

**Clinical trial results:****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****Summary**

EudraCT number	2020-004272-17
Trial protocol	BE DE
Global end of trial date	11 September 2024

Results information

Result version number	v1 (current)
This version publication date	12 January 2025
First version publication date	12 January 2025
Summary attachment (see zip file)	primary analysis (2022_Lancet_SPECTRA-Primary-Analysis.pdf) immunogenicity (2023_Vaccine_SPECTRA-Immunogenicity.pdf) 6 months follow-up (2023_Vaccine_SPECTRA-6-Month-Safety-Follow-Up.pdf)

Trial information**Trial identification**

Sponsor protocol code	CLO-SCB-2019-003
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Additional study identifiers

ISRCTN number	ISRCTN000000000
ClinicalTrials.gov id (NCT number)	NCT04672395
WHO universal trial number (UTN)	U0000-0000-0000

Notes:

Sponsors

Sponsor organisation name	Clover Biopharmaceuticals AUS Pty Ltd
Sponsor organisation address	Level 17, HWT Tower, 40 City Road, Southbank VIC, Melbourne, Australia, 3006
Public contact	Htay Htay Han, Clover Biopharmaceuticals AUS Pty Ltd, htayhtay.han@cloverbiopharma.com
Scientific contact	Htay Htay Han, Clover Biopharmaceuticals AUS Pty Ltd, htayhtay.han@cloverbiopharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 September 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 December 2021
Global end of trial reached?	Yes
Global end of trial date	11 September 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. Primary Efficacy Objective: Vaccine Efficacy 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.
2. Primary Safety and Reactogenicity Objective: To assess the safety and reactogenicity of CpG 1018/Alum-adjuvanted SCB-2019 vaccine compared to placebo.
3. Primary Immunogenicity Objective: To demonstrate that SCB-2019 vaccine when given as a booster dose (full dose) elicits an immune response that is noninferior to the immune response when given as primary 2-dose series, as measured by virus neutralization assay at 14 days after third (booster dose) or second (primary 2-dose series) vaccination in subjects without evidence of prior SARS-CoV-2 infection.

Protection of trial subjects:

The vaccine is cross-protective against D614G mutation SARS-CoV-2 strain, based on the hamster challenge study results which used the mut strain for challenge and VNT assay. Cross protection against SARS-CoV and other common cold coronaviruses are also being evaluated in nonclinical studies. The vaccine antigen is based on the full-length ectodomain spike (S1 and S2 domains), and S2 is more conserved across strains than S1.

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).

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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 March 2021
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Regulatory reason
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 709
Country: Number of subjects enrolled	Philippines: 13676
Country: Number of subjects enrolled	Colombia: 6696
Country: Number of subjects enrolled	Brazil: 7947
Country: Number of subjects enrolled	South Africa: 1100
Worldwide total number of subjects	30128
EEA total number of subjects	709

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	29712
From 65 to 84 years	416
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Initially only healthy adult individuals 18-64 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 18-64 years, DSMB made a recommendation regarding the extension of recruitment and inclusion of older adults aged ≥ 65 years and individuals with comorbidities.

Pre-assignment

Screening details:

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.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

An unblinded team, not involved in evaluations, handled dose preparation and administration. Syringes were opacified and doses given behind a curtain to prevent unblinding. Study and sponsor staff monitoring the study were blinded to the vaccine code. Labs tests were also blinded to avoid linking samples with treatments. The treatment code could only be revealed for medical necessity. Unblinding required sponsor approval unless medically urgent.

Arms

Are arms mutually exclusive?	No
Arm title	CpG 1018/alum/SCB-2019 group

Arm description:

approximately 15 000 adult subjects and 600 adolescents

Arm type	Experimental
Investigational medicinal product name	CpG 1018/alum/SCB-2019
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

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

Arm title	placebo arm
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Arm description:

approximately 15 000 adult subjects and 600 adolescents

Arm type	Placebo
Investigational medicinal product name	0.9% saline solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

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

Number of subjects in period 1	CpG 1018/alum/SCB- 2019 group	placebo arm
Started	15064	15064
Completed	15064	15064

Baseline characteristics

Reporting groups

Reporting group title	overall trial
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Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	30128	30128	
Age categorical			
Units: Subjects			
18-59 years	29345	29345	
≥ 60 years	783	783	
Gender categorical			
Units: Subjects			
Female	14119	14119	
Male	16009	16009	

End points

End points reporting groups

Reporting group title	CpG 1018/alum/SCB-2019 group
Reporting group description: approximately 15 000 adult subjects and 600 adolescents	
Reporting group title	placebo arm
Reporting group description: approximately 15 000 adult subjects and 600 adolescents	
Subject analysis set title	efficacy-PPS
Subject analysis set type	Per protocol
Subject analysis set description: For VE evaluation 14 days post Dose 2, subjects in the FAS - Efficacy (Dose 2) who correctly receive the full vaccination regimen and who have no other major protocol deviations that were judged to possibly impact the efficacy of the vaccine up to 14 days post Dose 2.	
Subject analysis set title	efficacy-FAS (dose 2)
Subject analysis set type	Full analysis
Subject analysis set description: Vaccine Efficacy in SARS-CoV-2-exposed Subjects [Efficacy-FAS (Dose 2) Including only Subjects with Evidence of Prior SARS-CoV-2 Infection]	
Subject analysis set title	phase 2-SAF
Subject analysis set type	Safety analysis
Subject analysis set description: Reactogenicity Subset	
Subject analysis set title	immunogenicity PPS
Subject analysis set type	Per protocol
Subject analysis set description: Subjects in the FAS – Immunogenicity who correctly receive the full vaccination regimen and who have no other major protocol deviations that were judged to possibly impact the immunogenicity of the vaccine	
Subject analysis set title	immunogenicity FAS
Subject analysis set type	Full analysis
Subject analysis set description: All adult subjects in the immunogenicity/reactogenicity subset and adolescent who are randomized, received at least one dose of study vaccine and provided immunogenicity data at Day 36 (Visit 3).	

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

End point title	Primary Efficacy Objective (H1) - VE against COVID-19 of any severity
End point description: 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.	
End point type	Primary
End point timeframe: 13 Sep 2024	

End point values	CpG 1018/alum/SCB-2019 group	placebo arm	efficacy-PPS	efficacy-FAS (dose 2)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	15064	15064	11745	14623
Units: %	52	155	52	11

Attachments (see zip file)	CSR/CLO-SCB-2019-003-compiled CSR V2.0-Oct 23 2024.pdf
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Statistical analyses

Statistical analysis title	Primary Efficacy Objective (H1) - VE against COVID
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Statistical analysis description:

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 (H10) and alternative (H1a) hypotheses for the primary endpoint are:

H10: VE \leq 30% vs H1a: VE $>$ 30%.

The VE was to be calculated as $100 \times [1 - \text{incidence rate ratio (IRR)}]$.

Comparison groups	CpG 1018/alum/SCB-2019 group v placebo arm v efficacy-FAS (dose 2) v efficacy-PPS
Number of subjects included in analysis	56496
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	< 0.05
Method	exact Binomail
Parameter estimate	Mean difference (final values)
Point estimate	150
Confidence interval	
level	95 %
sides	1-sided
lower limit	30
Variability estimate	Standard deviation

Notes:

[1] - 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. multi 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.

Primary: Primary Safety and Reactogenicity Objective

End point title	Primary Safety and Reactogenicity Objective
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End point description:

End point type	Primary
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End point timeframe:

Solicited Local Reactions (Phase 2 SAF): \leq 7-day after either dose

Solicited Systemic Adverse Events (Phase 2 SAF): \leq 7-day after either dose

Unsolicited AEs between Day 1 and Day 43 (Phase 2 SAF): \leq 6-week after 1st dose

End point values	CpG 1018/alum/SCB-2019 group	placebo arm	phase 2-SAF	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	14623	14623	14623	
Units: %	52	155	52	

Statistical analyses

Statistical analysis title	Primary Safety and Reactogenicity Objective
Comparison groups	placebo arm v CpG 1018/alum/SCB-2019 group
Number of subjects included in analysis	29246
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	> 0.05
Method	t-test, 2-sided

Secondary: Secondary immunogenicity objective

End point title	Secondary immunogenicity objective
End point description:	
End point type	Secondary
End point timeframe:	
For WT-VNA titers (in IU/ml) and in the SCB-2019 recipients at Day 36, 2-weeks after the 2nd dose compare to the baseline on Day 1.	

End point values	CpG 1018/alum/SCB-2019 group	placebo arm	immunogenicity PPS	immunogenicity FAS
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	381	47	428 ^[2]	722 ^[3]
Units: titre				
geometric mean (standard deviation)	220 (± 0)	28 (± 0)	224 (± 0)	211.3 (± 0)

Notes:

[2] - SCB-2019 arm 381, Placebo 47

[3] - SCB-2019 arm 636, Placebo 84

Statistical analyses

Statistical analysis title	Secondary immunogenicity objective
Statistical analysis description:	
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.	
Comparison groups	immunogenicity PPS v immunogenicity FAS

Number of subjects included in analysis	1150
Analysis specification	Pre-specified
Analysis type	superiority ^[4]
P-value	< 0.05 ^[5]
Method	Clopper-Pearson

Notes:

[4] - 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.

[5] - 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).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

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

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	CpG 1018/alum/SCB-2019 group
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Reporting group description: -

Reporting group title	placebo arm
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Reporting group description: -

Serious adverse events	CpG 1018/alum/SCB- 2019 group	placebo arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 808 (0.12%)	2 / 793 (0.25%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Vascular disorders			
hypertension			
subjects affected / exposed	1 / 808 (0.12%)	2 / 793 (0.25%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0.03 %

Non-serious adverse events	CpG 1018/alum/SCB- 2019 group	placebo arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	803 / 808 (99.38%)	793 / 793 (100.00%)	
General disorders and administration site conditions			

injection site pain			
subjects affected / exposed	803 / 808 (99.38%)	793 / 793 (100.00%)	
occurrences (all)	349	119	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 April 2022	Has updated Schedule of Activities, Objectives and Endpoints, Study Design, Contraindications to the Second or Third Vaccination, Inclusion Criteria, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information, Pregnancy, Immunological Markers of SARS-CoV-2 Infection, Immunogenicity (Primary Objective), Analysis Timing.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported