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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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Efficacy of the adjuvanted sub-unit protein Covid-19 vaccine, SCB-2019

Supplementary appendix

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Inclusion Criteria

Subjects are eligible for inclusion in the study only if all of the following criteria apply:

1. Male or females ≥ 12 years of age, inclusive*.
2. Participants who are 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 are in stable condition. A stable medical condition is defined as disease not requiring significant change in therapy or hospitalisation for worsening disease during the 3 months before enrolment.
4. Female subjects are eligible to participate in the study if not pregnant, not breastfeeding, and at least of the following criteria apply: Women of childbearing potential (WOCBP) must have a negative urine pregnancy test prior to each vaccination. A confirmatory serum pregnancy test may be conducted at the Investigator's discretion. They must be using a highly effective licensed method of birth control for 30 days prior to the first vaccination and must agree to continue such precautions during the study until 90 days after the second vaccination.
5. Male subjects must agree 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 refrain from donating sperm during this period.

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

Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

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 enrolment.

   **Note: A confirmation of SARS-CoV-2 infection by RT-PCR is required for subjects recruited in Brazil.*
2. Individuals with behavioural 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.
4. Individuals who receive 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 has been administered for treatment of an acute illness, participants

should not be enrolled into the study until corticosteroid therapy has been discontinued for at least 30 days before the first study vaccination. A unique dose of systemic steroids on single day would be allowed, as well as inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

5. Individuals who are pregnant, or breastfeeding, or planning to become pregnant during the study period.
6. Individuals who have 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 Aluminium hydroxide components as outlined in the latest IB).
7. Individuals who have a history of malignancy within year before screening (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix which have been cured, or other malignancies with minimal risk of recurrence).
8. Individuals who have received any other investigational product within 30 days prior to Day 1 or intent to participate in another clinical study at any time during the conduct of this study.
9. Individuals who have received previous vaccination with any coronavirus vaccine.
10. Individuals who have received any other licensed vaccines within 14 days prior to enrolment in this study or who are 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 injection.
12. Individuals who received any blood/plasma products or immunoglobulins within 60 days prior to Day 1 or plan to receive it during the study period.
13. Individuals with any condition that, in the opinion of the investigator, may increase the risk of study participation or interfere 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 days of randomisation. Participants meeting this criterion may be rescheduled within the relevant window. A febrile participant with minor illness can be enrolled at the discretion of the investigator.

Study procedures

Covid-19 cases were defined based on a pre-specified list of signs and symptoms according to the FDA Guidance [1]. At their first vaccination visit participants were trained on these signs and symptoms and instructed to spontaneously contact their study centre if any such symptom occurred. Following such contact participants were then invited for a standard case ascertainment work-up. As well as the routine contacts as per protocol the study sites contacted all participants weekly from two weeks after vaccination to ensure any suspected case was documented. Any suspected case was then confirmed by RT-PCR of nasopharyngeal swabs taken at the study centre.

In addition, participants were provided with the validated Rapid COVID-19 Antigen Test (RAT – Diagnostics Roche, Basel, Switzerland) and instructed in their use (including video demonstrations), with repeated reminders at each study visit. Each participant was reminded to use the RAT at weekly intervals by the ePro, irrespective of any symptoms, and those with positive results were to report to their study centre for confirmation of Covid-19 by RT-PCR.

For symptomatic cases meeting the case definition for Covid-19 a nasopharyngeal swab was obtained within 2 to 5 days (to allow for weekends) of symptom onset for confirmation of Covid-19 by RT-PCR, and Covid-19 symptoms were collected daily using the ePro including measurement and recording of body temperature, heart rate, and SpO_2 by study personnel. If a RT-PCR assessment was negative the participant returned to weekly assessments.

For confirmed Covid-19 cases a follow-up visit to the study centre was made 29 days (± 7 days) after symptom onset for

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

1. *Food and Drug Administration (FDA) Guidance for Industry: COVID-19: Developing Drugs and Biological Products for Treatment or Prevention (FDA, 2020)*

Definitions for study outcome

COVID-19 of any severity is defined as an episode of reverse transcription-polymerase chain reaction (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, non-productive cough, shortness of breath or difficulty breathing, fatigue, new loss of taste or smell, acute diarrhoea (≥ 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 is 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 is defined as change of negative test result at baseline to positive result at any time point during the study period.

Severe COVID-19 is defined as the 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 [FiO_2] < 300 mm Hg);
- Respiratory failure (defined as needing high-flow oxygen, non-invasive 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 is 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)9 , 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.
- 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;
- Diarrhoea (>3 episodes a day) for at least 2 consecutive days (in absence of any other diagnosed gastrointestinal infection).

Any SARS-CoV-2 infection is defined as:

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

***Supplementary table 1*. Primary and key secondary vaccine efficacy endpoints in the Full Analysis Set (FAS)**								
		No. at risk	Cumulative follow-up in person-yrs[a]	No. with event	No. at risk	Cumulative follow-up in person-yrs[a]	No. with event	**Vaccine efficacy with confidence intervals[b]**
Vaccine efficacy in Full Analysis Set (FAS)		**SCB-2019** (N = 12,989)			**Placebo** (N = 12,823)			
Any severity RT-PCR-confirmed Covid-19		12,153	1070·2	**63**	11,983	1045·8	**185**	**66·7% (55·5–75·4)**
Moderate-to-severe RT-PCR-confirmed Covid-19		12,153	1070·2	**7**	11,983	1045·8	**39**	**82·5% (60·3–93·4)**
Severe RT-PCR-confirmed Covid-19		12,153	1070·2	**0**	11,983	1045·8	**8** [c]	**100% (42·7–100)**
Any severity RT-PCR-confirmed Covid-19 associated **with hospitalization**		12,153	1070·2	**0**	11,983	1045·8	**8** [c]	**100% (42·7–100)**
VE endpoints in Full Analysis Set (FAS) against specific variants								
Any severity RT-PCR-confirmed Covid-19 in FAS participants	**Delta variant (B.1.617.2)**	12,153	1070·2	**13**	11,983	1045·8	**60**	**78·8% (61·0–89·3)**
	Gamma variant (P.1)	12,153	1070·2	**1**	11,983	1045·8	**12**	**91·9% (45·0–99·8)**
	Mu variant (B.1.621)	12,153	1070·2	**11**	11,983	11,983	**27**	**60·2% (17·1–82·2)**
	Other variants or not identified [d]	12,153	1070·2	**13**	11,983	11,983	**32**	**60·3% (22·2–80·9)**

a. Cumulative follow-up calculated among all participants at risk within each group, using the time period from 14 days post-dose 2 to analysis cut-off on August 10, 2021.

b. Confidence interval for vaccine efficacy calculated using Clopper-Pearson method based on conditional binomial distribution was 95% CI unless shown.

c. Of 8 severe cases of Covid-19 7 were hospitalised; of 8 hospitalised cases 7 had severe Covid-19 and one had moderate Covid-19 with pneumonia.

d. Includes cases where variant was not identified or cases were too few for variant-specific analysis (Alpha, Beta, B.1.623, Lambda, Theta, etc.)

Supplementary table 2. Reactogenicity in the Phase 2 and safety in the Phase 3 Safety Sets. Solicited reactogenicity showing rates of reporting of local and systemic adverse events in the 7 days following the first and second doses SCB-2019+CpG/alum or placebo as number of events with percentages (with 95% CI). Details of solicited local and systemic reactions are shown in *Supplementary Table 3 and Supplementary Figure 1*, and details of fatal AEs are provided in *Supplementary Table 4*.

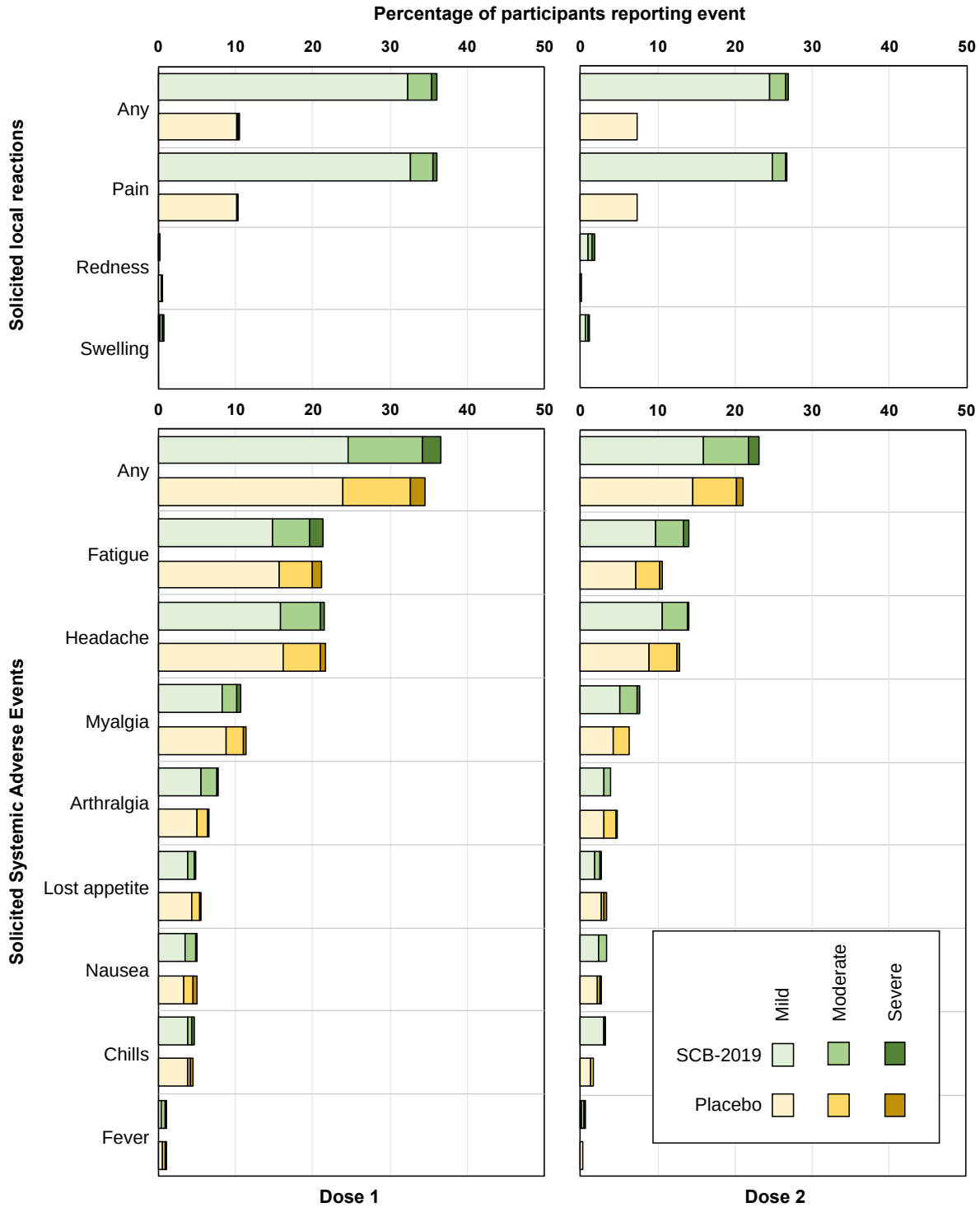
In the Phase 3 Safety Set consisting of any participant who received at least one study treatment rates are shown as number of events reported and percentages (with 95% CI).

Adverse event	SCB-2019+CpG/alum		Placebo	
	n	% (95% CI)	n	% (95% CI)
Phase 2 Safety Set				
First dose	N = 803		N = 786	
Any solicited local AE	290	36·1 (32·8–39·5)	89	11·3 (9·2–13·7)
Any solicited systemic AE	288	35·9 (32·5–39·3)	268	34·6 (30·8–37·5)
Second dose	N = 702		N = 699	
Any solicited local AE	198	28·2 (24·9–31·7)	57	8·2 (6·2–10·4)
Any solicited systemic AE	162	23·1 (20·0–26·4)	147	21·0 (18·1–24·2)
Phase 3 Safety Set				
	N = 15,064		N = 15,064	
Unsolicited AE	1859	12·3 (11·8–12·9)	1871	12·4 (11·9–13·0)
Related	694	4·6 (4·3–5·0)	469	3·0 (2·8–3·4)
Severe AE	34	0·2 (0·2–0·3)	48	0·3 (0·2–0·4)
Serious AE (SAE)				
Any	49	0·3 (0·2–0·4)	59	0·4 (0·3–0·5)
Related	4	0·0 (0·0–0·1)	1	0·0 (0·0–0·0)
Medically attended AE (MAAE)	659	4·4 (4·1–4·7)	776	5·2 (4·8–5·5)
AE of special interest (AESI)	185	1·2 (1·1–1·4)	271	1·8 (1·6–2·0)
Death	3	0·0 (0·0–0·1)	13	0·1 (0·0–0·1)

Supplementary table 3. Solicited reactogenicity in the phase 2 sub-sets. Reports of solicited local reactions and systemic adverse events in the 7 days after doses 1 and 2.

	SCB-2019		Placebo	
Solicited events	**Dose 1**	**Dose 2**	**Dose 1**	**Dose 2**
	N = 803	N = 702	N = 786	N = 699
Local reactions, n (%)				
• Any*	290 (36·1)	198 (28·2)	89 (11·3)	57 (8·2)
• Injection site pain	287 (35·7)	189 (26·9)	81 (10·3)	52 (7·4)
• Redness	14 (1·7)	35 (5·0)	14 (1·8)	10 (1·4)
• Swelling	22 (2·7)	25 (3·6)	9 (1·1)	9 (1·3)
Systemic adverse events, n (%)				
• Any*	288 (35·9)	162 (23·1)	268 (34·1)	147 (21·0)
• Fatigue	168 (20·9)	100 (14·2)	164 (20·9)	74 (10·6)
• Headache	170 (21·2)	98 (14·0)	166 (21·1)	89 (12·7)
• Myalgia	83 (10·3)	53 (7.5)	87 (11·1)	44 (6·3)
• Arthralgia	60 (7·5)	27 (3·8)	48 (6·1)	32 (4·6)
• Loss of appetite	39 (4·9)	19 (2·7)	42 (5·3)	23 (3·3)
• Nausea	38 (4·7)	24 (3·4)	39 (5·0)	19 (2·7)
• Chills	37 (4·6)	23 (3·3)	34 (4·3)	12 (1·7)
• Fever	5 (0·7)	5 (0·7)	2 (0·3)	2 (0·3)

Supplementary figure 1. Proportions of the phase 2 population who received two doses of SCB-2019 (n = 802) or placebo (n = 784) and reported the indicated solicited local reactions or systemic adverse events, with highest severity (mild, moderate or severe).



Supplementary table 4. Adverse events with an outcome of death by System Organ Class (SOC) and Preferred Term (PT) up to the Safety Analysis cut-off date (20 August 2021). Note, efficacy analysis cut-off date was 10 August 2021.

System organ class (SOC)/Preferred term (PT)	**SCB-2019 (N=15064)**	**Placebo (N=15064)**
	Number of subjects, (number of events)	**Number of subjects, (number of events)**
Any AE with outcome of death	3 (8)	13 (20)
Cardiac disorders	0 (0)	5 (7)
• Acute coronary syndrome	0 (0)	2 (2)
• Acute myocardial infarction	0 (0)	2 (2)
• Cardiogenic shock	0 (0)	2 (2)
• Cardio-respiratory arrest	0 (0)	1 (1)
General disorders and administration site conditions	1 (1)	3 (4)
• Death	1 (1)	0 (0)
• Fatigue	0 (0)	1 (1)
• Multiple organ dysfunction syndrome	0 (0)	1 (1)
• Pyrexia	0 (0)	1 (1)
• Sudden cardiac death	0 (0)	1 (1)
Infections and infestations	1 (2)	4 (5)
• Covid-19	0 (0)	3 (3)
• Covid-19pneumonia	0 (0)	1 (1)
• Pneumonia	1 (1)	0 (0)
• Septic shock	1 (1)	0 (0)
• Staphylococcal bacteremia	0 (0)	1 (1)
Injury, poisoning and procedural complications	1 (1)	1 (1)
• Road traffic accident	0 (0)	1 (1)
• Subdural hematoma	1 (1)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1)	0 (0)
• Lung adenocarcinoma stage IV	1 (1)	0 (0)
Nervous system disorders	1 (1)	0 (0)
• Intracranial mass	1 (1)	0 (0)
Respiratory, thoracic and mediastinal disorders	2 (2)	2 (3)
• Covid-19 pneumonia	0 (0)	1 (1)
• Chronic obstructive pulmonary disease	1 (1)	0 (0)
• Cough	0 (0)	1 (1)
• Dyspnoea	0 (0)	1 (1)
• Hemoptysis	1 (1)	0 (0)

AEs were collected from Day 1 up to the cut-off date for safety analysis.
AEs were excluded if they occurred after the administration of another Covid-19 vaccine.