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MAJOR ARTICLE

Phase 2 safety and antiviral activity of SAB-185, a novel polyclonal antibody therapy for non-hospitalized adults with COVID-19

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Background:SAB-185, a novel fully-human IgG polyclonal immunoglobulin product, underwent phase 2 evaluation for non-hospitalized adults with mild-moderate COVID-19.

Methods: Participants received intravenous SAB-185 3,840 units/kg (low-dose) or placebo, or 10,240 units/kg (high-dose) or placebo. Primary outcome measures were nasopharyngeal SARS-CoV-2 RNA <lower limit of quantification (LLoQ) at study days 3, 7, and 14, time to symptomatic improvement, and safety through day 28.

Results: Two-hundred thirteen participants received low-dose SAB-185/placebo (n=107/106) and 215 high-dose SAB-185/placebo (n=110/105). The proportions with SARS-CoV-2 RNA <LLoQ were higher for SAB-185 versus placebo at days 3 and 7 and similar at day 14, and significantly higher at day 7 for high-dose SAB versus placebo only, relative risk (95% CI) 1.23 (1.01, 1.49). At day 3, SARS-CoV-2 RNA levels were lower with low-dose and high-dose SAB-185 versus placebo, differences in medians of -0.78 $\log_{10}$copies/mL (p=0.08) and -0.71 $\log_{10}$copies/mL (p=0.10), respectively. No difference was observed in time to symptom improvement: median 11/10 days (p=0.24) for low-dose SAB-185/placebo and 8/10 days (p=0.50) for high-dose SAB-185/placebo. Grade ≥3 adverse events occurred in 5%/13% of low-dose SAB-185/placebo and 9%/12% of high-dose SAB-185/placebo.

Conclusions*: S*AB-185 was safe and generally well tolerated and demonstrated modest antiviral activity in predominantly low-risk non-hospitalized adults with COVID-19.

Key Words: polyclonal, antibody, COVID-19, treatment, SAB-185, transchromosomic

BACKGROUND

Globally, there have been almost 600 million cases of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, including almost 6.5 million deaths [1]. Some intravenous (IV) anti-SARS-CoV-2 monoclonal antibody (mAb)-based therapies received initial emergency use authorization (EUA) from regulatory agencies and were recommended for the treatment of COVID-19 in high-risk non-hospitalized persons. However, *in vitro* evidence of resistance among emerging SARS-CoV-2 variants, including the highly infectious Omicron (B.1.1.529) variant and its now dominant subvariants,

and availability of oral options, have led to changes in recommended outpatient COVID-19 treatment [2-8]. Ritonavir-boosted nirmatrelvir and remdesivir are the currently preferred antiviral agents, with bebtelovimab and molnupiravir as alternatives [3]. Given the unknown drug susceptibility of future SARS-CoV-2 variants, the limited breadth and vulnerability of mAb therapies to variants, logistical complexities of repeated outpatient remdesivir infusions, and contraindications to the oral treatment options, the therapeutic armamentarium against COVID-19 must be strengthened [9].

SAB-185 is a fully-human IgG polyclonal immunoglobulin derived from the plasma of hyperimmunized transchromosomic (Tc) bovines carrying a human artificial chromosome incorporating the human immunoglobulin gene repertoire [10]. Hyperimmunization of Tc bovines begins with priming with a plasmid DNA vaccine that expresses wild-type SARS-CoV-2 spike protein, followed by boosting immunizations with a recombinant spike protein from SARS-CoV-2 [11-13]. SAB-185 has demonstrated cross-variant neutralization [11-13]. Preliminary *in vitro* data support retained activity of SAB-185 against SARS-CoV-2 Variants of Concern (VOCs), including Omicron [11]. Here, we present results of the phase 2 evaluation of low- and high-dose SAB-185 in non-hospitalized adults with COVID-19 in the ACTIV-2/A5401 platform trial.

METHODS

Trial design and study intervention

ACTIV-2/A5401 was designed to evaluate the safety and efficacy of multiple investigational agents for the treatment of non-hospitalized adults with COVID-19. The trial is a randomized controlled platform that allowed use of a shared concurrent placebo control group to evaluate multiple agents in phase 2 evaluation in parallel**.** Because multiple agents were investigated simultaneously, participants were randomized in two steps to ensure an approximately equal number were assigned to an active agent and its pooled placebo control group. The randomization strategy for this platform trial provided a concurrent control group of participants consisting of those who were eligible to receive an investigational agent but who were randomized to receive the placebo for that agent or the placebo for other investigational agent(s) being evaluated in parallel. Randomization was stratified on time from symptom onset at study entry (≤5 versus >5 days).

Low-dose (3,840 units/kg) SAB-185 and high-dose (10,240 units/kg) SAB-185, given once by IV infusion, were selected for the phase 2 evaluation based on pre-clinical and phase 1 and 1b safety data after an interim analysis (NCT04468958). The placebo for SAB-185 was normal saline. Participants are followed for 72 weeks; the primary and key secondary outcomes at 28 days of follow-up are reported here. The protocol was approved by a central institutional review

board (IRB), Advarra (Pro00045266), with additional local IRB review and approval as required by participating sites. All participants provided written informed consent.

Participants

Participants were adults 18 years of age or older with a documented positive SARS-CoV-2 test by an FDA-authorized antigen or nucleic acid test from a respiratory sample collected within 10 days prior to study entry. Initially, participants were required to have no more than 8 days of COVID-19 symptoms at study entry; this was reduced to 7 days during the enrollment period. Also required were ongoing symptoms (not including loss of taste or smell) within 24 hours prior to study entry, resting peripheral oxygen saturation levels ≥92%, and no need for hospitalization as determined by the site investigator. Pregnancy and breastfeeding were exclusionary. Full eligibility criteria, including exclusion criteria with respect to underlying conditions and prior treatments are available at https://clinicaltrials.gov/ct2/show/NCT04518410.

In the initial design of ACTIV-2, eligibility for agents administered via IV infusion, including SAB-185, was restricted to individuals at protocol-defined higher risk for progression to hospitalization or death; however, after the standard of care for management of higher risk outpatients changed to include use of specific mAbs with EUA, the protocol was modified to enroll individuals at lower risk only considering its use of a placebo control.

Primary and secondary outcome measures

Study staff collected nasopharyngeal (NP) swabs on days 0 (day of study entry, prior to intervention), 3, 7, and 14 for quantitative SARS-CoV-2 RNA testing. Participants completed a daily symptom diary from day 0 to 28, where they recorded 13 targeted COVID-19 symptoms as absent, mild, moderate, or severe by self-assessment**.**

The primary outcome measures were 1) development of grade 3 or higher treatment-emergent adverse event (TEAE) through day 28; 2) NP SARS-CoV-2 RNA less than lower limit of quantification (LLoQ) at days 3, 7 and 14; and 3) time to improvement in COVID-19 symptoms, defined as number of days from study entry to the first of two consecutive days where all 13 targeted COVID-19 symptoms in the study diary were improved in severity from what was reported at entry or absent (symptoms initially reported as moderate or severe were required to be mild or absent, and symptoms initially reported as mild or absent were required to be absent). Secondary outcome measures included time to resolution in COVID-19 symptoms, defined as the number of days from study entry to the first of four consecutive days where all targeted symptoms were absent, quantitative NP SARS-CoV-2 RNA levels, time-averaged total symptom score from days 0-28, and all-cause hospitalization and death through day 28. For the total symptom score outcome, each symptom was scored 0 for absent, 1 for mild, 2 for moderate, and 3 for severe. Scores for the 13 symptoms were summed for each day, giving a total possible symptom score of 0-39 for a given day. Change in NP RNA from day 0 to day 3 among those with quantifiable RNA at day 0 was also examined in supplemental analysis.

Virology

NP samples were collected using standardized procedures and frozen and stored at -80°C (-65°C to -95°C) on the day of collection. Samples were shipped on dry ice to a central laboratory (University of Washington) for quantitative SARS-CoV-2 RNA testing using the Abbott m2000sp/rt platform with a validated internal standard. The collection, storage, processing, and assay methods have previously been described [14]. The assay limit of detection (LoD) was 1.4 $\log_{10}$ copies/mL, LLoQ was 2 $\log_{10}$ copies/mL, and upper limit of quantification (ULoQ) was initially 7, then 8 $\log_{10}$ copies/mL. For samples with RNA levels >ULoQ, the assay was rerun with dilutions to obtain a quantitative value.

Statistical analysis

Phase 2 evaluation was powered based on the virology outcome. The target sample size was 220 (110 for each dose of SAB and 110 for each placebo control group). With this sample size, there was at least 82% power to detect a 20% absolute increase in the proportion with SARS-CoV-2 RNA <LLoQ on a given measurement day in each SAB dose arm compared to its placebo control group using a two-sided 5% type I error rate.

Analyses were conducted separately by SAB-185 dose cohort, and the analysis populations included all participants who initiated the relevant SAB-185 dose or concurrent placebo. The analyses reported here are based on all available data through day 28.

The proportion of participants experiencing a grade 3 or higher TEAE was compared between each dose of SAB-185 and placebo using log-binomial regression and summarized with a risk ratio (RR), corresponding 95% CI and p-value based on the Wald test. The proportion of participants with SARS-CoV-2 RNA <LLoQ was compared between arms using Poisson regression for repeated measurements (days 3, 7 and 14) adjusted for day 0 $\log_{10}$ transformed SARS-CoV-2 RNA level, with Wald test across multiple measurement times and summarized with RR and 95% CI at each time; missing data are ignored in analysis. Quantitative SARS-CoV-2 RNA levels were compared between arms at each post-entry time using Wilcoxon rank-sum tests; results below the LoD were analyzed as the lowest rank and results above the LoD but below the LLoQ were analyzed as the second lowest rank. Changes in NP RNA from day 0 to day 3 were evaluated with linear regression models for censored data.

Time to symptom improvement and time to symptom resolution were compared between arms using a Gehan-Wilcoxon test, and time-averaged total symptom score from days 0-28 was compared between arms using a Wilcoxon rank sum test. The proportion of hospitalization/death events was compared between arms for the high-dose cohort using a Wald test for the ratio of cumulative proportions determined by Kaplan-Meier methods, and with Fisher's exact test for the low-dose cohort comparison due to small event numbers. All comparisons used a two-sided

5% type-I error rate, and no adjustment was made for the multiple comparisons. Statistical analyses were conducted using SAS version 9.4.

RESULTS

Participants and retention in follow-up

Participants were enrolled to the SAB-185 dose cohorts between April 20 and August 17, 2021 at 50 trial sites in the United States, including 221 participants randomized to the low-dose SAB-185 vs placebo cohort and 225 participants randomized to the high-dose SAB-185 vs placebo cohort. The final analysis included 213 participants who initiated low-dose SAB-185 or placebo (107 and 106, respectively) and 215 who initiated high-dose SAB-185 or placebo (110 and 105, respectively). Among the participants in the pooled placebo group for low-dose SAB-185, 35 (33%) were randomized to the placebo for low-dose SAB-185; for the pooled placebo group for high-dose SAB-185, 41 (39%) were randomized to placebo for high-dose SAB-185; the remainder in each pooled placebo group were randomized to placebo for the other SAB-185 dose or for other investigational agents in the platform **(Supplementary Table)**. Seven (3%) in the low-dose SAB cohort and 6 (3%) in the high-dose SAB-185 cohort prematurely discontinued the study prior to day 28 **(Fig. 1, Consort Flow Diagrams).**

Participants had a median age of 38 years, 86% identified as White and approximately half (48-50% for each dose cohort) as Hispanic/Latino, with 67-68% reporting ≤5 days of symptoms at study entry. The protocol definition of higher risk of progression to severe COVID-19 was met by 8% in the low-dose cohort and 9% in the high-dose cohort (**Table 1**). The only higher risk co-morbidities present in ≥5% of participants were hypertension in 5% of the low-dose SAB cohort and obesity (body mass index >35 kg/m^2) in 5% in both dose cohorts. The most frequently reported symptoms (>50% of participants) on day 0 across both dose cohorts included cough, fatigue, nasal obstruction or congestion, headaches, body/muscle pains/aches, nasal discharge, and chills; most symptoms were reported as mild or moderate (**Supplementary Figure 1).**

Virological outcomes

At day 0, the proportions of participants with NP SARS-CoV-2 RNA <LLoQ were 17% and 24% for low-dose SAB-185 and placebo, respectively, and 15% and 22% for high-dose SAB-185 and placebo, respectively, indicating a modest chance imbalance in pre-treatment NP SARS-CoV-2 RNA. The proportions of participants with NP SARS-CoV-2 RNA <LLoQ were higher for low-dose SAB than placebo at day 3 (46% versus 38%) and day 7 (70% versus 65%) but was similar at day 14 (91% versus 93%). The difference in proportions between arms (primary virologic outcome) was not significant across the three measurement times (overall p=0.30 adjusted for $\log_{10}$ RNA at day 0) or at each of days 3, 7, and 14, RR (95% CI) 1.29 (0.93, 1.79), 1.11 (0.92, 1.35), and 1.03 (0.91, 1.15), respectively **(Figure 2A**). The comparison of high-dose

SAB-185 and placebo was similar, with higher proportions <LLoQ for SAB-185 than placebo at day 3 (38% versus 36%), day 7 (76% versus 63%), and day 14 (93% versus 92%). The difference was not significant across the three measurement times (overall p=0.12 adjusted for $\log_{10}$ RNA at day 0) or at day 3 or 14, RR (95% CI) 1.12 (0.78, 1.61) and 1.06 (0.95, 1.18), respectively, but was significant at day 7, RR 1.23 (1.01, 1.49) (**Figure 2B**).

Distributions of SARS-CoV-2 RNA levels by visit and dose cohort are shown in **Figures 2C and 2D.** Although not statistically significant for either group, there was a trend of lower SARS-CoV-2 RNA levels in the SAB-185 arms versus placebo at day 3: in the low-dose cohort, median (quartiles) levels were 2.38 (0.70 [undetectable], 3.92) versus 3.16 (1.70 [detectable but <LLoQ], 4.95) $\log_{10}$ copies/mL (p=0.08) and in the high-dose cohort, medians were 2.61 (undetectable, 4.03) versus 3.32 (1.70 [detectable but <LLoQ], 5.20) $\log_{10}$ copies/mL (p=0.10) for SAB-185 vs placebo, respectively. Among those with RNA >LLoQ at day 0, there were significantly larger decreases in NP RNA from day 0 to day 3 for both low- and high-dose SAB-185 when compared to placebo, mean difference = -0.75 and -0.77 $\log_{10}$ copies/mL, p=0.017 and p=0.009, respectively; (Supplementary Table 2). In both dose cohorts, SARS-CoV-2 RNA levels by number of days of symptoms prior to treatment suggest greater early post-treatment differences between SAB-185 and placebo in participants treated within 5 days of symptoms compared to those treated later (**Figure 3).** SARS-CoV-2 RNA levels based on COVID-19 progression risk (higher versus lower) are shown in **Supplementary Figure 2** (the higher risk group was very small)**.**

Symptoms and other clinical outcomes

Time to symptom improvement (the primary symptom outcome) was not significantly different between SAB-185 and placebo for either dose cohort, median (quartiles) 11 (6, 20) versus 10 (5, 17) days for low-dose versus placebo, respectively (p=0.24), and 8 (5, 15) versus 10 (5, 17) days for high-dose versus placebo (p=0.50) **(Figure 4)**, nor was time to symptom resolution (Supplementary Table 3)**.** Time-averaged total symptom score for days 0-28 was also not significantly different between SAB-185 versus placebo: median (quartiles) 2.1 (0.9, 3.9) versus 2.1 (1.0, 4.7) days for the low-dose cohort (p=0.81) and 1.9 (0.9, 4.6) versus 2.0 (1.0, 4.4) for the high-dose cohort (p=0.74).

Through day 28, there were 2 (2%) hospitalizations in the low-dose SAB-185 arm versus 5 (5%) with placebo (p=0.28); and 5 (5%) in the high-dose SAB-185 arm versus 5 (5%) with placebo, RR (95%CI) = 0.95 (0.28, 3.18); there were no deaths in either dose cohort.

Safety

New grade 3 or higher TEAEs through day 28 (primary safety outcome) occurred more frequently in the placebo arms compared with the SAB-185 arms: in the low-dose cohort, 5 (4.7%) on SAB-185 versus 14 (13.2%) on placebo, RR (95% CI) = 0.35 (0.13, 0.95), p=0.039,

and in the high-dose cohort, 10 (9.1%) on SAB-185 versus 13 (12.4%) on placebo, RR (95% CI) = 0.73 (0.34, 1.60), p=0.44.

There were 8 (2 SAB-185, 6 placebo) participants with a serious TEAE through day 28 in the low-dose cohort and 11 (5 SAB-185, 6 placebo) participants in the high-dose cohort. With respect to adverse events of special interest (AESIs), two grade 2 hypersensitivity reactions were reported with high-dose SAB-185 and one grade 1 infusion-related reaction for corresponding placebo. Details of the TEAEs, treatment-emergent serious AEs, and AESIs through day 28 are presented in **Table 2.**

DISCUSSION

This blinded, placebo-controlled randomized clinical trial studied the safety and antiviral efficacy of SAB-185 in non-hospitalized adults with COVID-19. Most were enrolled amid the Delta variant surge, and most participants were at lower risk for severe COVID-19. The study allowed for a robust comparison of upper airway viral RNA shedding in active vs placebo-treated participants, which has been concordant with clinical outcome for most, but not all, EUA agents to date [15-20].

SAB-185 showed modest evidence of antiviral activity against SARS-CoV-2 in this cohort of predominantly young (median 38 years), lower risk individuals, 33%-39% of whom were SARS-CoV-2 vaccinated. There were consistent trends towards higher proportions of participants with unquantifiable NP SARS-CoV-2 RNA and lower quantitative SARS-CoV-2 RNA levels for both SAB-185 doses compared to placebo early post-treatment. As previously observed with other agents [21], the difference in SARS-CoV-2 RNA levels appeared more striking among participants treated within 5 days of symptom onset versus those treated later for both doses compared to placebo. This difference was likely due to higher SARS-CoV-2 RNA levels and limited immune response earlier in the disease course yielding greater opportunity for an antiviral intervention to impact the upper airway compartment. It is unknown if greater antiviral effects would have been observed in a higher risk, unvaccinated population given their low representation in the study. Both low-dose and high-dose SAB-185 were safe and generally well-tolerated compared to placebo.

Clinical endpoints are pivotal when characterizing the therapeutic value of investigational agents for SARS-CoV-2 [18]. We did not detect significant differences between either dose of SAB-185 and placebo in any of the symptom outcomes evaluated (time to symptom improvement, time to symptom resolution, or time-averaged total daily symptom score). This result may be explained, at least in part, by enrollment of a predominantly lower risk cohort. Young COVID-19 participants who are otherwise healthy are more likely to experience symptomatic recovery without antiviral therapy [22, 23], making a differential clinical effect of SAB-185 over placebo more difficult to detect. Consistent with this, there were too few events to draw conclusions on

clinical efficacy with respect to hospitalizations or deaths. Overall, assessment of clinical endpoints in patients at higher risk of disease progression, such as older persons with more co-morbidities or immune compromising conditions, is necessary to yield definitive conclusions, but the feasibility of conducting such large-scale clinical trials is limited with the lower hospitalization and death rates currently observed with COVID-19. Other limitations of this study include the lack of data on infectious SARS-CoV-2 titers or levels of neutralizing antibodies against the circulating or infecting strains with SAB-185 compared to placebo.

Interpretations of our results should consider that this phase 2 study was enrolled prior to the first reports of the Omicron (B.1.1.529) variant and its subsequently dominant subvariants [24, 25]. Compared to earlier pandemic variants, Omicron has more mutations (>30) in the spike protein, the target of neutralizing antibodies, and has shown clinically relevant differences compared to the Delta variant, the previously dominant strain, including requirement for boosting the mRNA based COVID vaccines for effective viral neutralization and resistance to some mAbs that had received initial EUA [26-29]. SAB-185 is produced through a novel platform that involves prime-boost vaccination of Tc bovines to generate large-volume, high-titer human antibodies targeting SARS-CoV-2 spike protein, which with the polyclonal configuration of SAB-185 confers broad neutralization breath and high barrier to viral escape. *In vitro* studies with lentiviral pseudovirus suggest that SAB-185 has mild to modest reduction in neutralization activity against the SARS-CoV-2 Omicron in comparison to wild type [11], but clinical trial data are needed to draw efficacy conclusions.

Based on a planned review of interim data from this trial, an independent data and safety monitoring board appointed by the National Institutes of Health concluded that both doses of SAB-185 met pre-specified criteria for phase 3 evaluation.

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*Data availability: T*he authors confirm that all data underlying the findings are fully available. 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 AIDS Clinical Trials Group (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.

Code availability: Not applicable.

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Table 1. Baseline Participant Characteristics by Dose Cohort and Treatment Arm.

	Low-Dose (3,840 Units/kg)			High-Dose (10,240 Units/kg)		
Characteristic	**SAB-185 (N=107)**	**Placebo (N=106)**	**Total (N=213)**	**SAB-185 (N=110)**	**Placebo (N=105)**	**Total (N=215)**
Age, years, median (quartiles)	38 (31, 49)	39 (29, 48)	38 (30, 48)	39 (30, 49)	38 (29, 47)	38 (30, 48)
Sex, n (%)						
Female	63 (59)	52 (49)	115 (54)	62 (56)	53 (50)	115 (53)
Male	44 (41)	54 (51)	98 (46)	48 (44)	52 (50)	100 (47)
Gender, n (%)						
Cis-gender	106 (99)	104 (98)	210 (99)	110 (100)	103 (98)	213 (99)
Transgender spectrum	1 (1)	2 (2)	3 (1)	0 (0)	2 (2)	2 (1)
Race, n (%)						
White	90 (84)	94 (89)	184 (86)	90 (83)	94 (90)	184 (86)
Black	9 (8)	6 (6)	15 (7)	14 (13)	5 (5)	19 (9)
Asian	4 (4)	3 (3)	7 (3)	3 (3)	3 (3)	6 (3)
Other[a]	4 (4)	3 (3)	7 (3)	2 (2)	3 (3)	5 (2)
Missing	0	0	0	1	0	1
Ethnicity, n (%)						
Hispanic/Latino	45 (42)	61 (58)	106 (50)	45 (41)	59 (56)	104 (48)
Not Hispanic/Latino	62 (58)	45 (42)	107 (50)	65 (59)	46 (44)	111 (52)
Days from symptom onset at study entry median (IQR)	4 (3, 6)	4 (3, 6)	4 (3, 6)	4 (3, 6)	4 (3, 6)	4 (3, 6)
≤5 days, n (%)	72 (67)	72 (68)	144 (68)	73 (66)	72 (69)	145 (67)
>5 days, n (%)	35 (33)	34 (32)	69 (32)	37 (34)	33 (31)	70 (33)

Risk of COVID-19 progression, n (%)						
Higher risk	10 (9)	8 (8)	18 (8)	11 (10)	8 (8)	19 (9)
Lower risk	97 (91)	98 (92)	195 (92)	99 (90)	97 (92)	196 (91)
History of SARS-CoV-2 Vaccination, n (%)	32 (30)	38 (36)	70 (33)	43 (39)	40 (38)	83 (39)
BMI (kg/m^2), median (IQR)	26.9 (23.3, 30.6)	27.7 (24.6, 31.6)	27.5 (23.6, 31.3)	27.2 (23.7, 31.9)	28.0 (24.9, 31.6)	27.6 (24.1, 31.7)
Missing	3	1	4	2	1	3

[a]Other includes American Indian or Alaskan, multiple races, and other
BMI = body mass index

Table 2. Adverse Events Through Day 28

	Low-Dose (3,840 Units/kg)			High-Dose (10,240 Units/kg)		
Event	**SAB-185 (N=107)**	**Placebo (N=106)**	**Risk Ratio (SAB-185 vs placebo) (95% CI), p-value[a]**	**SAB-185 (N=110)**	**Placebo (N=105)**	**Risk Ratio (SAB-185 vs placebo) (95% CI), p-value[a]**
Grade 3 or higher TEAEs through day 28 (primary safety outcome), number of participants (%)	5 (4.7)	14 (13.2)	0.35 (0.13, 0.95), p=0.039	10 (9.1)	13 (12.4)	0.73 (0.34, 1.60), p=0.44
Grade 2 or higher TEAEs through day 28, number of participants (%)	22 (20.6)	30 (28.3)	0.73 (0.45, 1.17), p=0.19	28 (25.5)	27 (25.7)	0.99 (0.63, 1.56), p=0.97
AEs leading to treatment changes, number of participants (%)	0	1 (0.9)	--	2 (1.8)	1 (1.0)	--
AESIs through day 28, number of participants (%)	0	0[b]	--	2 (1.8)	1 (2.4)[c]	--
*Infusion-related reaction	0	0[b]	--	0	1 (2.4)[c]	--
**Hypersensitivity reaction	0	0[b]	--	2 (1.8)	0[c]	--

Serious adverse events (SAEs) through day 28, number of participants (%)	2 (1.9)	6 (5.7)	--	5 (4.5)	6 (5.7)	--

TEAE = treatment emergent adverse event; AESI = adverse event of special interest;
[a]Wald test;
[b]Placebo group restricted to those who received placebo for SAB-185 (3,840 Units/kg), N=35;
[c]Placebo group restricted to those who received placebo for SAB-185 (10,240 Units/kg), N=41.
*Infusion reaction was reported as grade 1 nausea that occurred the day after the infusion
**Hypersensitivity reactions were reported as grade 2 urticaria during the infusion (treatment discontinued) and grade 2 chest heaviness on infusion day plus rash the following day (full dose received)

FIGURE LEGENDS

Figure 1. CONSORT Flow Diagrams

Figure 1A: CONSORT Flow Diagram, SAB-185 Low Dose Cohort

Figure 1B: CONSORT Flow Diagram, SAB-185 High Dose Cohort

Details of the screened population are not shown in the CONSORT diagram as screening was broad for evaluating multiple investigational agents in parallel and not specific to each agent.

Figure 1A. CONSORT Flow Diagram, SAB-185 Low Dose Cohort

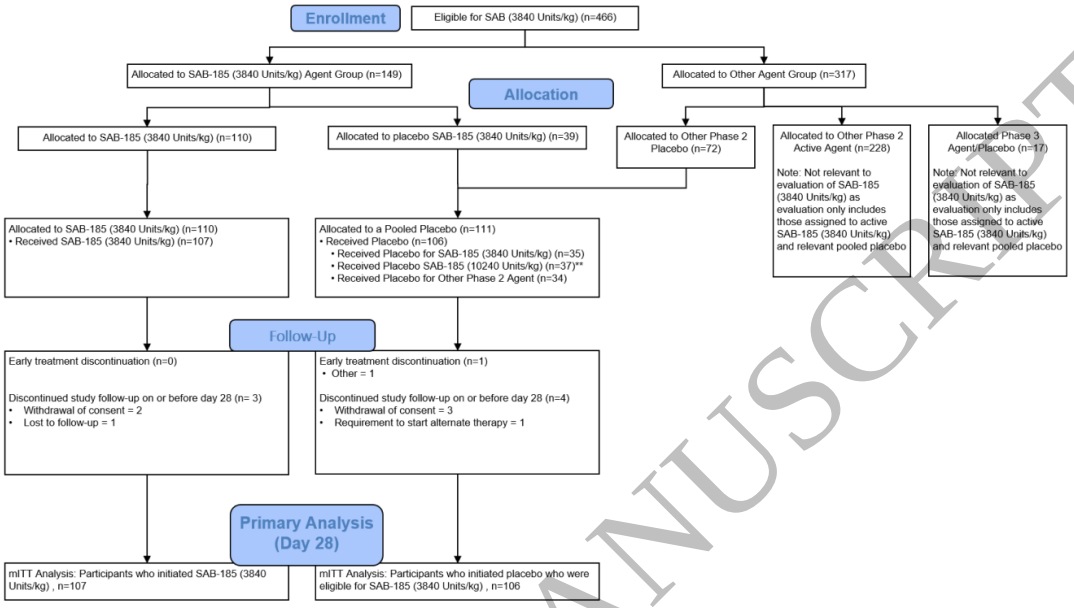

Figure 1B. CONSORT Flow Diagram, SAB-185 High Dose Cohort

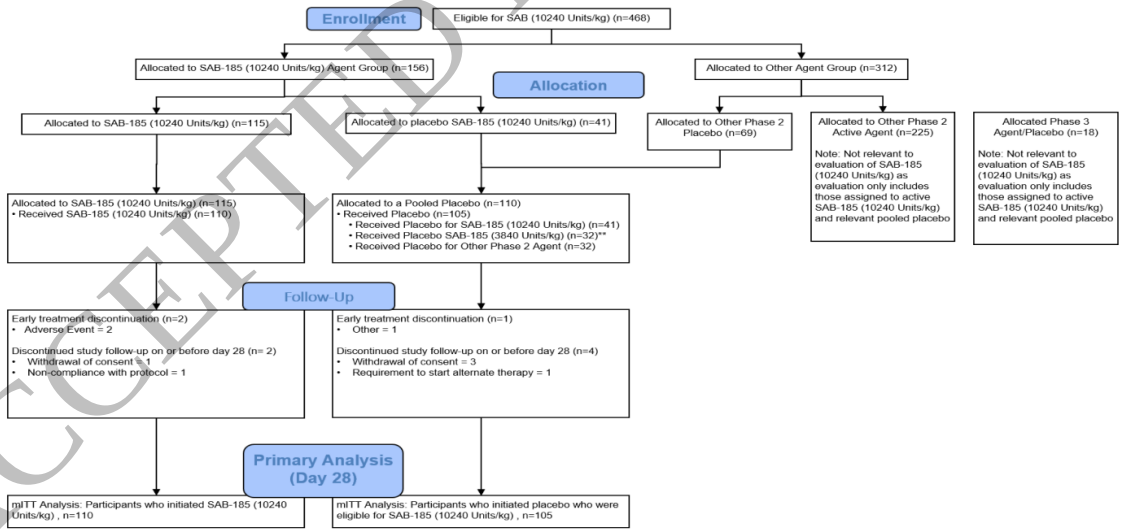

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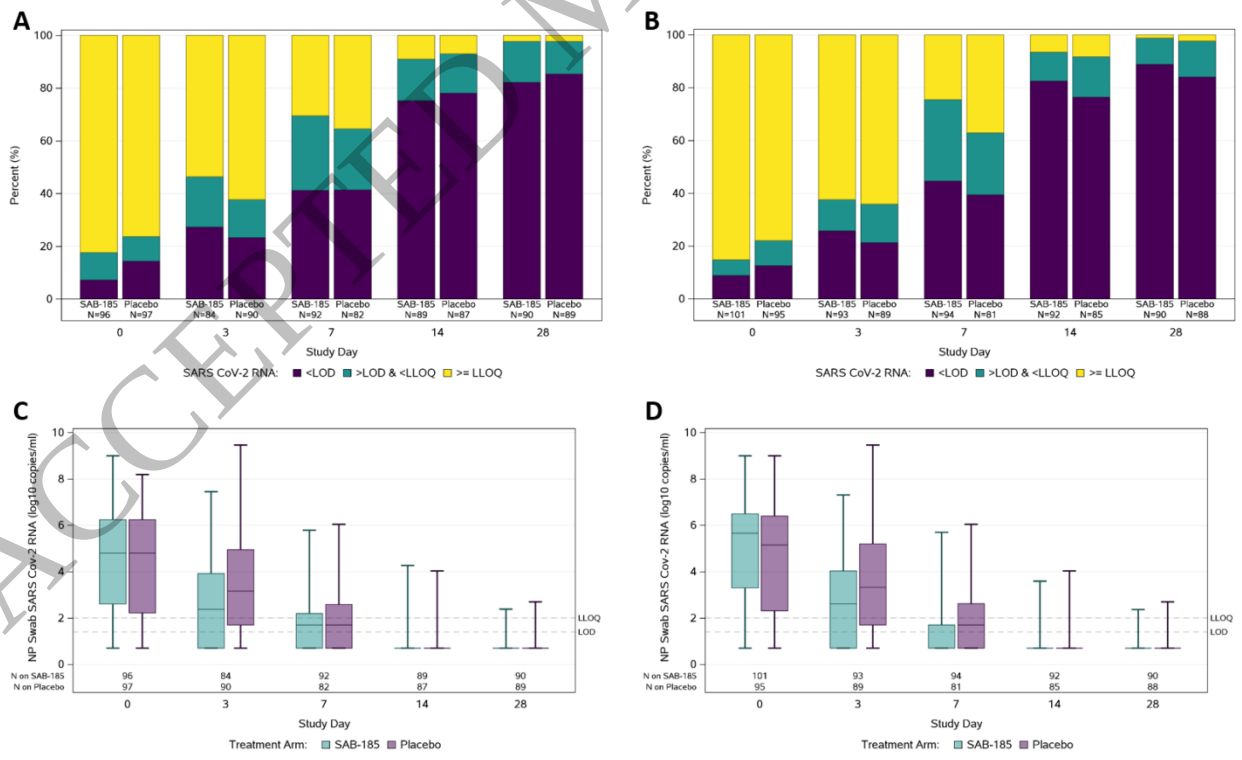
Figure 2. Nasopharyngeal SARS CoV-2 RNA by Study Visit

Distributions of SARS-CoV-2 RNA from nasopharyngeal (NP) swabs by randomized arm and study day for low-dose cohort (A and C) and high-dose cohort (B and D). For Figures (A) and (B), proportion with quantitative RNA (yellow), detectable but not quantifiable RNA (green), and undetectable (purple). For Figures (C) and (D), levels of RNA (log_{10} copies/mL) with horizontal line = median, box=interquartile range, whiskers=minimum/maximum. For Figures (C) and (D) results below the LOD were imputed as 0.7 log_{10} copies/mL (half the distance from zero to the LOD), results above the LOD but below the LLOQ were imputed as 1.7 log_{10} copies/mL (half the distance between the LOD and LLOQ), and values above the ULOQ that were not able to be quantified with dilution were imputed as 1 unit above the ULOQ. NP=Nasopharyngeal; LOD=limit of detection (1.4 log_{10} copies/mL); LLOQ=lower limit of quantification (2 log_{10} copies/mL); ULOQ=upper limit of quantification (7 or 8 log_{10} copies/mL).



DOI: 10.1093/infdis/jiad013

Figure 3. Nasopharyngeal SARS CoV-2 RNA by Days from Symptom Onset to Randomization (≤ 5 days or > 5 days)

Distributions of SARS-CoV-2 RNA from nasopharyngeal (NP) swabs by randomized arm and study day for low-dose cohort (A and C) and high-dose cohort (B and D). Those with ≤ 5 days of symptoms shown in (A) and (B) and those with > 5 days shown in (C) and (D).

Results below the LOD were imputed as 0.7 $\log_{10}$ copies/mL (half the distance from zero to the LOD), results above the LOD but below the LLOQ were imputed as 1.7 $\log_{10}$ copies/mL (half the distance between the LOD and LLOQ), and values above the ULOQ that were not able to be quantified with dilution were imputed as 1 unit above the ULOQ.

Horizontal line=median, box=interquartile range, whiskers=minimum/maximum, LOD=limit of detection (1.4 $\log_{10}$ copies/mL); LLOQ=lower limit of quantification (2 $\log_{10}$ copies/mL); ULOQ=upper limit of quantification (7 or 8 $\log_{10}$ copies/mL).

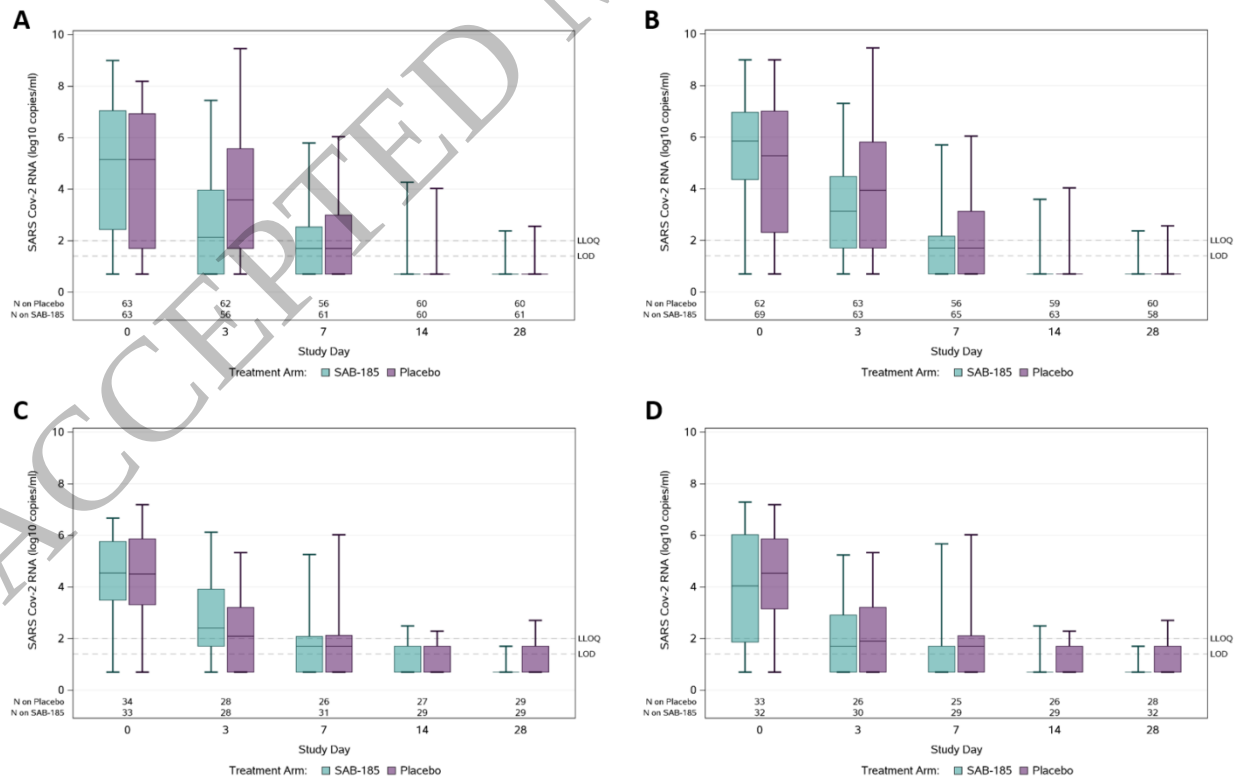


Figure 4. Time to Symptom Improvement from Day 0 for 2 Consecutive Days

Cumulative incidence by dose cohort (A: low-dose, B: high-dose) of participants meeting the primary symptom outcome of time to first of two consecutive days of symptom improvement. Symptom improvement defined as any symptoms scored as moderate or severe at day 0 were scored as mild or absent, and any symptoms scored as mild or absent at day 0 were scored as absent. Distributions compared between arms using two-sided Gehan-Wilcoxon test.