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Safety and Efficacy of SAB-185 for Nonhospitalized Adults With COVID-19: A Randomized Clinical Trial

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Background. We evaluated the fully human polyclonal antibody product SAB-185 in a phase 3 trial for COVID-19.

Methods. Nonhospitalized high-risk adults within 7 days of symptom onset were randomized 1:1 to open-label SAB-185 3840 units/kg or casirivimab/imdevimab 1200 mg. Noninferiority comparison was undertaken for pre-Omicron population (casirivimab/imdevimab expected to be fully active) and superiority comparison for the Omicron population (casirivimab/imdevimab not expected to be active). Primary outcomes were the composite of all-cause hospitalizations/deaths and grade ≥3 treatment-emergent adverse events (TEAEs) through day 28. A secondary outcome was time to sustained symptom resolution.

Results. Enrollment ended early due to low hospitalization/death rates upon Omicron emergence; 255 adults were in pre-Omicron and 392 in Omicron populations. Hospitalizations/deaths occurred in 6 (5.0%) and 3 (2.2%) of pre-Omicron SAB-185 and casirivimab/imdevimab arms (absolute difference 2.7%; 95% confidence interval [CI], −2.3%-8.6%); and 5 (2.5%) versus 3 (1.5%) (absolute difference 1.0%; 95% CI, −2.3%-4.5%) for Omicron. All risk ratios for grade ≥3 TEAEs were not significant. Time to symptom resolution was significantly shorter for SAB-185 for Omicron only: 18 versus >25 days; $P = .006$.

Conclusions. SAB-185 had an acceptable safety profile with faster symptom resolution in the Omicron population.

Clinical Trials Registration. NCT04518410.

Keywords. COVID-19; outpatient treatment; SAB-185; transchromosomic; casirivimab/imdevimab.

The coronavirus disease 2019 (COVID-19) pandemic continues to evolve [1]. Antibody-based therapies, including anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) monoclonal antibodies (mAbs), have played an important role in the pandemic [2–9], but no mAbs are currently authorized for COVID-19 treatment due to insufficient in vitro activity against circulating SARS-CoV-2 variants; a single mAb, pemivibart, was recently authorized for preexposure prophylaxis [10]. The recommended outpatient therapies for COVID-19 are limited by drug-drug interactions (nirmatrelvir/ritonavir), the resources required to administer an intravenous infusion daily for 3 days (remdesivir), and lower efficacy (molnupiravir) [11–14]. Additional treatment options are needed [15].

SAB-185 is a fully human anti-SARS-CoV-2 polyclonal immunoglobulin (IgG) derived from the plasma of transchromosomic bovines carrying an artificial chromosome incorporating the human immunoglobulin gene repertoire and immunized with the SARS-CoV-2 spike (S) protein [16–18]. This platform can be readily scaled for production of relatively large quantities of purified product (current capacity of 150 000 doses/year) [16, 19]. The clinical activity of SAB-185 is expected to be mediated by neutralizing antibodies against S epitopes, as well as potentially nonneutralizing antibodies with effector activity [18, 20]. In vitro data have indicated broad neutralizing antibody activity, including against BA.1.1.529, B.2.12.1, and BA.5 Omicron, supported by in vivo data in a small-animal prevention model [17, 18, 21, 22]. SAB-185 demonstrated antiviral activity in a phase 2 trial at both high (10 240 units/kg) and low (3840 units/kg) doses [23]. While interim analysis of phase 2 data by an independent data and safety monitoring board

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appointed by the National Institutes of Health concluded that both doses of SAB-185 met prespecified criteria for phase 3 evaluation [23], the 3840 units/kg (low) dose was selected for further phase 3 safety and efficacy evaluation based on available in vitro neutralization activity against variants of concern/variants of interest and similar clinical antiviral activity between the doses, wherein no justification for using the high dose was apparent. The results of the phase 3 trial are presented here.

METHODS

Trial Design and Study Intervention

Accelerating COVID-19 Therapeutic Interventions and Vaccines-2 (ACTIV-2)/A5401 was a master protocol designed to evaluate multiple investigational agents for outpatient COVID-19 treatment (see Supplementary Material for protocol and statistical analysis plan) [23–28]. For the phase 3 trial of SAB-185 on the ACTIV-2/A5401 platform, participants were randomized 1:1 to open-label SAB-185 (3840 units/kg) or casirivimab/imdevimab (600 mg/600 mg) given once by intravenous infusion. Randomization was stratified by time from symptom onset at study entry (≤ 5 vs >5 days; see Supplementary Material for additional details).

At the start of the trial, casirivimab/imdevimab was a standard-of-care treatment for COVID-19 [4], and the trial was designed as a noninferiority (NI) comparison of SAB-185 to casirivimab/imdevimab with planned sample size of 1200; enrollment began in September 2021. The Omicron variant emerged while enrollment was ongoing, and because casirivimab/imdevimab lacked in vitro activity against Omicron [4], enrollment was paused on 20 January 2022. As SAB-185 was expected to retain activity against Omicron [21, 22], the study underwent redesign to terminate the NI design and restart as a superiority trial comparing SAB-185 to placebo (with a planned sample size again of 1200). It was specified that previously enrolled participants with Omicron infection would be included in the superiority analysis, considering casirivimab/imdevimab as, functionally, a placebo. At a planned interim review that occurred while enrollment was still paused, the study Data and Safety Monitoring Board recommended enrollment termination due to operational futility—low event rates for the primary outcome of hospitalization or death among those randomized to casirivimab/imdevimab in the Omicron period made it unlikely that a conclusion on the efficacy of SAB-185 could be achieved with the planned sample size. Enrolled participants were followed through study completion. As a result of this sequence of events, all enrolled participants were randomized to receive SAB-185 or casirivimab/imdevimab and none received placebo.

Results are reported separately for pre-Omicron and Omicron populations due to the expected difference in efficacy of casirivimab/imdevimab in these 2 populations. Participants were assigned to 1 of 2 analysis populations, pre-Omicron (NI analysis) or Omicron (superiority analysis), defined by whether they were confirmed or likely to have pre-Omicron or Omicron infection. When variant determination by sequencing was not available, participants were assigned based on calendar date of enrollment. Participants enrolled before 15 December 2021 were assigned to the pre-Omicron population and participants enrolled on or after 15 December 2021 were assigned to the Omicron population. This cutoff date was chosen to likely best distinguish the 2 populations and determined by the study team upon review of blinded variant results from the trial (Supplementary Table 1).

For US sites, the protocol was approved by a central institutional review board (IRB), Advarra (Pro00045266), and local IRBs as required. Local ethics committee approval was obtained for sites outside the United States. All participants provided written informed consent.

Participants

Participants were adults 18 years of age or older with a positive antigen or nucleic acid SARS-CoV-2 test within 10 days and no more than 7 days of symptoms at study entry. Also required were symptoms within 24 hours prior to study entry, a resting peripheral oxygen saturation $\geq 92\%$, no indication for hospitalization, and being at high risk of COVID-19 progression (see study protocol in Supplementary Material for full eligibility criteria).

Assessments

Study visits were on days 0, 3, 7, 14, and 28. Adverse events (AEs) were assessed at all visits. SARS-CoV-2 serostatus was assessed by day 0 serum anti-nucleocapsid (N) and anti-S binding antibodies (Elecsys Anti-SARS-CoV-2; Roche Diagnostics), with seropositivity defined by either being detectable.

Participants completed a diary daily from day 0 (prior to study intervention) through day 28, where they self-reported the maximum severity of each of 13 targeted symptoms in the preceding 24 hours and whether they felt they had returned to their pre-COVID-19 health (see Supplementary Material for the diary).

Study staff collected nasopharyngeal (NP) swabs on days 0 and 3 for quantitative SARS-CoV-2 RNA testing at a central laboratory [29]. The assay limit of detection was 1.4 $\log_{10}$ copies/mL, lower limit of quantification (LLoQ) was 2 $\log_{10}$ copies/mL, and upper limit of quantification was 8 $\log_{10}$ copies/mL. SARS-CoV-2 RNA sequencing and variant calling were performed as described in the Supplementary Material.

Primary and Secondary Outcome Measures

The primary outcome measures were (1) the composite of all-cause hospitalization or death through day 28 and (2) grade ≥ 3

treatment-emergent AEs (TEAEs) through day 28. Secondary outcomes included (1) COVID-19-related hospitalization or death (adjudication by an independent committee); (2) time to sustained symptom improvement for 2 consecutive days; (3) time to sustained symptom resolution for 4 consecutive days; (4) time to sustained return to health (for 2 and 4 consecutive days); (5) time-averaged total symptom score from day 0 to 28; (6) NP SARS-CoV-2 RNA < LLoQ on day 3; (7) quantitative NP SARS-CoV-2 RNA level on day 3; and (8) grade ≥2 TEAEs through day 28. The symptom outcome measures were selected based on ACTIV-2 analyses that assessed the validity of various symptom improvement and resolution measures [30]. See Supplementary Methods for symptom outcome definitions. Serious AEs (SAEs) and AEs of special interest (AESI) were also assessed. The AESI definition was broader for SAB-185 than for casirivimab/imdevimab as SAB-185 had a less well-defined risk profile: grade ≥1 (SAB-185) or grade ≥2 (casirivimab/imdevimab) infusion-related and allergic/hypersensitivity reactions within 12 hours of administration deemed related to study product.

Statistical Analysis

The modified intent-to-treat analysis included all randomized participants who initiated SAB-185 or casirivimab/imdevimab. Due to concerns about data integrity, data from 5 sites were excluded from analyses (Figure 1). The analyses reported here are based on all available data as of 28 September 2023. Power and sample size considerations are given in Supplementary Methods.

In the pre-Omicron population, the absolute difference between arms in proportion hospitalized/died through day 28 was calculated with an exact 95% confidence interval (CI) [31]. NI was assessed by determining if the upper bound of the 95% CI was entirely below 3% (the prespecified NI margin). In the Omicron population, the prespecified comparison of proportion hospitalized/died through day 28 was evaluated using Fisher exact test; an exact 95% CI was calculated as a post hoc analysis [31].

To evaluate safety, the proportion of participants experiencing a grade ≥3 or grade ≥2 TEAE was compared between arms using log-binomial regression and summarized with a risk ratio (RR) and corresponding 95% CI.

Distributions of time to sustained symptom improvement, time to sustained symptom resolution, and time to sustained return to health were described using Kaplan-Meier estimates and compared between arms using Gehan-Wilcoxon test. Distributions of time-averaged total symptom scores were compared using a Wilcoxon rank sum test.

The proportion of participants with SARS-CoV-2 RNA < LLoQ at day 3 was compared using Poisson regression with robust variance, adjusted for day 0 $\log_{10}$-transformed SARS-CoV-2 RNA level and summarized with RR and 95% CI.

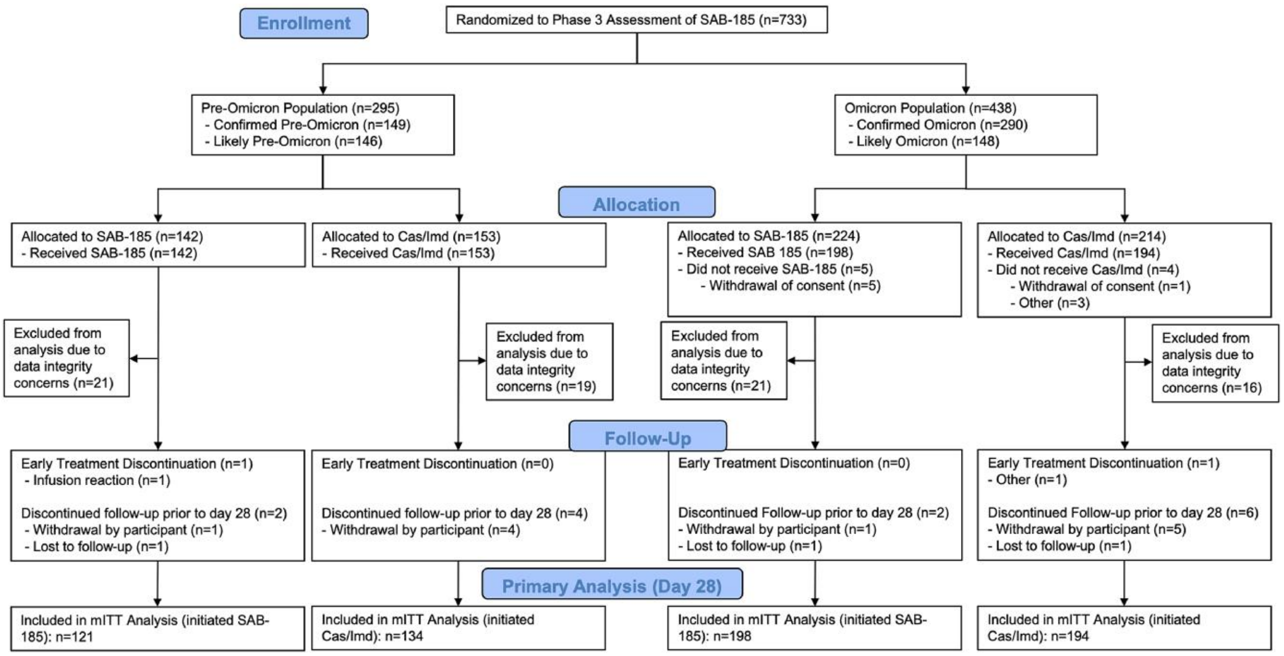

Figure 1. CONSORT diagram. Pre-Omicron population consists of all participants with a pre-Omicron variant result (confirmed pre-Omicron) and, for those without a variant determination, participants enrolled prior to 15 December 2021 (likely pre-Omicron). Omicron population consists of all participants with an Omicron variant result (confirmed Omicron) and, for those without a variant determination, participants enrolled on or after 15 December 2021 (likely Omicron). Participants who enrolled at sites with data integrity concerns (n = 77) were excluded from the analysis. Abbreviations: Cas, casirivimab; Imd, imdevimab; mITT, modified intent-to-treat.

Changes in NP RNA levels from day 0 to day 3 were evaluated with linear regression models for censored data, restricted to those with NP RNA > LLoQ at day 0 [32].

Although a NI margin was predefined for the primary efficacy comparison in the pre-Omicron population, there were no prespecified margins for other outcomes for this population. Thus, 95% CIs for differences in outcomes between arms are provided to allow evaluation of what magnitude of true difference might reasonably be ruled out. All comparisons used a 2-sided 5% type-I error rate, and no adjustment was made for the multiple comparisons across outcomes or for interim analyses that led to termination of the study based on operational futility. Statistical analyses were conducted using SAS version 9.4.

RESULTS

Study Participants

Seven hundred thirty-three participants were enrolled from 29 September 2021 to 20 January 2022 at 70 sites in the United States, Mexico, Argentina, Guatemala, and the Philippines. Ninety-eight percent of pre-Omicron and 89% of Omicron population participants were enrolled in the United States. Primary analysis included a total of 647 participants: 255 (121 SAB-185 and 134 casirivimab/imdevimab) pre-Omicron and 392 (198 SAB-185 and 194 casirivimab/imdevimab) Omicron (Figure 1 and Supplementary Table 2).

Baseline characteristics were reasonably balanced across arms within each analysis population (Table 1). The median age was 56 and 53 years for the pre-Omicron and Omicron populations, respectively. Across both populations, 55% were female sex, 52% identified as Hispanic/Latino, and 83% as White. Most participants enrolled within 5 days of symptom onset (70% pre-Omicron and 78% Omicron), 9% of the pre-Omicron and 20% of the Omicron populations reported a history of SARS-CoV-2 vaccination, and 54% of the pre-Omicron and 74% of the Omicron population were seropositive (Table 1).

Hospitalization/Death

In the pre-Omicron population, 6 of 121 (5.0%) participants in the SAB-185 arm were hospitalized (1 [0.8%] later died), and 3

Table 1. Baseline Participant Characteristics by Population and Treatment Arm

	Pre-Omicron Population			Omicron Population		
Characteristic	SAB-185 (n = 121)	Cas/Imd (n = 134)	Total (n = 255)	SAB-185 (n = 198)	Cas/Imd (n = 194)	Total (n = 392)
Age, y, median (quartiles)	56 (47, 62)	56 (45, 62)	56 (46, 62)	52 (40, 61)	53 (42, 65)	53 (41, 62)
Sex, No. (%)						
Female	72 (60)	67 (50)	139 (55)	108 (55)	107 (55)	215 (55)
Male	49 (40)	67 (50)	116 (45)	90 (45)	87 (45)	177 (45)
Cisgender, No. (%)	121 (100)	133 (100)	254 (100)	198 (100)	194 (100)	392 (100)
Race, No. (%)						
White	113 (93)	117 (87)	230 (90)	156 (80)	154 (80)	310 (80)
Black	4 (3)	12 (9)	16 (6)	17 (9)	16 (8)	33 (9)
Asian	0 (0)	0 (0%)	0 (0)	4 (2)	1 (1)	5 (1)
Other[a]	4 (3)	5 (4)	9 (4)	19 (10)	21 (11)	40 (10)
Ethnicity, No. (%)						
Hispanic/Latino	62 (51)	55 (41)	117 (46)	117 (59)	100 (52)	217 (55)
Not Hispanic/Latino	59 (49)	79 (59)	138 (54)	81 (41)	94 (48)	175 (45)
Days from symptom onset at study entry, median (quartiles)	4 (3, 6)	4 (3, 6)	4 (3, 6)	4 (3, 5)	4 (3, 5)	4 (3, 5)
≤ 5 d, No. (%)	85 (70)	93 (69)	178 (70)	150 (76)	155 (80)	305 (78)
> 5 d, No. (%)	36 (30)	41 (31)	77 (30)	48 (24)	39 (20)	87 (22)
History of SARS-CoV-2 vaccination,[b] No. (%)	11 (9)	12 (9)	23 (9)	39 (20)	39 (20)	78 (20)
SARS-CoV-2 seropositive at day 0,[c] No. (%)	65 (57)	64 (51)	129 (54)	137 (73)	128 (75)	265 (74)
Anti-N positive	31 (27)	29 (24)	60 (25)	46 (25)	45 (26)	91 (25)
Anti-S positive	64 (56)	61 (48)	125 (52)	133 (72)	122 (73)	255 (72)
SARS-CoV-2 RNA, $\log_{10}$ copies/mL, median (quartiles)	4.1 (<LOD, 7.0)	5.8 (<LOD, 7.3)	5.4 (<LOD, 7.2)	6.1 (3.5, 7.5)	6.1 (3.8, 7.3)	6.1 (3.7, 7.4)
≥ LLoQ, No. (%)	65 (55)	91 (68)	156 (62)	158 (83)	145 (81)	303 (82)
Detected, <LLoQ, No. (%)	2 (2)	2 (1)	4 (2)	9 (5)	11 (6)	20 (5)
<LOD, No. (%)	52 (44)	41 (31)	93 (37)	23 (12)	22 (12)	45 (12)
BMI, kg/m^2, median (quartiles)	30.5 (26.4, 35.9)	33.8 (28.3, 37.3)	31.8 (27.3, 36.4)	32.2 (26.5, 37.0)	32.7 (27.9, 36.8)	32.6 (27.4, 36.8)

Abbreviations: BMI, body mass index; Cas, casirivimab; Imd, imdevimab; LLoQ, lower limit of quantification; LOD, limit of detection; N, nucleocapsid; S, spike.

[a] Other includes participants who self-identified as American Indian or Alaskan, multiple races, or other.

[b] Defined as at least 1 dose of an authorized SARS-CoV-2 vaccine received prior to entry.

[c] Defined as detectable anti-N or anti-S antibodies.

Table 2. Primary and Secondary Outcomes of All-Cause Hospitalization/Death and COVID-19–Related Hospitalization/Death Through Day 28 by Treatment Arm and Analysis Population (Pre-Omicron and Omicron)

	Pre-Omicron Population (Noninferiority Analysis)			Omicron Population (Superiority Analysis)		
Event	SAB-185, No. (%) (n = 121)	Cas/Imd, No. (%) (n = 134)	Absolute Difference, SAB-185 vs Cas/Imd, % (95% CI)	SAB-185, No. (%) (n = 198)	Cas/Imd, No. (%) (n = 194)	Absolute Difference, SAB-185 vs Cas/Imd, % (95% CI) *P* value[a]
Composite of all-cause hospitalization or death, primary outcome	6 (5.0)	3 (2.2)	2.7 (−2.3 to 8.6)	5 (2.5)	3 (1.5)	1.0 (−2.3 to 4.5), *P* = .72
All-cause hospitalizations	6	3	…	5	3	…
Deaths,[b] cause of death	1[c]	1[d]	…	0	2[e]	…
Composite of COVID-19–related hospitalization, adjudicated, or all-cause death, secondary outcome	6 (5.0)	2 (1.5)	3.5 (−1.1 to 9.3)	4 (2.0)	3 (1.5)	0.5 (−2.7 to 3.8), *P* = 1.00
COVID-19–related hospitalizations	6	2	…	4	3	…
Deaths[b]	1	1	…	0	2	…

Abbreviations: Cas, casirivimab; CI, confidence interval; Imd, imdevimab.

[a] Fisher exact test.

[b] All deaths followed initial hospitalization.

[c] COVID-19 pneumonia, study day 20.

[d] COVID-19 pneumonia, study day 14.

[e] COVID-19/respiratory failure, study day 3, and multifocal COVID-19 pneumonia, study day 26.

of 134 (2.2%) casirivimab/imdevimab arm were hospitalized (1 [0.7%] died) (Table 2). The absolute difference in the proportion of participants hospitalized/died was 2.7% (95% CI, −2.3% to 8.6%). With the caveat of limited power, the analysis was inconclusive with respect to NI as this CI includes the NI margin of 3%.

In the Omicron population, 5 of 198 (2.5%) were hospitalized (none [0%] died) in the SAB-185 arm, and 3 of 194 (1.5%) were hospitalized (2 [1%] died) in the casirivimab/imdevimab arm. The absolute difference in the proportion hospitalized/died was 1.0% (95% CI, −2.3% to 4.5%).

Results were similar for the secondary outcome of COVID-19–related hospitalizations/deaths (Table 2). In each analysis population, all except 1 hospitalization occurred among participants enrolled ≤5 days from symptom onset (Supplementary Table 3).

Safety Outcomes

In the pre-Omicron population, 17 (14.0%) versus 20 (14.9%) participants in the SAB-185 and casirivimab/imdevimab arms, respectively, experienced grade ≥3 TEAEs through day 28 (RR = 0.94; 95% CI, .52–1.71), and in the Omicron population, counts were 28 (14.1%) versus 16 (8.2%), respectively (RR = 1.71; 95% CI, .96–3.07; Table 3 and Supplementary Table 4). No single AE occurred in >5% of participants in a given arm. The most common grade ≥3 TEAEs in SAB-185 recipients (reported for 3 or more participants) were COVID-19 pneumonia, increased creatinine, and increased glucose or diabetes mellitus, and for casirivimab/imdevimab recipients, were fatigue, pain, COVID-19 pneumonia, increased creatinine, increased glucose, and headache (Supplementary Table 4). Rates of grade ≥2 TEAEs were similar between arms in both analysis populations (Table 3). SAEs occurred in 6 (5.0%) participants in the SAB-185 and 4 (3.0%) in the casirivimab/imdevimab arm in the pre-Omicron population, and 5 (2.5%) in the SAB-185 and 3 (1.5%) in the casirivimab/imdevimab arm in the Omicron population. Five participants who received SAB-185 (3 pre-Omicron, 2 Omicron) experienced an AESI (2 hypersensitivity events, 2 infusion-related reactions, and 1 angioedema); 1 AESI (infusion-related reaction) occurred in a participant who received casirivimab/imdevimab across both populations (Table 3).

Symptom Outcomes

For any given study day through day 28, across all participants, 86% to 96% (220–244 of 255 pre-Omicron participants and 350–374 of 392 Omicron participants) completed the diary. In the pre-Omicron population, time to 2 days sustained symptom improvement and time to 4 days sustained symptom resolution were shorter for SAB-185, but were not significant: median 11 (quartiles 5, 24) for SAB-185 versus 14 (quartiles 5, 23) days for casirivimab/imdevimab, *P* = .95 (symptom improvement) and median 16 (quartiles 9, > 25) for SAB-185 versus 24 (quartiles 9, > 25) days for casirivimab/imdevimab, *P* = .27 (symptom resolution) (Figure 2*A* and 2*B*). The findings were similar across subgroups by days from symptom onset (≤ 5 or > 5 days) at study treatment, with the sample size being more limited for the >5 day subgroup (Supplementary Figure 1*A*–*D*). Differences were more modest (1 day) for time to 2 or 4 days return to usual pre-COVID health, and

Table 3. Safety Through Day 28

Event	Pre-Omicron Population			Omicron Population		
	SAB-185, No. (%) (n = 121)	Cas/Imd, No. (%) (n = 134)	Risk Ratio, SAB-185 vs Cas/Imd (95% CI), *P* Value[a]	SAB-185, No. (%) (n = 198)	Cas/Imd, No. (%) (n = 194)	Risk Ratio, SAB-185 vs Cas/Imd (95% CI), *P* Value[a]
Grade 3 or higher TEAEs through day 28, primary safety outcome	17 (14.0)	20 (14.9)	0.94 (.52–1.71), *P* = .84	28 (14.1)	16 (8.2)	1.71 (.96–3.07), *P* = .07
Deemed related by site investigator	1 (0.8)	0	…	2 (1.0)	0	…
Grade 2 or higher TEAEs through day 28	40 (33.1)	45 (33.6)	0.98 (.70–1.39), *P* = .93	57 (28.8)	60 (30.9)	0.93 (.69–1.26), *P* = .64
Deemed related by site investigator	3 (2.5)	1 (0.7)	…	4 (2.0)	2 (1.0)	…
TEAEs leading to treatment changes	2[b]	1[c]	…	2[d]	0	…
SAEs through day 28	6 (5.0)	4 (3.0)	…	5 (2.5)	3 (1.5)	…
SAEs through day 28 resulting in hospitalization	6 (5.0)[e]	3 (2.2)[f]	…	5 (2.5)[f]	3 (1.5)[e]	…
AESIs through day 28[g]	3 (2.5)[h]	1 (0.7)[i]	…	2 (1.0)[j]	0 (0)	…

Abbreviations: AESI, adverse event of special interest; Cas, casirivimab; Imd, imdevimab; SAE, serious adverse event; TEAE, treatment emergent adverse event.

[a] Wald test.

[b] One grade 3 drug hypersensitivity, 1 grade 2 infusion-related reaction.

[c] One grade 1 infusion-related reaction.

[d] One grade 1 infusion site reaction, 1 grade 3 hypertension.

[e] All hospitalizations deemed COVID-19 related.

[f] All but 1 hospitalization deemed COVID-19 related.

[g] The AESI definition was specific to each agent. For SAB-185: grade ≥1 infusion-related reactions and grade ≥1 allergic/hypersensitivity reactions within 12 hours of administration that were deemed related to study product as determined by the site investigator. For casirivimab/imdevimab: grade ≥2 infusion-related reactions and grade ≥2 allergic/hypersensitivity reactions within 12 hours of administration that were deemed related to study product as determined by the site investigator.

[h] One grade 3 drug hypersensitivity, 1 grade 2 hypersensitivity, 1 grade 2 infusion-related reaction.

[i] One grade 2 infusion-related reaction.

[j] One grade 3 infusion-related reaction, 1 grade 3 angioedema.

were also not significant (Supplementary Figure 2). Time to sustained symptom resolution for 2 days (Supplementary Figure 3) and time-averaged total symptom score from day 0 to 28 (Supplementary Table 5) also favored SAB-185 but were not significant.

In the Omicron population, for which casirivimab/imdevimab was not expected to be active, time to 2 days sustained symptom improvement and time to 4 days sustained symptom resolution were shorter for SAB-185: median 11 (quartiles 5, 19) for SAB-185 versus 13 (quartiles 7, 25) days for casirivimab/imdevimab, $P = .08$ (symptom improvement) and 18 (quartiles 10, > 25) for SAB-185 versus >25 (quartiles 12, > 25) days for casirivimab/imdevimab, $P = .006$ (symptom resolution), with more participants meeting both outcomes in the SAB-185 arm (Figure 2*C* and 2*D*). The findings were again similar across subgroups by days from symptom onset (≤ 5 or > 5 days), with the sample size being more limited for the >5 day subgroup (Supplementary Figure 4*A*–*D*). Time to 2 or 4 days sustained return to usual pre-COVID health was not different and was slightly longer for SAB-185 versus casirivimab/imdevimab, although more participants met the return to health outcome in the SAB-185 arm (Supplementary Figure 5). Time to sustained symptom resolution for 2 days was also significantly shorter for SAB-185 (Supplementary Figure 6) and time-averaged total symptom score from day 0 to 28 favored SAB-185 but was not significant (Supplementary Table 5).

Virological Outcomes

At entry, there was chance imbalance in the proportion of participants with NP SARS-CoV-2 RNA below LLoQ in the pre-Omicron population: 45% (54/119 with measurements) in the SAB-185 arm versus 32% (43/134) in the casirivimab/imdevimab arm (Supplementary Figure 7). At day 3, the proportion with SARS-CoV-2 RNA levels below LLoQ had increased modestly in both arms, to 50% (57/113) for SAB-185% and 43% (51/120) for casirivimab/imdevimab (RR adjusted for baseline of 0.94; 95% CI, .83–1.06 for SAB-185 vs casirivimab/imdevimab; Supplementary Figure 7 and Supplementary Table 6). Findings were similar examining quantitative viral RNA levels (Supplementary Table 6). Among those with quantifiable SARS-CoV-2 RNA at day 0, the adjusted mean reduction was 0.33 $\log_{10}$ copies/mL (95% CI, −.14 to .80) less for SAB-185 than casirivimab/imdevimab. Among those with RNA below LLoQ at day 0, only 1 participant had a quantifiable RNA value at day 3. No differences were observed by subgroups based on timing of treatment (≤5 or >5 days of symptoms) (Supplementary Table 7).

In the Omicron population, the proportion of participants with SARS-CoV-2 RNA below LLoQ at day 0 was 17% (32/190 with measurements) in the SAB-185 arm versus 19% (33/178) in the casirivimab/imdevimab arm (Supplementary Figure 8). At day 3, the proportion had increased to 28% (47/166 with measurements) in the SAB-185 arm versus 30% (47/158) in

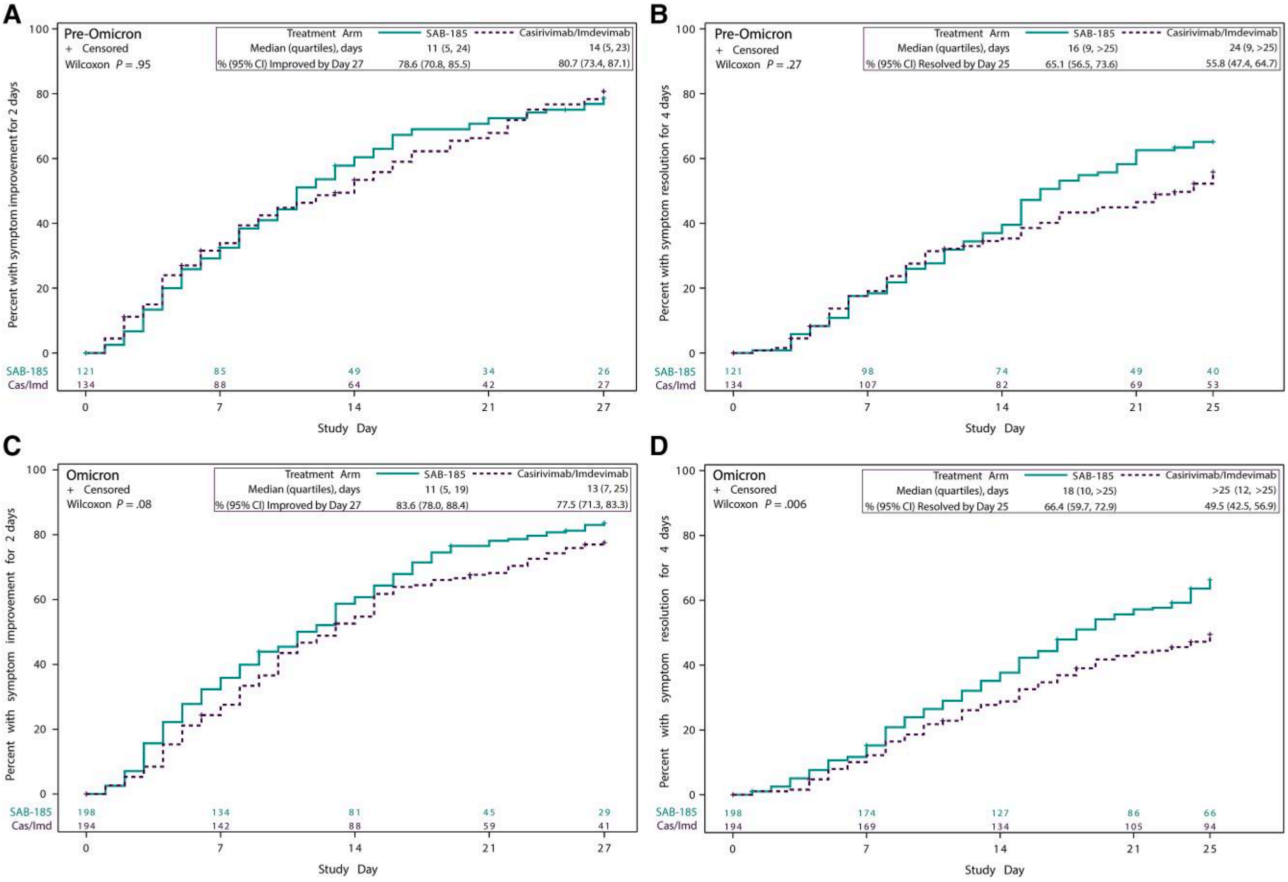

Figure 2. Time to sustained (2 days) symptom improvement and time to sustained (4 days) symptom resolution by treatment arm. The pre-Omicron population is shown in (*A*) (symptom improvement) and (*B*) (symptom resolution), and Omicron population is shown in (*C*) (symptom improvement) and (*D*) (symptom resolution). Values above the x-axis show the number of participants in each arm on selected days who are in follow-up and who have not yet met the symptom outcome.

the casirivimab/imdevimab arm (RR, 1.02; 95% CI, .81–1.29, adjusted for day 0 RNA level; Supplementary Figure 8 and Supplementary Table 8). Findings were similar examining quantitative viral RNA levels (Supplementary Table 9). Among participants with quantifiable SARS-CoV-2 RNA at day 0, there was no difference between arms in change from day 0 to day 3 in SARS-CoV-2 RNA levels (adjusted mean reduction 0.06 $\log_{10}$ copies/mL more for SAB-185; 95% CI, −.43 to .31) or when examining virologic outcomes by time from symptom onset (Supplementary Table 9). Among those with RNA < LLoQ at day 0, only 2 participants had a quantifiable RNA value at day 3.

DISCUSSION

Here, we present results from a randomized trial of SAB-185, a fully human anti-SARS-CoV-2 polyclonal antibody produced from the purified plasma of transchromosomic bovines [16, 18]. The trial was conducted during the global transition in the COVID-19 pandemic from Delta to Omicron variant, and prematurely closed to enrollment due to low hospitalization/death rates during the Omicron period. In the primary NI analysis of the pre-Omicron population, we observed hospitalization/death rates of 5.0% among 121 participants assigned SAB-185% and 2.2% among 134 participants assigned casirivimab/imdevimab. Definitive conclusions about noninferior efficacy of SAB-185 cannot be made as our analysis includes only 255 of 1200 planned participants. The planned assessment of SAB-185 superiority in the Omicron population was also underpowered due to a small sample size, compounded by low hospitalization/death event rates (2.5% with SAB-185% and 1.5% with casirivimab/imdevimab) as has been observed in other randomized controlled trials [33, 34] and cohorts in the Omicron era [35]. Overall, efficacy of SAB-185 on hospitalization/death cannot be determined from our trial. However, the study is of reasonable sample size to support the safety of SAB-185 as previously observed [23], with few reported infusion-related or hypersensitivity reactions (approximately 2% of treated).

Symptom outcomes, which have become the primary clinical efficacy end point in contemporary outpatient COVID-19 trials, were secondary measures in this study. In our trial, results for time to sustained symptom improvement and time to sustained symptom resolution generally favored SAB-185 over casirivimab/imdevimab, and significantly so for the Omicron population (for which casirivimab/imdevimab was not expected to be active), although these were not adjusted for multiple comparisons. While our previous data suggest a strong correlation between time to symptom improvement or resolution and time to return to health in a study population enrolled earlier in the pandemic [30], SAB-185 did not reduce time to sustained return to pre–COVID-19 health compared to casirivimab/imdevimab. In aggregate, the available data indicate a need to further evaluate the clinical effects of SAB-185.

Finally, no differences in NP viral levels were observed at day 3 posttreatment for SAB-185 compared to casirivimab/imdevimab in either the pre-Omicron or Omicron population. Nasal viral levels are challenging to interpret for a population in which approximately two-thirds had evidence of prior immunity. In addition, there is now some clinical evidence (noted to be available in a preprint and not peer-reviewed publication) to suggest that casirivimab/imdevimab may retain modest antiviral activity against Omicron variant despite lack of activity in vitro, which further limits assessment of antiviral activity of SAB-185 as casirivimab/imdevimab may not be a placebo equivalent as treated in the analysis [36]. Thus, our phase 3 data do not exclude antiviral activity of SAB-185, as was observed in the phase 2 trial [23].

Limitations of the study, in addition to the truncated sample size, include the open label design; unexpected high rates of nondetection of NP virus at study entry, particularly for the pre-Omicron population, that limited assessment of antiviral effects; the known limitations of nasal and NP compartment virus measures for assessing antiviral activity and as a surrogate for clinical activity [37, 38]; lack of variant determination for a substantial proportion of participants (with risk for contamination of each analysis population, although this impact is expected to be limited based on available variant data); and uncertain generalizability to currently circulating variants.

In conclusion, this trial of SAB-185 exemplifies the challenges of evaluating novel therapeutics for COVID-19 during a rapidly evolving pandemic. While limited in the conclusions on clinical efficacy, the overall safety of SAB-185 was demonstrated, and a potential benefit on COVID-19–related symptom outcomes was identified. Unlike anti–SARS-CoV-2 mAb therapeutics, which target single epitopes and thus render a potentially lower barrier to viral escape and loss of virologic activity, polyclonal SAB-185 antibodies are designed to target multiple extracellular regions of the SARS-CoV-2 S protein. This breadth of antigen targeting and the high-titer, high-avidity antibodies achieved on the platform may result in more durable neutralization of SARS-CoV-2 and clinical activity in the face of continued variant evolution [18]. The data from this trial highlight the potential of the transchromosomic fully human polyclonal antibody platform for safe and efficacious therapies for COVID-19 and possibly other respiratory viral infections.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). 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

Author contributions. K. W. C., B. O. T., and D. M. S. contributed study oversight, design, and implementation, analytic plan development, drafting of manuscript. C. M. contributed study design and implementation, analytic plan development, statistical analysis, drafting of manuscript. E. S. D. and D. A. W. contributed study design and implementation, manuscript review and edits. J. R. contributed study design and implementation, statistical analysis, drafting of manuscript. A. C. J. and C. V. F. contributed study design and implementation, manuscript review. J. Z. L. contributed study design, virologic analysis (viral sequencing, variant determination), manuscript review and edits. W. F. and C. B. contributed study design, manuscript review. A. L. G. performed virologic analysis (viral RNA quantification), manuscript review and edits. T. L. contributed study design, manuscript review and edits. R. C. and G. N. performed study enrollment, manuscript review. M. J. G. performed study implementation, statistical analysis, manuscript review. M. D. H. contributed study oversight, design, and implementation, analytic plan development, statistical analysis, manuscript review and edits. J. J. E. contributed study design and implementation, analytic plan development, manuscript review and edits. J. S. C. contributed study oversight, design, and implementation, analytic plan development, manuscript review and edits.

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Data availability. The authors confirm that all data underlying the findings are fully available. The next-generation sequencing data generated in this study have been deposited on the NCBI Short Read Archive under accession number PRJNA1023880. Other data are available under restricted access due to ethical restrictions. Access can be requested by submitting a data request at https://submit.mis.s-3.net/ and will require the written agreement of the ACTG and the manufacturer of the investigational product. Requests will be addressed as per ACTG standard operating procedures. Completion of an ACTG Data Use Agreement may be required.

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