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Six-month safety follow-up of an adjuvanted SARS-CoV-2 trimeric S-protein subunit vaccine (SCB-2019) in adults: A phase 2/3, double-blind, randomized study

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ABSTRACT

Background: We evaluated the safety of SCB-2019, a protein subunit vaccine candidate containing a recombinant SARS-CoV-2 spike (S) trimer fusion protein, combined with CpG-1018/alum adjuvants.
Methods: This ongoing phase 2/3, double-blind, placebo-controlled, randomized trial is being conducted in Belgium, Brazil, Colombia, the Philippines, and South Africa in participants ≥ 12 years of age. Participants were randomly assigned to receive 2 doses of SCB-2019 or placebo administered intramuscularly 21 days apart. Here, we present the safety results of SCB-2019 over the 6-month period following 2-dose primary vaccination series in all adult participants (≥18 years of age).
Results: A total of 30,137 adult participants received at least one dose of study vaccine (n = 15,070) or placebo (n = 15,067) between 24 March 2021 and 01 December 2021. Unsolicited adverse events, medically-attended adverse events, adverse events of special interest, and serious adverse events were reported in similar frequencies in both study arms over the 6-month follow-up period. Vaccine-related SAEs were reported by 4 of 15,070 SCB-2019 recipients (hypersensitivity reactions in two participants, Bell's palsy, and spontaneous abortion) and 2 of 15,067 placebo recipients (COVID-19, pneumonia, and acute respiratory distress syndrome in one participant and spontaneous abortion in the other one). No signs of vaccine-associated enhanced disease were observed.
Conclusions: SCB-2019 administered as a 2-dose series has an acceptable safety profile. No safety concerns were identified during the 6-month follow-up after the primary vaccination.
Clinical Trials Registration: NCT04672395; EudraCT: 2020–004272-17.

1. Introduction

The severe acute respiratory syndrome-related coronavirus-2 (SARS-CoV-2) pandemic has mobilized the global scientific community to develop effective vaccines for preventing coronavirus infectious disease caused by SARS-CoV-2 (COVID-19) [1,2]. A total of 41 vaccines against COVID-19 have been approved by Health Authorities in at least one country and 11 of them were granted emergency use authorization by World Health Organization [3]. As of 13 September 2022, more than 12.6 billion doses of COVID-19 vaccines have been administered around the world [4]. Various technologies have been employed to develop these vaccines, including inactivated and recombinant subunit protein vaccines, viral vector-based vaccines, and mRNA vaccines [5]. Due to the accelerated, global, multi-manufacturer development of COVID-19 vaccines, it is crucial that vaccine safety assessment including monitoring, investigation, and analysis is done throughout the life cycle of vaccine development in a harmonized and standardized manner [6]. The Safety Platform for Emergency vACcines (SPEAC) and the Brighton Collaboration have identified potential adverse events of special interest (AESIs) relevant to the development of COVID-19 vaccines [7,8]. Some of these AESIs have been previously identified with immunization in general (e.g., anaphylaxis, Guillain-Barré syndrome [GBS]), whereas some are relevant to certain vaccine platforms, and others are specific to COVID-19 vaccines (e.g., myocarditis, pericarditis) [9].

Most of the known side effects of COVID-19 vaccines are mild and short lived [10–14]. However, during clinical trials and through the safety monitoring systems, a few medically significant

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adverse events have been reported following immunization with the currently available COVID-19 vaccines. Post-marketing surveillance data demonstrated a rare risk of myocarditis and pericarditis associated with mRNA COVID-19 vaccination in adolescents and young adults, particularly within 7 days following the second dose [12,13,15]. Thrombosis associated with thrombocytopenia (TTS) has been reported in individuals vaccinated with adenovirus vector-based COVID-19 vaccines [10,11]. Currently available evidence supports a causal relationship between TTS and the Ad26.COV2-S (Janssen) COVID-19 vaccine. However, TTS following immunization with this vaccine is rare and has occurred in approximately 4 cases per million doses administered, with the highest reported rate in women aged 30–49 years (approximately 8 cases per million doses administered). Similarly, safety data suggest that the risk of TTS following vaccination with ChAdOx nCoV-19 (AstraZeneca) is approximately 4 cases per million adults in the United Kingdom and approximately 10 cases per million adults in the European Union [16–18]. Furthermore, very rare cases of GBS have been reported following vaccination with adenovirus vector-based COVID-19 vaccines but not with mRNA COVID-19 vaccines [19].

Hypersensitivity reactions, although rare (approximately 5.58 cases per million doses), associated with COVID-19 vaccines have also been reported [20,21]. Vaccine-associated enhanced disease (VAED) is also an important concern as some studies reported VAED in preclinical models of SARS-CoV-1 and the Middle East respiratory syndrome [22]. As SARS-CoV-2 is related to the coronaviruses causing these diseases, VAED has emerged as one of the major safety concerns for COVID-19 vaccines [6–8,22,23].

Clover Biopharmaceuticals developed SCB-2019, a recombinant protein-based subunit vaccine, using its innovative Trimer-Tag™ technology [24]. SCB-2019 contains the SARS-CoV-2 spike glycoprotein in a native-like prefusion trimeric conformation, adjuvanted with the Toll-like receptor agonist CpG-1018 and aluminum hydroxide (alum) [24,25]. The efficacy, immunogenicity, and safety of the SCB-2019 vaccine were evaluated in the SPECTRA study, a global phase 2/3 clinical trial with more than 30,000 study participants from five countries, including approximately 1,200 adolescents (aged 12 to 17 years) (NCT04672395; EudraCT: 2020–004272-17). In adults, SCB-2019 demonstrated 100 % efficacy against severe COVID-19 and COVID-19-associated hospitalizations, 83.7 % efficacy against moderate-to-severe COVID-19, and 67 % efficacy against COVID-19 of any severity for all evaluated SARS-CoV-2 strains [26]. Solicited local and systemic AEs reported in a subset of participants within 7 days after each vaccine dose have been previously published, as well as unsolicited AEs up to day 43 (21 days after the second dose) [26]. Here, we describe the safety results of SCB-2019 in adult participants from the phase 2/3 SPECTRA trial up to 6 months after the 2-dose primary vaccination series.

2. Materials and Methods

2.1. Study design

SPECTRA is a randomized, double-blind, placebo-controlled, phase 2/3 trial conducted in participants aged ≥ 12 years in five countries (Belgium, Brazil, Colombia, the Philippines, and South Africa) [26]. This trial was designed to assess the efficacy, immunogenicity, reactogenicity, and safety of SCB-2019.

Inclusion and exclusion criteria have been previously described [26]. Briefly, eligible study participants were healthy individuals or had a stable preexisting medical condition, were ≥ 12 years of age, and were willing to comply with the study requirements and procedures. Key exclusion criteria included pregnancy; breastfeeding; a history of severe adverse reaction or anaphylaxis to any vaccine component; any chronic condition or therapy likely to impact immune responses; and prior receipt of any approved coronavirus vaccine. Women of childbearing potential were required to use an approved contraception method from 30 days before their first dose until 90 days after their second dose. Men were required to use an approved contraception method from the day of their first dose until 6 months after their second dose.

We have previously described the primary efficacy and safety results of the SPECTRA trial up to the cutoff date of 10 August 2021, including the reactogenicity profile of SCB-2019 up to 7 days after each vaccination [26]. Here, we present the safety data obtained during the 6-month follow-up period after primary vaccination in all adult participants (≥18 years of age) who received at least one dose of SCB-2019 or placebo (1:1 randomization). At the time of this analysis, only 162 adolescents have been vaccinated. Results in adolescents will be disclosed once they become available.

The primary safety objective of this trial was to assess the safety of the SCB-2019 vaccine in study participants in terms of solicited and unsolicited AEs, medically-attended AEs (MAAEs), AEs of special interest, AEs leading to early termination from the study or vaccination, and serious AEs (SAEs). The secondary safety objective was to evaluate the immune response against the Trimer-Tag in a subset of approximately 800 exposed participants to address the theoretical concern that the glycine repeats of the mature collagen type I or the C-propeptide domain of the pro-collagen contained in the Trimer-Tag domain of SCB-2019 may trigger autoimmune disorders or enhance pre-existing immune-mediated diseases. In addition, one of the exploratory efficacy objectives was to evaluate the effect of SCB-2019 on the risk of disease enhancement including, but not limited to, enhanced respiratory disease.

The trial was conducted in accordance with the Declaration of Helsinki, the Council for International Organizations of Medical Sciences International Ethical Guidelines for Biomedical Research Involving Human Subjects, the Good Clinical Practice guidelines established by the International Council for Harmonization, and local regulations. All participants (or parents/legal representatives for minor participants) provided written informed consent before enrollment.

2.2. Vaccine

As previously described [26], the SCB-2019 vaccine, manufactured by Clover Biopharmaceuticals, was provided as 720 μg of SCB-2019 in 1 mL (20 doses) of solution for injection. The CpG-1018 adjuvant (Dynavax Technologies) was supplied in a 2-mL vial containing 12 mg/mL of a 22-mer phosphothioate oligodeoxynucleotide in Tris-buffered saline (24 mg per vial). Alum was supplied as a vial containing 10 mg/mL of aluminum hydroxide (Alhydrogel®, Croda Health Care). Vaccine components, except aluminum hydroxide, were stored at 2–8 °C and mixed to contain 30 μg SCB-2019, 1.5 mg CpG-1018, and 0.75 mg alum in each vaccine dose (0.5 mL per dose). The vaccine or placebo (0.9 % sodium chloride) was administered intramuscularly in the deltoid region of the non-dominant arm by an unblinded vaccinator. The study vaccine syringes were covered by masking labels to avoid unblinding of the subjects.

All adults were to receive two doses of the vaccine or placebo, 21 days apart (on days 1 and 22), according to the randomization stratified by site, age group (≥18 to 64 years vs ≥ 65 years of age), absence/presence of comorbidities associated with high risk of severe COVID-19, and a known history of COVID-19. The Cenduit Interactive Response Technology system (IQVIA, Durham, NC, USA) was used to randomly assign participants (1:1), using a block size of six. The randomization lists were generated by external

unmasked statisticians who played no further role in any statistical analyses.

2.3. Safety assessments

For all subjects, all AEs were to be collected within 30 min after each study vaccination, and all MAAEs, SAEs, AESIs, and AEs leading to early termination from the study or vaccination were to be collected during the entire study period. In addition, in adults enrolled in the phase 2 part of the study, solicited local AEs (pain, erythema, and swelling at the injection site) and systemic AEs (fatigue, headache, myalgia, arthralgia, loss of appetite, nausea, chills, fever [≥38.0 °C]) were to be recorded daily within 7 days after each study vaccination, and all unsolicited AEs were to be collected from the first vaccination (day 1) until 21 days post-second vaccination (day 43). Any AE not listed as solicited was considered as an unsolicited AE [26]. AESIs included potential immune-mediated diseases, inflammatory disorders, and/or neurologic disorders that may or may not have an autoimmune etiology [27]. Additionally, AEs potentially associated with COVID-19 were also reported as AESIs based on the SPEAC recommendations and were revised several times during the conduct of the study [9]. MAAEs were AEs that required medically attended visits (excluding routine visits) including hospital, emergency room, urgent care clinic, and visits to or from medical personnel. Participants were asked to actively report any signs or symptoms of suspected COVID-19. In addition, participants were recommended to perform weekly testing using a rapid antigen test to detect asymptomatic and pre-symptomatic cases of SARS-CoV-2. In all participants with suspected COVID-19 symptoms and positive result of rapid antigen test, a nasopharyngeal swab was collected for RT-PCR testing. All participants with diagnosed COVID-19 were followed for at least 28 days to assess the severity and outcome of each COVID-19 episode.

The effect of the SCB-2019 vaccine on the incidence of disease enhancement was assessed in comparison to the placebo. For this purpose, the ratio of severe COVID-19 to COVID-19 of any severity was evaluated from 14 days after the second dose to the data cutoff.

2.4. Immunogenicity assessments

We evaluated the humoral immune response to the Trimer-Tag domain of SCB-2019 in a subset of participants using a binding-antibody enzyme-linked immunosorbent assay (ELISA). We also evaluated cell-mediated immunity (CMI) to the Trimer Tag in a subset of 150 adult participants randomly enrolled at 3 selected study sites. To characterize CD4 + T cells responses to the Trimer-Tag domain, we performed intracellular cytokine staining of peripheral blood mononuclear cells followed by flow cytometry. Cytokines produced by *T*-helper type 1 cells (interferon gamma [IFNγ], interleukin [IL]-2, tumor necrosis factor alpha [TNFα]), *T*-helper type 2 cells (IL-4, IL-5), and *T*-helper type 17 cells (IL-17) were analyzed after in vitro stimulation with 15-mer peptide pools (with 11 overlapping amino acids per peptide) spanning across the entire Trimer-Tag molecule, or peptide pools spanning across the Trimer-Tag molecule's Glycine repeats or C-propeptide domain of procollagen (CICP). Post-vaccination results at day 36 were compared with the baseline, and results for the Trimer-Tag were compared with the placebo.

2.5. Statistical analysis

The statistical analysis methods, including sample size calculation, were previously described in detail [26]. Briefly, all adult participants who received at least one dose of either the SCB-2019 vaccine or the placebo were included in the safety set, which was used for all safety analyses. Missing data were not imputed. Frequencies and percentages of participants who reported at least one SAE, MAAE, or AESI, participant withdrawal or early termination from the study, and deaths were summarized by vaccine group along with 95 % CIs. Unsolicited AEs were presented by the MedDRA® system organ class (SOC) and preferred term (PT) for each vaccine group. The Clopper-Pearson method was used to calculate the confidence intervals (CIs). Descriptive statistics for age, height, weight, and body mass index were calculated overall and by study group at the time of enrollment. The distribution of participants by sex, ethnic origin, and risk of severe COVID-19 was summarized overall and by study group.

To assess the humoral immune responses, Trimer-Tag-specific antibody geometric mean titers (GMTs) and the percentage of subjects with Trimer-Tag binding antibody above the lower limit of quantification (LLOQ) were evaluated. To assess the cell-mediated immune responses to the Trimer-Tag, the numbers and frequency of T lymphocytes and cytokine-producing peripheral blood mononuclear cells were descriptively summarized. All statistical analyses and descriptive summaries were performed using SAS software version 9.4 (SAS Institute).

3. Results

3.1. Study population

Between 24 March 2021 (study start) and 01 December 2021 (cutoff date for analysis), a total of 30,137 adults received at least one dose of study vaccination and were included in the safety set of the SPECTRA trial: 15,070 participants received at least one dose of SCB-2019 and 15,067 received at least one dose of the placebo (Table 1). Of these, 14,011 (93.0 %) received two doses of the SCB-2019 vaccine and 13,861 (92.0 %) received two doses of the placebo, respectively.

In the safety set, 1059 (7.0 %) participants in the SCB-2019 arm and the 1206 (8.0 %) participants in the placebo arm discontinued from the vaccination schedule (did not receive the two planned vaccinations) and were encouraged to continue to be followed up for safety. The most frequent reason for vaccination discontinuation (2.3 % of participants overall) was associated with the participant's decision to receive an authorized COVID-19 vaccine. The second most frequent reason was an AE, which was reported by a similar percentage of participants in both arms (1.8 % in the SCB-2019 arm and 2.0 % in the placebo arm). Two participants in the placebo arm, died before receiving the second dose. Approximately 7 % of the participants in the safety set discontinued the study prematurely (988 [6.6 %] in the SCB-2019 arm and 1161 [7.7 %] in the placebo arm), mostly due to consent withdrawal and loss to follow up. A total of 30 participants died during the study (8 in the SCB-2019 arm and 22 in the placebo arm).

As of 01 December 2021, the median duration of participation in the study after the first vaccine dose was 177 days (range: 1–253 days) and was similar between arms. The demographic characteristics were generally similar between arms. Overall, in the safety set, the proportion of men was 53.1 % and the median age was 29 years (range: 18–86 years), with 2.6 % of participants being ≥ 60 years.

Nearly half of the participants were enrolled in the Philippines (45.4 %), followed by Brazil (26.4 %), Colombia (22.2 %), South Africa (3.6 %), and Belgium (2.4 %). Most subjects (45.5 %) were Asian, 20.2 % White, and 9.9 % Black or African American. Furthermore, 45.6 % were Hispanic or Latino.

3.2. Unsolicited AEs from day 1 to day 43

In the period comprised between the first vaccine dose and 21 days after the second dose, 2293 unsolicited AEs were reported

Table 1
Study population.

	SCB-2019	Placebo	Total
	n (%)	n (%)	n (%)
Enrolled set (Screening, ≥12 years)	–	–	31,483
Screen Failure	–	–	1105
No ICF signature	–	–	40
Randomized (≥12 years)	15,176	15,162	30,338
Did not receive any dose	24	15	39
Safety set (All exposed adults)	15,070 (99.5)	15,067 (99.5)	30,137 (99.5)
Received only one dose	1059 (7.0)	1206 (8.0)	2265 (7.5)
Treatment discontinuation	1018 (6.8)	1183 (7.9)	2201 (7.3)
Other	292 (1.9)	390 (2.6)	682 (2.3)
Adverse event	274 (1.8)	298 (2.0)	572 (1.9)
Withdrawal by subject	185 (1.2)	206 (1.4)	391 (1.3)
Lost to follow up	194 (1.3)	189 (1.3)	383 (1.3)
Protocol deviation	34 (0.2)	47 (0.3)	81 (0.3)
Pregnancy	21 (0.1)	26 (0.2)	47 (0.2)
Physician decision	18 (0.1)	25 (0.2)	43 (0.1)
Death	0	2 (0.0)	2 (0.0)
Received two doses	14,011 (93.0)	13,861 (92.0)	27,872 (92.5)
Early discontinued from study	988 (6.6)	1161 (7.7)	2149 (7.1)
Withdrawal by subject	419 (2.8)	547 (3.6)	966 (3.2)
Lost to follow up	307 (2.0)	327 (2.2)	634 (2.1)
Other	220 (1.5)	224 (1.5)	444 (1.5)
Physician decision	27 (0.2)	28 (0.2)	55 (0.2)
Death	8 (0.1)	22 (0.1)	30 (0.1)
Protocol deviation	6 (0.0)	8 (0.1)	14 (0.0)
Pregnancy	1 (0.0)	4 (0.0)	5 (0.0)
Adverse event	0	1 (0.0)	1 (0.0)
Per-Protocol set (Efficacy)[a]	6336 (41.8)	6216 (41.0)	12,552 (41.4)

n is the number of participants in the study arm.
[a] Per-Protocol Efficacy set includes participants who were seronegative for SARS-CoV-2 S protein at baseline and correctly received the full vaccination regimen and had no major protocol deviations up to 14 days after the second dose that could affect the vaccine efficacy. About half of the study participants were seropositive for SARS-Cov-2 S protein at baseline and were excluded from the Per-Protocol set.

by 1543 of 15,070 (10.2 %) SCB-2019 recipients, and 2040 unsolicited AEs were reported by 1414 of 15,067 (9.4 %) placebo recipients. The most frequently reported events were classified under the SOCs General disorders and administration site conditions, Nervous system disorders, and Gastrointestinal system disorders. COVID-19, vaccination site pain, headache, and anosmia (loss of smell) were the most common unsolicited AEs by PT (data not shown). Thirty-three participants in each arm (0.2 % each) reported at least one severe unsolicited AE during this period. When classified by PT, the most common event was COVID-19, which was reported by 4 SCB-2019 recipients and 5 placebo recipients (<0.05 % in each group).

Among unsolicited AEs, 1024 events in 690 SCB-2019 recipients (4.6 % [95 % CI: 4.3–4.9]) and 616 events in 459 placebo recipients (3.0 % [95 % CI: 2.8–3.3]) were considered related to vaccination. General disorders and administration site conditions were the most frequent vaccination-related unsolicited AEs and were reported by 511 (3.4 %) SCB-2019 recipients and 263 (1.7 %) placebo recipients. Among them, the most frequently reported AE was vaccination site pain (2.0 % and 0.6 %, respectively). Nervous system disorders were reported by 142 SCB-2019 recipients and 129 placebo recipients (0.9 % in both arms), with headache being the most frequently reported AE (0.8 % and 0.7 %, respectively).

3.3. Overall SCB-2019 safety profile from day 1 to the 6-month follow-up cutoff date

Less than half of the AEs occurring during the follow-up period required medical visits, with MAAEs reported by 1071 SCB-2019 recipients (7.1 % [(95 % CI: 6.7–7.5]) and 1211 placebo recipients (8.0 % [95 % CI: 7.6–8.5]) (Table 2). Upper respiratory tract infections (1.9 % of recipients in both arms), COVID-19 (1.5 % and 2.5 %, respectively), systemic viral infections (0.7 % and 0.8 %, respectively), and gastroenteritis (0.6 % and 0.5 %, respectively) were the most frequent MAAEs.

Overall, SAEs were reported by 90 (0.6 %) participants in the SCB-2019 arm and 114 (0.8 %) participants in the placebo arm (Table 2). The most frequently reported SAEs, listed in Table 3, were classified under the SOCs Infections and infestations (in 23 [0.2 %] SCB-2019 recipients and 46 [0.3 %] placebo recipients), followed by Injury, poisoning and procedural complications (in 18 [0.1 %] SCB-2019 recipients and 20 [0.1 %] placebo recipients). The most common SAEs were COVID-19 (reported by 2 SCB-2019 recipients and 19 placebo recipients), COVID-19 pneumonia (reported by 9 placebo recipients), and spontaneous abortion (reported by 4 SCB-2019 recipients and 8 placebo recipients).

In the SCB-2019 arm, 4 of the SAEs were considered related to vaccination by the investigator (Table 2). These SAEs included hypersensitivity (2 events), Bell's palsy, and spontaneous abortion. In the placebo arm, 4 SAEs, reported by 2 participants, were considered related to vaccination by the investigator. One participant reported COVID-19, pneumonia, and acute respiratory distress syndrome and the other participant experienced spontaneous abortion.

Adverse events of special interest, including potential immune-mediated diseases, were reported by 323 (2.1 % [95 % CI: 1.9–2.4]) participants in the SCB-2019 arm and 496 (3.3 % [95 % CI: 3.0–3.6]) participants in the placebo arm (Table 2). Most of these AESIs were reported under the SOCs Nervous system disorders (Table 4). Among them, the most frequently reported AESIs were anosmia (reported by 1.7 % participants in the SCB-2019 arm and 2.5 % in the placebo arm), and ageusia (reported by 1.3 % participants in the SCB-2019 arm and 2.3 % in the placebo arm), which were associated with diagnosed COVID-19 in most participants. Both of these AESIs were reported at a lower frequency in the SCB-2019 arm than in the placebo arm. Besides anosmia and ageusia, no notable differences were observed in the frequency of AESIs between study arms. Two cases of Bell's palsy were observed in the SCB-2019 arm but none in the placebo arm.

A total of 26 AESIs considered related to vaccination were reported by 12 SCB-2019 recipients (0.1 % [95 % CI: 0.0–0.1]) and 13 placebo recipients (0.1 % [95 % CI: 0.0–0.1]) (Table 2). Of these, the most frequently reported events were hypersensitivity (reported by 4 SCB-2019 recipients and 2 placebo recipients), urticaria (reported by 3 SCB-2019 recipients and 2 placebo recipients), and alopecia areata (reported by 1 SCB-2019 recipient and 2 placebo recipients). Three of the vaccine-related AESIs reported by SCB-2019 recipients were also potential immune-mediated disease events, notably the single events of Bell's palsy (already mentioned above), alopecia areata, and dermatitis herpetiformis (which occurred in a participant with a history of chickenpox who presented with dermatomal lesions on the abdomen and back characteristic of herpes zoster and was treated with acyclovir).

4. Potential risk of disease enhancement associated with SCB-2019

We also evaluated the risk of disease enhancement after vaccination with SCB-2019 in participants without evidence of prior SARS-CoV-2 infection. We analyzed all RT-PCR-confirmed COVID-19 cases of any severity starting from 14 days post-dose 2 in SCB-2019 and placebo recipients. Among the 256 participants with RT-PCR-confirmed COVID-19 in the SCB-2019 arm, none had severe disease

Table 2
Safety overview during the 6–month follow-up.

Adverse events	SCB-2019 N = 15,070		Placebo N = 15,067	
	n_s (n_e)	% (95 % CI)	n_s (n_e)	% (95 % CI)
Any unsolicited adverse events	2497 (4132)	16.6 (16.0–17.2)	2597 (4419)	17.2 (16.6–17.8)
Related to vaccination	712 (1057)	4.7 (4.4–5.1)	480 (645)	3.2 (2.9–3.5)
Severe	73 (93)	0.5 (0.4–0.6)	93 (144)	0.6 (0.5–0.8)
Any medically-attended adverse events	1071 (1697)	7.1 (6.7–7.5)	1211 (1910)	8.0 (7.6–8.5)
Any serious adverse events	90 (114)	0.6 (0.5–0.7)	114 (176)	0.8 (0.6–0.9)
Related to vaccination	4 (4)	0.0 (0.0–0.1)	2 (4)	0.0 (0.0–0.0)
Any adverse events of special interest	323 (509)	2.1 (1.9–2.4)	496 (791)	3.3 (3.0–3.6)
Related to vaccination	12 (12)	0.1 (0.0–0.1)	13 (14)	0.1 (0.0–0.1)
Any adverse events 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)

Abbreviations: CI, confidence interval.
N is the number of participants in the study arm used as denominator for percentage calculation; n_e is the number of events; n_s is the number of participants reporting the adverse event (AE).
For a participant reporting greater than 1 AE for a given symptom within 7 days post-vaccination, the most severe AE was included in the calculation of percentage.
A related AE was an AE that was considered to be probably or possibly caused by the study vaccination.

Table 3
Serious adverse events reported by ≥ 3 participants in any group by system organ class and preferred term.

Serious adverse events	SCB-2019 N = 15,070		Placebo N = 15,067	
	n_s (n_e)	% (95 % CI)	n_s(n_e)	% (95 % CI)
Any serious adverse event	90 (114)	0.6 (0.5–0.7)	114 (176)	0.8 (0.6–0.9)
Cardiac disorder	8 (8)	0.1 (0.0–0.1)	8 (11)	0.1 (0.0–0.1)
Acute myocardial infarction	2 (2)	0.0 (0.0–0.0)	3 (3)	0.0 (0.0–0.1)
Acute coronary syndrome	1 (1)	0.0 (0.0–0.0)	3 (3)	0.0 (0.0–0.1)
Cardiogenic shock	0 (0)	0.0 (0.0–0.0)	3 (3)	0.0 (0.0–0.1)
General disorders and administration site conditions	3 (3)	0.0 (0–0.1)	2 (2)	0.0 (0.0–0.0)
Hepatobiliary disorders	2 (2)	0.0 (0.0–0.0)	6 (7)	0.0 (0.0–0.1)
Cholelithiasis	0 (0)	0.0 (0.0–0.0)	4 (4)	0.0 (0.0–0.1)
Immune system disorders	3 (3)	0.0 (0.0–0.1)	1 (1)	0.0 (0.0–0.0)
Hypersensitivity	3 (3)	0.0 (0.0–0.1)	0 (0)	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 (0.0–0.1)	4 (4)	0.0 (0.0–0.1)
COVID-19	2 (2)	0.0 (0.0–0.0)	19 (19)	0.1 (0.1–0.2)
Pneumonia	2 (2)	0.0 (0.0–0.0)	6 (6)	0.0 (0.0–0.1)
Appendicitis	1 (1)	0.0 (0.0–0.0)	4 (4)	0.0 (0.0–0.1)
COVID-19 pneumonia	0 (0)	0.0 (0.0–0.0)	9 (9)	0.1 (0.0–0.1)
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 (0.0–0.1)	1 (1)	0.0 (0.0–0.0)
Animal bite	1 (2)	0.0 (0.0–0.0)	4 (4)	0.0 (0.0–0.1)
Gunshot wound	0 (0)	0.0 (0.0–0.0)	3 (3)	0.0 (0.0–0.1)
Neoplasms benign, malignant and unspecified	3 (3)	0.0 (0.0–0.1)	3 (3)	0.0 (0.0–0.1)
Nervous system disorders	7 (7)	0.0 (0.0–0.1)	12 (14)	0.1 (0.0–0.1)
Pregnancy, puerperium and perinatal conditions	9 (12)	0.1 (0.0–0.1)	12 (12)	0.1 (0.0–0.1)
Spontaneous abortion	4 (4)	0.1 (0.0–0.1)	8 (8)	0.1 (0.0–0.1)
Psychiatric disorders	5 (5)	0.0 (0.0–0.1)	1 (2)	0.0 (0.0–0.0)
Renal and urinary disorders	3 (3)	0.0 (0.0–0.1)	6 (6)	0.0 (0.0–0.1)
Reproductive system and breast disorders	4 (4)	0.0 (0.0–0.1)	2 (2)	0.0 (0.0–0.0)
Respiratory, thoracic and mediastinal disorders	5 (6)	0.0 (0.0–0.1)	11 (14)	0.1 (0.0–0.1)
Acute respiratory distress syndrome	1 (1)	0.0 (0.0–0.0)	3 (3)	0.0 (0.0–0.1)
Acute respiratory failure	0 (0)	0.0 (0.0–0.0)	4 (4)	0.0 (0.0–0.1)

Abbreviations: AE; adverse event; CI, confidence interval; COVID-19, coronavirus disease.
N is the number of participants in the study arm used as the denominator for calculating percentages; n_e is the number of events; n_s is the number of participants reporting the adverse event.
Serious adverse events were collected up to the cutoff date for safety analysis (01 December 2021).
Adverse events were coded using MedDRA version 24.1 mixed.

(0 %), in contrast to 20/486 participants (4.1 %) in the placebo arm. (Table 5). No signs of disease enhancement were observed during the study period following one or two doses of SCB-2019 vaccine. A total of 11 deaths were associated with COVID-19: 1 case (0.01 %) in the SCB-2019 group after the first dose and 10 cases (0.1 %) in the placebo group after the second dose.

4.1. Assessment of potential risks associated with COVID-19 vaccines

Severe local injection-site reactions: In addition to the solicited AEs collected in a subset of participants within 7 days after each vaccination previously described [26], all participants were encouraged to report any post-vaccination reactions of concern. In total, 3 cases of severe local reactions were reported as unsolicited AEs: 2 cases of vaccination site pain and 1 case of vaccination site erythema. These events started on the day of vaccination or the following day and were deemed related to vaccination. All cases lasted for 2 days and resolved without requiring a medical visit or treatment.

Syncope: Five cases of syncope were reported, 2 in the SCB-2019 arm and 3 in placebo arm. Three events occurred within 30 min post-vaccination, one occurred 10 days post-vaccination, and one

Table 4
Adverse events of special interest reported by ≥ 2 participants in any group by system organ class and preferred term.

Adverse event of special interest	SCB-2019 (N = 15,070)		Placebo (N = 15,067)	
	n_s (n_e)	% (95 % CI)	n_s(n_e)	% (95 % CI)
Any adverse event of special interest	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)

N is the number of participants in the study arm used as the denominator for calculating percentages; n_e is the number of events; n_s is the number of participants reporting the adverse event.
Serious adverse events were collected up to the cutoff date for safety analysis (01 December 2021).
Adverse events were coded using MedDRA version 24.1 mixed.

Table 5
Risk of disease enhancement in participants with COVID-19 in SARS-CoV-2-naïve participants.

	SCB-2019 N = 6336	Placebo N = 6216
Participants with RT-PCR-confirmed COVID-19 of any severity from 14 days after the second dose	256	486
Participants with RT-PCR-confirmed severe COVID-19 from 14 days after the second dose	0	20
Ratio of severe COVID-19 to COVID-19 of any severity (%)	0.0	4.1

Abbreviations: RT-PCR, reverse transcriptase-polymerase chain reaction; COVID-19, coronavirus disease.
This analysis was performed in participants who had no evidence of prior SARS-CoV-2 infection at baseline (per-protocol set for efficacy).

occurred 13 days post-vaccination. Two of them were considered as vaccination-related. All events were assessed as mild-to-moderate in intensity and resolved on the same day.

Hypersensitivity reactions: Thirteen participants experienced hypersensitivity reactions (9 in the SCB-2019 arm and 4 in the placebo arm), 3 of which in the SCB-2019 arm were reported as SAEs. Two of these SAEs were considered vaccination-related: a 28 year-old male with medical history of allergic rhinitis experienced a hypersensitivity reaction of moderate intensity 15 min after receiving the first dose. The participant experienced dizziness, drowsiness, itching on the face and the limbs, and hives in the upper limbs. He also reported a sensation of dyspnea, although no changes in vital signs were recorded. The second case occurred in a 23 year-old male without a significant medical history who experienced a serious hypersensitivity reaction 3 days after the second dose. He presented with nausea, diarrhea, abdominal pain, and generalized pruritic wheals, followed by shortness of breath. Both SAEs considered vaccination-related required treatment (epinephrine, antihistamines, and hydrocortisone) and resolved the next day. Six participants experienced non-serious hypersensitivity reactions, 3 after the first dose and 3 after the second one. They were mild-to-moderate in intensity and resolved following anti-allergic and steroid treatments. No cases of vaccine-related anaphylaxis have been reported.

Bell's palsy: Two events of Bell's palsy were reported in the SCB-2019 group between day 1 and the cutoff date. Both were considered mild. One participant, a 31-year-old male with medical history of obesity, developed Bell's palsy-one day after the second vaccine dose. This event was deemed related to the study vaccine and resolved completely within 17 days with treatment. The other participant, a 23-year-old male without any known medical history or concomitant medications, developed Bell's palsy 156 days after the second dose of SCB-2019. The event was considered unrelated to the study vaccine and resolved in approximately-one month with treatment.

Myocarditis and pericarditis: No cases of myocarditis or pericarditis were reported between the first vaccination and the cutoff date.

Thrombosis associated with thrombocytopenia: To evaluate potential events of TTS, we examined all serious thromboembolic events, which were retrieved from the datasets using the Standardized MedDRA Queries of *Embolic and thrombolic events*. The

retrieved cases were analyzed to determine if there was a contemporaneous event of thrombocytopenia reported. The PTs used to search for thrombocytopenia included *thrombocytopenia*, *immune thrombocytopenia*, and *platelet count decreased*. None of the retrieved cases were consistent with TTS associated with the administration of SCB-2019.

Pregnancy: A total of 125 pregnancies were reported (60 in SCB-2019 recipients and 65 in placebo recipients). Spontaneous abortions were experienced by 9 (0.06 % [95 % CI: 0.0–0.1]) SCB-2019 recipients and 10 (0.07 % [95 % CI: 0.0–0.1]) placebo recipients. Overall, no imbalance in the number of subjects with abnormal pregnancy outcomes was observed between the study arms.

4.2. Assessment of the immune responses to the Trimer-Tag

As part of SCB-2019 safety assessment, we also evaluated the humoral and cell-mediated immune responses to the Trimer-Tag that is used to stabilize the recombinant SARS-CoV-2 Spike protein in the native prefusion trimeric conformation. Specific antibodies against the Trimer-Tag were not induced above the LLoQ in SCB-2019 recipients after the first (day 22) or the second dose (day 36) (**Table S1**). Moreover, CD4 + T cells were neither activated following in vitro stimulation with the Trimer-Tag (**Table S2**), nor with the Glycine repeats or the CICP portion of the Trimer-Tag molecule (data not shown).

5. Discussion

The safety of licensed COVID-19 vaccines is continuously monitored [28]. All COVID-19 vaccines have an acceptable safety profile. The vast majority of known adverse events are mild and of short duration, and vaccine-related serious adverse events are rare (<0.1 %) [14]. The 6-month safety results of the SPECTRA trial reported here are consistent with the initial safety results from the same trial [26], suggesting that SCB-2019 has an acceptable safety profile with no differences in frequencies of SAEs, MAAEs, and AESIs compared to placebo. Certain AESIs have been monitored throughout the study, because these events have been reported previously for other vaccines, including COVID-19 vaccines. Potential immune-mediated diseases are commonly monitored for all vaccines including adjuvants [27].

Hypersensitivity reactions, although rare (approximately 5.58 cases per million doses), have been reported in association with COVID-19 vaccines [20,21]. In our study, a higher rate of hypersensitivity reactions was observed, with two serious reactions deemed related to SCB-2019 vaccination among approximately 15,000 participants. However, no cases of anaphylaxis related to SCB-2019 vaccine have been reported. Two events of Bell's palsy were reported in this study, one related to the SCB-2019 vaccination one day post-vaccination which resolved with treatment.

In post-marketing surveillance, a few risks have been identified with the current authorized COVID-19 vaccines [29]. Rare cases of GBS have been reported following vaccination with adenovirus vector-based COVID-19 vaccines [19]. As of June 2021, 227 cases of GBS have been reported after approximately 51.4 million doses of the ChAdOx nCoV-19 vaccine (AstraZeneca) and 100 cases of GBS after approximately 12.2 million doses of the Ad26.COV2-S vaccine (Janssen) [19]. Also, TTS has been reported after vaccination with adenovirus vector-based COVID-19 vaccines, at a rate of approximately 4 cases per million doses administered [16–18]. Furthermore, rare cases of myocarditis and pericarditis occurred most frequently in male adolescents and young adults within 7 days following the second dose of an mRNA COVID-19 vaccine (approximately 40.6 cases per million second doses among males) [30,31].

In our study, no cases of GBS, TSS, myocarditis and pericarditis were reported. However, the number of participants exposed to the SCB-2019 vaccine in the study is not sufficient to detect these events in this setting. Therefore, these events will be closely monitored as part of the post-marketing safety surveillance.

Vaccine-associated enhanced disease is a rare phenomenon reported in preclinical models with other coronaviruses whereby vaccination promotes immune responses that exacerbate the disease caused by a subsequent infection with the pathogen [22]. This exacerbation is generally associated with antibody responses. We did not observe any signs of VAED during the study period, when looking at the severity of the COVID-19 cases following the administration of at least one SCB-2019 dose. Our data showed that fewer deaths occurred in SCB-2019-recipients than in placebo-recipients, mostly due to the decrease in deaths associated with COVID-19.

Although pregnancy was an exclusion criterion and appropriate contraception methods were required in this study, 125 pregnancies were reported. Similar numbers of abnormal pregnancy outcomes and spontaneous abortions were observed in both study arms and were consistent with the expected rate in this population (15 %–20 %) [32].

At enrolment, participants were stratified by age, prior history of COVID-19, and absence/presence of comorbidities associated with a high risk of severe COVID-19 [33]. Overall, safety profiles of SCB-2019 and placebo were similar within different subgroups in terms of age, sex, risk of COVID-19, or in SARS-CoV-2–exposed participants (data not shown).

There are a few limitations to this study. Although the surveillance period has increased from a median follow-up of 82 to 177 days compared to the results previously published [26], it remains relatively short. Longer surveillance is ongoing and is planned to continue up to 12 months after the second vaccination (day 389). Nevertheless, the placebo arm will not be maintained for the rest of the follow-up. For ethical reasons, the adult participants in the placebo arm of the study were unblinded at 6 months after the second dose to allow vaccination with SCB-2019 or with an approved COVID-19 vaccine. Another limitation is that the safety analysis was limited to adult participants and does not include adolescents and children. Because they generally have milder COVID-19 than adults, worries about safety are prevailing in the general public and higher safety standards are expected to ensure that the benefits of COVID-19 vaccination outweigh the risks, both for the individuals and the population. Lastly, the sample size in this study is insufficient to rule out rare AEs like myocarditis, pericarditis, or TTS [15,29].

6. Conclusions

The SCB-2019 vaccine has a favorable safety profile in adults aged $\geq$ 18 years in the 6-month follow-up period after primary vaccination, with no major safety concerns identified.

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Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing

interests: RH, PA, IS, PL, HQ, CV, BH, and YH are employees of Clover Biopharmaceuticals and may own stocks in the company. CB is an employee of Clover Biopharmaceuticals and owns stocks in Clover Biopharmaceuticals, GSK, and Sanofi. PR was an employee of Clover Biopharmaceuticals at the time of the study conduct and owns stocks in the company.

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Appendix A. Supplementary material

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