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Persistence of the Immune Responses and Cross-Neutralizing Activity With Variants of Concern Following 2 Doses of Adjuvanted SCB-2019 Coronavirus Disease 2019 Vaccine

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Background. We have previously reported the safety and immunogenicity 4 weeks after 2 doses of the Clover coronavirus disease 2019 (COVID-19) vaccine candidate, SCB-2019, a stabilized prefusion form of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein (S-trimer). We now report persistence of antibodies up to 6 months after vaccination, and cross-neutralization titers against 3 variants of concern (VoCs).

Methods. In a phase 1 study, adult (18–54 years of age) and elderly (55–75 years of age) volunteers received 2 vaccinations 21 days apart with placebo or 3-, 9-, or 30-μg. We measured immunoglobulin G (IgG) antibodies against SCB-2019, angiotensin-converting enzyme 2 (ACE2) competitive binding antibodies, and neutralizing antibodies against wild-type SARS-CoV-2 (Wuhan-Hu-1) at days 101 and 184, and neutralizing antibodies against 3 VoCs, Alpha (B.1.1.7), Beta (B.1.351), and Gamma (P.1), in day 36 sera.

Results. Titers waned from their peak at days 36–50, but SCB-2019 IgG antibodies, ACE2 competitive binding antibodies, and neutralizing antibodies against wild-type SARS-CoV-2 persisted at 25%–35% of their observed peak levels at day 184. Day 36 sera also demonstrated dose-dependent increases in neutralizing titers against the 3 VoCs.

Conclusions. SCB-2019 dose-dependently induced immune responses against wild-type SARS-CoV-2, which persisted up to day 184. Neutralizing antibodies were cross-reactive against 3 of the most prevalent VoCs.

Keywords. COVID-19; vaccine; immunogenicity; persistence; variants of concern.

The coronavirus disease 2019 (COVID-19) pandemic, due to infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has seen a major campaign by many research groups and companies to develop safe and effective vaccines. Most are based around the glycosylated spike protein (S-protein) of the viral membrane, which is an essential component of the interaction with human cell-surface angiotensin-converting enzyme 2 (ACE2) for viral uptake [1, 2]. Clover Biopharmaceuticals has developed a vaccine candidate, SCB-2019, comprising a stabilized prefusion form for the trimeric S-protein using Trimer-Tag technology [3].

We have previously reported on the safety and reactogenicity of 3 dose levels (3 μg, 9 μg, or 30 μg) in different nonadjuvanted and adjuvanted formulations of the Clover vaccine candidate when given as 2 doses 21 days apart to adults from 18–54 years of age and elderly adults from 55 to 75 years of age [4]. That report presented immunogenicity data up to 4 weeks after the second vaccination. We now present data on the persistence of antibody responses to the 3 dose levels of the SCB-2019 formulation adjuvanted with the Toll-like receptor agonist CpG-1018 combined with alum, in both age groups up to 6 months after vaccination.

With the increasing occurrence around the world of mutations of the original SARS-CoV-2, resulting in variants of concern (VoCs), with new variants having been first detected in the United Kingdom, India, and Brazil, for example [5–7], we have also tested sera from placebo and SCB-2019 recipients 2 weeks after completion of vaccination for neutralizing activity against these viruses.

MATERIALS AND METHODS

Study Design

This phase 1 study is ongoing at Linear Clinical Research, a specialized clinical trial center in Perth, Australia, since 19 June 2020. It is being performed in concordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and Good Clinical Practice

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guidelines and with the signed informed consent of all volunteer participants [4]. The study protocol and amendments were approved by the center's institutional review board and registered at ClinicalTrials.gov (NCT04405908). Participants are 18- to 75-year-old men or women who met the required inclusion criteria without any exclusion criteria. Main inclusion criteria were being healthy, not having any prior exposure to SARS-CoV-2 by vaccination or infection (tested by serological screening and reverse-transcription polymerase chain reaction), and being available for the duration of the study. Principal exclusion criteria included evidence from the screening of SARS-CoV-2 exposure, any chronic condition or therapy likely to impact immune responses, or any serological evidence of human immunodeficiency virus, hepatitis B virus, or hepatitis C virus infection.

Vaccine

The experimental vaccine formulation SCB-2019 (Clover Biopharmaceuticals, Chengdu, China) was stored at 2°C–8°C in single-use vials as a sterile, clear, colorless solution for injection. Three different doses were tested: 3 µg, 9 µg, or 30 µg SCB-2019, in sodium phosphate buffer and 0.05 mg polysorbate 80 in 0.9% sodium chloride (NaCl), with or without adjuvant. For use, the appropriate dose of SCB-2019 was diluted in a vial with NaCl (0.9%) for nonadjuvanted preparations, or with 1.5 mg CpG 1018 (Dynavax Technologies, Emeryville, California) plus 0.75 mg alum (Alhydrogel, Croda, Goole, United Kingdom) per dose added to the vial and mixed by gentle inversion at room temperature a maximum of 1 hour before administration. The same 3 dose levels of SCB-2019 were also used in experimental formulations with another adjuvant, 0.25 mL of AS03 (GSK Vaccines, Wavre, Belgium). These experimental AS03 formulations are not being taken into further clinical development but results are presented in the Supplementary Materials. Each 0.5 mL was administered by intramuscular injection in the deltoid region. Placebo was 0.5 mL 0.9% NaCl for injection.

Immunogenicity

Blood samples were obtained on days 1 and 22, before administration of the first and second doses of vaccine or placebo, and subsequently on days 36, 50, 101, and 184. Sera were stored at –80°C or lower until shipment to the immunological analysis laboratory (360biolabs, Melbourne, Australia) to assess immune responses using 3 immunological assays: (1) the anti-SCB-2019 immunoglobulin G (IgG) antibody titer measured by enzyme-linked immunosorbent assay (ELISA); (2) anti–wild-type (WT) SARS-CoV-2 neutralizing activity measured by WT microneutralization assay (WT-MN_{50}); (3) and the inhibition of SCB-2019 binding to human ACE2 receptor by serum IgG antibodies using an ACE2-competitive ELISA [4]. Each assay was also applied to a panel of 20 human convalescent serum (HCS) samples collected 20–57 days (mean, 39 days) after symptom onset from 3 hospitalized adults and 17 nonhospitalized adults with COVID-19 (mean age, 37 years; standard deviation, 11 years; range, 18–54 years).

With the recent emergence of mutated SARS-CoV-2 viruses, we also assessed the neutralizing antibody responses against 3 of the main VoCs: Alpha (B.1.1.7) [5], Beta (B.1.351) [6], and Gamma (P.1) [7]. These were assessed by Vismederi (Siena, Italy) using available serum samples from adult and elderly vaccinees who received either placebo as control or who had seroconverted against the Wuhan-Hu-1 strain after 1 of the 3 different dose levels of SCB-2019 adjuvanted with CpG/alum at the day 36 timepoint, and compared with responses in the same assay to the World Health Organization (WHO) International Standard 20/136, which is a pooled HCS sample containing high titers of antibodies against SARS-CoV-2 [8].

Statistical Analysis

All analyses are descriptive and no formal sample size calculations were performed for this phase 1 dose selection study. Immune responses are described as geometric mean values (with 95% confidence intervals [CIs]) for each study group at each timepoint and for the panel of HCS samples in each assay. Seroconversion rates (SCRs) are the percentages of each group who displayed 4-fold or greater increases in antibody titers from day 1. Initially seronegative samples were assigned a value of half the lower limit of quantitation (LLOQ) for the calculation, the LLOQs being 20 MN_{50} for neutralizing titers, 25 for anti–SCB-2019 IgG, and 10 for the ACE2 competitive binding ELISA.

RESULTS

As described in our original report, we enrolled 151 volunteers (91 adults and 60 elderly) [4]. Persistency results are reported in this manuscript for the 48 participants who received 3-, 9-, or 30-µg doses of SCB-2019 formulated with CpG/alum (24 adults and 24 elderly). As expected, the adult and elderly participants who received 2 placebo injections did not display any SARS-CoV-2–specific immune responses and the 25 adults who received nonadjuvanted SCB-2019 did not mount any consistent specific response [4] over the course of the study up to day 184 (Supplementary Tables 1–3). Data for those participants who received vaccine formulations of 30 µg SCB-2019 combined with the AS03 adjuvant, which is not being further pursued for clinical development, also have their results presented in Supplementary Tables 1–3.

Compliance through day 184 was good: Only 2 adults, 1 each in the 3-µg and 30-µg groups, and 1 elderly participant from the 9-µg group did not provide sera for the full study duration. A total of 4 serious adverse events have been reported in the study to date, all in older adults (55–69 years of age), none of which were considered to be related to vaccination. Two were

previously reported (cellulitis in a 55-year-old woman after a cat bite and hypernatremia associated with a pituitary adenoma in a 59-year-old man [4]). Two new events occurred in this follow-up period: A pulmonary embolism not associated with thrombocytopenia occurred in a 69-year-old man with onset 144 days after the second dose of 3 µg SCB-2019 + AS03, and a 63-year-old man who ruptured his gluteus medius tendon following strenuous exercise after a second dose of 30 µg SCB-2019 + CpG/alum. No safety signals have been observed so far in the ongoing surveillance.

Immune responses to the different doses of SCB-2019 + CpG/alum assessed as neutralizing antibodies against WT SARS-CoV-2, IgG against SCB-2019, and ACE2 competitive binding antibodies are illustrated as geometric mean titers (GMTs) in Figure 1, with the data from the HCS panel for comparison. In the younger adults, 2 doses of the CpG/alum adjuvanted formulations led to high SARS-CoV-2–specific immune responses measured by all 3 assays, at levels that overlapped the range of those measured in the HCS. Responses were highest in the 30-µg group, especially for elderly participants. Antibody

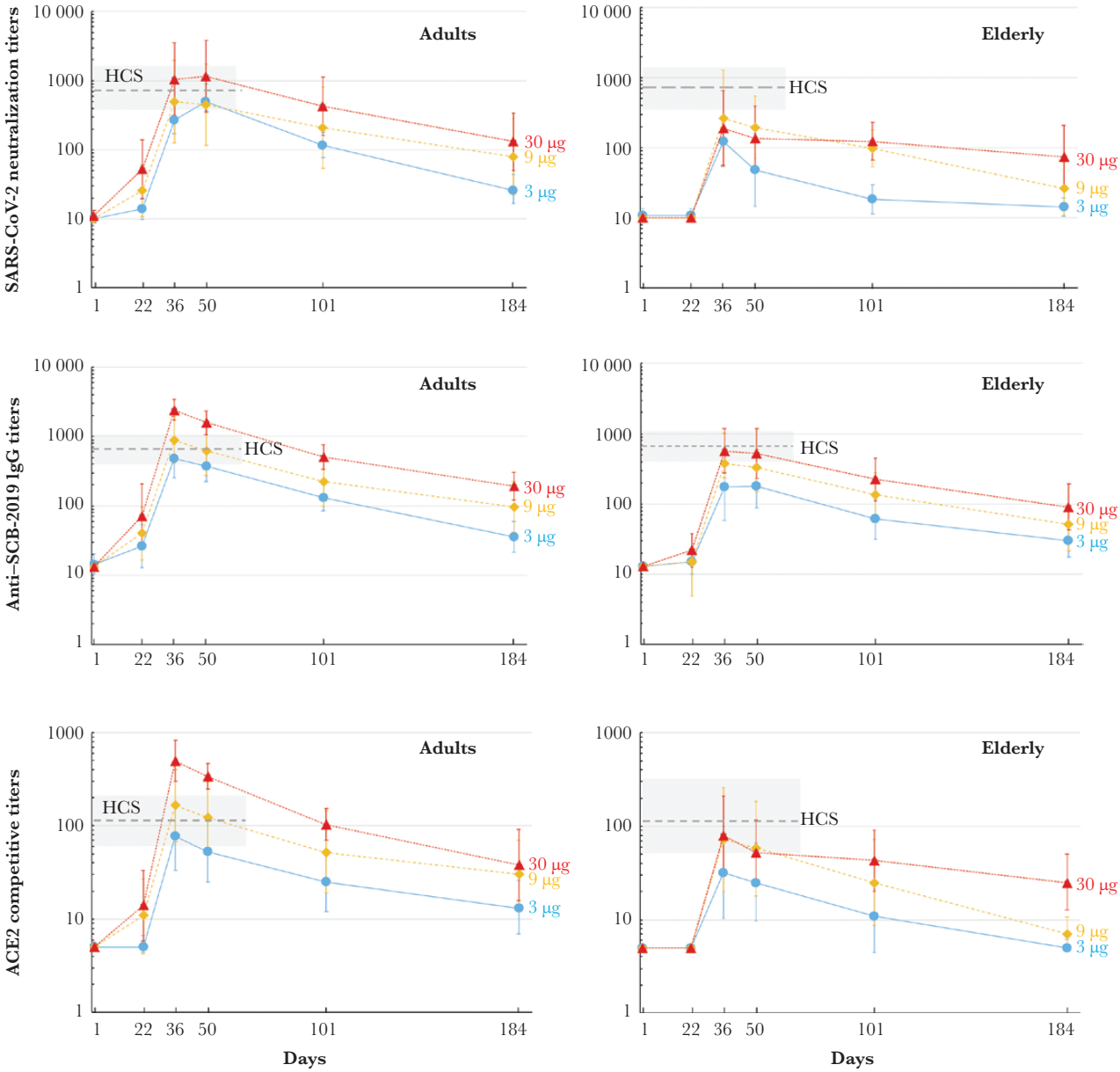

Figure 1. Immune responses to vaccinations at days 1 and 22 of the 3 different doses of SCB-2019 + CpG/alum (3 µg in blue, 9 µg in yellow, and 30 µg in red) in adult (left panels) and elderly (right panels) groups assessed by wild-type severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) neutralizing antibodies (top panels), anti–SCB-2019 immunoglobulin G (IgG) by enzyme-linked immunosorbent assay (middle panels), and angiotensin-converting enzyme 2 (ACE2) competitive binding antibodies (lower panels). Values show geometric mean titers per group (n = 7 or 8) with 95% confidence bars at each timepoint. Also shown is the mean value in each assay determined in human convalescent sera (HCS) obtained 20–57 days after symptom onset. Gray shading represents 95% confidence interval.

levels in each assay peaked at days 36–50, and then waned as expected, but GMTs at day 184 in the 30-μg group were still at much higher levels than baseline. Neutralizing antibody levels represented 8%–11% of the peak GMTs achieved at days 36–50. Peak levels achieved by the elderly participants were lower than those of the younger adults, but titers of WT SARS-CoV-2 neutralizing antibodies and ACE2 competitive binding antibodies in the elderly 30-μg group still remained above baseline at day 184, at 38% and 31% of their peaks.

When expressed as SCRs—that is, the presence of any antibodies in the initially seronegative participants—rates with WT SARS-CoV-2 neutralizing antibodies were 88%–100% in adults 2 weeks after the second dose (day 36) for the 3 SCB-2019-CpG/alum formulations; only one 9-μg recipient did not respond (Table 1). The SCRs remained high up to day 101, after which they decreased to 14%, 63%, and 86% in the 3-μg, 9-μg, and 30-μg groups, respectively, by day 184. The SCRs for neutralizing antibodies in elderly participants were lower, peaking at 75%, 86%, and 88% in the 3-μg, 9-μg, and 30-μg groups, respectively at day 36, and then falling to 0%, 38%, and 63% by day 184. In contrast, SCRs measured as IgG against SCB-2019 were 100% in adult and elderly participants by day 50 and were still 100% in all participants at day 184. SCRs for ACE2 competitive binding antibodies peaked by day 50, but at lower rates than anti–SCB-2019 IgG or WT SARS-CoV-2 neutralizing antibodies, and this response waned more rapidly.

The relationships between the immune responses measured in the different assays were assessed by calculating the Pearson correlation coefficient (*R*) between the results with each assay at day 184 (Figure 2). This showed significant positive linear

Table 1. Antibody Seroconversion Rates[a] in Young and Elderly Adult Groups

Day		Placebo Adults and Elderly Pooled	3 μg SCB-2019 + CpG/Alum		9 μg SCB-2019 + CpG/Alum		30 μg SCB-2019 + CpG/Alum	
			Adult	Elderly	Adult	Elderly	Adult	Elderly
Wild-type SARS-CoV-2 neutralizing antibodies								
22	No.	30	8	8	8	7	8	8
	SCR, No. (%)	0	0	0	2 (25)	0	4 (50)	0
36	No.	30	8	8	8	7	7	8
	SCR, No. (%)	0	8 (100)	6 (75)	7 (88)	6 (86)	7 (100)	7 (88)
50	No.	28	8	8	8	7	7	8
	SCR, No. (%)	0	8 (100)	4 (50)	7 (88)	6 (86)	7 (100)	7 (88)
101	No.	26	8	8	8	7	7	8
	SCR, No. (%)	0	7 (88)	0	7 (88)	5 (71)	7 (100)	7 (88)
184	No.	27	7	8	8	8	7	8
	SCR, No. (%)	0	1 (14)	0	5 (63)	3 (38)	6 (86)	5 (63)
Anti–SCB-2019 IgG antibodies								
22	No.	30	8	8	8	7	8	8
	SCR, No. (%)	0	7 (88)	1 (13)	5 (63)	4 (57)	8 (100)	6 (75)
36	No.	30	8	8	8	7	7	8
	SCR, No. (%)	0	8 (100)	8 (100)	8 (100)	7 (100)	7 (100)	6 (75)
50	No.	29	8	8	8	7	8	8
	SCR, No. (%)	0	8 (100)	8 (100)	8 (100)	7 (100)	7 (100)	8 (100)
101	No.	27	8	8	8	7	7	8
	SCR, No. (%)	0	8 (100)	8 (100)	8 (100)	7 (100)	7 (100)	8 (100)
184	No.	28	7	8	8	8	7	8
	SCR, No. (%)	0	7 (100)	8 (100)	8 (100)	8 (100)	7 (100)	8 (100)
ACE2 receptor competitive binding IgG antibodies								
22	No.	30	8	8	8	7	8	8
	SCR, No. (%)	0	0	0	2 (25)	0	1 (13)	0
36	No.	30	8	8	8	7	7	8
	SCR, No. (%)	0	6 (75)	2 (25)	7 (88)	5 (71)	7 (100)	7 (88)
50	No.	29	8	8	8	7	7	8
	SCR, No. (%)	0	5 (63)	3 (38)	7 (88)	5 (71)	7 (100)	7 (88)
101	No.	27	8	8	8	7	7	8
	SCR, No. (%)	0	2 (25)	1 (13)	5 (63)	3 (43)	7 (100)	6 (75)
184	No.	28	7	8	8	8	7	8
	SCR, No. (%)	0	0	0	4 (50)	0	4 (57)	3 (38)

Abbreviations: ACE2, angiotensin-coverting enzyme 2; IgG, immunoglobulin G; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SCR, seroconversion rate.

[a]Seroconversion is defined as a 4-fold increase in antibody level postvaccination. In participants who were seronegative at baseline, the baseline titer was assigned as half the lower limit of quantitation.

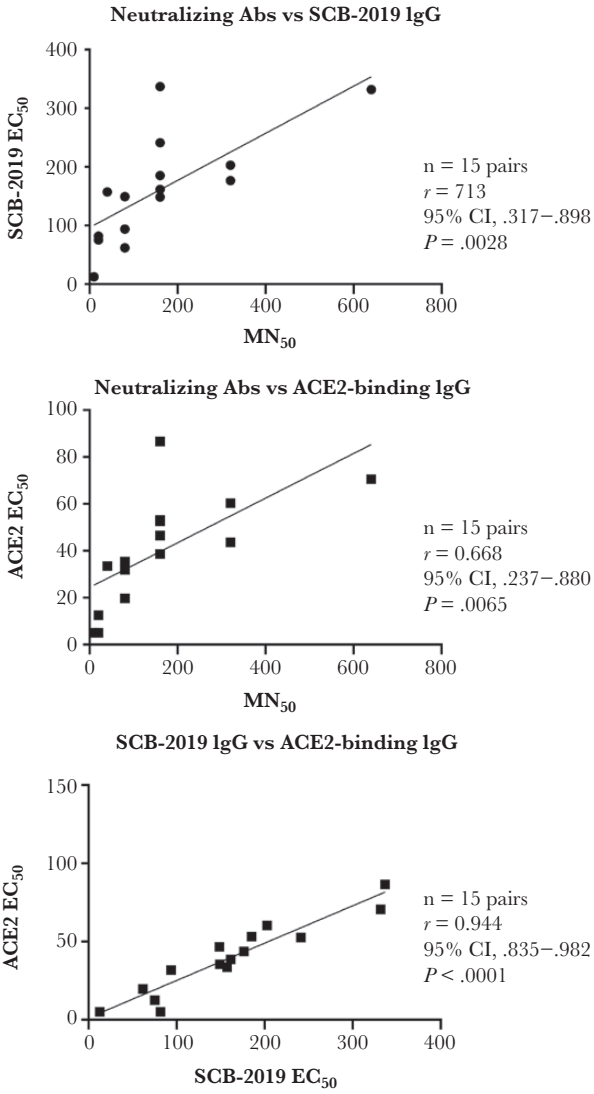

Figure 2. Pairwise Pearson regression analyses between the individual data obtained for the 3 different assays in the adult and elderly participants who received SCB-2019 + CpG/alum obtained at day 184. Abbreviations: Abs, antibodies; ACE2, angiotensin-converting enzyme 2; CI, confidence interval; EC_{50}, ELISA concentration; IgG, immunoglobulin G; MN_{50}, microneutralization titer.

correlations for all 3 pairwise comparisons, for adult or elderly groups assessed separately, or the pooled data for both age groups. This confirms the observations made with the data from days 36 and 50 in our original report, in which the ratios of WT neutralizing antibodies to SCB-2019–binding IgG were also similar to those observed in HCS samples [4].

We measured the neutralizing immune responses against 3 SARS-CoV-2 VoCs—Alpha (B.1.1.7), Beta (B.1.351), and Gamma (P.1)—in 46 serum samples obtained at day 36 after the 2 vaccinations with 3 different dosages of SCB-2019 adjuvanted with CpG/alum administered on days 1 and 22 to adult and elderly participants and 12 placebo recipients, as well as the WHO International Standard 20/136. Data, presented as individual titers and GMTs with 95% CIs in Figure 3, show dose-dependent neutralizing responses against all 3 VoCs. The WHO International Standard 20/136 showed good cross-reactive neutralizing activity against the Alpha and Gamma VoCs, but also appreciable activity against the Beta variant. In vaccinees, the highest responses were to the Alpha variant and then to the Gamma variant. In adults who received the 30-μg dosage of SCB-2019 + CpG/alum, the responses were in the same range as against the original Wuhan-Hu-1 strain. There was also a low but measurable neutralizing response against the Beta variant. Elderly participants showed low levels of neutralizing responses against Alpha and Gamma variants, but little to no cross-reactivity with the Beta variant. A total of 38 of 46 (82.6%) SCB-2019 + CpG/alum vaccinees displayed seroconversion (ie, $MN_{50} \geq 40$) against the Wuhan-Hu-1 strain. Of those 38 who seroconverted, 29 (76.3%), 15 (39.5%), and 37 (97.3%) had measurable neutralizing activity ($MN_{50} \geq 20$) against Alpha, Beta, and Gamma strains, respectively (Table 2). None of the 12 placebo controls tested displayed any activity against any of the 4 strains tested.

DISCUSSION

This presentation of our ongoing assessment of immune responses to different SCB-2019 formulations demonstrates that the originally reported immune responses persist above baseline in a dose-dependent manner up to 6 months after the first vaccination with no emergent safety signals. Six-month levels of WT SARS-CoV-2 neutralizing antibodies, which correlated strongly with levels of anti–SCB-2019 IgG antibodies, were markedly higher than baseline in groups of young and elderly adults who received the 30-μg doses. We have confirmed that there was no evidence of a SARS-CoV-2–specific immune response in any recipient of placebo and only low, inconsistent responses in those who received unadjuvanted SCB-2019 [4]. These data support the selection of the 30-μg SCB-2019 + CpG/alum formulation for further clinical development.

Six months after administration of the first of two 30-μg doses of SCB-2019 + CpG/alum to adult and elderly participants who were all seronegative before vaccination, 100% still had IgG antibodies against SCB-2019, and 86% and 63% had neutralizing antibodies against WT SARS-CoV-2 virus for the adult and elderly groups, respectively. Although titers of both binding and neutralizing antibody had waned by this time, the GMTs still remained higher than post–first dose GMT responses in both groups (Figure 1). This is consistent with observations of the immune response in convalescing COVID-19 patients in whom significant decreases in IgG antibodies been observed by 6 months postinfection [9]. Neutralizing antibodies were shown to decrease over time, becoming undetectable in 37% of convalescing patients over a similar time period [10]. Binding IgG antibody titers against the S-protein and receptor-binding domain (RBD) are relatively stable over the

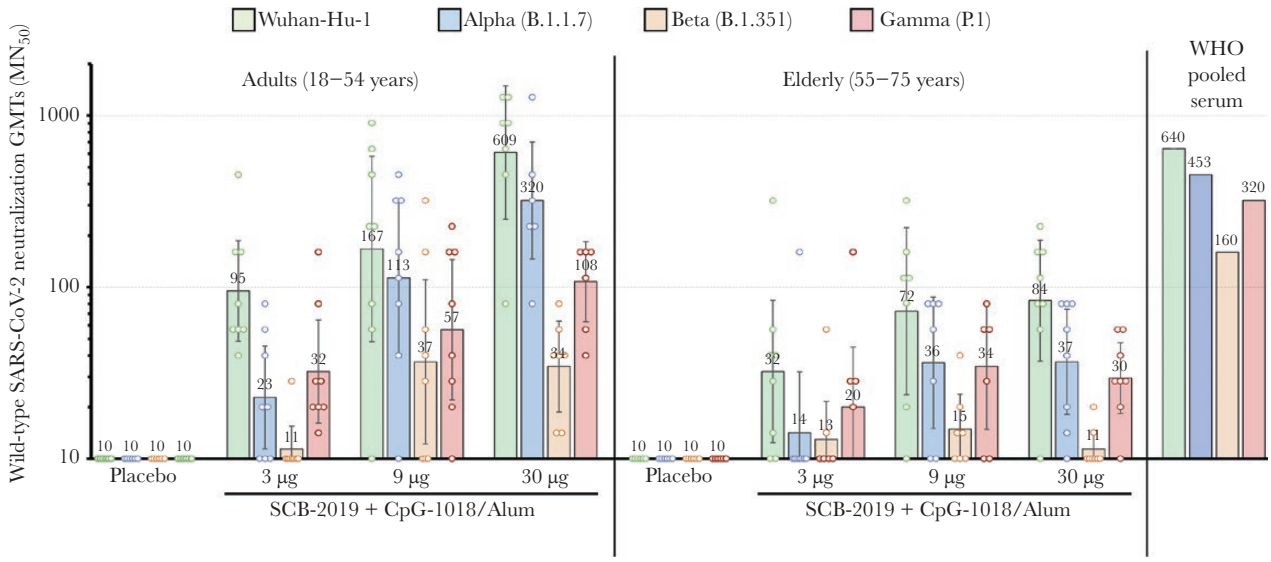

Figure 3. Neutralizing immune responses against the original severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Wuhan-Hu-1) and 3 variants of concern (Alpha, Beta, and Gamma) in day 36 sera after 3 different dosages of SCB-2019 adjuvanted with CpG/alum were administered on days 1 and 22 to adult (18–54 years) and elderly (55–75 years) participants, and World Health Organization (WHO) human convalescent sera International Standard 20/136. Circles show individual titers; columns are geometric mean titers (GMTs; microneutralization titer [MN_{50}]) with 95% confidence intervals.

6-month postinfection period with calculated half-lives of 140 and 83 days, respectively, although with wide variation between individuals [10]. Another group found that IgG levels to RBD peaked at 56 days postinfection before waning [11].

Several other COVID vaccines based on immunity to the S-protein are already in widespread use after being developed and tested clinically for immunogenicity and efficacy against COVID infection [12–15]. One approach for such vaccines is the use of messenger RNA (mRNA) coding for the S-protein, which have been demonstrated to elicit neutralizing immunity against SARS-CoV-2 and efficacy against COVID-19 disease [12, 13]. The mRNA-1273 vaccine has been shown to elicit 94% protective efficacy against COVID-19 after 2 doses 28 days apart [13]. Two doses of mRNA-1273 in this schedule were found to elicit peak neutralizing antibody titers, measured in a pseudovirus neutralization assay, at day 43 in 18- to 55-year-old adults and at day 43–57 in older adults (56–70 years of age), which declined to 22% and 13% of the peak titers, respectively, 6 months after the second vaccination [16]. In our study of 30 μg SCB-2019 + CpG/alum, the analysis of WT SARS-CoV-2 neutralization titers at day 184 had declined to similar absolute levels in the adult and elderly groups, representing 11% and 38% of the peak titers in these groups, respectively.

There is currently no serologic correlate of protection against COVID-19 illness with which to assess the present results. Neutralizing antibodies have been proposed to be predictive of immune protection against symptomatic COVID-19 infection, with levels significantly lower than those measured in HCS samples providing protection against symptomatic illness—20.2% (95% CI, 14%–28%) of the mean convalescent level providing 50% protection against infection, and only 3% (95% CI, .7%–13%) of the mean convalescent level providing 50% protection against severe infection [17]. This may indicate that the levels we found through 6 months postvaccination are predictive of at least moderate or higher efficacy against illness for that period. Several other groups have demonstrated vaccine efficacy against the illness [12–15]. While these vaccines have been assessed using different serologic methods and assays,

Table 2. Neutralizing Antibody Responses Against Variants of Concern in Participants Who Displayed Seroconversion Against Wild-Type Severe Acute Respiratory Syndrome Coronavirus 2 (Wuhan-Hu-1) Following 2 Doses of SCB-2019 + CpG/Alum, and in Placebo Recipients

			Cross-Neutralizing Activity (MN_{50} ≥20) vs VoCs		
Group		Seroconversion Against WT SARS-CoV-2	Alpha (B.1.1.7)	Beta (B.1.351)	Gamma (P.1)
SCB-2019 + CpG/alum	no./No. (%)	38/46 (82.6)	29/38 (76.3)[a]	15/38 (39.5)[a]	37/38 (97.3)[a]
Placebo	no./No. (%)	0/12 (0)	0/12 (0)	0/12 (0)	0/12 (0)

Data are presented as total number of participants who seroconverted or displayed measurable neutralizing activity/total number tested.

Abbreviations: MN_{50}, xxx; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VoCs, variants of concern; WT, wild-type.

[a]VoCs were only tested in sera of the 38 participants who seroconverted against Wuhan-Hu-1.

Earle et al [18] have attempted to compensate for this by correlating efficacy rates and neutralizing titers across studies calibrated with the internal HCS controls from each study as GMT ratios. They found significant correlations between neutralizing titers and efficacy ($\rho = 0.79$) and SARS-CoV-2 spike IgG antibody titers and efficacy ($\rho = 0.93$). If we apply the same analysis to our neutralizing data from vaccinees and convalescent sera, we find GMT ratios of 0.783 (95% CI, .219–2.806) for adults and 0.265 (95% CI, .077–.920) for elderly participants at day 36, which are indicative of efficacies against disease of any severity of at least 70%–80% for adults and 50%–60% for the elderly according to the correlation by Earle et al [18]. This speculative extrapolation of our data to efficacy assessed in other studies with different vaccines is encouraging, but true efficacy will only be demonstrated by our currently ongoing large efficacy study of SCB-2019 + CpG/alum involving >30 000 participants (EudraCT number 2020-004272-17).

COVID-19 infection also leads to an adaptive immune response in patients in whom robust $CD4^+$ T-cell responses have been demonstrated, with some contribution by $CD8^+$ T cells [19–21]. These SARS-CoV-2–specific $CD4^+$ and $CD8^+$ T-cell responses also decline over the same period as IgG, with a half-life of 3–5 months [20]. We have demonstrated a T-cell response to SCB-2019 + CpG/alum [4], but we have not investigated the persistence of that response in this study, nor the potential contribution of any vaccine-induced immune memory against future exposure to SARS-CoV-2 or variants of the virus.

The recent appearance of genetic variation of the original Wuhan-Hu-1 strain of SARS-CoV-2 has led to VoCs that are displaying different characteristics of transmission and disease severity [5–7]. Sera obtained from adults at day 36 after the 2 vaccinations with 3 different dosages of SCB-2019 adjuvanted with CpG/alum displayed robust cross-reactive neutralizing activity against the Alpha (B.1.1.7) and Gamma (P.1) VoCs and some activity against the Beta (B.1.351) variant. Samples from elderly displayed lower levels of cross-reactivity against the Alpha and Gamma variants, but little or no activity against the Beta variant. This post hoc analysis of responses against VoCs, including the widespread Delta variant, will be extended in sera obtained at 6 months postvaccination. The global distribution of these and other new VoCs will affect any current or future phase 3 study of COVID-19 vaccines, particularly the phase 3 efficacy studies [22]. The SCB-2019 + CpG/alum efficacy trial is currently ongoing in countries where the Alpha, Beta, and Gamma VoCs as well as the B.1.621 variant, first described in Colombia [23], are predominating with very little remaining circulation of the ancestor strain. This is a unique opportunity to generate efficacy data against those variants but also leads to the fact that overall efficacy data across vaccines are not comparable and are dependent upon the variant-specific efficacies and the distribution of these variants in the final analysis.

This assessment of the persistence of the immune responses to 2 doses of the selected formulation of 30 μg SCB-2019 + CpG/alum shows that the IgG and neutralizing antibodies that were elicited persist above baseline levels up to 6 months after the first dose, with similar kinetics to other COVID-19 vaccines with proven efficacy. Protein vaccines may also be a very advantageous platform to boost immunity in previously vaccinated individuals. Further ongoing investigations of the immune response to this vaccine formulation include studies of the SCB-2019 vaccine as a heterologous booster dose in individuals who have received 1 or 2 doses of inactivated virion or viral-vectored vaccines. Based on data from preclinical studies, these trials will also include arms using fractional doses of SCB-2019 + CpG/alum as well as SCB-2019 with alum alone.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Disclaimer. Any opinions, findings, and conclusions expressed in this manuscript are those of the authors.

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