P6m**).

Table 74 AEs Leading to Early Termination from the Study, Reported ≥2 Subjects in any arm, by PT up to the Cutoff Date for Safety Analysis (SAF)

Adverse event (AE) leading to early termination from the study by System organ class/Preferred term (PT)*	SCB-2019 (N=15070)		Placebo (N=15067)	
	Number of subjects, n_s (number of events, n_e)	% subjects (95% CI)	Number of subjects, n_s (number of events, n_e)	% subjects (95% CI)
Any AE	9 (10)	0.1 (0.0–0.1)	24 (30)	0.2 (0.1–0.2)
Cardiac disorders	3 (3)	0 (0.0–0.1)	7 (8)	0 (0.0–0.1)
• Acute myocardial infarction	1 (1)	0 (0.0-0.0)	3 (3)	0 (0.0–0.1)
• Cardiogenic shock	0 (0)	0 (0.0-0.0)	3 (3)	0 (0.0–0.1)
General disorders and administration site conditions	2 (2)	0 (0–0)	2 (2)	0 (0–0)
• Death	2 (2)	0 (0.0-0.0)	0 (0)	0 (0-0)
Infections and infestations	2 (3)	0 (0.0–0.0)	8 (11)	0.1 (0.0–0.1)
• COVID-19	1 (1)	0 (0.0–0.0)	5 (5)	0 (0.0–0.1)
• Pneumonia	1 (1)	0 (0.0–0.0)	3 (3)	0 (0.0–0.1)
Respiratory, thoracic, and mediastinal disorders	1 (1)	0 (0.0–0.0)	3 (3)	0.0 (0.0–0.1)
• Acute respiratory failure	0 (0)	0 (0.0–0.0)	2 (2)	0 (0.0–0.0)

Source **Table 14.3.2.10_P6m**. Percentage of subjects was calculated as $100 \times n_s/N$, where n_s=number of subjects reporting the AE, and N=number of subjects in the SAF by arm. AEs were collected from Day 1 up to the cutoff date for safety analysis (1 December 2021). CI, confidence interval. *Note, these AEs include AEs that were reported by subjects after their receipt of another COVID-19 vaccine.

12.2.3.2 Secondary Objective: Assessment of Trimer-Tag-Specific Antibodies

There was no evidence in the adult recipients of SCB-2019 of the induction of Abs specific for the Trimer-Tag in the SCB-2019 antigen. After 1 dose (Day 22) or 2 doses (Day 36), no Trimer-Tag-specific Ab titer above the LLoQ was observed in any SCB-2019 recipient in the Immunogenicity subset of the PPS (i.e. GMTs = LLoQ/2 and GMFRs =1; **Table 14.3.3.1.1** and **14.3.3.2.1**).

12.2.3.2.1 *Supplementary analysis: Assessment of Trimer-Tag-Specific Antibodies in the Immunogenicity FAS*

In the Immunogenicity FAS, there was no evidence in the adult recipients of SCB-2019 of the induction of Abs specific for the Trimer-Tag in the SCB-2019 antigen. After 1 dose (Day 22) or 2 doses (Day 36), no Trimer-Tag-specific Ab titer above the LLoQ was observed in any SCB-2019 recipient (i.e. GMTs = LLoQ/2 and GMFRs =1; **Table 14.3.3.1.2** and **14.3.3.2.2**).

12.2.3.3 Unsolicited Adverse Events (Phase 2 SAF and SAF)

12.2.3.3.1 *Unsolicited AEs reported between Day 1 and Day 43 (Phase 2 SAF)*

Table 75 summarizes the unsolicited AEs, grouped by MedDRA SOC and PT, and reported during the vaccination period (Day 1 through Day 43).

- At least one unsolicited AE was reported during the vaccination period by 12% (94/808) of SCB-2019 recipients and 14% (112/793) of placebo recipients.
- The most frequently reported unsolicited AEs by SOC in the SCB-2019 and Placebo arms were Infections and infestations (5.6% and 7.8% respectively), General disorders and administration site conditions (2.6% and 2% respectively), Nervous system disorders (1.2% and 2.5% respectively), and Gastrointestinal disorders (1.1% and 0.4% respectively).
- The most frequently reported unsolicited AEs by PT in the SCB-2019 and Placebo arms were COVID-19 (2.2% and 3.3% respectively), injection site pain (1.0% and 0.5% respectively), upper respiratory tract infection (0.7% and 0.9% respectively) and headache (0.5% and 0.9% respectively).

Table 75 Unsolicited AEs Reported by ≥3 Subjects in any Group by PT in Phase 2 SAF (Day 1 to 43)

Unsolicited adverse event (AE) by System organ class/Preferred term	**SCB-2019 (N=808)**		**Placebo (N=793)**	
	Number of subjects, n_s (number of events, n_e)	**% subjects (95% CI)**	**Number of subjects, n_s (number of events, n_e)**	**% subjects (95% CI)**
Any	94 (123)	11.6 (9.5-14.0)	112 (140)	14.1 (11.8-16.7)
Gastrointestinal disorder	9 (10)	1.1 (0.5-2.1)	3 (3)	0.4 (0.1-1.1)
• Diarrhea	7 (8)	0.9 (0.3-1.8)	1 (1)	0.1(0.0-0.7)
General disorders and administration site conditions	21 (23)	2.6 (1.6-3.9)	16 (20)	2.0 (1.2-3.3)
• Injection site pain	8 (8)	1.0 (0.4-1.9)	4 (4)	0.5 (0.1-1.3)
• Fatigue	4 (4)	0.5 (0.1-1.3)	4 (6)	0.5 (0.1-1.3)
• Influenza like illness	2 (3)	0.2 (0.0-0.9)	5 (5)	0.6 (0.2-1.5)
• Pyrexia	4 (4)	0.5 (0.1-1.3)	1 (1)	0.5 (0.0-0.7)
Infections and infestations	45 (48)	5.6 (4.1-7.4)	62(65)	7.8 (6.0-9.9)
• COVID-19	18 (18)	2.2 (1.3-3.5)	26 (26)	3.3 (2.2-4.8)
• Upper respiratory tract infection	6 (6)	0.7 (0.3-1.6)	7 (7)	0.9 (0.4-1.8)
• Nasopharyngitis	5 (5)	0.6 (0.2-1.4)	6 (6)	0.8 (0.3-1.6)
• Asymptomatic COVID-19	1 (1)	0.1 (0.0-0.7)	5 (5)	0.6 (0.2-1.5)
• Gastroenteritis	2 (2)	0.2 (0.0-0.9)	3 (3)	0.4 (0.1-1.1)
• Pulpitis dental	2 (2)	0.2 (0.0-0.9)	3 (3)	0.4 (0.1-1.1)
Musculoskeletal and connective tissue disorders	5 (5)	0.6 (0.2-1.4)	4 (5)	0.5 (0.1-1.3)
• Myalgia	2 (2)	0.2 (0.0-0.9)	3 (3)	0.4 (0.1-1.1)
Nervous system disorders	10 (14)	1.2 (0.6-2.3)	20 (24)	2.5 (1.5-3.9)
• Headache	4 (5)	0.5 (0.1-1.3)	7 (7)	0.9 (0.4-1.8)
• Anosmia	2 (2)	0.2 (0.0-0.9)	4 (4)	0.5 (0.1-1.3)
• Tension headache	2 (2)	0.2 (0.0-0.9)	4 (4)	0.5 (0.1-1.3)
• Aguesia	2 (2)	0.2 (0.0-0.9)	3 (3)	0.4 (0.1-1.1)
• Dizziness	3 (3)	0.4 (0.1-1.1)	2 (3)	0.3 (0.0-0.9)
Respiratory, thoracic and mediastinal disorders	6 (6)	0.7 (0.3-1.6)	5 (5)	0.6 (0.2-1.5)
• Oropharyngeal pain	2 (2)	0.2 (0.0-0.9)	4 (4)	0.5 (0.1-1.3)
Vascular disorders	4 (4)	0.5 (0.1-1.3)	2 (2)	0.3 (0.0-0.9)
• Hypertension	3 (3)	0.4 (0.1-1.1)	1 (1)	0.1 (0.0-0.7)

Source **Table 14.3.2.2**. Percentage of subjects was calculated as $100 \times n_s/N$, where n_s=number of subjects reporting the AE, and N=number of subjects in the Phase 2 SAF by arm. Unsolicited AEs were collected from Day 1 and Day 43. CI, confidence interval.

Subgroup analysis for Unsolicited Adverse Events (Phase 2 SAF)

No notable differences in frequency and severity of unsolicited AEs were observed in the subgroup analysis. The results of the subgroup analyses were in line with the overall analysis (the results by age: **Table 14.3.2.2.1**, by sex: **Table 14.3.2.2.2**, by race: **Table 14.3.2.2.3**, by country: **Table 14.3.2.2.4**, by evidence of prior SARS-CoV-2 infection: **Table 14.3.2.2.5**, by baseline risk factors: **Table 14.3.2.2.6**).

12.2.3.3.2 *Related unsolicited adverse events reported between Day 1 and Day 43 (Phase 2 SAF)*

Table 76 summarizes the unsolicited AEs, assessed as related to the study vaccine, grouped by MedDRA SOC and PT, and reported during the vaccination period (Day 1 through Day 43):

- At least one related unsolicited AE was reported during the vaccination period by 3.1% (25/808) of SCB-2019 recipients and 3.3% (26/793) of placebo recipients.
- The most frequently reported related unsolicited AEs by SOC in the SCB-2019 and Placebo arms were General disorders and administration site conditions (1.6% and 1.1% respectively), and Nervous system disorders (0.5% and 0.9% respectively).
- The most frequently reported related unsolicited AEs by PT in the SCB-2019 and Placebo arms were injection site pain (1.0% and 0.5% respectively, and headache (0.4% and 0.5% respectively).

The majority of reported unsolicited AEs were mild or moderate in intensity and resolved within short duration. Only three severe unsolicited AEs were reported in the Phase 2 – SAF: two cases of hypertension (one in each arm) and one case of stab wound in the Placebo arm (**Table 14.3.2.4**).

Table 76 Related Unsolicited AEs Reported by ≥2 Subjects in any Group by PT in Phase 2 SAF (Day 1 to 43)

Related unsolicited adverse event (AE) by System organ class/Preferred term	**SCB-2019 (N=808)**		**Placebo (N=793)**	
	Number of subjects, (n_s) (number of events, n_e)	**% subjects (95% CI)**	**Number of subjects, (n_s) (number of events, n_e)**	**% subjects (95% CI)**
Any	25 (31)	3.1 (2.0-4.5)	26 (33)	3.3 (2.2-4.8)
Gastrointestinal disorders	2 (2)	0.2 (0.0-0.9)	1 (1)	0.1 (0.0-0.7)
• Diarrhoea	2 (2)	0.2 (0.0-0.9)	0 (0)	0.0 (0.0-0.5)
General disorders and administration site conditions	13 (15)	1.6 (0.9-2.7)	9 (12)	1.1 (0.5-2.1)
• Injection site pain	8 (8)	1.0 (0.4-1.9)	4 (4)	0.5 (0.1-1.3)
• Fatigue	1 (1)	0.1 (0.0-0.7)	3 (5)	0.4 (0.1-1.1)
Musculoskeletal and connective tissue disorders	0 (0)	0.0 (0.0-0.5)	2 (3)	0.3 (0.0-0.9)
• Arthralgia	0 (0)	0.0 (0.0-0.5)	2 (2)	0.3 (0.0-0.9)
Nervous system disorders	4 (6)	0.5 (0.1-1.3)	7 (8)	0.9 (0.4-1.8)
• Headache	3 (4)	0.4 (0.1-1.1)	4 (4)	0.5 (0.1-1.3)
• Dizziness	2 (2)	0.2 (0.0-0.9)	1 (2)	0.1 (0.0-0.7)
Respiratory, thoracic and mediastinal disorders	3 (3)	0.4 (0.1-1.1)	2 (2)	0.3 (0.0-0.9)
• Oropharyngeal pain	2 (2)	0.2 (0.0-0.9)	2 (2)	0.3 (0.0-0.9)

Source **Table 14.3.2.3**. Percentage of subjects was calculated as $100 \times n_s/N$, where n_s=number of subjects reporting the AE, and N=number of subjects in the SAF by arm. Unsolicited AEs were collected from Day 1 and Day 43. A related AE was an AE which the investigator considered to be probably or possibly caused by the study vaccine. CI, confidence interval.

Subgroup Analyses for Related Unsolicited Adverse Events (Phase 2 SAF)

No notable differences in frequency and severity of unsolicited AEs, assessed as related to the study vaccination, were observed in the subgroup analysis. The results of the subgroup analyses

were in line with the overall analysis (the results by age: **Table 14.3.2.3.1**, by sex: **Table 14.3.2.3.2**, by race: **Table 14.3.2.3.3**, by country: **Table 14.3.2.3.4**, by evidence of prior SARS-CoV-2 infection: **Table 14.3.2.3.5**, by baseline risk factors: **Table 14.3.2.3.6**).

12.2.3.3.3 *Unsolicited AEs from Day 1 to Day 43 (SAF)*

At least one unsolicited AE was reported from Day 1 to Day 43 by 10.2% (1543/15070) of SCB-2019 recipients and 9.4% (1414/15067) of placebo recipients. The most frequently reported unsolicited AEs by SOC in the SCB-2019 and Placebo arms were Infections and infestations (reported by 3.8% and 4.3% of subjects, respectively), General disorders and administration site conditions (reported by 3.7% and 2.0% of subjects, respectively), Nervous system disorders (reported by 2.2% and 2.4% of subjects, respectively), and Gastrointestinal disorders (0.7% in both arms). The most frequently reported unsolicited AEs by PT in the SCB-2019 and Placebo arms were COVID-19 (reported by 1.9% and 2.3% of subjects, respectively), vaccination site pain (reported by 2.0% and 0.6% of subjects, respectively), headache (reported by 1.1% and 1.0%, respectively), and anosmia (reported by 0.8% of subjects in both arms). These events are consistent with the unsolicited AEs reported in the CSR V1.0 dated 10 November 2021 (Section 12.2) (**Table 14.3.2.2_P6m**).

12.2.3.3.4 *Related unsolicited AEs from Day 1 to Day 43 (SAF)*

At least one related unsolicited AE was reported from Day 1 to Day 43 by 4.6% (690/15070) of SCB-2019 recipients and 3.0% (459/15067) of placebo recipients. The most frequently reported related unsolicited AEs by SOC in the SCB-2019 and Placebo arms were General disorders and administration site conditions (reported by 3.4% and 1.7% of subjects, respectively), and Nervous system disorders (reported by 0.9% of subjects in both arms). The most frequently reported related unsolicited AEs by PT in the SCB-2019 and Placebo arms were vaccination site pain (reported by 2.0% and 0.6% of subjects, respectively), and headache (reported by 0.8% and 0.7%, of subjects respectively) (**Table 14.3.2.3_P6m**).

12.2.3.3.5 *Severe Unsolicited AEs from Day 1 to Day 43 (SAF)*

At least one severe unsolicited AE was reported from Day 1 to Day 43 by 0.2% (33/15070) of SCB-2019 recipients and 0.2% (33/15067) of placebo recipients (**Table 14.3.2.4_P6m**). The most frequently reported severe unsolicited AEs by SOC in the SCB-2019 and Placebo arms were Infections and infestations (reported by 8/15070 and 12/15067 subjects, respectively), and by PT were COVID-19 reported by 4 subjects in the SCB-2019 arm and 5 subjects in the Placebo arm.

12.2.3.3.6 *Unsolicited AEs reported within 30 minutes after any vaccination (SAF)*

Table 77 summarizes the unsolicited AEs, reported within 30 minutes after any study vaccination, grouped by MedDRA SOC and PT.

- At least one unsolicited AE was reported within 30 minutes post-vaccination by 1.3% (193/15064) of SCB-2019 recipients and 1.0% (144/15064) of placebo recipients.
- The most frequently reported related unsolicited AEs by SOC in the SCB-2019 and Placebo arms were General disorders and administration site conditions (1.0% and 0.6% respectively), and Nervous system disorders (0.1% and 0.2% respectively).

- The most frequently reported related unsolicited AEs by PT in the SCB-2019 and the Placebo arms were vaccination site pain (0.6% and 0.3% respectively), injection site pain (0.3% and 0.2% respectively), and headache (0.1% and 0.1% respectively).
- Two cases of hypersensitivity were reported in the SCB-2019 group (**Table 14.3.2.5**). The detailed description of these cases is presented in Section 12.3.2.2.

Table 77 Unsolicited AEs, Occurred within 30 Minutes after any Vaccination, Reported by ≥2 Subjects in any Group by PT (SAF)

Unsolicited adverse event (AE) by System organ class/Preferred term	**SCB-2019 (N=15064)**		**Placebo (N=15064)**	
	Number of subjects, (n_s) (number events, n_e)	**% subjects (95% CI)**	**Number of subjects, (n_s) (number events, n_e)**	**% subjects (95% CI)**
Any Unsolicited AE	193 (220)	1.3 (1.1-1.5)	144 (156)	1.0 (0.8-1.1)
Cardiac disorders	2 (2)	0.0 (0-0)	0 (0)	0.0 (0-0)
• Sinus tachycardia	2 (2)	0.0 (0-0)	0 (0)	0.0 (0-0)
Gastrointestinal disorders	4 (5)	0.0 (0–0.1)	9 (9)	0.1 (0–0.1)
• Nausea	3 (3)	0.0 (0–0.1)	8 (8)	0.1 (0–0.1)
General disorders and administration site conditions	151 (163)	1.0 (0.8-1.2)	95 (98)	0.6 (0.5-0.8)
• Vaccination site pain	92 (95)	0.6 (0.5-0.7)	50 (51)	0.3 (0.2-0.4)
• Injection site pain	47 (47)	0.3 (0.2-0.4)	29 (29)	0.2 (0.1-0.3)
• Vaccination site paraesthesia	4 (4)	0.0 (0–0.1)	7 (7)	0.0 (0–0.1)
• Fatigue	3 (3)	0.0 (0–0.1)	0 (0)	0.0 (0-0)
• Asthenia	0 (0)	0.0 (0-0)	2 (2)	0.0 (0-0)
Infections and infestations	3 (3)	0.0 (0–0.1)	0 (0)	0.0 (0-0)
• COVID-19	2 (2)	0.0 (0-0)	0 (0)	0.0 (0-0)
Investigations	3 (3)	0.0 (0–0.1)	1 (1)	0.0 (0-0)
• Blood pressure increased	3 (3)	0.0 (0–0.1)	1 (1)	0.0 (0-0)
Musculoskeletal and connective tissue disorders	16 (17)	0.1 (0.1-0.2)	12 (12)	0.1 (0–0.1)
• Myalgia	12 (12)	0.1 (0.0-0.1)	9 (9)	0.1 (0.0-0.1)
• Pain in extremity	3 (3)	0.0 (0–0.1)	1 (1)	0.0 (0–0)
Nervous system disorders	19 (20)	0.1 (0.1-0.2)	28 (32)	0.2 (0.1-0.3)
• Headache	13 (13)	0.1 (0–0.1)	15 (15)	0.1 (0.1–0.2)
• Dizziness	1 (1)	0.0 (0-0)	9 (9)	0.1 (0–0.1)
• Somnolence	1 (1)	0.0 (0-0)	2 (2)	0.0 (0-0)
• Syncope	1 (1)	0.0 (0-0)	2 (2)	0.0 (0-0)
• Tension headache	3 (3)	0.0 (0–0.1)	0 (0)	0.0 (0-0)
• Hypoaesthesia	0 (0)	0.0 (0-0)	2 (2)	0.0 (0-0)

Source **Table 14.3.2.5**. Percentage of subjects was calculated as $100 \times n_s/N$, where n_s=number of subjects reporting the AE, and N=number of subjects in the SAF by arm. Unsolicited AEs were collected within 30 minutes after any dose administration. CI, confidence interval.

12.2.3.4 Safety Evaluation for Specific Populations

This section presents the safety evaluation for specific populations in the study CLO-SCB-2019-003.

12.2.3.4.1 *Safety Evaluation for Elderly Participants (≥60 years of age)*

Summaries of serious adverse events (SAEs) and adverse events of special interest (AESIs) reported in the elderly population from Day 1 up to the safety cut-off date (20 August 2021) are provided in **Table 14.3.2.6.2** and **Table 14.3.2.9.2**.

No SAEs were reported in the elderly population.

A total of 4 AESIs were reported by 3 elderly subjects in the SCB-2019 arm: one considered related and the remaining 3 were evaluated as unrelated to SCB-2019. Events reported were: 1 event of Covid-19, 1 event of gout, 1 event of anosmia and 1 event of urticaria (related).

12.2.3.4.2 *Safety Evaluation for Subjects with HIV Infection*

An overall summary of the unsolicited adverse events (AEs) reported in the HIV infected population from Day 1 up to the safety cut-off date (20 August 2021) is provided in Table 78. Summaries of serious adverse events (SAEs), medically attended adverse events (MAAEs) and adverse events of special interest (AESIs) reported in the HIV infected population from Day 1 up to the safety cut-off date are provided in **Table 14.3.2.6b_HIV**, **Table 14.3.2.8b_HIV** and **Table 14.3.2.9b_HIV**.

In the HIV infected population, 7 unsolicited events were reported by 6 subjects: 4 subjects experienced 5 events in the SCB-2019 arm and 2 subjects experienced 2 events in the Placebo arm (**Table 14.3.2.1b_HIV**). One subject in the SCB-2019 arm reported COVID-19 which was assessed by the investigator as grade 3 severity and one subject in the SCB-2019 arm reported vaccination site pain which was considered related to the vaccine (**Table 14.3.2.12_HIV**). No SAEs, AESIs or AEs leading to early termination (**Table 14.3.2.10_HIV**) from the study were reported in the HIV infected population up to the safety cut-off date. A total of 4 MAAEs were reported by 3 subjects: 2 subjects in the SCB-2019 arm (headache, dyspnea, oropharyngeal pain) and 1 subject in the Placebo arm (hypertension). No cases of COVID-19 were reported in the HIV infected population up to the safety cut-off date.

Table 78 Overall Summary of SAEs MAAEs, AESIs and AE Leading to Study Termination (Safety Set - HIV infected subjects)

	SCB-2019 (N=33)		**Placebo (N=29)**	
Unsolicited adverse event [AE]	**Number of subjects, n_s (number of events, n_e)**	**% subjects (95% CI)**	**Number of subjects, n_s (number of events, n_e)**	**% subjects (95% CI)**
Unsolicited AEs	4 (5)	12.1 (3.4–28.2)	2 (2)	6.9 (0.8-22.8)
• Related	1 (1)	3.0 (0.1-15.8)	0 (0)	0.0 (0.0–11.9)
• Severe	1 (1)	3.0 (0.1-15.8)	0 (0)	0.0 (0.0–11.9)
Serious AE [SAE]	0 (0)	0.0 (0.0–10.6)	0 (0)	0.0 (0.0–11.9)
• Related	0 (0)	0.0 (0.0–10.6)	0 (0)	0.0 (0.0–11.9)
Medically attended AE [MAAE]	2 (3)	6.1 (0.7–20.2)	1 (1)	3.4 (0.1–17.8)
AE of special interest [AESI]	0 (0)	0.0 (0.0–10.6)	0 (0)	0.0 (0.0–11.9)
AE leading to early study termination	0 (0)	0.0 (0.0–10.6)	0 (0)	0.0 (0.0–11.9)
Death	0 (0)	0.0 (0.0–10.6)	0 (0)	0.0 (0.0–11.9)

Source **Table 14.3.2.1b_HIV**. Percentage of subjects was calculated as $100 \times n_s/N$, where n_s=number of subjects reporting the AE, and N=number of subjects in the SAF by arm. These AEs were collected from Day 1 up to cut-off date of the CSR for safety analysis (20 August 2021). A related AE was an AE which the investigator considered to be probably or possibly caused by the study vaccine. CI, confidence interval. AE were excluded if occurring after other COVID-19 Vaccine.

12.2.3.4.3 *Safety Evaluation for Participants of Chinese Origin*

Up to the safety cut-off date (20 August 2021), no SAEs and AESIs) were reported in the Chinese origin population.

12.2.3.4.4 *Safety Evaluation for Subjects in the Manufacturing Scales Comparability Assessment*

Summaries of serious adverse events (SAEs) and adverse events of special interest (AESIs) reported from Day 1 up to the safety cut-off date (20 August 2021) in subjects who received SCB-2019 DS from 2000L or 200L fermenter are provided in **Table 14.3.2.6.3** and **Table 14.3.2.9.3**.

One SAE of pelvic inflammatory disease was reported by 1 subject in the SCB-2019 2000L group and 2 SAEs (1 event of abdominal wall abscess and 1 event of bipolar disorder) were reported by 2 subjects in the SCB-2019 200L group. None of these SAEs were considered as related to vaccination.

Three AESIs (1 event of ageusia, 1 event of anosmia and 1 event of dermatitis herpetiformis) were reported by 2 subjects in the SCB-2019 2000L group. The event of dermatitis herpetiformis was considered as related to vaccination. No AESIs were reported by subjects in the SCB-2019 200L group.

12.2.4 Listing of Adverse Events by Subject

AEs are listed by subject in **Listing 16.2.7.**

12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1 Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Listing of deaths, other SAEs, and other significant AEs are provided in **Section 14.3.2**.

12.3.1.1 Deaths

From Dose 1 up to the cutoff date (1 December 2021), 32 deaths associated with 38 AEs were reported; 9 (0.1%) deaths were reported in the SCB-2019 arm (N=15070) and 23 (0.2%) deaths were reported in the Placebo arm (N=15067).

Of the nine deaths reported among SCB-2019 recipients, one was associated with COVID-19 (Table 79 and **Table 14.2.5.4.2_P6m**). Of the 23 deaths reported among placebo recipients, 10 were associated with COVID-19 (Table 79 and **Table 14.2.5.4.2_P6m**). No death cases were considered to be associated with the study vaccine (**Listing 14.3.2.8_P6m**).

Table 79 AEs with Outcome of Death by PT and SOC up to the Cutoff Date for Safety Analysis - (SAF)

System organ class (SOC)/ Preferred term (PT)	**SCB-2019 (N=15070)**		**Placebo (N=15067)**	
	Number of subjects, n_s (number of events, n_e)	**% subjects (95% CI)**	**Number of subjects, n_s (number of events, n_e)**	**% subjects (95% CI)**
Any AE with outcome of death*	9 (9)	0.1 (0–0.1)	23 (29)	0.2 (0.1–0.2)
Cardiac disorders	3 (3)	0.0 (0–0.1)	7 (8)	0.0 (0–0.1)
• Acute myocardial infarction	1 (1)	0.0 (0–0)	3 (3)	0.0 (0–0.1)
• Acute coronary syndrome	1 (1)	0.0 (0–0)	0 (0)	0.0 (0–0)
• Cardiopulmonary failure	1 (1)	0.0 (0–0)	0 (0)	0.0 (0–0)
• Cardiogenic shock	0 (0)	0.0 (0–0)	3 (3)	0.0 (0–0.1)
• Cardio-respiratory arrest	0 (0)	0.0 (0–0)	1 (1)	0.0 (0–0)
• Myocardial ischemia	0 (0)	0.0 (0–0)	1 (1)	0.0 (0–0)
General disorders and administration site conditions	2 (2)	0.0 (0–0)	2 (2)	0.0 (0–0)
• Death	2 (2)	0.0 (0–0)	0 (0)	0.0 (0–0)
• Multiple organ dysfunction syndrome	0 (0)	0.0 (0–0)	1 (1)	0.0 (0–0)
• Sudden cardiac death	0 (0)	0.0 (0–0)	1 (1)	0.0 (0–0)
Infections and infestations	2 (2)	0.0 (0–0)	7 (9)	0.0 (0–0.1)
• Pulmonary tuberculosis	1 (0)	0.0 (0–0)	0 (0)	0.0 (0–0)
• Septic shock	1 (1)	0.0 (0–0)	0 (0)	0.0 (0–0)
• COVID-19	0 (0)	0.0 (0–0)	4 (4)	0.0 (0–0.1)
• COVID-19 pneumonia	0 (0)	0.0 (0–0)	1 (1)	0.0 (0–0)
• Pneumonia	0 (0)	0.0 (0–0)	1 (1)	0.0 (0–0)
• Sepsis	0 (0)	0.0 (0–0)	1 (1)	0.0 (0–0)
• Staphylococcal sepsis	0 (0)	0.0 (0–0)	1 (1)	0.0 (0–0)
• Suspected COVID-19	0 (0)	0.0 (0–0)	1 (1)	0.0 (0–0)
Injury, poisoning and procedural complications	0 (0)	0.0 (0–0)	2 (2)	0.0 (0–0)
• Road traffic accident	0 (0)	0.0 (0–0)	1 (1)	0.0 (0–0)
• Gunshot wound	0 (0)	0.0 (0–0)	1 (1)	0.0 (0–0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1)	0.0 (0–0)	0 (0)	0.0 (0–0)
• Pancreatic carcinoma stage IV	1 (1)	0.0 (0–0)	0 (0)	0.0 (0–0)
Nervous system disorders	0 (0)	0.0 (0–0)	2 (2)	0.0 (0–0)
• Cerebral hemorrhage	0 (0)	0.0 (0–0)	1 (1)	0.0 (0–0)
• Hypoxic-ischaemic encephalopathy	0 (0)	0.0 (0–0)	1 (1)	0.0 (0–0)
Renal and urinary disorders	0 (0)	0.0 (0–0)	1 (1)	0.0 (0–0)
• End stage renal disease	0 (0)	0.0 (0–0)	1 (1)	0.0 (0–0)
Respiratory, thoracic and mediastinal disorders	1 (1)	0.0 (0–0)	5 (5)	0.0 (0–0.1)
• Haemoptysis	1 (1)	0.0 (0–0)	0 (0)	0.0 (0–0)
• Acute respiratory failure	0 (0)	0.0 (0–0)	3 (3)	0.0 (0–0.1)
• Acute respiratory distress syndrome	0 (0)	0.0 (0–0)	2 (2)	0.0 (0–0)

Source **Table 14.3.2.11_P6m**. Percentage of subjects was calculated as $100 \times n_s/N$, where n_s=number of subjects reporting the AE, and N=number of subjects in the SAF by arm. AEs were collected from Day 1 up to the cutoff date for safety analysis (1 December 2021). CI, confidence interval. *Note, these AEs include AEs that were reported by subjects after their receipt of another COVID-19 vaccine.

12.3.1.2 Serious Adverse Events

Up to the cutoff date of 1 December 2021, 290 SAEs were reported by 204 subjects; 90 subjects in the SCB-2019 arm (N=15070) and 114 subjects in the Placebo arm (N=15067; **Table 14.3.2.6_P6m**). Eight SAEs considered by the investigator as related to vaccination were reported by 4 SCB-2019 recipients (4 events) and 2 placebo recipients (3 events by one subject, and 1 event by the remaining subject, respectively) (**Table 14.3.2.7_P6m**, **Listing 14.3.2.2_P6m** and **Section 14.3.3**).

12.3.1.3 Important Medical Events and Other Significant Adverse Events

No subjects with long-term sequelae of COVID-19, including respiratory disorders, neurologic disorders, and other organ dysfunctions were identified in the study up to the cutoff date for safety analysis.

Up to the cutoff date of 1 December 2021, 40 AEs were associated with 33 subjects withdrawing from the study; 9 subjects in the SCB-2019 arm (N=15070) and 24 subjects in the Placebo arm (N=15067; **Table 14.3.2.10_P6m**).

12.3.2 Narratives of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

All full narratives of deaths, other SAEs, and other significant AEs are provided in **Section 14.3.3**. Short narratives of the deaths reported in the SCB-2019 arm are presented below.

12.3.2.1 Deaths

- Subject 6061140, a 52-year-old male with medical history of hypertension at baseline received one dose of SCB-2019 vaccine and developed COVID-19 shortly after vaccination. The subject hospitalized for 34 days for Grade 4 COVID-19 pneumonia which required ventilatory support. The subject died of massive hemoptysis probably secondary to bronchiectasis 6 days after being discharged from the hospital. The investigator assessed the death as not related to the study vaccine. As part of the adjudication process of the COVID-19 cases reported in the study, the death was assessed as being associated with COVID-19.
- Subject 6052215, a 65-year-old male with medical history of hypertension died unexpectedly due to undetermined cause about 3.5 weeks after the second dose of the study vaccine. This subject had complained of exertional dyspnea one day before he died which points to a cardiovascular etiology for the fatal event per investigator's assessment. The investigator assessed the death as not related to the study vaccine.
- Subject 6051001, 70-year-old Asian male with no known medical history received one dose of SCB-2019 vaccine and was newly diagnosed with adenocarcinoma of lung and brain metastasis after developing symptoms 42 days vaccination. The subject died of septic shock and pneumonia. The investigator assessed the death as not related to the study vaccine.
- Subject 3070575, a 69-year-old male participant with medical history of gastritis and osteoarthritis received two doses of SCB-2019 vaccine. Approximately 58 days after the

second dose and 86 days after the first dose of SCB-2019 the participant died due to an unknown cause. The investigator assessed the death as not related to the study vaccine.

- Subject 6100795, a 32-year-old male participant without any medical history received two doses of SCB-2019 vaccine. Approximately 119 days after the second dose of SCB-2019 vaccine, participant experienced body stiffness and cyanosis. A physician was called, and the participant was reported to have cardiopulmonary failure. The investigator and sponsor assessed the event cardiopulmonary failure as not related to the SCB-2019 vaccine.
- Subject 6130165 a 28-year-old male participant without any previous medical history received two doses of SCB-2019 vaccine. Approximately 80 days after the second dose of SCB-2019 vaccine, the participant developed COVID-19 that recovered in three weeks and developed pneumonia few days later that recovered in approximately 4 weeks. In another 1.5 months the participant developed productive cough and high grade fever (38 to 39°C), occasional dyspnea, loss of appetite, easy fatigability and observed weight loss. Approximately after a week, the participant was diagnosed with pulmonary tuberculosis that was confirmed on chest X-ray. Few weeks later, the participant experienced worsening of symptoms and died in few days. The primary cause of death was pulmonary tuberculosis (Grade 5). The investigator and sponsor assessed the event pulmonary tuberculosis as not related to the SCB-2019 vaccine.
- Subject 6031175, a 34-year-old male participant with medical history of obesity, gouty arthritis and smoking received two doses of SCB-2019 vaccine. Approximately 113 days after the second dose of SCB-2019 vaccine participant had an episode of non-projectile vomiting with coffee grounded particles mixed with mucus and experienced a sudden onset of severe on-and-off chest pain under the sternum. The participant subsequently lost consciousness and was declared dead on arrival in the emergency room. The cause of the death was reported as acute coronary syndrome (Grade 5) and acute myocardial infarction. The participant did not receive any treatment for this event. An autopsy was not performed. The investigator and sponsor assessed the event acute coronary syndrome as not related to the SCB-2019 vaccine.
- Subject 6030155, a 52-year-old male participant with medical history of obesity and hypertension received two doses of SCB-2019 vaccine. Approximately 135 days after the second dose SCB-2019 vaccine the participant presented to the emergency department with symptoms of sudden onset of severe, progressive abdominal pain. The participant became unconscious in the ED and developed asystole and was diagnosed with myocardial infarction and died due to the event of acute myocardial infarction (Grade 5). No autopsy was performed. The investigator and sponsor assessed the event acute myocardial infarction as not related to the SCB-2019 vaccine.
- Subject 6020039 a 39-year-old male participant without medical history was diagnosed approximately 77 days after receiving the second dose of SCB-2019 vaccine with pancreatic carcinoma stage IV. The participant died in two months due to multiple organ failure secondary to liver cirrhosis and pancreatic carcinoma stage IV. The investigator and sponsor assessed the event pancreatic carcinoma stage IV as not related to the SCB-2019 vaccine.

12.3.2.2 Other Serious Adverse Events

The short narratives of the related SAEs for SCB-2019 recipients are presented below and in Section 12.3.2.3:

- Subject 3030492 (SCB-2019 vaccine arm), a 31 year-old male with medical history of obesity developed Bell's Palsy 1 day after receiving the second dose of SCB-2019 vaccine. He initially reported the appearance of "tic" in the right eye. Over the next several days he experienced a sensation of numbness on the right side of the face and a sensation of deviation from the labial corner on the left. At the time, the subject's physical examination showed symmetrical facial muscles at rest, inability to wrinkle right eyebrow, complete occlusion of the eye with minimal effort and deviation of the labial commissure to the left when smiling. He was treated with naproxen and steroids and the event was reported as mild and resolved completely in 17 days. The subject did not require hospitalization. The investigator assessed the event as related to the study vaccine.
- Subject 3040045 (SCB-2019 vaccine arm), a 28 year-old male with medical history of allergic rhinitis experienced a serious hypersensitivity reaction of moderate intensity approximately 15 minutes after receiving the first dose of SCB-2019 vaccine. The subject experienced a sensation of dizziness, drowsiness, itching in the upper limbs and appearance of hives in the upper limbs. The subject was treated with epinephrine and referred to the ER. The subject also reported itching on the face and itching in the lower limbs. The subject received further treatment in the ER which included, hydrocortisone and Loratadine. The subject also reported a "sensation of dyspnea". The events completely recovered the following day. The study treatment was withdrawn due to the event, and second dose was not administered. The events were considered as related to SCB-2019 vaccine.
- Subject 6120202 (SCB-2019 vaccine arm), a 23 year-old male with no significant medical history of hypersensitivity experienced serious hypersensitivity reaction 3 days after the second dose of study vaccine. The subject presented nausea, diarrhea and abdominal pain. He noted the appearance of generalized and pruritic wheals. Later, the subject developed shortness of breath which prompted him to attend the ER. Treatment included oxygen, epinephrine, antihistamines and hydrocortisone. The events recovered completely the following day. The event was initially reported as anaphylactic reaction and was updated by the investigator after CSR data lock point for this report, to serious hypersensitivity reaction as it does not meet the Brighton collaboration definition of anaphylaxis due to delayed onset. The event was considered as related to the study vaccine by the investigator.

12.3.2.3 Events Leading to Discontinuation

- Subject 3030366 (SCB-2019 vaccine arm), a 20 year-old female had a spontaneous abortion 31 days after the first dose of SCB-2019 vaccine. The subject had no prior pregnancies and was found to be pregnant at the second study visit, 29 days after receiving the first dose of SCB-2019 vaccine. No second dose of study vaccine was administered. 31 days after receiving the first dose of study vaccine she presented to the ER with vomiting, intense colic-type abdominal pain and vaginal bleeding and was hospitalized. She had an incomplete spontaneous abortion for which an obstetric curettage under general anesthesia was performed without complications. The event resolved on the same day and she was

discharged. The investigator assessed the spontaneous abortion as related to the study vaccine.

12.3.2.4 Other Events of Special Interest

- Subject 3030634 (SCB-2019 vaccine arm), a 48-year-old female with history of chickenpox at 12 years of age experienced moderate severity dermatitis herpetiformis 18 days after receiving the second dose of study vaccine. She presented initially with dermatomal lesions on the abdomen and back, which appeared as pruritic papules. Next day the lesions evolved to pustules and blistered with pain, burn, heat, redness, itching associated with subjective fever. The diagnosis was made on clinical presentation, and no biopsy or immunofluorescence studies were performed to support the diagnosis. The treatment was initiated as the lesions had characteristic of herpes zoster with secondary bacterial infection. She was treated with acyclovir, dicloxacillin, naproxen, tramadol, and acetaminophen. Twelve days from the appearance of the initial lesions she was asymptomatic, and the event resolved. The event was evaluated as related to the study vaccine by the investigator.
- Two events of Bell's palsy have been reported in the study from Day 1 to the cutoff date of 1 December 2021. One case is presented in Section 12.3.2.2 (subject 3030492) and an additional case is presented below:
- Subject 6020296, a 23-year-old male without any known medical history or concomitant medications, developed Bell's palsy (grade 1) 156 days after receiving the 2nd dose of the SCB-2019. Subject presented with difficulty in closing his right eye and loss of muscle tone on the right side of his mouth. Physical examination showed significant facial asymmetry, shallow nasolabial folds, and a drooping eyelid on the right side. There was no weakness of extremities, slurring of speech, or decrease in sensation. Subject was treated with oral prednisone with improvement of symptoms treated with steroid, vitamins and antibiotics which resolved in approximately one month. The event was assessed by both, the investigator and sponsor, as not related to the SCB-2019.

12.3.2.5 Other Significant Events

Hypersensitivity reactions were considered an important medical event in this study.

Overall, 13 subjects experienced hypersensitivity reactions, nine in SCB-2019 group and four in the Placebo (**Section 14.3.3**). Three of the subjects in SCB-2019 arm experienced hypersensitivity reactions that were reported as SAEs. Two of those serious hypersensitivity reactions were considered related and are described in Section 12.3.2.2. Six subjects experienced non-serious hypersensitivity reactions, three after the second dose and 3 after the first dose of study vaccine, events reported were mild (four cases) to moderate (two cases) in intensity and recovered completely. These non-serious hypersensitivity reactions required treatment with antiallergics and steroids.

The summary of two hypersensitivity reactions reported as related SAEs is presented in Section 12.3.2.2. The description of 7 other hypersensitivity reactions is presented below:

- Subject 2041860 (SCB-2019 vaccine arm), a 20 year-old female experienced a severe hypersensitivity reaction 6 days after the first dose of study vaccine. The subject developed swollen hands and feet, difficulty in breathing and had a closed-throat feeling. The subject

was treated in the ER with dexamethasone, promethazine and levocetirizine dihydrochloride. The subject reported exposure to eating granola that could have contributed to the event. The events recovered in less than 3 hours. This event was reported as an SAE and was considered not related to the study vaccine by the investigator.

- Subject 2031532 (SCB-2019 vaccine arm), a 40 year-old female with medical history of food allergy (shellfish) and drug allergy (amoxicillin). After the first study vaccination, the subject experienced dyspnea without decrease in oxygen saturation and vital signs within reference range (less than an hour), malaise (less than an hour) and injection site erythema (for 3 days). These events resolved completely, and no treatment was provided. After the second study vaccination the subject developed a generalized urticarial rash with intense itching but without respiratory or cardiac symptoms. The subject was treated with one dose of adrenaline and oral prednisone after which her symptoms completely resolved within the same day. The event was assessed as moderate intensity, non-serious and related to the study vaccine. Hypersensitivity reaction does not meet Brighton collaboration criteria for anaphylaxis due to the absence of major/minor respiratory or cardiac criteria.
- Subject 6151209 (SCB-2019 vaccine arm), a 41 year-old female without medical history of allergic reactions experienced a delayed type IV hypersensitivity reaction moderate intensity. She developed generalized urticaria with pruritus 11 days after the first dose of the study vaccine. The hypersensitivity reaction was treated with prednisone, levocetirizine and montelukast and the symptoms resolved in 4 days. This case was reported as a non-serious AE, related to the study vaccine.
- Subject 6151129 (SCB-2019 vaccine arm), a 33 year old female without history of allergic reactions experienced rash, generalized pruritus, runny nose and eyelid swelling 1 day after the first dose of study vaccine. The event was reported as generalized a hypersensitivity reaction of mild intensity. The subject was treated with prednisone, cetirizine and montelukast and the outcome recovered in 9 days. Subject was not given second dose of study vaccine. The event was reported as non-serious AE and assessed as related to study vaccine by investigator.
- Subject 6131083 (SCB-2019 vaccine arm), a 20 year old female developed non serious drug hypersensitivity reaction approximately 5 hours after 2nd dose of SCB-2019 vaccine. The event was mild in intensity and was evaluated to be related to study vaccine. Subject was treated with paracetamol and antihistamine and recovered completely in 5 days.
- Subject 6021032 (SCB-2019 vaccine arm), a 68 year old male developed non serious hypersensitivity reaction 46 days after 1st dose of SCB-2019 vaccine. The event was mild in intensity and was evaluated to be not related to study vaccine. The subject was treated with antihistamine and recovered completely in 28 days. The subject had developed community acquired pneumonia and pulmonary tuberculosis prior to the event and were considered plausible confounding factors. The subject received the 2nd dose of the study vaccine on Day 70 of the study.
- Subject 6020646 (SCB-2019 vaccine arm), a 29 year old male developed non serious hypersensitivity reaction approximately 6 days after 2nd dose of SCB-2019 vaccine. The event was mild in intensity and was evaluated to be not related to study vaccine. The subject had history of egg allergy that may have caused the event as confounding factor. The subject was treated with emollients without any medication and recovered completely in 11 days.

The hypersensitivity events reported with SCB-2019 vaccine were mostly mild or moderate in intensity and few severe events were reported as well. The events were treated with standard clinical care, including antihistamines and steroids and recovered completely.

12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

From Dose 1 up to 1 December 2021, eight SAEs considered by the investigator as related to vaccination were reported by 4 SCB-2019 recipients (4 events) and 2 placebo recipient (4 events). For the SCB-2019 recipients, these SAEs included a mild case of Bell's palsy one day after the second dose; a moderate hypersensitivity reaction 15 minutes after receiving the first dose which resolved the next day; a serious hypersensitivity reaction 3 days after the second dose; and a severe spontaneous abortion 31 days after the first dose. Three related SAEs were reported by one placebo recipient and were a life-threatening case of COVID-19, pneumonia, and acute respiratory syndrome 53 days after the second dose. A fourth related SAE was reported by one placebo recipient and was a severe spontaneous abortion 39 days after the second dose (**Listing 14.3.2.2_P6m** and **Section 14.3.3**).

From Dose 1 up to 1 December 2021, 32 deaths associated with 38 AEs were reported. Nine deaths were reported in the SCB-2019 arm, including one which was associated with COVID-19 (**Table 14.2.5.4.2_P6m**),and 23 deaths were reported in the Placebo arm, of which 10 were associated with COVID-19 (**Table 14.2.5.4.2_P6m**). No death was considered to be associated with the study vaccine (**Listing 14.3.2.8_P6m**).

12.4 Clinical Laboratory Evaluations

No laboratory evaluations were made for this study.

12.4.1 Individual Clinically Significant Abnormalities

No individual clinically significant abnormalities were identified for this study.

12.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

12.5.1 Vital Signs

Vital signs collected for subjects are listed in **Listing 16.2.9**.

12.5.2 Physical Examination

Physical examination data collected for subjects are listed in **Listing 16.2.10**.

12.5.3 Prior and Concomitant Medication

At the start of the study, 0.5% (73/15070) of SCB-2019 recipients and 0.5% (76/15067) of Placebo recipients reported prior medication (**Table 14.1.5.1_P6m**). From Dose 1 up to 1 December 2021, 43.2% (6510/15070) of SCB-2019 recipients and 46.8% (7053/15067) of Placebo recipients reported concomitant medication (**Table 14.1.5.2_P6m**).

12.5.4 Pregnancies

From Dose 1 up to 1 December 2021, 125 pregnancies were reported; 60 pregnancies were reported by SCB-2019 recipients and 65 were reported by Placebo recipients. Nine (0.06 %) spontaneous abortions were reported in SCB-2019 vaccine arm and 10 (0.07 %) in the placebo arm. Overall, no imbalance in the number of subjects with abnormal pregnancy outcomes was observed between the study arms (**Listing 16.2.8.4_P6m**).

12.6 Safety Conclusions

12.6.1 Conclusions Relating to the Primary Safety Objective

SCB-2019 had and acceptable safety profile with no major safety concerns in the adult study population:

- Although solicited local AEs were reported more frequently by SCB-2019 recipients than placebo recipients (44% versus 15%), AEs of moderate or severe intensity were infrequent in SCB-2019 recipients (4% and 1%, respectively) and transient.
- Solicited systemic AEs were reported by SCB-2019 recipients at a similar frequency to that reported by placebo recipients (44% and 40%, respectively). In SCB-2019 recipients, moderate or severe intensity symptoms were infrequent (12% and 4%, respectively).
- Solicited AEs of any intensity and of severe intensity were reported less frequently by SCB-2019 recipients after the second dose than after the first dose.
- Solicited AEs reported by SCB-2019 recipients were transient and mostly resolved within 3 days.
- Unsolicited AEs considered related to vaccination up to 21 days after the second dose were reported by SCB-2019 recipients at a similar frequency to that reported by placebo recipients in Phase 2-SAF (3.7% and 3.4% respectively).
- Overall and throughout the study, a lower proportion of subjects experienced SAEs, MAAEs, AESIs and AE leading to early study termination with SCB-2019 than with placebo, possible reflecting a lower frequency of AEs categorized under preferred terms related to COVID-19 symptoms.
- SAEs considered related to vaccination were infrequent and reported by 4 SCB-2019 recipients and 2 placebo recipients in a population of 30 000 adults.

12.6.2 Conclusions Relating to the Secondary Safety Objective

- There was no evidence in the adult SCB2019 recipients of the induction of Abs specific for the Trimer-Tag in the SCB-2019 antigen.

12.6.3 Other Safety Conclusions

- No evidence of enhanced respiratory disease was identified in subjects received SCB-2019 vaccine. No long-term sequelae of COVID-19, including respiratory disorders, neurologic disorders, and other organ dysfunctions were identified in the study up to the cut-off date for safety analysis.

- No difference in reactogenicity and safety profile of SCB-2019 was observed in subgroup of subjects with and without evidence of prior SARS-CoV-2 infection. No notable differences in frequency and severity of solicited and unsolicited AEs were observed in the subgroup analyses by age group, sex, race, country, and baseline risk factors.

12.6.4 Safety Conclusions in Special Populations

- Overall, the SCB-2019 vaccine had an acceptable safety profile with no major safety concerns up to the safety cut-off date (20 August 2021) in the following populations: elderly (≥60 years of age), HIV positive individuals, subjects of Chinese origin, and subjects receiving SCB-2019 vaccine from two different manufacturing scales.

13.0 DISCUSSION AND OVERALL CONCLUSIONS

13.1 Discussion

This Phase 2/3 double-blind, randomized, controlled study of over 30000 adults in 5 countries across 4 continents, was designed to demonstrate the efficacy of the SCB-2019 vaccine against COVID-19, and evaluate its safety and immunogenicity. The population was young (mean age 32 years) and balanced between arms for all baseline characteristics. About half of the study population was SARS-CoV-2-exposed at baseline and was excluded from the Efficacy PPS.

The primary efficacy objective was met in demonstrating that two doses of SCB-2019 protected against COVID-19 of any severity in SARS-CoV-2 naïve adults. Overall, 207 cases were included in the analysis for primary efficacy endpoint, 8 severe COVID-19 cases, 42 moderate-to-severe cases, and 165 cases of COVID-19 that did not meet definition of moderate or severe disease. The efficacy was 67.2% (95.72% CI: 54.3–76.8), and the lower bound of the CI was above the pre-specified success threshold of 30%. The key secondary efficacy objectives were met in demonstrating significant efficacy of two doses of SCB-2019 against moderate-to-severe COVID-19 and against severe COVID-19 in SARS-CoV-2–naïve adults. Here, the efficacy estimates were 83.7% (97.86% CI 55.9–95.4) and 100% (97.86% CI 25.3–100.0), with the lower bound of the CIs above the pre-specified success threshold of 0%. The efficacy of SCB-2019 against any laboratory-confirmed SARS-CoV-2 infection met pre-specified success criteria with estimate of 34.4% (95% CI 27.1-41.0). No efficacy against asymptomatic SARS-CoV-2 infection was demonstrated in SARS-CoV-2 naïve subjects.

Another secondary objective suggested that SCB-2019 vaccine showed protection against COVID-19 of any severity in SARS-CoV-2–naïve adults who were at high risk of severe COVID-19. Here, vaccine efficacy was estimated at 65.9% (95% CI 35.7–82.9). Vaccine efficacy against any COVID-19 in subjects previously exposed to SARS-CoV-2 was 64.2% (95% CI 26.5-83.8).

SCB-2019 induced protection against all three dominant variants of SARS-CoV-2 virus circulating during the study period. In SARS-CoV-2 naïve subjects at baseline, VE against COVID-19 of any severity caused by the Delta variant was 78.7% (95% CI: 57.3–90.4), Mu variant, 58.6% (95% CI: 13.3–81.5), and Gamma variant, 91.8% (95% CI: 44.9–99.8). In SARS-CoV-2-exposed subjects, vaccine efficacy against any COVID-19 due to the Delta variant was 79.1% (95% CI 25.1–96.1).

During the 6-month follow-up analysis, SCB-2019 vaccine demonstrated sustained protection against severe COVID-19 (100%, 95% CI: 80.9-100) and COVID-19-associated hospitalizations (95.0%, 95% CI: 68.8-99.9) in SARS-CoV-2 naïve subjects. The protection against mild disease appeared to reduce over the time with VE estimate against any COVID-19 of 50.4% (95% CI 42.1–57.5) within 6 months after primary vaccination in SARS-CoV-2 naïve subjects. In subjects previously infected with SARS-CoV-2, no reduction in the efficacy of SCB-2019 vaccine was observed for at least 6 months after vaccination.

SCB-2019 also provided long-term protection against COVID-19 in older adults ≥60 years of age, VE against any COVID-19 was 54.5% (95% CI: 18.2-75.5). Vaccine efficacy was higher against moderate-to-severe COVID-19 and severe COVID-19: 88.0% (95% CI: 48.9-98.7) and 100% (95% CI: 33.3 – 100.0), respectively.

Two doses of SCB-2019 were immunogenic in the adult study population in terms of the induction of neutralizing antibodies specific for SARS-CoV-2. Those are potentially relevant to protecting against SARS-CoV-2 entry into cells. In addition, 2 doses of SCB-2019 vaccine elicited ACE2 receptor binding Abs, and Abs specific for the SCB-2019 antigen. In SARS-CoV-2 naïve subjects without evidence of SARS-CoV-2 infection during the study period, 2 doses of SCB-2019 vaccine induced a peak of neutralizing antibodies at Day 36 (279.9), which demonstrated good persistence with titer of 111.1 at 6 months after the last immunization. In SARS-CoV-2 exposed individuals, a similar kinetics of neutralizing antibody waning was observed (1803.3 at Day 36 and 803.4 at Day 205).

SCB-2019 had an acceptable safety profile with no major safety concerns in the adult study population. For the safety objectives, reactogenicity and unsolicited AEs reported from Day 1 through 21 days post the second dose were monitored in the Phase 2 cohort of 1601 subjects, and SAE and other AEs of interest were monitored through the entire study period in the exposed Phase 3 study population. Although local AEs were reported more frequently by SCB-2019 recipients than placebo recipients (44% versus 15%), local solicited AEs of moderate or severe intensity were infrequent in SCB-2019 recipients (4% and 1%, respectively). Also, systemic AEs were reported by SCB-2019 recipients at a similar frequency to that reported by placebo recipients. It is important to note that local or systemic AEs were less frequent after the second dose than after the first dose of SCB-2019, and generally of short duration (less than 3 days). In the entire population and throughout the study (to the safety cut-off date of December 2021), SAEs, MAAEs, AESIs were reported by SCB-2019 recipients at a marginally lower frequency to those reported by placebo recipients, possibly reflecting a lower frequency of AEs categorized under Preferred Terms related to COVID-19 symptoms. SAEs considered related to vaccination were infrequent and reported by 4 SCB-2019 recipients and 2 placebo recipients in a population of 30 000 adults. AEs of severe hypersensitivity reactions and Bell's Palsy were reported with very rare frequency in the adult subjects. No difference in the safety profile was observed when comparing different subgroups in terms of sex, risk of COVID-19 disease, or in the SARS-CoV-2–exposed subjects. It is important to note that no signs of disease enhancement were observed during the study period, when looking at the severity of the COVID-19 cases observed following one or two doses of the SCB-2019 vaccine. No antibody titers against Trimer Tag domain of the SCB-2019 vaccine were detected in the study. This data dismisses a theoretical concern that the SCB-2019 vaccine may induce immune response against Trimer-Tag or non-vaccine-derived human autoantigens and trigger autoimmune disorders.

In summary, the study has demonstrated clinical benefit and a favorable risk/benefit profile of SCB-2019 vaccine in adults ≥18 years of age.

13.2 Overall Conclusions

13.2.1 Efficacy

- The primary efficacy objective was met in demonstrating that two doses of the SCB-2019 vaccine protected against COVID-19 of any severity in SARS-CoV-2 naïve adults.
- The key secondary efficacy objectives were met in demonstrating significant efficacy of two doses of the SCB-2019 vaccine against moderate-to-severe COVID-19 and against severe COVID-19 in SARS-CoV-2–naïve adults.

  - SCB-2019 vaccine induces protection against laboratory-confirmed SARS-CoV-2 infection of any severity and reduces the burden of COVID-19 disease in SARS-CoV-2-naïve adults. Protection against asymptomatic RT-PCR-confirmed SARS-CoV-2 infection was observed in SARS-CoV-2-exposed adults, but not in SARS-CoV-2 naïve adults.
  - Two doses of the SCB-2019 vaccine protected against COVID-19 caused by various lineages of SARS-CoV-2 variants.
- In SARS-CoV-2 naïve subjects, VE against severe COVID-19 and COVID-19-associated hospitalizations remain high at 6 months after vaccination.
- In subjects previously infected with SARS-CoV-2, SCB-2019 induces protection against any COVID-19, with no reduction in the efficacy of SCB-2019 vaccine for at least 6 months after vaccination.
- SCB-2019 vaccine induces protection against COVID-19 in healthy subjects and individuals with co-morbidities associated with high risk of severe COVID-19 across the entire age range, including subjects 60 years of age and above.

13.2.2 Immunogenicity

  - Two doses of the SCB-2019 vaccine were immunogenic in SARS-CoV-2–naïve adults, in terms of the induction of functional Abs specific for SARS-CoV-2.
  - In SARS-CoV-2 exposed subjects, a single dose induced a rapid, significant and specific humoral response at 21 days after vaccination. The second dose was associated with further increase in antibody titers.
- Neutralizing antibodies persist for at least 6 months after the primary immunization series in SARS-CoV-2-naïve and SARS-CoV-2 exposed individuals.
- In SARS-CoV-2 naïve study participants, a robust cross neutralizing response was observed against Alpha, Beta, Gamma, Delta, Mu and Omicron BA.2 and BA.5 variants but not against Omicron BA.1 and BA.4. In SARS-CoV-2 exposed study participants, a cross neutralizing response was observed against all variants at antibody levels associated with clinical protection.
- A Th1 CD4+ T cell response was observed against S1 subunit peptide pool in PBMCs from subjects who received 2 doses of SCB-2019. This Th1 response tended to be lower against S2 subunit peptide and was not observed with Trimer-tag, Gly repeats or CICP. No Th2 or Th17 type responses were detected with any of the stimulating pools of peptides.

13.2.3 Safety

  - The SCB-2019 vaccine had an acceptable safety profile with no major safety concerns in the adult study population.

14.0 TABLES, FIGURES, AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 Demographic Data

14.2 Efficacy Data

14.3 Safety Data

14.3.1 Displays of Adverse Events

14.3.2 Listings of Deaths, Other Serious Adverse Events, and Certain Other Significant Adverse Events

14.3.3 Narratives of Deaths, Other Serious, and Certain Other Significant Adverse Events

14.3.4 Abnormal Laboratory Value Listing

15.0 REFERENCES

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16.0 APPENDICES

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

16.1.2 Sample Case Report Form and Data Collection Tools

16.1.3 IEC Information, Sample Informed Consent Form, and Representative Written Information for Subjects

16.1.4 Investigators and Other Important Participants in the Study

16.1.5 Signatures of Coordinating Investigators

16.1.6 List of Subjects Receiving Investigational Vaccine(s) From Specific Batches

16.1.7 Randomization Scheme and Codes

16.1.8 Audit Certificates

16.1.9 Documentation of Statistical Methods

16.1.10 Documentation of Inter-laboratory Standardization Methods and Quality Assurance Procedures

16.1.11 Publications Based on the Study

16.1.12 Important Publications Referenced in the Report

16.1.13 Data Safety Monitoring Board Charter

16.1.14 Endpoint Adjudication Committee Charter

16.2 Subject Data Listings

16.2.1 Discontinued Subjects

16.2.2 Protocol Deviations

16.2.3 Subjects Excluded From the Efficacy Analyses

16.2.4 Demographic Data

16.2.5 Compliance and/or Vaccine Content Data

16.2.6 Individual Efficacy Response Data

16.2.7 Adverse Event Listings (Each Subject)

16.2.8 Listing of Individual Laboratory Measurements by Participant if Required by Regulatory Authorities

16.2.9 Vital Signs

16.2.10 Physical Examination

16.3 Case Report Forms**

16.3.1 CRFs of deaths, other serious adverse events, and withdrawals for AE

16.3.2 Other CRFs submitted

16.4 Individual Subject Data Listings**

*List of subjects with available electronic case report forms (eCRFs) is provided in Sections 16.3. The eCRFs that are included in this submission are those required by the regulations of the region in which this document is submitted. The audit trails for these eCRFs are not included but are available upon request.

Please see **Listing 16.2 for subject data listings.