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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.

Supplement to: Smolenov I, Han HH, Li P, et al. Impact of previous exposure to SARS-CoV-2 and of S-Trimer (SCB-2019) COVID-19 vaccination on the risk of reinfection: a randomised, double-blinded, placebo-controlled, phase 2 and 3 trial. *Lancet Infect Dis* 2022; published online April 18. https://doi.org/10.1016/S1473-3099(22)00144-X.

Smolenov 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.

Supplementary appendix

Table of Contents

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.

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).

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 bpm, 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), 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 bpm.
- 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.

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

Definitions for SARS-CoV-2 status

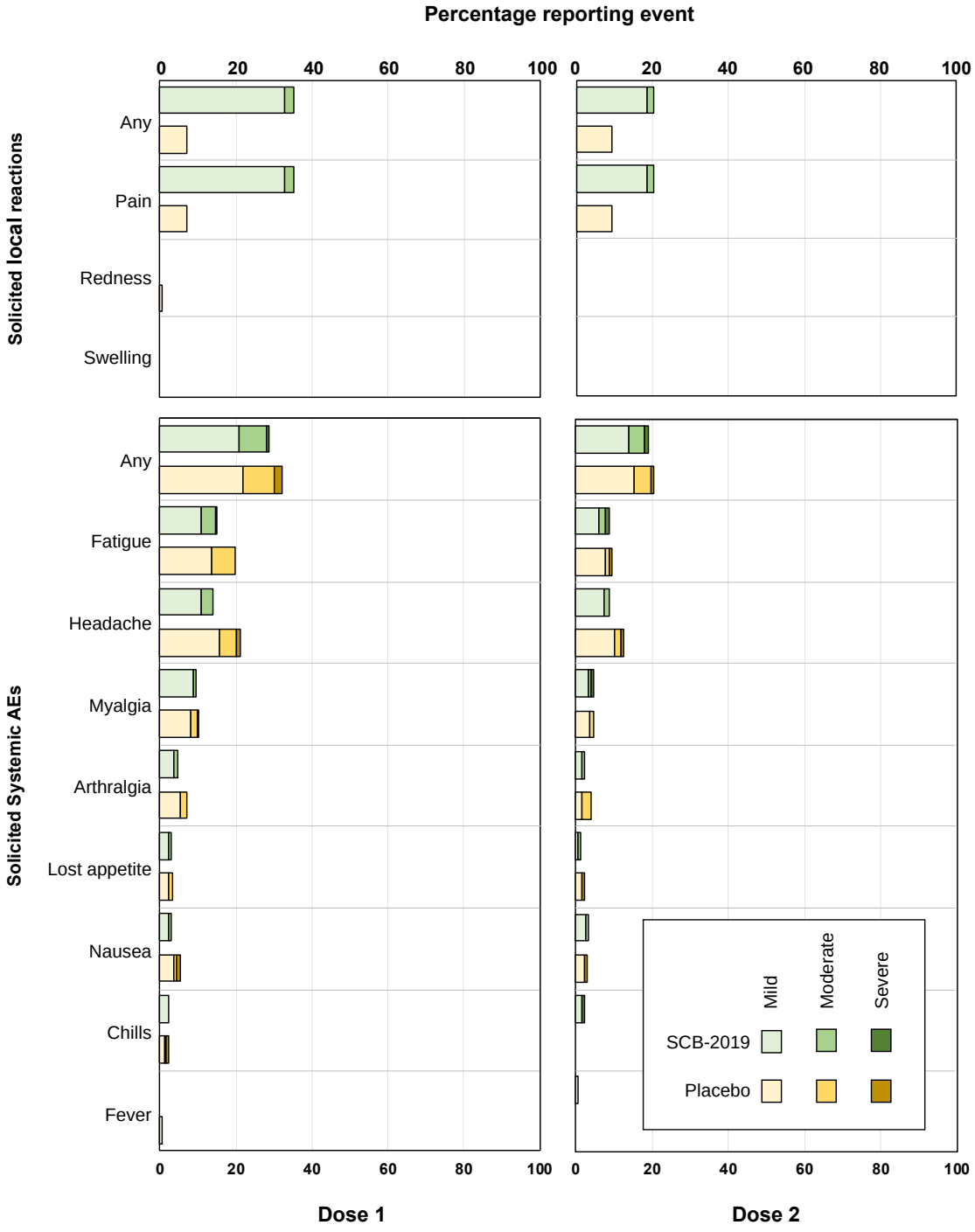
Participant without evidence of prior SARS-CoV-2 infection is defined as

- An individual with a negative result of anti-SARS-CoV-2 enzyme-linked immunosorbent assay (ELISA) immunoglobulin (Ig) test to Receptor-Binding Domain (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
- An individual with a negative Rapid COVID-19 Antigen test at baseline, and
- An individual without documented history of SARS-CoV-2 infection.

Participant with evidence of prior SARS-CoV-2 infection is defined as

- An 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
- An individual with a documented history of SARS-CoV-2 infection.

Supplementary figure 1. Solicited local and systemic reactogenicity in initially seropositive participants in the phase 2 subset. Rates represent occurrence in the 7 days after doses 1 and 2 of the solicited events at maximum severity as percentages of the groups who received dose 1 of SCB-2019 (n = 192) or placebo (n = 183), or dose 2 of SCB-2019 (n = 178) or placebo (n = 168).



Supplementary table 1. Solicited reactogenicity in the phase 2 sub-sets in the pre-exposed population. 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 = 263	N = 243	N = 239	N = 218
Local reactions, n (%)				
Any	91 (34·6)	43 (17·7)	18 (7·5)	19 (8·7)
Injection site pain	89 (33·8)	41 (16·9)	16 (6·7)	17 (7·8)
Redness	4 (1·5)	4 (1·6)	5 (2·1)	2 (0·9)
Swelling	8 (3·0)	3 (1·2)	3 (1·3)	2 (0·9)
Systemic adverse events, n (%)				
Any	74 (28·1)	35 (14·4)	71 (29·7)	38 (17·4)
Fatigue	37 (14·1)	18 (7·4)	41 (17·2)	30 (13·8)
Headache	38 (14·4)	16 (6·6)	48 (20·1)	25 (11·5)
Myalgia	22 (8·4)	9 (3.7)	21 (8·8)	8 (3·7)
Arthralgia	13 (4·9)	4 (1·6)	15 (6·3)	7 (3·2)
Loss of appetite	7 (2·3)	2 (0·8)	7 (2·9)	4 (1·8)
Nausea	8 (3·0)	6 (2·5)	10 (4·2)	5 (2·3)
Chills	7 (2·7)	4 (1·63)	4 (1·7)	0 (0)
Fever	1 (0·4)	5 (0·7)	1 (0·4)	0 (0)