ORIGINAL ARTICLE

Early Treatment for Covid-19 with SARS-CoV-2 Neutralizing Antibody Sotrovimab

Anil Gupta, M.D., Yaneicy Gonzalez-Rojas, M.D., Erick Juarez, M.D., Manuel Crespo Casal, M.D., Jaynier Moya, M.D., Diego R. Falci, M.D., Ph.D., Elias Sarkis, M.D., Joel Solis, M.D., Hanzhe Zheng, Ph.D., Nicola Scott, M.Sc., Andrea L. Cathcart, Ph.D., Christy M. Hebner, Ph.D., Jennifer Sager, Ph.D., Erik Mogalian, Pharm.D., Ph.D., Craig Tipple, M.B., B.S., Ph.D., Amanda Peppercorn, M.D., Elizabeth Alexander, M.D., Phillip S. Pang, M.D., Ph.D., Almena Free, M.D., Cynthia Brinson, M.D., Melissa Aldinger, Pharm.D., and Adrienne E. Shapiro, M.D., Ph.D., for the COMET-ICE Investigators*

ABSTRACT

BACKGROUND

Coronavirus disease 2019 (Covid-19) disproportionately results in hospitalization or death in older patients and those with underlying conditions. Sotrovimab is a pan-sarbecovirus monoclonal antibody that was designed to prevent progression of Covid-19 in high-risk patients early in the course of disease.

METHODS

In this ongoing, multicenter, double-blind, phase 3 trial, we randomly assigned, in a 1:1 ratio, nonhospitalized patients with symptomatic Covid-19 (≤5 days after the onset of symptoms) and at least one risk factor for disease progression to receive a single infusion of sotrovimab at a dose of 500 mg or placebo. The primary efficacy outcome was hospitalization (for >24 hours) for any cause or death within 29 days after randomization.

RESULTS

In this prespecified interim analysis, which included an intention-to-treat population of 583 patients (291 in the sotrovimab group and 292 in the placebo group), 3 patients (1%) in the sotrovimab group, as compared with 21 patients (7%) in the placebo group, had disease progression leading to hospitalization or death (relative risk reduction, 85%; 97.24% confidence interval, 44 to 96; P=0.002). In the placebo group, 5 patients were admitted to the intensive care unit, including 1 who died by day 29. Safety was assessed in 868 patients (430 in the sotrovimab group and 438 in the placebo group). Adverse events were reported by 17% of the patients in the sotrovimab group and 19% of those in the placebo group; serious adverse events were less common with sotrovimab than with placebo (in 2% and 6% of the patients, respectively).

CONCLUSIONS

Among high-risk patients with mild-to-moderate Covid-19, sotrovimab reduced the risk of disease progression. No safety signals were identified. (Funded by Vir Biotechnology and GlaxoSmithKline; COMET-ICE ClinicalTrials.gov number, NCT04545060.)

From the Albion Finch Medical Centre, William Osler Health Centre, Toronto (A.G.); Optimus U (Y.G.-R.) and Florida International Medical Research (E.J.), Miami, Pines Care Research Center, Pembroke Pines (J.M.), and Sarkis Clinical Trials, Gainesville (E.S.) — all in Florida; Álvaro Cunqueiro Hospital, IIS Galicia Sur, Vigo, Spain (M.C.C.); Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil (D.R.F.); Centex Studies, McAllen (J. Solis), and Central Texas Clinical Research, Austin (C.B.) — both in Texas; Vir Biotechnology, San Francisco (H.Z., A.L.C., C.M.H., J. Sager, E.M., E.A., P.S.P., M.A.); GlaxoSmithKline, Stevenage, United Kingdom (N.S., C.T.); GlaxoSmithKline, Cambridge, MA (A.P.); Pinnacle Research Group, Anniston, AL (A.F.); and the Departments of Global Health and Medicine, University of Washington, and Fred Hutchinson Cancer Research Center, Seattle (A.E.S.). Dr. Shapiro can be contacted at aeshapir@uw.edu or at the Fred Hutchinson Cancer Research Center, Mailstop E5-110, 1100 Fairview Ave. N., Seattle, WA 98109.

*A list of the COMET-ICE investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on October 27, 2021, at NEJM.org.

N Engl J Med 2021;385:1941-50.
DOI: 10.1056/NEJMoa2107934

CME at NEJM.org

A Quick Take is available at NEJM.org

More than 4.8 million persons worldwide have died from coronavirus disease 2019 (Covid-19) during the global pandemic.[1] In the United States alone, an estimated 960,000 to 2.4 million Covid-19–related hospitalizations occurred through the fall of 2020 and, at the peak of the pandemic in January 2021, 79% of hospital beds in intensive care units (ICUs) were occupied by patients with this disease.[1-3] Older patients with Covid-19 and those with certain coexisting conditions such as obesity, diabetes mellitus, chronic obstructive pulmonary disease, and chronic kidney disease have been identified as being at highest risk for hospitalization or death.[4-8]

Highly effective therapeutic agents directed against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes Covid-19, are needed for these high-risk persons. Recent data suggest that one option is monoclonal antibody therapy, which can reduce the risk of hospitalization[9,10]; however, the emergence and proliferation of SARS-CoV-2 variants that confer resistance to some antibodies are troubling.[11,12] Furthermore, because additional variants of concern will probably continue to emerge, there is a great unmet need for therapeutic agents that, alone or in combination, can remain effective as the virus evolves. One possible solution is a monoclonal antibody that neutralizes SARS-CoV-2 by targeting an evolutionarily conserved epitope that lies outside the rapidly evolving receptor-binding motif. This antibody would be anticipated to have a high barrier to resistance, and because of its nonoverlapping resistance profile, it could be combined with receptor-binding motif–targeted antibodies when necessary to further heighten the barrier to resistance.

Sotrovimab, formerly known as VIR-7831, is an engineered human monoclonal antibody that neutralizes SARS-CoV-2 and multiple other sarbecoviruses, including SARS-CoV-1, the virus responsible for the SARS outbreak two decades ago.[13] In fact, the parental form of sotrovimab, S309, was isolated from a patient with SARS-CoV-1.[13] We hypothesized that a monoclonal antibody that neutralizes all sarbecoviruses would target a highly conserved epitope that would be functionally retained as SARS-CoV-2 evolves (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Consistent with this hypothesis, we subsequently found that, in vitro, sotrovimab retained activity against variants of interest and concern, including the alpha, beta, gamma, delta, and lambda variants.[11,14,15] In contrast, many of the other monoclonal antibodies under development for Covid-19 bind to the receptor-binding motif that engages the angiotensin-converting enzyme 2 (ACE2) receptor and is one of the most mutable and immunogenic regions of the virus; in some cases, these antibodies do not retain activity against the variants.[16-19]

Sotrovimab contains a two–amino acid Fc modification (termed LS) to increase half-life and potentially improve bioavailability in the respiratory mucosa through enhanced engagement with the neonatal Fc receptor.[20-22] This modification may permit therapeutic concentrations for longer durations.[20-22] Sotrovimab has been shown to have potent effector functions in vitro that may result in immune-mediated viral clearance.[13,14]

Here, we report the results of a prespecified interim analysis of the Covid-19 Monoclonal Antibody Efficacy Trial–Intent to Care Early (COMET-ICE), which was designed to evaluate the efficacy and safety of sotrovimab in high-risk, ambulatory patients with mild-to-moderate Covid-19. The trial is currently closed for enrollment; data collection is ongoing. Additional analyses of efficacy, safety, and laboratory data, as well as initial immunogenicity data, are under way.

METHODS

TRIAL OBJECTIVES AND OVERSIGHT

In this phase 3, multicenter, randomized, double-blind, placebo-controlled trial, we evaluated a single intravenous infusion of sotrovimab at a dose of 500 mg for the prevention of progression of mild-to-moderate Covid-19 in high-risk, nonhospitalized patients. For this prespecified interim analysis, patients were recruited beginning on August 27, 2020, and were followed through March 4, 2021, at 37 trial sites in four countries (the United States, Canada, Brazil, and Spain). The protocol and statistical analysis plan are available at NEJM.org, and changes made to these documents after the trial began are summarized in the Supplementary Appendix.

The trial, which was sponsored by Vir Biotech-

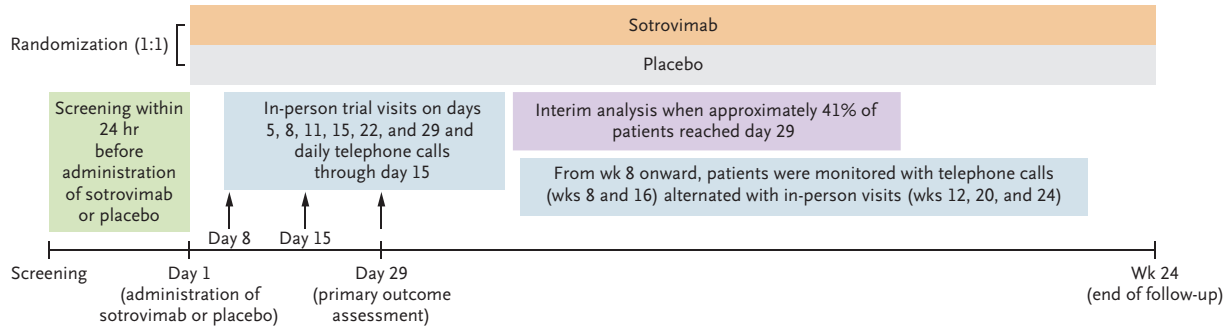

Figure 1. Trial Design.

Patients were stratified according to age (≤70 years or >70 years), symptom duration (≤3 days or 4 or 5 days), and geographic region. The trial pharmacists reconstituted and dispensed sotrovimab and placebo within equal time frames in order to maintain blinding.

nology in collaboration with GlaxoSmithKline, was conducted in accordance with the principles of the Declaration of Helsinki and the ethical guidelines of the Council for International Organizations of Medical Sciences, applicable International Council for Harmonisation Good Clinical Practice guidelines, and applicable laws and regulations. All the patients provided written informed consent. The sponsors designed the trial, and the sponsors and trial investigators participated in data collection, analysis, and interpretation. The authors made the decision to submit the manuscript for publication and vouch for the accuracy and completeness of the data presented and for the fidelity of the trial to the protocol. Medical writers who were funded by Vir Biotechnology assisted in drafting the manuscript under the authors' direction. All the authors had confidentiality agreements with the sponsors.

PATIENTS AND PROCEDURES

Adult patients (≥18 years of age) who had a positive result on reverse-transcriptase–polymerase-chain-reaction or antigen SARS-CoV-2 testing and an onset of Covid-19 symptoms within the previous 5 days were screened for eligibility; screening was performed within 24 hours before the administration of sotrovimab or placebo. The patients were at high risk for progression of Covid-19 because of older age (≥55 years) or because they had at least one of the following risk factors: diabetes for which medication was warranted, obesity (body-mass index [BMI; the weight in kilograms divided by the square of the height in meters], >30), chronic kidney disease (estimated glomerular filtration rate, <60 ml per minute per 1.73 m^2 of body-surface area),[23] congestive heart failure (New York Heart Association class II, III, or IV), chronic obstructive pulmonary disease, and moderate-to-severe asthma.[24] Patients with already severe Covid-19, defined as shortness of breath at rest, an oxygen saturation below 94%, or the use of supplemental oxygen, were excluded. Full inclusion and exclusion criteria are described in the Supplementary Methods section in the Supplementary Appendix.

Eligible patients were randomly assigned in a 1:1 ratio with the use of an interactive Web-based response system to receive either a single 500-mg, 1-hour infusion of sotrovimab or an equal volume of saline placebo on day 1 (Fig. 1). The trial design did not mandate any treatment for Covid-19 other than sotrovimab or placebo; as a result, the patients received treatment at the discretion of their physicians according to the local standard of care.

EFFICACY ASSESSMENTS

The primary outcome was the percentage of patients who were hospitalized for more than 24 hours or who died from any cause through day 29 after randomization. Secondary efficacy outcomes included the percentage of patients with an emergency department visit, hospitalization, or death and the percentage of patients who had disease progression that warranted the use of supplemental oxygen.

SAFETY ASSESSMENTS

The safety outcomes included adverse events, serious adverse events, and adverse events of special interest, which were defined as infusion-related reactions (including hypersensitivity reactions). Immunogenicity testing for antidrug antibodies was performed, and antibody-dependent enhancement was evaluated. All hospitalizations, including those due to Covid-19, were counted as serious adverse events.

STATISTICAL ANALYSIS

A prespecified interim analysis for safety, futility, and efficacy was triggered when approximately 41% of the required number of trial patients reached day 29. Sample-size calculations were based on a group-sequential design with two interim analyses to assess both futility due to lack of efficacy and efficacy. A Lan–DeMets alpha-spending function was used to control type I error, with the use of a Pocock analogue rule for futility and a Hwang–Shih–DeCani analogue rule for efficacy (with the value of $\gamma=1$).[25] The overall sample of 1360 patients would have provided approximately 90% power to detect a 37.5% relative efficacy in reducing progression of Covid-19 through day 29 at the overall two-sided 5% significance level, with an assumed incidence of progression of 16% in the placebo group.

In the interim analysis, the intention-to-treat population included all the patients who underwent randomization through the prespecified interim analysis cutoff date of January 19, 2021, irrespective of whether they received sotrovimab or placebo. The safety analysis population in the interim analysis included all the patients who received sotrovimab or placebo and underwent randomization through February 17, 2021; patients were grouped according to the actual agent received. The primary outcome was analyzed in the intention-to-treat population with the use of a Poisson regression model with robust sandwich estimators to adjust for trial agent, duration of symptoms, age, and sex. Missing progression status was imputed under a missing-at-random assumption with the use of multiple imputation. On the basis of this analysis model, the statistical significance testing, the relative risk of progression, and its appropriate confidence interval are provided with the adjusted significance level for this interim analysis.

An independent data monitoring committee recommended that enrollment in the trial be stopped on March 10, 2021, because of efficacy, at which time 1057 patients had undergone randomization. Analyses of all secondary and exploratory outcomes are planned when all the patients have completed day 29.

RESULTS

PATIENTS

Of 795 patients who underwent screening, 583 underwent randomization by January 19, 2021, and were assigned to receive sotrovimab (291 patients) or placebo (292 patients); these patients composed the intention-to-treat population for the interim analysis (Fig. S2 and Table S1). In this intention-to-treat population, both the numbers of patients who withdrew from or continued in the trial and the durations of follow-up were similar in the two trial groups. Overall, 4 patients each in the sotrovimab and placebo groups withdrew from the trial (3 patients in the sotrovimab group withdrew before they received sotrovimab). The median duration of follow-up in the intention-to-treat population was 72 days (range, 5 to 190) in the sotrovimab group and 72 days (range, 16 to 190) in the placebo group.

Overall, 868 patients (430 patients in the sotrovimab group and 438 in the placebo group) underwent randomization and received sotrovimab or placebo by February 17, 2021; these patients composed the safety analysis population for the interim analysis. The median duration of follow-up in this population was 56 days (range, 5 to 190) in the sotrovimab group and 55 days (range, 2 to 190) in the placebo group.

In the intention-to-treat population, baseline demographic and disease characteristics were similar in the sotrovimab and placebo groups (Table 1). Overall, 22% of the patients were 65 years of age or older, 7% were Black, 63% were Hispanic or Latino, and 42% had two or more conditions that were considered to be risk factors for progression of Covid-19. The most common risk factors were obesity, an age of 55 years or older, and diabetes for which medication was warranted. The most common presenting symp-

Table 1. Baseline Demographic and Disease Characteristics (Intention-to-Treat Population).*

Characteristic	Sotrovimab (N = 291)	Placebo (N = 292)	Total (N = 583)
Age			
Median (range) — yr	53.0 (18–96)	52.5 (18–88)	53.0 (18–96)
≥65 yr — no. (%)	63 (22)	65 (22)	128 (22)
>70 yr — no. (%)	33 (11)	32 (11)	65 (11)
Male sex — no. (%)	135 (46)	131 (45)	266 (46)
Race or ethnic group — no./total no. (%)†			
White	254/290 (88)	252/291 (87)	506 (87)
Black	16/290 (6)	22/291 (8)	38 (7)
Asian	17/290 (6)	17/291 (6)	34 (6)
Mixed race	2/290 (<1)	0/291	2 (<1)
American Indian or Alaska Native	1/290 (<1)	0/291	1 (<1)
Hispanic or Latinx	190/290 (66)	178/291 (61)	368 (63)
BMI‡	32.0±6.4	32.1±6.3	32.1±6.3
Duration of symptoms — no. (%)§			
≤3 days	167 (57)	171 (59)	338 (58)
4 or 5 days	123 (42)	121 (41)	244 (42)
Any risk factor for Covid-19 progression — no. (%)	291 (100)	290 (99)	581 (>99)
Age ≥55 yr	135 (46)	141 (48)	276 (47)
Diabetes for which medication was warranted	66 (23)	66 (23)	132 (23)
Obesity: BMI >30	182 (63)	187 (64)	369 (63)
Chronic kidney disease¶	1 (<1)	4 (1)	5 (<1)
Congestive heart failure: NYHA class II, III, or IV	1 (<1)	3 (1)	4 (<1)
Chronic obstructive pulmonary disease	14 (5)	10 (3)	24 (4)
Moderate-to-severe asthma	46 (16)	46 (16)	92 (16)
No. of concurrent risk factors for Covid-19 progression — no. (%)			
0	0	2 (<1)	2 (<1)
1	170 (58)	168 (58)	338 (58)
2	91 (31)	86 (29)	177 (30)
≥3	30 (10)	36 (12)	66 (11)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. NYHA denotes New York Heart Association.
† Race and ethnic group were reported by the patients.
‡ Body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.
§ The duration of symptoms in one patient in the sotrovimab group was 6 days.
¶ Chronic kidney disease was defined according to the Modification of Diet in Renal Disease criteria as an estimated glomerular filtration rate less than 60 ml per minute per 1.73 m^2 of body-surface area.

toms (in ≥62% of all the patients) were cough, muscle aches or myalgia, headache, and fatigue (Table S2). Baseline demographic and disease characteristics in the safety analysis population were similar in the two trial groups and are reported in Table S3.

EFFICACY OUTCOMES

A total of 3 of 291 patients in the sotrovimab group (1%), as compared with 21 of 292 patients in the placebo group (7%), had disease progression leading to hospitalization (for >24 hours) for any cause or death (relative risk reduction,

Table 2. Efficacy Outcomes through Day 29 (Intention-to-Treat Population).*

Outcome	Sotrovimab (N = 291)	Placebo (N = 292)
Primary outcome		
Hospitalization for >24 hr for any cause or death from any cause — no. (%)	3 (1)	21 (7)
Hospitalization for >24 hr for any cause	3 (1)	21 (7)
Death from any cause	0	1 (<1)†
Alive and not hospitalized — no. (%)	284 (98)	270 (92)
Data missing — no. (%)		
All patients with missing data	4 (1)	1 (<1)
Patients with missing data because of withdrawal of consent before receipt of sotrovimab or placebo	3 (1)	1 (<1)
Relative risk reduction (97.24% CI)	85 (44–96)	—
P value	0.002	—
Other clinical outcomes‡		
Emergency department visit or hospitalization for any cause or death from any cause — no. (%)	6 (2)	28 (10)
Emergency department visit for any cause§	2 (<1)	8 (3)
Hospitalization for any cause	4 (1)¶	21 (7)‖
Death from any cause	0	1 (<1)†
Emergency department visit without hospitalization, or hospitalization for <24 hr for any cause — no. (%)**	3 (1)	7 (2)
Severe or critical progression — no. (%)††	2 (<1)	19 (7)
Low-flow nasal cannula or face mask	2 (<1)	11 (4)
Nonrebreather mask, high-flow nasal cannula, or noninvasive ventilation	0	5 (2)
Invasive mechanical ventilation	0	2 (<1)
Death from any cause	0	1 (<1)
Admission to ICU for any cause — no. (%)	0	5 (2)

* CI denotes confidence interval, and ICU intensive care unit.
† The contributing event in Patient K was hospitalization for more than 24 hours; this patient later was included in the category "death from any cause."
‡ Inferential testing of secondary outcomes was not performed at this interim analysis.
§ "Emergency department visit for any cause" was defined as any inpatient or outpatient emergency department visit (regardless of whether the patient was hospitalized).
¶ One patient was hospitalized for less than 24 hours for diabetes management.
‖ The contributing event in Patient L was an "emergency department visit for any cause"; this patient later was included in the category "hospitalization for any cause."
** "Emergency department visit without hospitalization, or hospitalization for less than 24 hours for any cause" was defined as any emergency department visit without hospitalization, or hospitalization for less than 24 hours for any cause.
†† Severe or critical progression was manifested by the use of supplemental oxygen.

85%; 97.24% confidence interval [CI], 44 to 96; P=0.002) (Table 2). The primary reasons for the 24 hospitalizations were consistent with progressive Covid-19 (Table 3), with one probable exception: 1 patient in the sotrovimab group who had a notable medical history of small-intestinal obstruction presented 22 days after infusion with a small-intestinal obstruction.

All 5 patients who were admitted to the ICU were in the placebo group; 2 of these 5 patients received invasive mechanical ventilation, and a third patient declined to undergo intubation and

subsequently died by day 29. Emergency department visits without hospitalization or hospitalization for less than 24 hours were observed in fewer patients in the sotrovimab group than in the placebo group (Table 2).

SAFETY

In the safety analysis population, 73 of 430 patients in the sotrovimab group (17%) and 85 of 438 patients in the placebo group (19%) reported an adverse event (Table 4). The percentage of patients who reported grade 3 or 4 adverse events was lower in the sotrovimab group (2%) than in the placebo group (6%). Overall, the only adverse event that occurred in at least 1% of the patients who received sotrovimab was diarrhea, which occurred in 6 patients (1%) in the sotrovimab group (5 cases of diarrhea that were mild in severity and 1 case that was moderate in severity). Diarrhea occurred in 3 patients (<1%) in the placebo group.

The percentage of patients with infusion-related reactions was the same in the two groups (1% in each). One patient who received sotrovimab had an infusion-related reaction (moderate [grade 2] dyspnea) that was considered by the investigators to be related to sotrovimab.

Serious adverse events occurred in 2% of the patients who received sotrovimab and in 6% of those who received placebo. Most of these events were hospitalizations for Covid-19–related causes. No serious adverse events were considered by the investigators to be related to sotrovimab. One patient in the placebo group died after day 29; this patient died from Covid-19 pneumonia on day 37.

No trends were observed in hematologic values, liver-function values, or other laboratory data. Overall, laboratory results were similar in the sotrovimab and placebo groups.

DISCUSSION

In this prespecified interim analysis of COMET-ICE involving high-risk adults with symptomatic Covid-19, the relative risk reduction in hospitalization (for >24 hours) or death between patients who received a single 500-mg dose of sotrovimab and those who received placebo was 85%. Among patients who were hospitalized, none of the patients who received sotrovimab were admitted to the ICU, as compared with five patients who received placebo; this finding suggests that sotrovimab prevented more severe complications of Covid-19 in addition to preventing hospitalization. Furthermore, as a result of investigator site selection, more than 60% of the trial population consisted of patients who identified as Hispanic or Latinx; thus, this trial showed efficacy in a population that has been underrepresented in clinical trials involving patients with Covid-19, despite the disproportionately negative effect that the pandemic has had on this ethnic group. Overall, no safety signals were identified in this trial. There was also no evidence of antibody-dependent enhancement with sotrovimab, which would have manifested as more patients with worsening of disease in the sotrovimab group than in the placebo group.[26]

Sotrovimab is a potential therapeutic agent in the fight against Covid-19, for which there remains an unmet medical need despite the recent success of preventative measures such as vaccines. Challenges associated with access to vaccines, vaccine hesitancy, medical contraindications to vaccines, immunocompromised persons who may not have a response to a vaccine, and most important, the potential emergence of variant viruses that escape vaccine-derived immunity, may all contribute to what is likely to be a large and enduring number of patients with Covid-19 for whom treatment is warranted.

Treatments for Covid-19 that retain activity even in the face of a rapidly evolving virus are needed. To that end, sotrovimab was selected to have an intrinsically higher barrier to resistance as a result of targeting a pan-sarbecovirus epitope.[14] In one analysis, among more than 1.7 million SARS-CoV-2 sequences in the Global Initiative on Sharing All Influenza Data database, amino acid positions composing the sotrovimab epitope were at least 99.8% conserved in naturally occurring viruses.[14] Moreover, when necessary to further enhance breadth and barrier to resistance, sotrovimab can probably be combined with currently authorized receptor-binding motif–targeted antibodies because of its nonoverlapping resistance profile.

This interim analysis has several major limitations. First, with only three hospitalizations in the sotrovimab group, it is not possible to determine which patient or disease characteristics might be associated with sotrovimab treatment

Table 3. Primary Reasons for Hospitalization Longer than 24 Hours (Intention-to-Treat Population).

Group and Patient	Age	Sex	Hospitalization Day	Duration of Hospitalization	Primary Reason for Hospitalization	ICU Admission	Invasive Mechanical Ventilation	Died
	yr			*days*				
Sotrovimab group								
Patient A	96	M	19	14	Covid-19	No	No	No
Patient B	65	F	22	3	Small-intestinal obstruction	No	No	No
Patient C	71	F	2	16	Covid-19–related pneumonia	No	No	No
Placebo group								
Patient D	52	F	4	6	Covid-19–related pneumonia	No	No	No
Patient E	50	F	4*	20	Covid-19–related pneumonia	No	No	No
Patient F	66	F	6	7	Covid-19–related pneumonia	No	No	No
Patient G	38	M	9*	5	Covid-19–related pneumonia	No	No	No
Patient H	50	F	4*	8	Covid-19–related pneumonia	Yes†	No	No
Patient I	82	F	7	6	Acute respiratory failure	No	No	No
Patient J	70	M	12	13	Respiratory distress	Yes‡	Yes§	No
Patient K	70	M	5	14	Pneumonia	Yes¶	No	Yes
Patient L	65	M	6	7	Dehydration	No	No	No
Patient M	52	F	5	4	Covid-19–related pneumonia	No	No	No
Patient N	62	M	7	6	Covid-19–related pneumonia	No	No	No
Patient O	57	M	6	4	Pneumonia	No	No	No
Patient P	65	M	12	4	Pneumonia	No	No	No
Patient Q	68	M	7	4	Covid-19–related pneumonia	No	No	No
Patient R	55	F	7	3	Pulmonary embolism	No	No	No
Patient S	60	M	10	5	Covid-19–related pneumonia	No	No	No
Patient T	71	F	10	28	Covid-19–related pneumonia	Yes‖	Yes**	Yes
Patient U	37	F	6*	8	Covid-19–related pneumonia	No	No	No
Patient V	83	M	8	2	Dyspnea	No	No	No
Patient W	56	M	2	24	Covid-19–related pneumonia	Yes††	No	No
Patient X	55	M	7	5	Covid-19–related pneumonia	No	No	No

Table 3. (Continued.)

* The adverse event associated with the hospitalization began the day before the patient was admitted to the hospital.
† The duration of ICU stay was 8 days.
‡ The duration of ICU stay was 13 days.
§ The duration of invasive mechanical ventilation was 9 days.
¶ The duration of ICU stay was 2 days.
‖ The duration of ICU stay was 28 days.
** The duration of invasive mechanical ventilation was 16 days.
†† The duration of ICU stay was 24 days.

failure. Second, the number of patients in the sotrovimab group in the safety analysis population was modest (430 patients), and thus a rare adverse event (in <1% of the patients) may not have been observed, although one would not be expected because sotrovimab was derived from an antibody isolated from a patient who had recovered from SARS-CoV-1 infection, has minimal engineering, and targets a viral epitope (not a host epitope). Third, the presence of a baseline autologous antibody response to SARS-CoV-2 has not yet been analyzed to determine what effect emerging autologous immunity may have on the safety and efficacy of sotrovimab. Finally, secondary and exploratory outcome analyses were excluded from this interim analysis because the trial is ongoing; such analyses to further determine the potential additional benefits of sotrovimab are under way.

This trial has implications beyond showing the therapeutic value of sotrovimab. First, the results indicate that a single binding antibody against the non–receptor-binding motif, which does not directly block the ACE2 receptor interaction, can be clinically therapeutic, and thus the results suggest a role for other receptors.[27] Second, because sotrovimab has potent effector function, the efficacy and absence of safety signals suggest that effector function is neither detrimental nor associated with antibody-dependent enhancement.[26] In fact, preclinical models of Covid-19 suggest that the potent effector function of this agent may be beneficial.[13,14]

The results of this interim analysis of COMET-ICE indicate that sotrovimab can be a therapeutic agent for outpatients with Covid-19. Notably, a 500-mg dose may also permit intramuscular administration, which may increase the convenience of and access to therapeutic antibody agents for patients with Covid-19. Studies are currently under way to evaluate this route of administration. Given its in vitro activity against variants of interest and concern,[14] as well as its ability to neutralize other sarbecoviruses, we speculate that sotrovimab has the potential to remain therapeutically active even as SARS-CoV-2 continues to evolve.

Table 4. Adverse Events (Safety Analysis Population).

Adverse Events	Sotrovimab (N = 430)	Placebo (N = 438)
	no. of patients (%)	
Any adverse event*	73 (17)	85 (19)
Related to sotrovimab or placebo†	8 (2)	8 (2)
Leading to dose interruption or delay	2 (<1)‡	0
Any infusion-related reaction*§	6 (1)	5 (1)
Related to sotrovimab or placebo†	1 (<1)	2 (<1)
Leading to dose interruption or delay	0	0
Any grade 3 or 4 adverse event	7 (2)	27 (6)
Any serious adverse event	7 (2)	26 (6)
Related to sotrovimab or placebo†	0	1 (<1)
Death		
All deaths	0	2 (<1)¶
Related to sotrovimab or placebo†	0	0

* None of the patients had an adverse event (i.e., a life-threatening infusion-related reaction, including a severe allergic or hypersensitivity reaction during the intravenous infusion) leading to permanent discontinuation of sotrovimab or placebo.
† Relatedness was determined by individual trial investigators while they were unaware of the trial-group assignments.
‡ For both patients, the adverse event was infusion extravasation; both infusions were completed.
§ Infusion-related reactions were defined as adverse events according to the preferred terms of pyrexia, chills, dizziness, dyspnea, pruritus, rash, and infusion-related reaction within 24 hours after administration of sotrovimab or placebo.
¶ In addition to the patient in the placebo group who died by day 29, another patient in the placebo group died from Covid-19–related pneumonia on day 37; this patient was admitted to the hospital before day 29 and was thus considered to have had the primary-outcome event of Covid-19 progression.

Supported by Vir Biotechnology and GlaxoSmithKline.
Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank Caryn Gordon, Pharm.D., and Courtney St. Amour, Ph.D., of Cello Health Communications–SciFluent for medical-writing support and Krystyna Grycz, B.A., Jordan Clark, B.S., and Minnie Kuo, M.S., of Vir Biotechnology for clinical operations support.

REFERENCES

1. Coronavirus Resource Center home page (https://coronavirus.jhu.edu).
2. Angulo FJ, Finelli L, Swerdlow DL. Estimation of US SARS-CoV-2 infections, symptomatic infections, hospitalizations, and deaths using seroprevalence surveys. JAMA Netw Open 2021;4(1):e2033706.
3. Reese H, Iuliano AD, Patel NN, et al. Estimated incidence of coronavirus disease 2019 (COVID-19) illness and hospitalization — United States, February–September 2020. Clin Infect Dis 2021;72(12):e1010-e1017.
4. Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ 2020;369:m1966.
5. Liang W, Liang H, Ou L, et al. Development and validation of a clinical risk score to predict the occurrence of critical illness in hospitalized patients with COVID-19. JAMA Intern Med 2020;180:1081-9.
6. Cariou B, Hadjadj S, Wargny M, et al. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. Diabetologia 2020;63:1500-15.
7. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
8. CDC COVID-19 Response Team. Severe outcomes among patients with coronavirus disease 2019 (COVID-19) — United States, February 12–March 16, 2020. MMWR Morb Mortal Wkly Rep 2020;69:343-6.
9. Chen P, Nirula A, Heller B, et al. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with Covid-19. N Engl J Med 2021;384:229-37.
10. Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. N Engl J Med 2021;384:238-51.
11. Wang P, Nair MS, Liu L, et al. Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7. Nature 2021;593:130-5.
12. Chen RE, Zhang X, Case JB, et al. Resistance of SARS-CoV-2 variants to neutralization by monoclonal and serum-derived polyclonal antibodies. Nat Med 2021;27:717-26.
13. Pinto D, Park Y-J, Beltramello M, et al. Cross-neutralization of SARS-CoV-2 by a human monoclonal SARS-CoV antibody. Nature 2020;583:290-5.
14. Cathcart AL, Havenar-Daughton C, Lempp FA, et al. The dual function monoclonal antibodies VIR-7831 and VIR-7832 demonstrate potent in vitro and in vivo activity against SARS-CoV-2. August 6, 2021 (https://www.biorxiv.org/content/10.1101/2021.03.09.434607v6). preprint.
15. McCallum M, Bassi J, De Marco A, et al. SARS-CoV-2 immune evasion by variant B.1.427/B.1.429. April 1, 2021 (https://www.biorxiv.org/content/10.1101/2021.03.31.437925v1). preprint.
16. Focosi D, Maggi F. Neutralising antibody escape of SARS-CoV-2 spike protein: risk assessment for antibody-based Covid-19 therapeutics and vaccines. Rev Med Virol 2021 March 16 (Epub ahead of print).
17. Tada T, Dcosta BM, Zhou H, Vaill A, Kazmierski W, Landau NR. Decreased neutralization of SARS-CoV-2 global variants by therapeutic anti-spike protein monoclonal antibodies. February 19, 2021 (https://www.biorxiv.org/content/10.1101/2021.02.18.431897v1). preprint.
18. Starr TN, Greaney AJ, Dingens AS, Bloom JD. Complete map of SARS-CoV-2 RBD mutations that escape the monoclonal antibody LY-CoV555 and its cocktail with LY-CoV016. Cell Rep Med 2021;2:100255.
19. Liu H, Wei P, Zhang Q, et al. 501Y.V2 and 501Y.V3 variants of SARS-CoV-2 lose binding to bamlanivimab *in vitro*. February 16, 2021 (https://www.biorxiv.org/content/10.1101/2021.02.16.431305v1). preprint.
20. Ko S-Y, Pegu A, Rudicell RS, et al. Enhanced neonatal Fc receptor function improves protection against primate SHIV infection. Nature 2014;514:642-5.
21. Zalevsky J, Chamberlain AK, Horton HM, et al. Enhanced antibody half-life improves in vivo activity. Nat Biotechnol 2010;28:157-9.
22. Gaudinski MR, Coates EE, Houser KV, et al. Safety and pharmacokinetics of the Fc-modified HIV-1 human monoclonal antibody VRC01LS: a phase 1 open-label clinical trial in healthy adults. PLoS Med 2018;15(1):e1002493.
23. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Intern Med 1999;130:461-70.
24. COVID-19: developing drugs and biological products for treatment or prevention. May 2020 (https://www.fda.gov/media/137926/download).
25. Hwang IK, Shih WJ, De Cani JS. Group sequential designs using a family of type I error probability spending functions. Stat Med 1990;9:1439-45.
26. Arvin AM, Fink K, Schmid MA, et al. A perspective on potential antibody-dependent enhancement of SARS-CoV-2. Nature 2020;584:353-63.
27. Lempp FA, Soriaga L, Montiel-Ruiz M, et al. Membrane lectins enhance SARS-CoV-2 infection and influence the neutralizing activity of different classes of antibodies. April 4, 2021 (https://www.biorxiv.org/content/10.1101/2021.04.03.438258v1). preprint.