Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Efficacy and safety of two neutralising monoclonal antibody therapies, sotrovimab and BRII-196 plus BRII-198, for adults hospitalised with COVID-19 (TICO): a randomised controlled trial

ACTIV-3/Therapeutics for Inpatients with COVID-19 (TICO) Study Group†*

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See Online for appendix

Summary

Background We aimed to assess the efficacy and safety of two neutralising monoclonal antibody therapies (sotrovimab [Vir Biotechnology and GlaxoSmithKline] and BRII-196 plus BRII-198 [Brii Biosciences]) for adults admitted to hospital for COVID-19 (hereafter referred to as hospitalised) with COVID-19.

Methods In this multinational, double-blind, randomised, placebo-controlled, clinical trial (Therapeutics for Inpatients with COVID-19 [TICO]), adults (aged ≥18 years) hospitalised with COVID-19 at 43 hospitals in the USA, Denmark, Switzerland, and Poland were recruited. Patients were eligible if they had laboratory-confirmed SARS-CoV-2 infection and COVID-19 symptoms for up to 12 days. Using a web-based application, participants were randomly assigned (2:1:2:1), stratified by trial site pharmacy, to sotrovimab 500 mg, matching placebo for sotrovimab, BRII-196 1000 mg plus BRII-198 1000 mg, or matching placebo for BRII-196 plus BRII-198, in addition to standard of care. Each study product was administered as a single dose given intravenously over 60 min. The concurrent placebo groups were pooled for analyses. The primary outcome was time to sustained clinical recovery, defined as discharge from the hospital to home and remaining at home for 14 consecutive days, up to day 90 after randomisation. Interim futility analyses were based on two seven-category ordinal outcome scales on day 5 that measured pulmonary status and extrapulmonary complications of COVID-19. The safety outcome was a composite of death, serious adverse events, incident organ failure, and serious coinfection up to day 90 after randomisation. Efficacy and safety outcomes were assessed in the modified intention-to-treat population, defined as all patients randomly assigned to treatment who started the study infusion. This study is registered with ClinicalTrials.gov, NCT04501978.

Findings Between Dec 16, 2020, and March 1, 2021, 546 patients were enrolled and randomly assigned to sotrovimab (n=184), BRII-196 plus BRII-198 (n=183), or placebo (n=179), of whom 536 received part or all of their assigned study drug (sotrovimab n=182, BRII-196 plus BRII-198 n=176, or placebo n=178; median age of 60 years [IQR 50–72], 228 [43%] patients were female and 308 [57%] were male). At this point, enrolment was halted on the basis of the interim futility analysis. At day 5, neither the sotrovimab group nor the BRII-196 plus BRII-198 group had significantly higher odds of more favourable outcomes than the placebo group on either the pulmonary scale (adjusted odds ratio sotrovimab 1·07 [95% CI 0·74–1·56]; BRII-196 plus BRII-198 0·98 [95% CI 0·67–1·43]) or the pulmonary-plus complications scale (sotrovimab 1·08 [0·74–1·58]; BRII-196 plus BRII-198 1·00 [0·68–1·46]). By day 90, sustained clinical recovery was seen in 151 (85%) patients in the placebo group compared with 160 (88%) in the sotrovimab group (adjusted rate ratio 1·12 [95% CI 0·91–1·37]) and 155 (88%) in the BRII-196 plus BRII-198 group (1·08 [0·88–1·32]). The composite safety outcome up to day 90 was met by 48 (27%) patients in the placebo group, 42 (23%) in the sotrovimab group, and 45 (26%) in the BRII-196 plus BRII-198 group. 13 (7%) patients in the placebo group, 14 (8%) in the sotrovimab group, and 15 (9%) in the BRII-196 plus BRII-198 group died up to day 90.

Interpretation Neither sotrovimab nor BRII-196 plus BRII-198 showed efficacy for improving clinical outcomes among adults hospitalised with COVID-19.

Funding US National Institutes of Health and Operation Warp Speed

Introduction

Finding effective therapies for patients admitted to hospital (hereafter referred to as hospitalised) for COVID-19 remains an important priority. Remdesivir, corticosteroids, and other anti-inflammatory medications have shown efficacy among subsets of patients hospitalised with COVID-19.[1–3] However, morbidity and mortality from COVID-19 remain substantial, creating an urgent need for more effective therapies for severely ill patients with COVID-19. Neutralising monoclonal antibody therapies targeting SARS-CoV-2 accelerate reduction in viral loads and reduce the risk of disease progression for outpatients

Research in context

Evidence before this study

Neutralising monoclonal antibody therapies targeting SARS-CoV-2 have been considered promising potential therapies for COVID-19 since the beginning of the pandemic. Three anti-SARS-CoV-2 monoclonal antibody therapies have received emergency use authorisation by the US Food and Drug Administration for treatment of outpatients: sotrovimab, bamlanivimab plus etesevimab, and casirivimab plus imdevimab. However, efficacy for anti-SARS-CoV-2 monoclonal antibody therapies for patients admitted to hospital (hereafter referred to as hospitalised) with more severe COVID-19 has not been established and no trials to date have reported results for patients hospitalised with COVID-19 treated with either of sotrovimab or BRII-196 plus BRII-198. Both sotrovimab and BRII-196 plus BRII-198 are investigational human neutralising IgG monoclonal antibodies that potently inhibit SARS-CoV-2 replication. We searched PubMed for research articles published between database inception and Oct 30, 2021, for clinical trials of anti-SARS-CoV-2 monoclonal antibody therapies among patients hospitalised with COVID-19 using various combinations of the terms "COVID-19", "SARS-CoV-2", "monoclonal antibody", and "clinical trial." No language restrictions were applied. Two trials, described in three publications (two of which were preprint pieces), reported results of treatment with anti-SARS-CoV-2 monoclonal antibodies among patients hospitalised with COVID-19: bamlanivimab in a trial conducted by the ACTIV-3 investigators, and casirivimab plus imdevimab in a trial conducted by the RECOVERY investigators. Both of these trials reported no clinical benefit for anti-SARS-CoV-2 monoclonal antibody therapy overall but suggested potential benefit for patients without endogenous anti-SARS-CoV-2 antibodies at the time of treatment, including a significant survival benefit for casirivimab plus imdevimab.

Added value of this study

This study is the first clinical trial to report results of two anti-SARS-CoV-2 monoclonal antibody therapies with unique mechanisms (sotrovimab and BRII-196 plus BRII-198) for the treatment of patients hospitalised with COVID-19. Neither therapy showed efficacy over placebo for the overall trial population; results for BRII-196 plus BRII-198 suggested potential heterogeneity of treatment effect, possibly with more favourable treatment effects among patients without than with endogenous neutralising anti-SARS-CoV-2 antibodies.

Implications of all the available evidence

Clinical trials completed to date do not support indiscriminate use of anti-SARS-CoV-2 monoclonal antibody therapies for patients hospitalised with COVID-19. This trial, along with other recent trials, suggest targeted therapy using anti-SARS-CoV-2 monoclonal antibodies for patients hospitalised with COVID-19 who have not mounted an endogenous antibody response against SARS-CoV-2 could be a beneficial approach, although larger studies in this population are neeed.

with mild COVID-19.[4–10] However, whether neutralising monoclonal antibody therapy can provide benefit for more severely ill patients hospitalised with COVID-19 remains a question of active investigation.

The US National Institutes of Health (NIH) established the third Accelerating COVID-19 Therapeutic Interventions and Vaccines platform (ACTIV-3) to rapidly test antiviral therapies among patients hospitalised with COVID-19.[11] In the first ACTIV-3 trial, we reported that the neutralising monoclonal antibody bamlanivimab did not have clinical efficacy in this setting.[12] Therefore, we retired bamlanivimab from the platform trial and added two different neutralising monoclonal antibody therapies that target different SARS-CoV-2 epitopes: sotrovimab (VIR-7831; Vir Biotechnology and GlaxoSmithKline) and BRII-196 paired with BRII-198 administered as a two-antibody cocktail (BRII-196 plus BRII-198; Brii Biosciences).

Both sotrovimab and BRII-196 plus BRII-198 are investigational human neutralising IgG monoclonal antibodies that potently inhibit SARS-CoV-2 replication and have shown efficacy among outpatients with COVID-19 for preventing disease progression to death or hospitalisation.[6,10,13] Sotrovimab was derived from a SARS-CoV survivor and tightly binds a highly conserved epitope of the SARS-CoV and SARS-CoV-2 spike protein outside the angiotensin-converting enzyme 2 (ACE2) receptor-binding motif. Sotrovimab has a two amino acid modification in its fragment crystallisable (Fc) domain (Met428Leu and Asn434Ser) designed to increase lung penetration and half-life while maintaining Fc effector function.[14,15] BRII-196 and BRII-198 are two monoclonal antibodies isolated from COVID-19 survivors that bind distinct and complementary epitopes of the SARS-CoV-2 spike protein.[16] The Fc regions of BRII-196 and BRII-198 are engineered with triple amino acid modifications (Met252Tyr, Ser254Thr, and Thr256Glu) to extend half-life and reduce the binding affinity to Fc-γ receptors with the goal of reducing the potential for antibody-dependent enhancement.

Here, we report the results of the ACTIV-3 trial comparing sotrovimab versus placebo and BRII-196 plus BRII-198 versus placebo among adults hospitalised with COVID-19.

Methods

Study design and participants

Therapeutics for Inpatients with COVID-19 (TICO) is a double-blind, randomised, controlled trial within the

ACTIV-3 programme focused on testing antiviral therapies for severely ill adults hospitalised with COVID-19. The rationale and design of TICO have been previously described[11,12] and the protocol is in the appendix (pp 65–238). Briefly, TICO facilitates the simultaneous testing of multiple agents using a common placebo group. Before an initial futility assessment, patients with moderate or severe COVID-19, defined as admitted to hospital with COVID-19 without organ failure or major extrapulmonary manifestations of COVID-19, are randomly assigned to an active agent or placebo. After approximately 150 patients in each group have been followed-up for at least 5 days, an early futility assessment is done for each agent using two seven-category ordinal outcome scales measured at day 5: the pulmonary and pulmonary-plus ordinal scales. If an agent does not pass the futility assessment, enrolment to that agent ceases. If an agent passes the futility assessment, enrolment expands without delay and without data unblinding to include patients with moderate, severe, and critical COVID-19 and continues until approximately 843 patients combined in the active group and the pooled concurrent placebo group have the primary outcome (sustained clinical recovery). Further methodological detail is in the appendix (pp 11–20).

For TICO, we recruited patients from 43 hospital in the USA, Denmark, Switzerland, and Poland (appendix p 27). We enrolled adults (aged ≥18 years) admitted to hospital for acute medical care for COVID-19 with laboratory-confirmed SARS-CoV-2 infection (PCR or nucleic acid test) and COVID-19 symptoms for up to 12 days. If patients had received any SARS-CoV-2 neutralising monoclonal antibodies, hyperimmune immunoglobulin to SARS-CoV-2, or convalescent plasma from a person recovered from COVID-19 any time before admission to hospital they were excluded. Before the early futility assessment, patients were eligible for enrolment if they were receiving no oxygen therapy or standard oxygen therapy via a nasal cannula or mask, but were excluded if they were receiving high-flow oxygen via nasal cannula, non-invasive ventilation, or invasive mechanical ventilation, or met any of the other criteria for acute organ failure or major extrapulmonary manifestations of COVID-19, as detailed in the protocol. Full eligibility criteria and relevant definitions are in the appendix (pp 13–15).

The protocol was approved by a governing institutional review board for each enrolling site. Written informed consent for trial participation was obtained from each enrolled patient or a legally authorised representative, as applicable. The trial was overseen by a data and safety monitoring board (DSMB) appointed by the National Institute of Allergy and Infectious Diseases.

Randomisation and masking

Participants were randomly assigned to one of two active therapies (sotrovimab or BRII-196 plus BRII-198) or placebo using a web-based application that verified eligibility before randomisation. For sites consenting patients to both investigational agents (all but one site), randomisation allocation was 2:1:2:1 to sotrovimab, matching placebo for sotrovimab, BRII-196 plus BRII-198, or matching placebo for BRII-196 plus BRII-198. One site did not obtain regulatory approval for BRII-196 plus BRII-198, and so participants were randomly assigned 1:1 to sotrovimab or matching placebo. For the analysis, the concurrent placebo groups (placebo matching sotrovimab and placebo matching BRII-196 plus BRII-198) were pooled, resulting in approximately a 1:1:1 allocation of sotrovimab to BRII-196 plus BRII-198 to placebo. Randomisation was stratified by trial site pharmacy (geographically close clinical sites shared a single trial pharmacy in some cases). The study infusion was prepared by unmasked study pharmacists. The following people were masked to treatment allocation: the patient, the patient's family, clinical personnel caring for the patient, investigators in the trial, study personnel who collected data, and all outcome assessors.

Procedures

Each study product was administered as a one-time intravenous dose over 60 min as soon as possible after randomisation. Patients randomly assigned to the sotrovimab group received a single 500 mg dose of sotrovimab (Vir Biotechnology and GlaxoSmithKline). Patients randomly assigned to the BRII-196 plus BRII-198 group received 1000 mg of BRII-196 immediately followed by 1000 mg of BRII-198 (Brii Biosciences). The doses of sotrovimab and BRII-196 plus BRII-198 were selected on the basis of in-vitro and in-vivo animal model data suggesting that these doses would provide lung concentrations with maximal antiviral activity for at least 3 weeks.[17] Patients randomly assigned to the placebo groups received an intravenous infusion of 0·9% sodium chloride solution in a manner that mimicked administration of either sotrovimab or BRII-196 plus BRII-198, depending on their matched group assignment. Infusion of the placebo solution was visibly indistinguishable from the solutions containing active agents.

The trial protocol instructed investigators to administer remdesivir (Gilead Sciences) 200 mg intravenously on the first day, then 100 mg daily for up to 10 days while the participant was in hospital for those who did not have a contraindication to it; remdesivir was provided by the trial. Participants were not treated with other passive immunotherapies, such as COVID-19 convalescent plasma or open-label neutralising monoclonal antibodies. Other treatments for COVID-19, including oxygen, respiratory support, and corticosteroids, were administered at the discretion of the treating clinician per local standard of care.

Participants were assessed for study data, including outcomes and adverse events, daily from randomisation until day 7 (inclusive), and then on days 14, 28, 60, and 90.

Longer-term assessments, including at 6 months, 12 months, and 18 months, are planned for the future and are not reported here. Blood samples were collected from participants before administration of the study infusion for plasma measurement of neutralising IgG antibody concentrations against the receptor binding domain of the SARS-CoV-2 spike protein (GenScript SARS-CoV-2 Surrogate Virus Neutralisation assay; GenScript, Piscataway, NJ, USA), total IgG concentration against SARS-CoV-2 nucleocapsid antigen (BioRad Platelia SARS-CoV-2 Total Ab assay; BioRad, Hercules, CA, USA), and SARS-CoV-2 nucleocapsid antigen concentrations (Quanterix assay; Quanterix, Billerica, MA, USA). These assays are described in detail in the appendix (pp 15–16).

Adverse events were graded for severity using the toxicity table of the Division of AIDS from the National Institute of Allergy and Infectious Diseases. Adverse events were categorised according to codes in the Medical Dictionary for Regulatory Activities (MedDRA; version 23.1) and grouped by System Organ Class. Infusion-related reactions were reported on a checklist during and for 2 h after infusion. After the infusion and for the first 7 days of hospitalisation, patients were assessed in-person daily and adverse event data were collected via direction interaction between the study team and the patient and via medical record review. After hospital discharge, adverse event data were collected via in-person visits and telephone visits. Relatedness of adverse events to study procedures was assessed. The protocol specified some serious events anticipated to be common in COVID-19, including death, that were exempt from being reported as serious adverse events, except when the event was classified as related or possibly related to study procedures.

Outcomes

The early futility assessment included two intermediate efficacy outcomes assessed at day 5 after randomisation: the seven-category pulmonary ordinal outcome scale, which classifies patients on the basis of the intensity of respiratory support, and the seven-category pulmonary-plus ordinal outcome scale, which is the same as the pulmonary scale but with added extrapulmonary manifestations of COVID-19 (appendix pp 16–17) . These ordinal scales were derived from COVID-19 outcome scales recommended by WHO and previously used in COVID-19 trials.[1,18,19] The pulmonary ordinal outcome scale includes the following seven categories: (1) able to independently undertake usual activities with minimal or no symptoms; (2) symptomatic and currently unable to independently undertake usual activities but no need for supplemental oxygen (or not above premorbid requirements); (3) need for supplemental oxygen at less than 4 L/min or less than 4 L/min above premorbid requirements; (4) need for supplemental oxygen at 4 L/min or higher or 4 L/min or higher than premorbid requirements but no need for high-flow oxygen; (5) need for non-invasive ventilation or high-flow oxygen (ie, high-flow nasal cannula); (6) need for invasive ventilation, extracorporeal membrane oxygenation, mechanical circulatory support, or renal replacement therapy; and (7) death. The pulmonary-plus ordinal scale includes the same classifications as the pulmonary scale with additional extrapulmonary manifestations that result in a category 4 classification (stroke with NIH Stroke Scale [NIHSS] score of ≤14, meningitis, encephalitis, myelitis, myocardial infarction, myocarditis, pericarditis, new onset congestive heart failure of New York Heart Association class III or IV or worsening to class III or IV, or arterial or deep venous thromboembolic events), a category 5 classification (stroke with NIHSS score of >14), or a category 6 classification (vasopressor therapy).

The primary efficacy outcome was time to sustained clinical recovery up to day 90, defined as time between randomisation and return to home (with home defined as the patient's residence before COVID-19 or a location that provided similar or less intensive medical care) for 14 consecutive days. Key secondary outcomes were all-cause death up to day 90 after randomisation and time to discharge from index hospitalisation.

Composite safety outcomes were ascertained on day 5, day 28, and day 90. On days 5 and 28 the composite included all-cause death, serious adverse events, grade 3 or 4 adverse events, incident organ failure, and serious coinfection. On day 90, the composite included all outcomes on days 5 and 28 except grade 3 and 4 adverse events. Definitions and additional outcomes are described in the appendix (pp 16–20).

Statistical analysis

The prespecified criteria used by the DSMB to assess futility stated that an agent would pass the early futility assessment if it showed more favourable odds ratios (OR) for both the pulmonary and pulmonary-plus ordinal scales than placebo with one-sided p values of less than 0·30. In the early futility assessment, comparison of 150 patients in an active group with 150 patients in the placebo group provided 95% power to detect an OR of 1·60 or higher for a more favourable outcome on the pulmonary or pulmonary-plus ordinal scales in the active group versus placebo group with a one-sided type 1 error of 0·30 (appendix p 22).

The population for all efficacy and safety analyses was the modified intention-to-treat (mITT) population, which included patients randomly assigned to treatment who received all or part of the assigned study product infusion. We analysed outcomes among patients with non-missing data for each outcome, and report denominators for each analysis; we did not impute missing outcome data. We did separate analyses to compare the sotrovimab group with the placebo group and the BRII-196 plus BRII-198 group with the placebo group for each outcome.

We analysed the pulmonary and pulmonary-plus ordinal outcome scales at day 5 with proportional odds models

adjusted for two prespecified variables: baseline pulmonary ordinal scale category and trial pharmacy, with trial pharmacies with fewer than 15 participants grouped by geographical region (appendix p 28). In a post-hoc sensitivity analysis, we varied the strategy for grouping of trial pharmacies. We also fit proportional odds models with the same covariates for the ordinal outcomes at days 1–4, 6, 7, 14, and 28. We did a score test for the proportional odds assumption. The test for proportional odds was done by comparing the results of fitting two models, one in which a common odds ratio was assumed for each of the six dichotomised analyses of seven-category ordinal scale and compared with a second model that allowed the odds ratios to vary. The score test refers to the comparison of the two models with the six degree of freedom χ^2 statistic, which was used to calculate a p value.

We analysed time to sustained recovery up to day 90, time to discharge, and time to the two most favourable categories of the pulmonary ordinal scale using a Fine-Gray model to account for the competing risk of death, stratified by trial pharmacy. We refer to summary statistics from the stratified analyses as adjusted analyses. The primary analyses were pooled over strata defined by study site pharmacy to obtain an overall summary statistic. The pooling takes into account the size of each stratum. We analysed time to death up to day 90 using a proportional hazards model stratified by trial pharmacy. We analysed the composite safety outcome at day 5 using logistic regression adjusted for trial pharmacy and we analysed the day 28 and day 90 composite safety outcomes using proportional hazards regression. Additional analyses for each outcome are described in the appendix (pp 17–20).

We analysed heterogeneity of treatment effect by adding an interaction term in the models for sustained clinical recovery and the composite safety outcome up to day 90. The baseline characteristics we considered in the analyses of heterogeneity of treatment effect included antibody and antigen levels, demographics, and duration of symptoms; a full list is in the appendix (pp 20–21). Our primary hypothesis regarding baseline antibody levels, which was added as an addendum to the statistical analysis plan after completion of enrolment and before any antibody results were revealed, was that patients without endogenous neutralising anti-SARS-CoV-2 antibodies would benefit more from sotrovimab and BRII-196 plus BRII-198 compared with placebo than would patients with these neutralising antibodies. For the subgroup analysis based on SARS-CoV-2 antigen levels, we used a single threshold at the median value for participants in this trial (1450 pg/mL) to dichotomise the population into those with high and low antigen levels, with a hypothesis that patients with higher antigen levels would be more likely to benefit from monoclonal antibody therapy than those with lower antigen levels.

Reported p values are two-sided unless otherwise stated. Unless otherwise stated, we considered p values of less than 0·05 to be significant. We did all statistical analyses using SAS (version 9.4) and R (version 4.0). This study is registered with ClinicalTrials.gov, NCT04501978

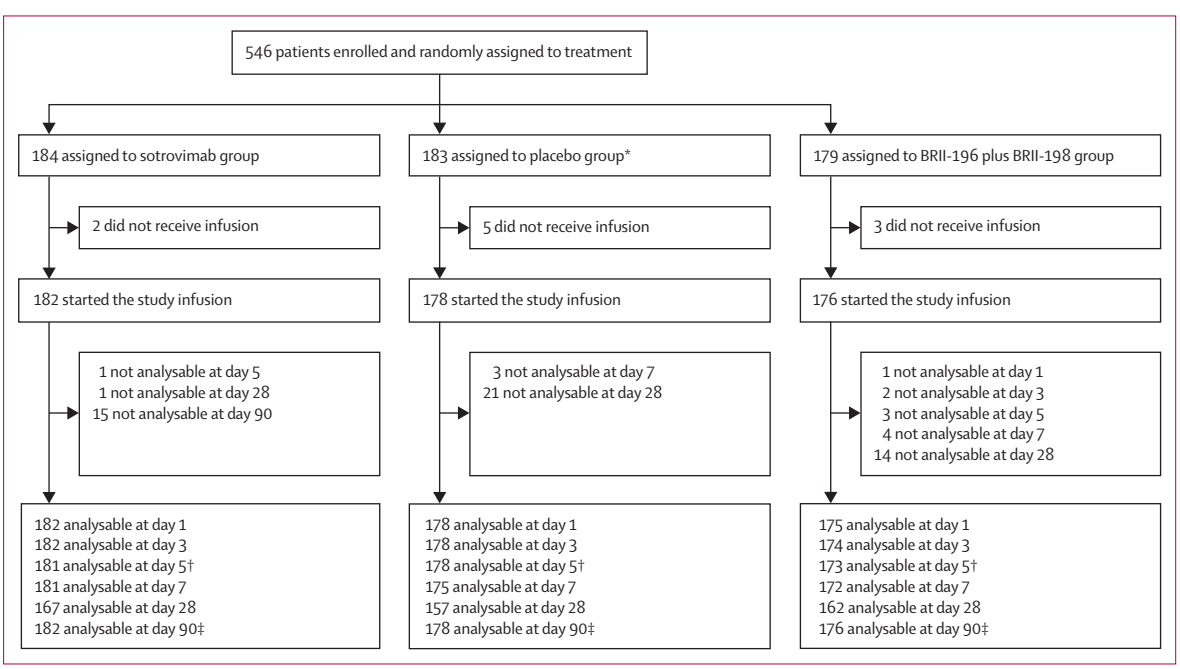


Figure 1: **Study profile**
*One patient who was randomly assigned to the placebo group was enrolled at a site not using the BRII-196 plus BRII-198 agent. This patient was not included in the placebo group for comparisons with BRII-196 plus BRII-198. †Day 5 outcomes were used for the early futility assessment. ‡Day 90 outcome of sustained clinical recovery was the primary efficacy outcome; patients lost to follow-up were censored.

	Sotrovimab group (n=182)	Placebo group (n=178)*	BRII-196 plus BRII-198 group (n=176)
Age, years	61 (50–74)	60 (49–70)	61 (50–71)
Sex			
Female	75 (41%)	75 (42%)	78 (44%)
Male	107 (59%)	103 (58%)	98 (56%)
Race or ethnicity†			
Asian	7 (4%)	9 (5%)	12 (7%)
Non-Hispanic Black	40 (22%)	37 (21%)	37 (21%)
Hispanic	30 (16%)	32 (18%)	34 (19%)
Non-Hispanic White	101 (55%)	92 (52%)	87 (49%)
Other	4 (2%)	8 (4%)	6 (3%)
Body-mass index category			
≥30 kg/m² (obese)	102 (56%)	99 (56%)	90 (51%)
≥40 kg/m² (severely obese)	31 (17%)	25 (14%)	26 (15%)
Co-existing chronic illness			
Any	134 (74%)	136 (76%)	133 (76%)
Hypertension treated with medication	103 (57%)	104 (58%)	97 (55%)
Diabetes treated with medication	71 (39%)	62 (35%)	59 (3%)
Renal impairment	27 (15%)	19 (11%)	13 (7%)
Asthma	19 (10%)	17 (10%)	23 (13%)
Heart failure	13 (7%)	8 (4%)	15 (9%)
Chronic supplemental oxygen use before COVID-19	2 (1%)	5 (3%)	4 (2%)
Previous receipt of ≥1 dose of a COVID-19 vaccine	15 (8%)	10 (6%)	16 (9%)
Time since symptom onset, days	8 (5–9)	8 (5–9)	8 (6–9)
Medication use before randomisation			
Remdesivir	120 (66%)	112 (63%)	108 (61%)
Antibacterial agent	46 (2%)	54 (30%)	42 (24%)
Corticosteroid	109 (60%)	120 (67%)	98 (56%)
Therapeutic anticoagulation‡	25 (14%)	16 (9%)	18 (10%)
Prophylactic or intermediate anticoagulation	122 (67%)	126 (71%)	115 (65%)
Pulmonary ordinal scale category§			
Category 2: unable to do usual activities and no supplemental oxygen	64 (35%)	52 (29%)	60 (34%)
Category 3: supplemental oxygen <4 L/min	76 (42%)	80 (45%)	74 (42%)
Category 4: supplemental oxygen ≥4 L/min	42 (23%)	46 (26%)	42 (24%)
Neutralising anti-spike antibody positive	68/173 (39%)	76/171 (44%)	68/169 (40%)
Anti-nucleocapsid antibody positive	100/173 (58%)	108/171 (63%)	104/169 (62%)
Negative on both anti-nucleocapsid and neutralising anti-spike antibody assays	67/173 (39%)	54/171 (32%)	57/169 (34%)
Nucleocapsid antigen concentration >1450 pg/mL	84/173 (49%)	80/171 (47%)	82/169 (49%)

Data are n (%), n/N (%), or median (IQR). *One patient in the common placebo group was enrolled at a site that was not enrolling patients into the BRII-196 plus BRII-198 group of the trial; this patient was not included in the placebo group for comparison with BRII-196 plus BRII-198. †Race or ethnicity was self-reported. ‡Therapeutic anticoagulation was defined as receipt of therapeutic doses of heparin, warfarin, or a direct-acting oral anticoagulant. §For patients on chronic supplemental oxygen therapy before COVID-19, categorisation on the pulmonary ordinal scale was based on oxygen flow rates above the pre-COVID-19 oxygen flow rate. For example, a patient who chronically used supplemental oxygen at 2 L/min before COVID-19 would be categorised as category 2 if using 2 L/min at randomisation, category 3 if using >2 L/min and <6 L/min, and category 4 if using ≥6 L/min of supplemental oxygen.

Table 1: **Baseline characteristics of patients (modified intention-to-treat population)**

Role of the funding source

Investigators from NIH were directly involved in all aspects of this study, including study design, data collection, data analysis, data interpretation, and writing of the report.

Results

On March 1, 2021, the DSMB reviewed data for the early futility assessment for both sotrovimab and BRII-196 plus BRII-198. Based on DSMB recommendations, which were consistent with prespecified criteria for futility, enrolment to both agents was halted (appendix pp 23–26).

Between Dec 16, 2020, and March 1, 2021, 546 patients were enrolled and randomly assigned to treatment at 43 sites in the USA, Denmark, Switzerland, and Poland. Ten patients who were randomly assigned to treatment did not receive any volume of study product infusion,

	Sotrovimab group (n=182)	Placebo group (n=178)*	BRII-196 plus BRII-198 group (n=176)	Sotrovimab *vs* placebo†		BRII-196 plus BRII-198 *vs* placebo†	
				Point estimate (95% CI)	p value	Point estimate (95% CI)	p value
Efficacy outcomes							
Pulmonary ordinal outcome scale at day 5 (futility assessment)	..	..	..	aOR 1·07 (0·74–1·56)‡	0·72	aOR 0·98 (0·67–1·43)‡	0·91
Category 1: can independently do usual activities	42/181 (23%)	40/178 (22%)	44/173 (25%)	..	..	..	..
Category 2: no supplemental oxygen; symptomatic and unable to do usual activities	66/181 (36%)	58/178 (33%)	58/173 (34%)	..	..	..	..
Category 3: supplemental oxygen <4 L/min	42/181 (23%)	42/178 (24%)	33/173 (19%)	..	..	..	..
Category 4: supplemental oxygen ≥4 L/min	19/181 (10%)	20/178 (11%)	18/173 (10%)	..	..	..	..
Category 5: high-flow nasal canula or non-invasive ventilation	10/181 (6%)	14/178 (8%)	15/173 (9%)	..	..	..	..
Category 6: invasive ventilation, ECMO, mechanical circulatory support, or RRT	2/181 (1%)	3/178 (2%)	4/173 (2%)	..	..	..	..
Category 7: death	0/181 (0%)	1/178 (1%)	1/173 (1%)	..	..	..	..
Pulmonary-plus ordinal outcome scale at day 5 (futility assessment)	..	..	..	aOR 1·08 (0·74–1·58)‡	0·68	aOR 1·00 (0·68–1·46)‡	0·99
Category 1: can independently do usual activities	42/181 (23%)	40/178 (22%)	44/173 (25%)	..	..	..	..
Category 2: no supplemental oxygen; symptomatic and unable to do usual activities	66/181 (36%)	57/178 (32%)	58/173 (34%)	..	..	..	..
Category 3: supplemental oxygen <4 L/min	40/181 (22%)	42/178 (24%)	32/173 (18%)	..	..	..	..
Category 4: supplemental oxygen ≥4 L/min or extrapulmonary manifestations	20/181 (11%)	21/178 (12%)	18/173 (10%)	..	..	..	..
Category 5: high-flow nasal canula or non-invasive ventilation or severe stroke	9/181 (5%)	14/178 (8%)	15/173 (9%)	..	..	..	..
Category 6: invasive ventilation, ECMO, mechanical circulatory support, RTT, or vasopressor	4/181 (2%)	3/178 (2%)	5/173 (3%)	..	..	..	..
Category 7: death	0/181 (0%)	1/178 (1%)	1/173 (1%)	..	..	..	..
Sustained clinical recovery up to day 90 (primary outcome)	160 (88%)	151 (85%)	155 (88%)	aRR 1·12 (0·91–1·37)§	0·29	aRR 1·08 (0·88–1·32)§	0·48
Death up to day 90	14 (8%)	13 (7%)	15 (9%)	aHR 1·02 (0·48–2·17)§	0·96	aHR 1·15 (0·54–2·41)§	0·72
Safety outcomes							
Composite safety outcomes							
Up to day 5	36 (20%)	44 (25%)	46 (26%)	aOR 0·75 (0·44–1·26)§	0·28	aOR 1·14 (0·69–1·86)§	0·62
Up to day 28	51 (28%)	57 (32%)	58 (33%)	aHR 0·87 (0·60 – 1·27)§	0·48	aHR 1·10 (0·76–1·59)§	0·62
Up to day 90	42 (23%)	48 (27%)	45 (26%)	aHR 0·84 (0·55–1·27)§	0·40	aHR 1·00 (0·66–1·51)§	>0·99
Infusion reaction	18 (10%)	14 (8%)	23 (13%)	aOR 1·30 (0·61–2·76)§	0·50	aOR 1·83 (0·89–3·77)§	0·10

Data are n/N (%) or n (%) unless otherwise stated. aOR=adjusted odds ratio. aHR=adjusted hazard ratio. aRR=adjusted rate ratio. ECMO=extracorporeal membrane oxygenation. HR=hazard ratio. RRT=renal replacement therapy. *One patient in the common placebo group was enrolled at a site that was not enrolling patients into the BRII-196 plus BRII-198 group of the trial; this patient was not included in the placebo group for comparison with BRII-196 plus BRII-198; thus, the placebo group in the analyses of BRII-196 plus BRII-198 included 177 patients. †The difference between the active agent (sotrovimab or BRII-196 plus BRII-198) group and the placebo group was calculated as an odds ratio, rate ratio, or hazard ratio. A ratio >1·0 indicated more favourable results with the active agent compared with placebo for the following outcomes: pulmonary ordinal outcome scale, and sustained clinical recovery. A ratio >1·0 indicated more favourable results with placebo compared with the active agent for the following outcomes: death, composite safety outcomes, and infusion reaction. ‡Adjusted for baseline pulmonary ordinal scale category and trial pharmacy, with trial pharmacies with fewer than 15 participants grouped by geographical region. §Adjusted for trial pharmacy.

Table 2: **Summary of key clinical outcomes**

resulting in 536 patients being included in the mITT population for analysis, including 182 patients in the sotrovimab group, 176 in the BRII-196 plus BRII-198 group, and 178 in the placebo group (figure 1). One patient in the placebo group was enrolled at a site that was not open to the BRII-196 plus BRII-198 agent; this patient was not included in analyses of BRII-196 plus BRII-198. Among the 536 patients in the mITT population, 527 (98%) received the full volume of study product. Nine participants received a partial infusion due to adverse events (five patients), staffing error (three patients), or technical problems with the infusion pump (one patient).

In the mITT population, the median age was 60 years (IQR 50–72) and 228 (43%) patients were female and 308 (57%) were male (table 1). At the time of randomisation, median duration of COVID-19 symptoms was 8 days (IQR 5–9), 360 (67%) patients were receiving supplemental oxygen, 340 (63%) had received remdesivir, 327 (61%) had received corticosteroids, and 41 (8%) had received at least one dose of a COVID-19 vaccine (table 1). Baseline endogenous anti-SARS-CoV-2 antibody and antigen levels were available for 513 (96%) patients,

among whom 212 (41%) were positive for neutralising anti-spike protein antibodies, 312 (61%) were positive for anti-nucleocapsid antibodies, 178 (35%) were negative for both antibody assays, and 488 (95%) had detectable plasma nucleocapsid antigens. Neutralising anti-spike antibodies and anti-nucleocapsid antibodies at baseline were detected less frequently in patients with shorter duration of symptoms, with higher SARS-CoV-2 plasma antigen levels, and who were older (appendix p 30).

During the entire stay in hospital, including time both before and after randomisation, 487 (91%) of 536 patients received at least one dose of remdesivir (appendix p 31).

The number of patients who had an improvement in the seven-category pulmonary ordinal scale between baseline and day 5 was 85 (47%) of 181 in the sotrovimab group, 77 (45%) of 173 in the BRII-196 plus BRII-198 group, and 91 (51%) of 178 in the placebo group. Compared with placebo, the adjusted OR (active treatment *vs* placebo) for patients being in a more favourable category on the pulmonary scale on day 5 was 1·07 (95% CI 0·74 to 1·56) for sotrovimab and 0·98 (0·67 to 1·43) for BRII-196 plus BRII-198 (table 2; figure 2A). Adjusted ORs for the pulmonary ordinal scale on other days during the first week of follow-up and days 14 and 28 also did not differ significantly (appendix p 35). Outcomes for the pulmonary-plus ordinal outcome scale were nearly identical to the pulmonary ordinal outcome scale; the number of patients with improvement between baseline and day 5 on the pulmonary-plus scale was 85 (47%) of 181 in the sotrovimab group, 77 (45%) of 173 in the BRII-196 plus BRII-198 group, and 91 (51%) of 178 in the placebo group. The adjusted OR for a more favourable day 5 pulmonary-plus category with active treatment than with placebo was 1·08 (95% CI 0·74 to 1·58) for sotrovimab and 1·00 (0·68 to 1·46) for BRII-196 plus BRII-198 (table 2; figure 2B). Adjusted ORs for the pulmonary-plus ordinal scale on other days during the first week of follow-up and days 14 and 28 also did not differ (appendix p 35). We found no evidence that the proportional odds assumption was not met for the proportional odds models. In a post-hoc sensitivity analysis, varying how trial pharmacies with small numbers of participants were pooled in each stratum did not have a substantive effect on the results (appendix p 36).

By day 90, sustained clinical recovery was seen in 151 (85%) of 178 patients in the placebo group, compared with 160 (88%) of 182 in the sotrovimab group (rate ratio 1·12 [95% CI 0·91–1·37]) and 155 (88%) of 176 in the BRII-196 plus BRII-198 group (1·08 [0·88–1·32]; table 2; figure 3). Time to hospital discharge and time to the two most favourable categories on the pulmonary ordinal scale for patients on supplemental oxygen at entry were not significantly different between sotrovimab and placebo or between BRII-196 plus BRII-198 and placebo (appendix pp 58–59). Among those discharged within 14 days, 37 (26%) of 142 patients in the placebo group, 31 (22%) of 144 in the sotrovimab group, and 39 (26%) of 148 in the BRII-196 plus BRII-198 group continued to receive supplemental oxygen above pre-morbid levels at home.

By day 90, 42 (8%) patients had died, including 14 (8%) in the sotrovimab group, 15 (9%) in the BRII-196 plus

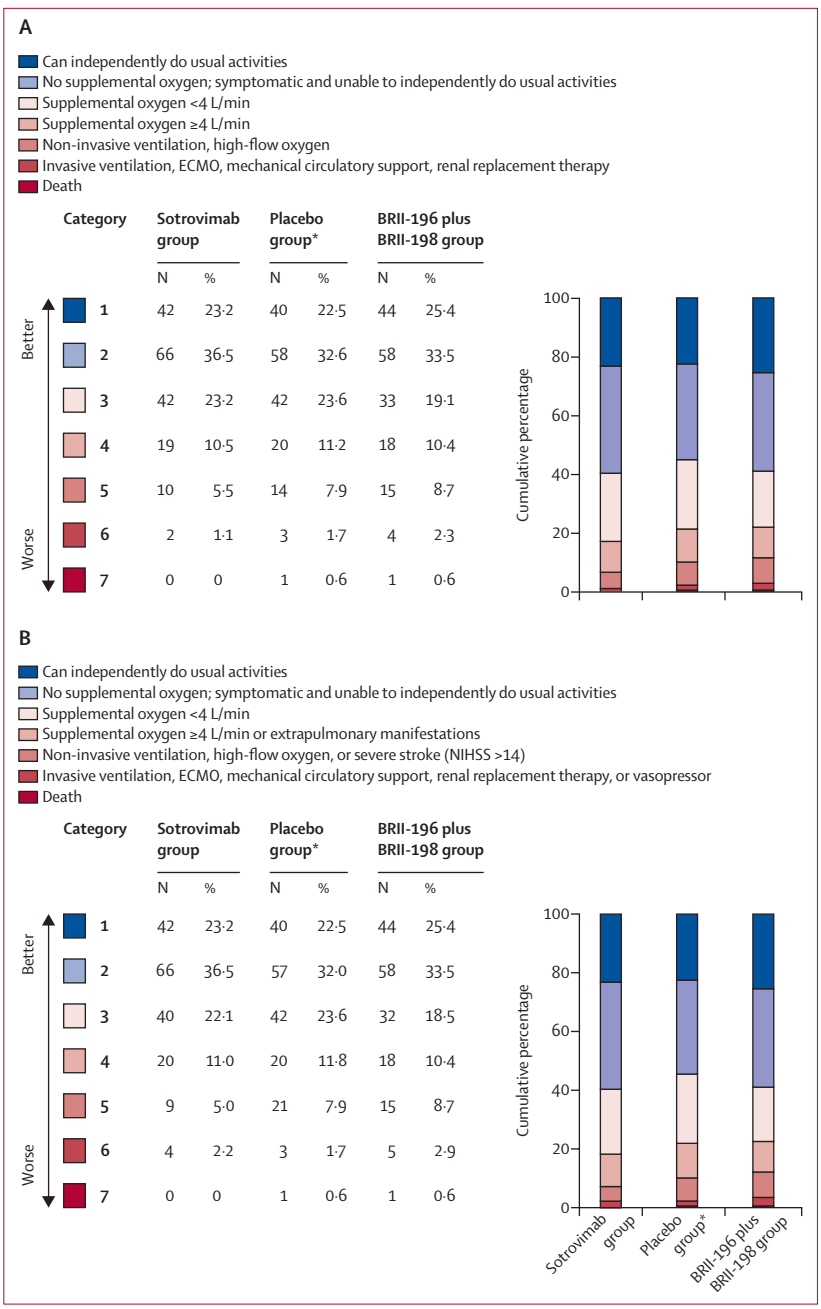


Figure 2: **Distribution of patients on the pulmonary ordinal scale (A) and the pulmonary-plus ordinal scale (B) on day 5**

The sotrovimab group and the BRII-196 plus BRII-198 group were each compared with the placebo group. ECMO=extracorporeal membrane oxygenation. NIHSS=National Institutes of Health Stroke Scale. *One patient in the common placebo group was enrolled at a site that was not enrolling patients into the BRII-196 plus BRII-198 group of the trial; this patient was not included in the placebo group for comparison with BRII-196 plus BRII-198.

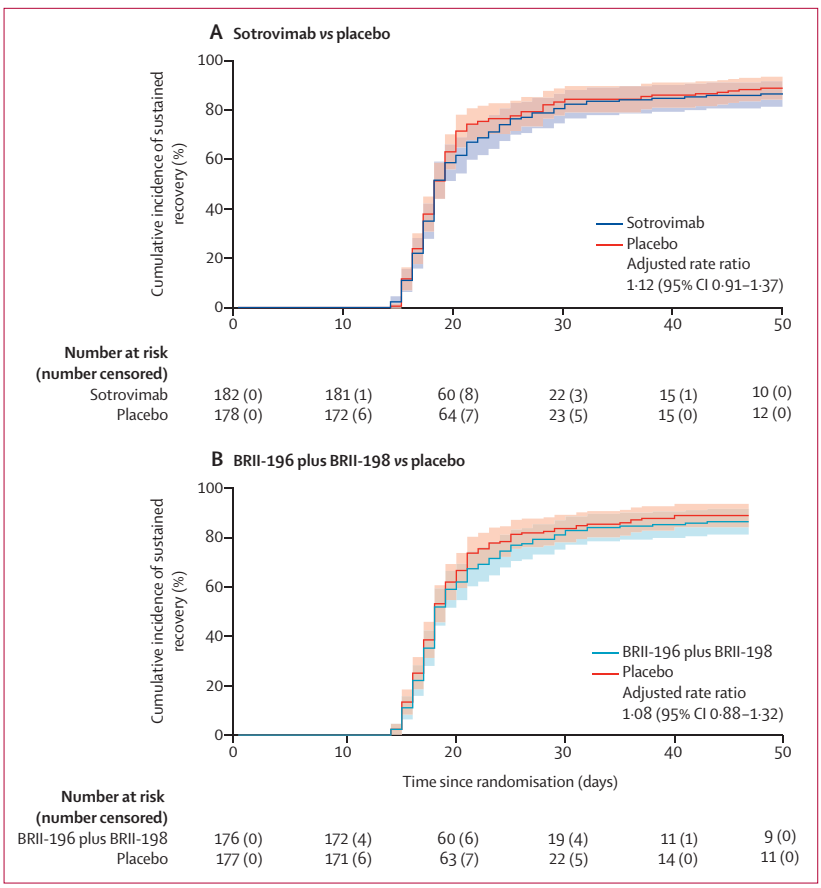


***Figure 3*: Time to sustained clinical recovery up to day 90 for sotrovimab versus placebo (A) and BRII-196 plus BRII-198 versus placebo (B)**

The rate ratios were calculated with Fine-Gray models to account for the competing risk of death and stratified according to trial pharmacy. Reasons for censoring included death before sustained recovery was reached (11 patients in the sotrovimab and placebo groups and 13 in the BRII-196 plus BRII-198 group), loss to follow-up (five patients in the sotrovimab and BRII-196 plus BRII-198 groups and nine in the placebo group), and not reaching sustained recovery by day 90 (six patients in the sotrovimab group, three in the BRII-196 plus BRII-198 group, and seven in the placebo group) .

BRII-198 group, and 13 (7%) in the placebo group (table 2). Median time between randomisation and death was 24 days (IQR 15–31). Compared with the placebo group, the hazard ratio (HR) for death for sotrovimab was 1·02 (95% CI 0·48–2·17) and for BRII-196 plus BRII-198 was 1·15 (0·54–2·41; table 2; appendix p 60).

At least one infusion-related adverse event was reported for 18 (10%) patients in the sotrovimab group, 23 (13%) patients in the BRII-196 plus BRII-198 group, and 14 (8%) patients in the placebo group (table 2). Epinephrine was used to treat anaphylaxis for one (1%) patient in the sotrovimab group, one (1%) patient in the BRII-196 plus BRII-198 group, and no patients in the placebo group.

The composite safety outcome up to day 90 was met by 48 (27%) patients in the placebo group compared with 42 (23%) patients in the sotrovimab group (adjusted HR 0·84 [95% CI 0·55–1·27]) and 45 (26%) patients in the BRII-196 plus BRII-198 group (1·00 [0·66–1·51]; table 2). Respiratory failure was the most common incident organ failure up to day 28, experienced by 19 (10%) patients in the sotrovimab group, 24 (14%) in the BRII-196 plus BRII-198 group, and 21 (12%) in the placebo group (appendix p 41). Additional safety outcome results are detailed in the appendix (pp 37–50).

For sotrovimab, point estimates favoured active agent over placebo among both patients with and without endogenous neutralising antibodies for both the sustained recovery and composite safety outcomes, with no heterogeneity of treatment effect observed (figure 4). For BRII-196 plus BRII-198, point estimates for patients without endogenous neutralising antibodies favoured active agent over placebo for both the sustained recovery outcome and the composite safety outcome, whereas point estimates for patients with endogenous neutralising antibodies favoured placebo over the active agent for both outcomes with overlapping 95% CIs. For BRII-196 plus BRII-198, an interaction was observed between baseline neutralising antibody status and the composite safety outcome at 90 days (figure 4). For BRII-196 plus BRII-198, point estimates also favoured active agent over placebo for patients with high antigen levels and favoured placebo over active agent for patients with low antigen levels. Comparisons of individual components of the composite day 90 safety outcome by endogenous neutralising antibody status and treatment are summarised in the appendix (pp 49–50). We did not find evidence of heterogeneity of treatment effect for sotrovimab or BRII-196 plus BRII-198 on the basis of demographic or other clinical characteristics (appendix pp 51–56).

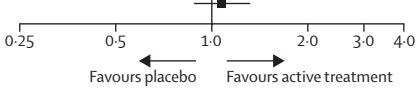
Discussion

In this randomised, double-blind, clinical trial among adults hospitalised with COVID-19 without organ failure and with symptoms for up to 12 days, treatment with either of two anti-SARS-CoV-2 neutralising monoclonal antibody therapies (sotrovimab or BRII-196 plus BRII-198) that have been shown to potently inhibit SARS-CoV-2 replication[13,20] did not improve day 5 pulmonary status, time to clinical recovery, or other clinical outcomes compared with placebo. Both therapies had reassuring findings for safety.

In other clinical trials, both sotrovimab and BRII-196 plus BRII-198 have shown efficacy for reducing disease progression to hospitalisation or death among outpatients with mild or moderate COVID-19 when treatment was given within 5 days (sotrovimab in the COMET-ICE trial[21]) or 10 days (BRII-196 plus BRII-198 in the ACTIV-2 platform[10]) of symptom onset. Similarly, other anti-SARS-CoV-2 neutralising monoclonal antibody therapies, including bamlanivimab plus etesevimab[5,12,22] and casirivimab plus imdevimab,[4,23] have exhibited benefit among outpatients with early COVID-19 in both peer-reviewed and preprint studies. This resulted in emergency use authorisation by the US Food and Drug Administration for sotrovimab,[24] bamlanivimab plus

A Time to sustained recovery

	Active		Placebo		Rate ratio (95%CI)	Rate ratio (95%CI)	$p_{interaction}$
	Patients	Events (%)	Patients	Events (%)			
Sotrovimab group							
GenScript antibody							0·57
Negative	105	88 (83·8%)	95	73 (76·8%)		1·05 (0·78–1·40)	
Positive	68	65 (95·6%)	76	72 (94·7%)		1·21 (0·88–1·65)	
Quanterix antigen							0·41
>1450	87	74 (85·1%)	83	63 (75·9%)		1·17 (0·85–1·61)	
≤1450	86	79 (91·9%)	88	82 (93·2%)		0·97 (0·73–1·28)	
Overall	**182**	**160 (87·9%)**	**178**	**151 (84·8%)**		**1·12 (0·91–1·37)**	
BRII-196 plus BRII-198 group							
GenScript antibody							0·22
Negative	101	87 (86·1%)	94	73 (77·7%)		1·19 (0·89–1·59)	
Positive	68	62 (91·2%)	76	72 (94·7%)		0·90 (0·66–1·24)	
Quanterix antigen							0·50
>1450	82	68 (82·9%)	83	63 (75·9%)		1·14 (0·83–1·59)	
≤1450	87	81 (93·1%)	87	82 (94·3%)		0·98 (0·74–1·29)	
Overall	**176**	**155 (88·1%)**	**177**	**151 (85·3%)**		**1·08 (0·88–1·32)**	



B Composite safety outcome up to day 90

	Active		Placebo		Hazard ratio (95%CI)	Hazard ratio (95%CI)	$p_{interaction}$
	Patients	Events (%)	Patients	Events (%)			
Sotrovimab group							
GenScript antibody							0·95
Negative	105	28 (26·7%)	95	30 (31·6%)		0·79 (0·47–1·33)	
Positive	68	11 (16·2%)	76	16 (21·1%)		0·76 (0·35–1·65)	
Quanterix antigen							0·48
>1450	87	23 (26·4%)	83	29 (34·9%)		0·71 (0·41–1·24)	
≤1450	86	16 (18·6%)	88	17 (19·3%)		0·96 (0·48–1·89)	
Overall	**182**	**42 (23·1%)**	**178**	**48 (27·0%)**		**0·84 (0·55–1·27)**	
BRII-196 plus BRII-198 group							
GenScript antibody							0·045
Negative	101	23 (22·8%)	94	29 (30·9%)		0·69 (0·40–1·20)	
Positive	68	21 (30·9%)	76	16 (21·1%)		1·65 (0·86–3·16)	
Quanterix antigen							0·22
>1450	82	24 (29·3%)	83	29 (34·9%)		0·79 (0·46–1·36)	
≤1450	87	20 (23·0%)	87	16 (18·4%)		1·35 (0·70–2·61)	
Overall	**176**	**45 (25·6%)**	**177**	**47 (26·6%)**		**1·00 (0·66–1·51)**	

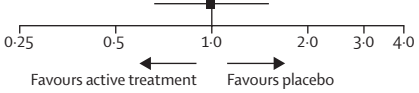


Figure 4: **Subgroup analysis for time to sustained recovery up to day 90 (A) and the composite safety outcome at day 90 (B) by antibody status and antigen levels at baseline**

These analyses tested for heterogeneity of treatment effects for sotrovimab and BRII-196 plus BRII-198 by baseline measurements of endogenous neutralising antibodies against the SARS-CoV-2 receptor binding domain and concentrations of SARS-CoV-2 nucleocapsid antigens. Antibody and antigen measurements were done on plasma collected before study drug infusion. Samples with >30% binding inhibition against the SARS-CoV-2 receptor binding domain on the GenScript SARS-CoV-2 Surrogate Virus Neutralization Test assay were classified as positive for endogenous neutralising antibodies. Nucleocapsid antigen concentration >1450 pg/mL on a Quanterix assay, which was approximately the median value in the trial population, was considered a high antigen concentration.

etesevimab,[25] and casirivimab plus imdevimab[26] for the treatment of outpatients with COVID-19.

Meanwhile, a treatment strategy using neutralising monoclonal antibodies for patients hospitalised with severe COVID-19 remains under development. In addition to the overall null results reported here for sotrovimab and BRII-196 plus BRII-198, previous trials of bamlanivimab[12] and casirivimab plus imdevimab[23] have

also reported null results for the overall population of patients hospitalised with COVID-19. However, evidence is emerging that patients hospitalised with COVID-19 without endogenous anti-SARS-CoV-2 antibodies might benefit from neutralising monoclonal antibody therapy. In our study, approximately 301 (58%) of 513 patients were negative for neutralising anti-SARS-CoV-2 antibodies at the time of randomisation and, among these patients, point estimates suggested treatment with BRII-196 plus BRII-198 could potentially be beneficial for both time to sustained clinical recovery and the composite safety outcome. Meanwhile, point estimates for patients positive at baseline for neutralising antibodies who were treated with BRII-196 plus BRII-198 were found to usually indicate worse outcomes. These results for BRII-196 plus BRII-198, which were based on underpowered subgroup analyses and should be interpreted with caution, are similar to findings reported for bamlanivimab[27] and casirivimab plus imdevimab,[23] in which subgroup analyses by endogenous antibody status indicated that patients hospitalised with COVID-19 without endogenous anti-SARS-CoV-2 antibodies potentially benefited from neutralising monoclonal antibody therapies, whereas those with endogenous antibodies did not. Future studies assessing neutralising monoclonal antibody therapies among patients hospitalised with COVID-19 should assess antibody status to understand if these findings are broadly applicable to monoclonal antibody therapies and if only patients without endogenous anti-SARS-CoV-2 antibodies should be targeted for treatment. Notably, although rapid SARS-CoV-2 antibody testing is not routinely available in all clinical settings, substantial progress has been made towards making rapid antibody testing a feasible route for guiding early treatment decisions in the near future.[28]

Results for sotrovimab in this trial did not suggest heterogeneity of treatment effect by baseline endogenous antibody status. This observation could be related to different antibody characteristics of sotrovimab, including a target epitope outside the ACE2 receptor-binding motif and differences in Fc modifications,[15] or it might be due to random chance alone.

In addition to trials of patients hospitalised with COVID-19 probably having a greater proportion of patients with endogenous anti-SARS-CoV-2 antibodies than outpatient trials, increased use of concomitant COVID-19 therapies for inpatients might be an alternative or supplementary explanation for null overall results in inpatient trials and beneficial results in outpatient trials.[29] For example, in our trial, more than 90% of patients received remdesivir during their hospital stay and more than 60% received corticosteroids before randomisation, which have both shown benefit for some patients hospitalised with COVID-19.[1,2] The additional antiviral activity from neutralising monoclonal antibody therapies might not provide incremental benefit above background therapy with remdesivir and corticosteroids. Additionally, inpatients with COVID-19 usually have longer duration of symptoms than do outpatients with COVID-19 seeking care,[10,21] and neutralising monoclonal antibody therapies might have reduced efficacy later in the disease course, regardless of endogenous antibody status and concomitant medications.

A potential harm signal for treatment with neutralising monoclonal antibody therapies among patients with endogenous anti-SARS-CoV-2 antibodies needs to be better understood. Among patients with endogenous anti-SARS-CoV-2 antibodies, trends toward worse clinical outcomes among patients treated with BRII-196 plus BRII-198 than treated with placebo were observed in this trial, although the 95% CIs crossed unity and the study was underpowered for subgroup analyses. This finding is consistent with findings reported in other recent trials for bamlanivimab[27] and casirivimab plus imdevimab.[23] Theoretically, neutralising monoclonal antibodies might cause harm in some patients through antibody-dependent enhancement of inflammation or viral replication, or both;[30,31] however, evidence of clinically important antibody-dependent enhancement has not been clearly observed in trials to date.

Limitations of this trial include its small sample size because of early stopping due to futility, which prevented robust subgroup analyses, including a well powered assessment of patients without endogenous anti-SARS-CoV-2 antibodies. Small beneficial effects from sotrovimab and BRII-196 plus BRII-198 could not be ruled out by this trial, which was designed to rapidly assess multiple agents for large clinical effects among a heterogenous population of patients hospitalised with COVID-19 and without consideration of serostatus. Early futility in this trial was based on two ordinal outcome scales (the pulmonary and pulmonary-plus scales) measured 5 days after randomisation; these are intermediate clinical outcomes and their correlation with long-term outcomes that are relevant to the patient has not been established. Critically ill patients, such as those treated with high-flow oxygen therapy or mechanical ventilation, were not included in this trial, and so the results are not generalisable to this more severely ill population. Although the doses of sotrovimab and BRII-196 plus BRII-198 used in this trial were selected on the basis of preclinical studies showing strong antiviral activity in the lungs in animals, robust dose-finding studies have not been completed and it is possible that higher doses could have been more efficacious than the doses used in this study.[17] Additionally, the effect of sotrovimab and BRII-196 plus BRII-198 on SARS-CoV-2 clearance was not analysed.

In conclusion, in this multinational, double-blind, placebo-controlled, randomised clinical trial, the neutralising anti-SARS-CoV-2 monoclonal antibodies sotrovimab and BRII-196 plus BRII-198 did not show efficacy over placebo for improving clinical outcomes among adults hospitalised with COVID-19. Prespecified subgroup analyses suggested heterogeneity of treatment

effect in the BRII-196 plus BRII-198 group by baseline endogenous neutralising antibody status, suggesting potential opportunity for monoclonal antibody therapies to be targeted to patients hospitalised with COVID-19 who have not developed endogenous antibodies.

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Author and collaborator contributions, including responsibility for decision to submit the manuscript, drafting of the initial manuscript, study conceptualisation, investigation, data curation, formal analysis, study supervision, and review and editing of the manuscript, are provided in the appendix (pp 4–11). JDN and GG directly accessed and verified the underlying study data. JDN had access to all the study data and had final responsibility for the decision to submit the paper for publication.

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Data sharing

Deidentified data from TICO trials will be made available 1 year after publication of final results from the platform. Supporting documents will be made available, including the protocol, statistical analysis plan, informed consent document, and data dictionary. Data will be made available to researchers after approval of a proposal for use of the data. Proposals for data use should be submitted using the Research Proposal Form on the INSIGHT website, www.insight-trials.org.

For the **INSIGHT website** see www.insight-trials.org

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