JAMA | Original Investigation

Effect of Sotrovimab on Hospitalization or Death Among High-risk Patients With Mild to Moderate COVID-19
A Randomized Clinical Trial

Anil Gupta, MD; Yaneicy Gonzalez-Rojas, MD; Erick Juarez, MD; Manuel Crespo Casal, MD; Jaynier Moya, MD; Diego Rodrigues Falci, MD, PhD; Elias Sarkis, MD; Joel Solis, MD; Hanzhe Zheng, PhD; Nicola Scott, MSc; Andrea L. Cathcart, PhD; Sergio Parra, MD, MSc; Jennifer E. Sager, PhD; Daren Austin, PhD; Amanda Peppercorn, MD; Elizabeth Alexander, MD, MSc; Wendy W. Yeh, MD; Cynthia Brinson, MD; Melissa Aldinger, PharmD; Adrienne E. Shapiro, MD, PhD; for the COMET-ICE Investigators

IMPORTANCE Older patients and those with comorbidities who are infected with SARS-CoV-2 may be at increased risk of hospitalization and death. Sotrovimab is a neutralizing antibody for the treatment of high-risk patients to prevent COVID-19 progression.

OBJECTIVE To evaluate the efficacy and adverse events of sotrovimab in preventing progression of mild to moderate COVID-19 to severe disease.

DESIGN, SETTING, AND PARTICIPANTS Randomized clinical trial including 1057 nonhospitalized patients with symptomatic, mild to moderate COVID-19 and at least 1 risk factor for progression conducted at 57 sites in Brazil, Canada, Peru, Spain, and the US from August 27, 2020, through March 11, 2021; follow-up data were collected through April 8, 2021.

INTERVENTIONS Patients were randomized (1:1) to an intravenous infusion with 500 mg of sotrovimab (n = 528) or placebo (n = 529).

MAIN OUTCOMES AND MEASURES The primary outcome was the proportion of patients with COVID-19 progression through day 29 (all-cause hospitalization lasting >24 hours for acute illness management or death); 5 secondary outcomes were tested in hierarchal order, including a composite of all-cause emergency department (ED) visit, hospitalization of any duration for acute illness management, or death through day 29 and progression to severe or critical respiratory COVID-19 requiring supplemental oxygen or mechanical ventilation.

RESULTS Enrollment was stopped early for efficacy at the prespecified interim analysis. Among 1057 patients randomized (median age, 53 years [IQR, 42-62], 20% were ≥65 years of age, and 65% Latinx), the median duration of follow-up was 103 days for sotrovimab and 102 days for placebo. All-cause hospitalization lasting longer than 24 hours or death was significantly reduced with sotrovimab (6/528 [1%]) vs placebo (30/529 [6%]) (adjusted relative risk [RR], 0.21 [95% CI, 0.09 to 0.50]; absolute difference, −4.53% [95% CI, −6.70% to −2.37%]; $P < .001$). Four of the 5 secondary outcomes were statistically significant in favor of sotrovimab, including reduced ED visit, hospitalization, or death (13/528 [2%] for sotrovimab vs 39/529 [7%] for placebo; adjusted RR, 0.34 [95% CI, 0.19 to 0.63]; absolute difference, −4.91% [95% CI, −7.50% to −2.32%]; $P < .001$) and progression to severe or critical respiratory COVID-19 (7/528 [1%] for sotrovimab vs 28/529 [5%] for placebo; adjusted RR, 0.26 [95% CI, 0.12 to 0.59]; absolute difference, −3.97% [95% CI, −6.11% to −1.82%]; $P = .002$). Adverse events were infrequent and similar between treatment groups (22% for sotrovimab vs 23% for placebo); the most common events were diarrhea with sotrovimab (n = 8; 2%) and COVID-19 pneumonia with placebo (n = 22; 4%).

CONCLUSIONS AND RELEVANCE Among nonhospitalized patients with mild to moderate COVID-19 and at risk of disease progression, a single intravenous dose of sotrovimab, compared with placebo, significantly reduced the risk of a composite end point of all-cause hospitalization or death through day 29. The findings support sotrovimab as a treatment option for nonhospitalized, high-risk patients with mild to moderate COVID-19, although efficacy against SARS-CoV-2 variants that have emerged since the study was completed is unknown.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT04545060

JAMA. 2022;327(13):1236-1246. doi:10.1001/jama.2022.2832
Published online March 14, 2022.

Visual Abstract

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: A list of the COMET-ICE Investigators appears in Supplement 3.

Corresponding Author: Adrienne E. Shapiro, MD, PhD, Fred Hutchinson Cancer Research Center, E5-110, 1100 Fairview Ave N, Seattle, WA 98109 (aeshapir@uw.edu).

As of January 2022, more than 5.4 million people worldwide have died from COVID-19.[1] The most common serious manifestations of COVID-19 are respiratory failure and acute respiratory distress syndrome, but diverse effects have been observed in other organ systems.[2] Patient characteristics associated with a greater risk of severe COVID-19 include older age, obesity, and chronic kidney disease.[3]

Since its identification, mutations in the SARS-CoV-2 spike gene have resulted in the global spread of variants of concern that may increase transmissibility and disease severity while decreasing response to vaccines and treatment options.[4,5] Recently, B.1.617.2 (Delta) and B1.1.529 (Omicron) have emerged as the leading variants of concern, with increased transmissibility and immune evasion, including vaccine breakthrough infections.[4] Effective therapies are needed because of these mutations, limited vaccine availability, and vaccine hesitancy to provide a high barrier against viral escape and enduring coverage.[6] In the US, current treatment guidelines for outpatients with mild to moderate COVID-19 who are at high risk for clinical progression recommend monoclonal antibody treatment.[6]

Sotrovimab is an Fc-engineered human monoclonal antibody that contains the LS modification to enhance half-life and respiratory mucosal delivery.[7,8] In contrast to other monoclonal antibodies,[9] sotrovimab targets a highly conserved epitope in the SARS-CoV-2 spike protein at a region that does not compete with binding of the angiotensin-converting enzyme 2.[10,11] In addition to neutralizing SARS-CoV-2, sotrovimab has demonstrated effector functions in vitro that may contribute to immune-mediated viral clearance.[7,12] Data also suggest that sotrovimab may prevent cell-cell fusion (ie, syncytia formation) unlike other antibodies that target the receptor-binding domain.[13]

The COVID-19 Monoclonal Antibody Efficacy Trial–Intent to Care Early (COMET-ICE) evaluated the efficacy and tolerability of sotrovimab administered intravenously in high-risk patients with mild to moderate COVID-19. The results from a preplanned interim analysis were recently published.[14] The full results of this trial through the primary outcome at day 29 are presented here.

Key Points

Question Among patients at risk of disease progression, does early treatment of mild to moderate COVID-19 with the neutralizing antibody sotrovimab prevent progression to severe disease?

Findings In this randomized clinical trial of 1057 participants, treatment with a single intravenous dose of sotrovimab, compared with placebo, resulted in a statistically significant reduction in the proportion of patients who experienced a composite outcome of all-cause hospitalization lasting longer than 24 hours or death through day 29 (1% vs 6%, respectively; adjusted relative risk, 0.21).

Meaning Findings support sotrovimab as a treatment option for nonhospitalized, high-risk patients with mild to moderate COVID-19, although efficacy against SARS-CoV-2 variants that have emerged since the study was completed is unknown.

Methods

Study Design

The early treatment of mild to moderate COVID-19 with sotrovimab was assessed in this phase 3, double-blind, placebo-controlled, multicenter randomized clinical trial. There were 57 participating centers (6 sites in Brazil; 2 sites in Canada; 1 site in Peru; 3 sites in Spain; and 45 sites in the US). The protocol and statistical analysis plan, including changes made after trial commencement, appear in Supplement 1. The study was conducted in accordance with the principles of the Declaration of Helsinki and the Council for International Organizations of Medical Sciences international ethical guidelines, applicable Good Clinical Practice guidelines from the International Council for Harmonisation, and applicable laws and regulations. Ethics approval was obtained from institutional review boards and ethics committees at all participating sites. All patients or their representatives provided written informed consent, and the appropriate institutional forms were archived.

Patients

Eligible patients were aged 18 years or older, tested positive for SARS-CoV-2 by reverse transcriptase–polymerase chain reaction (RT-PCR) test or an antigen test, and had symptom onset within the prior 5 days. The study population represented patients at high risk for COVID-19 progression requiring hospitalization or death. As such, patients were required to have at least 1 of the following risk factors: age of 55 years or older, diabetes requiring medication, obesity (body mass index >30; calculated as weight in kilograms divided by height in meters squared), chronic kidney disease (estimated glomerular filtration rate <60 mL/min/1.73 m^2),[15] congestive heart failure (≥New York Heart Association class II), chronic obstructive pulmonary disease, or moderate to severe asthma.[16] Patients were excluded if they were hospitalized or if they had signs or symptoms of severe COVID-19 (shortness of breath at rest, oxygen saturation level <94%, or required supplemental oxygen).

Race and ethnicity were collected for regulatory reporting purposes and were self-reported by the patients from a predefined list of racial and ethnic categories. If a patient identified as multiracial, the terms *mixed White race*, *mixed Asian race*, or *mixed race* were used in accordance with regulatory guidance.

Randomization and Intervention

Eligibility screening was performed within 24 hours before study drug administration. Using an interactive web response system, eligible patients were randomized 1:1 to receive a single intravenous infusion with 500 mg of sotrovimab or an equal volume of saline placebo over 1 hour on day 1. Patients were observed for approximately 2 hours after the infusion. Randomization was stratified by age

(≤70 years vs >70 years), duration of COVID-19 symptoms (≤3 days vs 4-5 days), and region (North America vs South America vs Europe) and based on a block size of 6. Participants and investigators (and treatment administrators) were all blinded to treatment allocation.

Outcomes

Primary and Secondary Outcomes

The primary efficacy outcome was the proportion of patients with COVID-19 progression through day 29 (defined as all-cause hospitalization lasting >24 hours for acute illness management or death due to any cause). To capture clinical events that may not have required prolonged hospitalization but were potentially clinically relevant, a secondary composite outcome of the proportion of patients with all-cause emergency department visit, hospitalization of any duration for acute illness management, or death due to any cause through day 29 was measured.

Additional prespecified clinical secondary outcomes included the proportion of patients with progression to severe or critical respiratory COVID-19 requiring supplemental oxygen (severe disease) or mechanical ventilation (critical disease) through day 29 and all-cause mortality at day 29. Symptom severity and duration were measured using the COVID-19-adapted version of the Influenza Patient-Reported Outcome Plus (FLU-PRO Plus) questionnaire and assessed as mean change in total score (an average of responses from the 32-item questionnaire; scores range from 0 [symptom-free] to 4 [very severe symptoms]) from baseline through day 7 (additional information on the FLU-PRO Plus questionnaire appears in the eMethods in Supplement 2).[17] There is no established minimal clinically important difference for the FLU-PRO Plus questionnaire in a population with COVID-19. Changes from baseline to day 8 in viral load (in nasal secretions) were determined by quantitative RT-PCR test.

Exploratory Outcomes

Prespecified exploratory outcome measures included total hospital length of stay, total intensive care unit length of stay, total number of days requiring mechanical ventilation from randomization through day 29, and detection of SARS-CoV-2 in nasal secretions by RT-PCR test through day 29. Further details regarding other outcomes not reported in this article appear in the eMethods in Supplement 2.

Adverse Events

Adverse events and serious adverse events, including all hospitalizations and deaths (regardless of their relationship to COVID-19), were assessed. Adverse events of special interest were defined as infusion-related reactions (including hypersensitivity reactions) and the potential for antibody-dependent enhancement (a phenomenon in which an antibody against a pathogen worsens its virulence by a mechanism that is shown to be antibody-dependent). Candidate antibody-dependent enhancement events were assessed at the site level by investigators and adjudicated centrally by the trial sponsors and an independent data monitoring committee; the process is detailed in §2.3.1 of the trial protocol (Supplement 1).

Sample Size

A sample size of 1360 patients (680 per treatment group) was determined to provide approximately 90% power to detect a relative efficacy of 37.5% in reducing COVID-19 progression through day 29 at the overall 2-sided 5% significance level. The assumed progression rate for COVID-19 was 10% in the sotrovimab group and 16% in the placebo group. Using these progression rates, which were based on data from early in the COVID-19 pandemic, the minimal detectable relative risk (RR) was approximately 0.75 for the day 29 analysis.[18]

Statistical Analysis

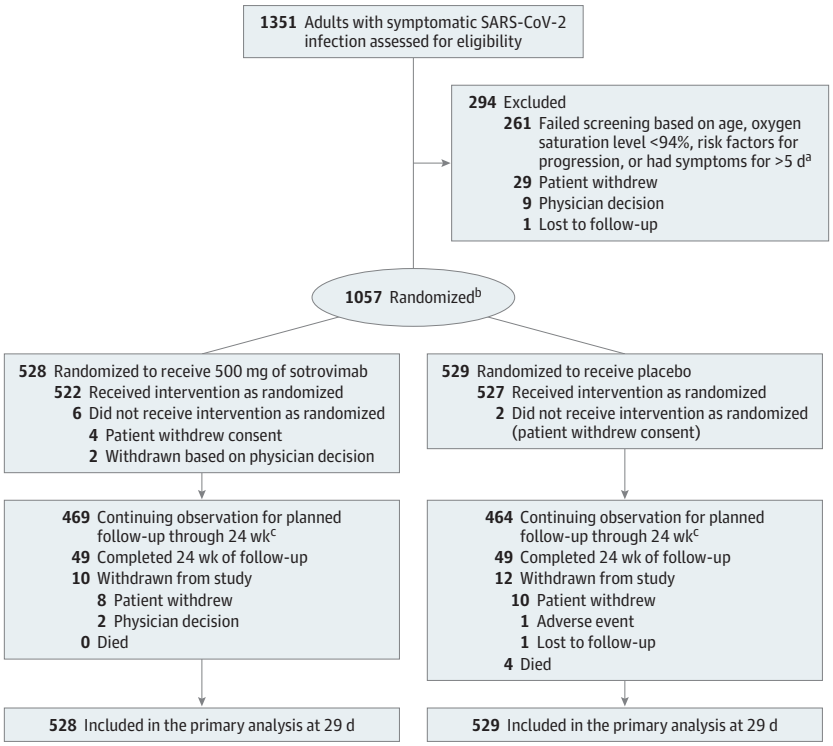
The as-randomized population included all randomized patients irrespective of the study treatment they received. The as-treated population included all patients who received either treatment. The virology population was a subset of the as-randomized population that included only patients with a central laboratory–confirmed quantifiable baseline nasopharyngeal swab.

The study used a group sequential design with 2 interim analyses to assess both futility (due to lack of efficacy) and overwhelming efficacy that were conducted when approximately 41% and 64% of the required number of patients reached the day 29 visit. A Lan-DeMets[19] α-spending function was used to control the type I error for the primary outcome, with a Pocock analog rule for futility and a Hwang-Shih-DeCani ($\gamma = 1$) analog rule for efficacy.[20] The 2-sided significance thresholds at the first interim analysis were $P < .02758$ for efficacy and $P > .38790$ for futility. Based on the adjusted significance level of $P < .02758$, the 97.24% CIs were calculated. The 97.24% CIs and the 95% CIs are presented for the day 29 as-randomized analysis for ease of comparison with the interim analysis.[14]

The primary outcome was analyzed in the as-randomized population using a Poisson regression model with robust sandwich estimators adjusting for the duration of symptoms, age, and sex to determine the RR. Missing data were imputed under a missing at random assumption using a multiple imputation model. A post hoc analysis was conducted to determine the absolute difference with the Wald CI and missing data were imputed as no COVID-19 progression, which is more likely given the low number of COVID-19 progression events overall.

The secondary outcomes were formally analyzed in the as-randomized population (except the viral load outcome, which was assessed in the virology population) at the final day 29 analysis using a 2-sided α level of 5%. Statistical testing of secondary outcomes was adjusted for multiplicity using a hierarchy in which the full α ($P \le .05$) was transferred down between each outcome measure. The order of hierarchical testing for the secondary outcomes was COVID-19 progression (all-cause emergency department visit, hospitalization of any duration for acute illness management, or death through day 29), change in viral load, progression to severe or critical respiratory COVID-19 requiring supplemental

Figure. Patient Enrollment and Treatment Assignment for the As-Randomized Population in COMET-ICE



COMET-ICE indicates COVID-19 Monoclonal Antibody Efficacy Trial–Intent to Care Early.

[a] Patients may have met more than 1 exclusion criterion based on eligibility criteria. The eligibility criteria were based on composites of age, high risk of COVID-19 progression and protocol-specified risk factors, oxygen saturation level, and duration of symptoms. The details of these composites and other eligibility criteria leading to study exclusion appear in eTable 1 in Supplement 2.

[b] One patient who was randomized to the placebo group received sotrovimab and was included in the sotrovimab group of the as-treated population but in the placebo group of the as-randomized population. This patient had no adverse events or hospitalizations.

[c] At the time of database lock.

oxygen or mechanical ventilation, change in FLU-PRO Plus total score, and all-cause mortality. The proportion of patients with an all-cause emergency department visit, hospitalization of any duration for acute illness management, or death through day 29 and the proportion of patients with progression to severe or critical respiratory COVID-19 were analyzed in a similar manner as the primary outcome.

The mean change in FLU-PRO Plus total score was analyzed as area under the curve through day 7 using analysis of covariance that was adjusted for baseline value, age group, time to symptom onset, sex, and region. Missing data for FLU-PRO Plus total score were imputed using a modified last observation carried forward approach for the final assessment only. The mean change in $\log_{10}$-transformed nasal viral load was analyzed using a mixed model for a repeated-measures model and was adjusted for baseline value, baseline value by visit, age, duration of symptoms, and sex. An analysis of all-cause mortality was planned a priori; however, because less than 5% of the deaths overall occurred through day 29, no analysis was performed.

Region (North America vs South America vs Europe) was considered a priori as a covariate for disease progression outcomes in the statistical analysis plan; however, due to the North American region dominating the interim analysis, region was removed from the models to overcome convergence issues. An analysis of the primary outcome has not been conducted by study center due to the varied number of participants randomized at the study centers, and in conjunction with the low number of primary outcome progression events.

Testing was performed for the exploratory outcomes at the 2-sided 5% significance level. The statistical analyses were performed using SAS version 9.4 (SAS Institute Inc).

Results

The first interim analysis (n = 583 for efficacy and n = 868 for safety) at the data cutoff date of March 4, 2021, was performed by an independent statistical data analysis center, and the data were reviewed by the independent data monitoring committee on March 10, 2021. As planned prospectively in the independent data monitoring committee charter, the *P* values at the interim analysis were plotted against predetermined stopping boundaries. The efficacy success boundary was crossed; therefore, the independent data monitoring committee recommended the study be stopped and recruitment was terminated on March 11, 2021. For the first interim analysis of the primary outcome, 583 patients were in the as-randomized data set.[14]

Patient Demographics and Clinical Characteristics

In the current analysis, of the 1351 patients screened from August 27, 2020, through March 11, 2021, 1057 (1-156 per study site) were randomly assigned to sotrovimab (n = 528) or placebo (n = 529), comprising the as-randomized population (**Figure**). Database lock occurred in April 2021. Eight randomized patients did not receive the study drug and were not included in the as-treated population (n = 1049).

The median duration of follow-up was 103 days (IQR, 79-128 days) for the sotrovimab group and 102 days (IQR, 77-128 days) for the placebo group. Follow-up data were collected through April 8, 2021.

The baseline demographics and clinical characteristics were well balanced between treatment groups (**Table 1**). The median age was 53 years (IQR, 42-62 years) and 20% of patients were aged 65 years or older. The majority of patients (65%) were Latinx. Most patients (953/1057 [90%]) were recruited from 45 sites in the US and recruitment was generally balanced across the treatment groups. Given this dominance of the North American recruitment, and a lower than anticipated number of severe or critical COVID-19 progression events, region was removed as a covariate to aid convergence. The 4 most common predefined risk factors or comorbidities in both treatment groups at screening were obesity, age of 55 years or older, diabetes requiring medication, and moderate to severe asthma. Most patients (59%) had symptoms for 3 or fewer days. Presenting symptoms were similar between treatment groups; cough, headache, myalgia, and fatigue were the most common.

Primary Outcome

Of 528 patients treated with sotrovimab, 6 (1%) progressed to all-cause hospitalization lasting longer than 24 hours for acute illness management or death due to any cause through day 29 vs 30 of 529 patients (6%) who received placebo, resulting in a statistically significant reduction (adjusted RR, 0.21 [95% CI, 0.09 to 0.50], $P < .001$; **Table 2**). Using a post hoc Wald CI with missing data imputed as no COVID-19 progression, the absolute difference in the primary outcome was -4.53% (95% CI, -6.70% to -2.37%). In a post hoc review of all progression events to assess the relationship with COVID-19, of the patients receiving sotrovimab who were hospitalized, 3 had respiratory conditions associated with COVID-19 and 3 were hospitalized for reasons potentially unrelated to COVID-19 (small intestinal obstruction, non-small cell lung cancer, and diabetic foot ulcer; eTable 2 in Supplement 2).

Secondary Outcomes

Of the 5 secondary outcomes tested in hierarchal order, 4 met statistical significance (Table 2). The fifth outcome, all-cause mortality at day 29, was not formally analyzed due to fewer than anticipated deaths. The percentage of patients who progressed to the composite outcome of all-cause emergency department visit, hospitalization of any duration for acute illness management, or death due to any cause through day 29 was significantly reduced with sotrovimab (13/528 [2%]) vs placebo (39/529 [7%]) (adjusted RR, 0.34 [95% CI, 0.19 to 0.63]; absolute difference, -4.91% [95% CI, -7.50% to -2.32%], $P < .001$). Sotrovimab significantly reduced progression to severe or critical respiratory COVID-19 through day 29 (7/528 [1%]) compared with placebo (28/529 [5%]) (adjusted RR, 0.26 [95% CI, 0.12 to 0.59]; absolute difference, -3.97% [95% CI, -6.11% to -1.82%], $P = .002$). No patients treated with sotrovimab required high-flow oxygen, oxygen via a nonrebreather mask, or mechanical ventilation. Among patients who received placebo, 10 required oxygen support (high-flow nasal cannula, nonrebreather mask, or noninvasive ventilation) and 4 required mechanical ventilation (eFigure in Supplement 2). By day 29, there were no deaths in the sotrovimab group and 2 deaths in the placebo group.

Among patients in the virology population (n = 733), the mean decline from baseline in viral load at day 8 was significantly greater with sotrovimab (-2.589 $\log_{10}$ copies/mL) vs placebo (-2.357 $\log_{10}$ copies/mL) (absolute difference, -0.232 $\log_{10}$ copies/mL [95% CI, -0.399 to -0.065 $\log_{10}$ copies/mL], $P = .007$; Table 2 and eTable 3 in Supplement 2). Among patients in the as-randomized population, 57% of those receiving sotrovimab and 56% of those receiving placebo completed the FLU-PRO Plus questionnaire through day 7. The least-squares mean difference in FLU-PRO Plus total score from baseline to day 7 was significantly greater in the sotrovimab group (area under the curve, -3.05) compared with the placebo group (area under the curve, -1.98) (least-squares mean difference, -1.07 [95% CI, -1.38 to -0.76], $P < .001$; Table 2 and eTable 3 in Supplement 2).

Exploratory Outcomes

Compared with placebo, treatment with sotrovimab reduced the number of patients who were admitted to the hospital for longer than 24 hours for any reason. Among patients who required hospitalization, patients treated with sotrovimab had a shorter duration of hospitalization compared with patients who received placebo (**Table 3**). In addition, 0 patients receiving sotrovimab required an intensive care unit stay or mechanical ventilation while hospitalized compared with 10 patients (2%) in the placebo group who required an intensive care unit stay and 6 patients (1%) in the placebo group who required mechanical ventilation. By day 8, approximately 60% of patients had a negative nasal SARS-CoV-2 result in both study groups. By day 29, the majority of patients had SARS-CoV-2 viral clearance as evidenced by a negative result.

Adverse Events

In the as-treated population (n = 1049), adverse events were reported for 22% (114 of 523) of patients in the sotrovimab group and 23% (123 of 526) of patients in the placebo group (**Table 4**). No deaths were reported for patients receiving sotrovimab. Four deaths occurred in patients receiving placebo (2 occurred prior to day 29 and 2 occurred after day 29). Two of the deaths were classified as due to COVID-19 pneumonia, 1 as pneumonia, and 1 as respiratory failure. Serious adverse events and grade 3 or 4 adverse events were less common in patients receiving sotrovimab compared with placebo. No serious adverse events were considered related to sotrovimab.

Most adverse events occurring in more than 1% of patients in either treatment group were more frequent in the placebo group vs the sotrovimab group. However, diarrhea occurred in more patients receiving sotrovimab (8 [2%]) than in those receiving placebo (4 [<1%]; Table 4). Of the 8 sotrovimab-treated patients who reported diarrhea, all had grade 1 or 2 events, and diarrhea resolved for all but 1 patient at the data cutoff date for the day 29 analysis.

The proportion of patients with any systemic infusion-related reaction was the same in each treatment group (Table 4).

Table 1. Baseline Demographics and Clinical Characteristics of the As-Randomized Population

	No. (%)[a]	
	Sotrovimab (n = 528)	Placebo (n = 529)
Demographics		
Age, median (IQR), y	53 (41.5-62)	53 (43-63)
Age group, y		
≥65	105 (20)	108 (20)
>70	56 (11)	56 (11)
Sex		
Female	299 (57)	273 (52)
Male	229 (43)	256 (48)
Race[b]	(n = 527)	(n = 528)
American Indian or Alaska Native	1 (<1)	2 (<1)
Asian	24 (5)	21 (4)
Black or African American	40 (8)	42 (8)
Multiracial[c]	4 (<1)	0
White	458 (87)	463 (88)
Ethnicity		
Latinx	345 (65)	346 (65)
Not Latinx	183 (35)	183 (35)
Region		
North America	503 (95)	502 (95)
Europe	14 (3)	15 (3)
South America	11 (2)	12 (2)
Body mass index, median (IQR)[d]	31.9 (27.6-36.0)	31.7 (27.7-35.8)
Clinical characteristics		
Method of diagnosis		
RT-PCR test	444 (84)	450 (85)
Antigen test	84 (16)	79 (15)
Nasopharyngeal swab viral load[e]	(n = 451)	(n = 470)
Not detectable or <lower limit of quantification	93 (21)	95 (20)
≤Log 10^5 copies/mL	68 (15)	83 (18)
>Log 10^5 copies/mL-≤log 10^7 copies/mL	134 (30)	113 (24)
>Log 10^7 copies/mL	156 (35)	179 (38)
Duration of symptoms, d		
≤3	314 (59)	310 (59)
4-5	213 (40)	219 (41)
>5	1 (<1)[f]	0
Any risk factor for COVID-19 progression	525 (>99)	526 (>99)
Risk factors for COVID-19 progression		
Obesity (body mass index >30)[d]	330 (63)	341 (64)
Age ≥55 y	243 (46)	256 (48)
Diabetes requiring medication	119 (23)	109 (21)
Moderate to severe asthma[g]	90 (17)	88 (17)
Chronic obstructive pulmonary disease	34 (6)	27 (5)
Chronic kidney disease[h]	5 (<1)	8 (2)
Congestive heart failure (≥NYHA class II)[i]	4 (<1)	3 (<1)
No. of concurrent risk factors for COVID-19 progression		
0	3 (<1)	3 (<1)
1	290 (55)	304 (57)
2	178 (34)	153 (29)
≥3	57 (11)	69 (13)

Abbreviations: NYHA, New York Heart Association; RT-PCR, reverse transcriptase–polymerase chain reaction.

[a] Data are expressed as No. (%) unless otherwise indicated.

[b] Self-reported and not available for 1 patient in each treatment group.

[c] If a patient identified as multiracial, the terms *mixed White race*, *mixed Asian race*, or *mixed race* were used in accordance with regulatory guidance.

[d] Calculated as weight in kilograms divided by height in meters squared.

[e] Measured by the central laboratory. Data only reported for patients with an available value at baseline.

[f] Patient had a symptom duration of 6 days.

[g] Patients who required an inhaled corticosteroid to control symptoms or had been prescribed a course of oral corticosteroids within the past year.

[h] Defined as estimated glomerular filtration rate of less than 60 mL/min/1.73 m^2 by the Modification of Diet in Renal Disease equation.

[i] Functional classification based on physical activity limitations from class I (no limitation) to class IV (unable to perform any physical activity without discomfort).

Table 2. Primary and Secondary Efficacy Outcomes for the As-Randomized Population[a]

	Sotrovimab (n = 528)	Placebo (n = 529)	Absolute difference (95% CI), %[b]	Adjusted relative risk (95% CI)	*P* value[c]
Primary efficacy outcome, No. (%)[d]					
All-cause hospitalization lasting >24 h for acute illness management or death due to any cause through 29 d	6 (1)	30 (6)	-4.53 (-6.70 to -2.37)	0.21 (0.09 to 0.50)[e]	<.001
Components of the primary outcome, No. (%)					
All-cause hospitalization lasting >24 h for acute illness management	6 (1)	29 (5)			
Death due to any cause	0	2 (<1)[f]			
Secondary outcomes[g]					
Composite outcome of all-cause emergency department visit, hospitalization of any duration, or death due to any cause through 29 d, No. (%)	13 (2)	39 (7)	-4.91 (-7.50 to -2.32)	0.34 (0.19 to 0.63)	<.001
Change from baseline in viral load at 8 d, least-squares mean difference (95% CI), $\log_{10}$ copies/mL[h]	(n = 294) -2.589 (-2.708 to -2.470)	(n = 305) -2.357 (-2.475 to -2.240)	-0.232 (-0.399 to -0.065)[i]		.007
Progression to severe or critical respiratory COVID-19 through 29 d, No. (%)[j]	7 (1)	28 (5)	-3.97 (-6.11 to -1.82)	0.26 (0.12 to 0.59)	.002
Low-flow nasal cannula or face mask (severe)	7 (1)	12 (2)			
Nonrebreather mask, high-flow nasal cannula, or noninvasive ventilation (including CPAP support; severe)	0	10 (2)			
Mechanical ventilation or extracorporeal membrane oxygenation (critical)	0	4 (<1)			
Change from baseline in FLU-PRO Plus total score through 7 d, least-squares mean difference (95% CI)[k]	(n = 412) -3.05 (-3.27 to -2.83)	(n = 399) -1.98 (-2.20 to -1.76)	-1.07 (-1.38 to -0.76)[i]		<.001
All-cause mortality at 29 d, No. (%)	0	2 (<1)			

Abbreviations: CPAP, continuous positive airway pressure; FLU-PRO, Influenza Patient-Reported Outcome.

[a] Includes all randomized patients, irrespective of the treatment received. In the sotrovimab group, 515 patients (98%) were alive and not hospitalized at 29 days vs 494 patients (93%) in the placebo group. There were missing data for patients who withdrew from the study prior to day 29 and progression status was unknown for 7 (1%) in the sotrovimab group (included 4 patients who withdrew consent prior to treatment, 2 who were withdrawn due to physician decision prior to treatment, and 1 who withdrew consent on day 5 due to personal reasons) vs 5 (<1%) in the placebo group (included 2 patients who withdrew consent prior to treatment, 1 who withdrew consent on day 3, 1 who withdrew consent on day 15, and 1 who was withdrawn due to an adverse event of intermittent nausea on day 11).

[b] Unless otherwise indicated.

[c] Compares the preplanned analysis of adjusted relative risk.

[d] The absolute difference was calculated using Wald CI with missing data imputed as no COVID-19 progression. The adjusted relative risk used multiple imputation for missing data and adjusted for duration of symptoms (≤3 days vs 4-5 days), age (≤70 years vs >70 years), and sex (male vs female). Region was considered a priori as a covariate for progression outcomes. However, region was removed from the models (due to domination by North America for the interim analysis) to overcome convergence issues.

[e] For ease of comparison with the interim analysis, the adjusted relative risk was 0.15 (97.24% CI, 0.08 to 0.56).

[f] One patient died at home due to COVID-19 pneumonia without hospitalization and 1 patient died at the hospital due to pneumonia.

[g] Hierarchical statistical testing of the secondary outcomes was performed in order of presentation; this hierarchy was ordered based on descending order of importance to assess the effect of COVID-19 on health care use and patient outcomes.

[h] Evaluated in the virology population, which includes patients with a central laboratory–confirmed quantifiable baseline nasopharyngeal swab. Additional data at each time point appear in eTable 3 in Supplement 2.

[i] Least-squares mean difference (95% CI).

[j] Defined as a requirement for supplemental oxygen (severe disease) and mechanical ventilation (critical disease).

[k] Calculated as area under the curve through day 7 for patients with available data. The FLU-PRO Plus total score is an average of responses from the 32-item questionnaire, ranging from 0 (symptom-free) to 4 (very severe symptoms). There is no established minimal clinically important difference for the FLU-PRO Plus score in a COVID-19 population. This analysis includes all nonmissing total scores and a last observation carried forward imputation between day 2 and day 7 as appropriate. Additional data at each time point appear in eTable 3 in Supplement 2.

Table 3. Exploratory Outcomes Through Day 29 for the As-Randomized Population

	No. (%)	
	Sotrovimab (n = 528)	Placebo (n = 529)
Hospital length of stay		
0 d	521 (99)	499 (94)
≤24 h	1 (<1)	0
1-≤8 d	3 (<1)	19 (4)
9-≤15 d	2 (<1)	3 (<1)
16-≤22 d	1 (<1)	4 (<1)
23-≤29 d	0	4 (<1)
Intensive care unit length of stay, d		
0	528 (100)	519 (98)
1-≤8	0	2 (<1)
9-≤15	0	3 (<1)
16-≤22	0	2 (<1)
23-≤29	0	3 (<1)
Duration of mechanical ventilation, d		
0	528 (100)	523 (99)
1-≤8	0	0
9-≤15	0	2 (<1)
16-≤22	0	3 (<1)
23-≤29	0	1 (<1)
Nasal SARS-CoV-2 viral detection[a]		
At 8 d	(n = 59)	(n = 68)
Positive	19 (32)	27 (40)
Negative	36 (61)	39 (57)
Inconclusive	4 (7)	2 (3)
At 29 d	(n = 68)	(n = 77)
Positive	3 (4)	5 (6)
Negative	64 (94)	72 (94)
Inconclusive	1 (1)	0

[a] Assessed with reverse transcriptase–polymerase chain reaction test.

All systemic infusion-related reactions were grade 1 or 2 and clinically manageable. Changes in laboratory parameters and vital signs were consistent with underlying disease and similar in both treatment groups.

Discussion

In this phase 3, double-blind, placebo-controlled, multicenter randomized clinical trial that evaluated the efficacy and adverse effects of a single 500-mg intravenous dose of sotrovimab in high-risk patients with mild to moderate COVID-19, the primary outcome, a composite of all-cause hospitalization or death, was significantly reduced with sotrovimab. The reduction in the proportion of patients who progressed to hospitalization or died through day 29 was consistent with the magnitude of effect observed for the primary outcome at the interim analysis of this trial.[14] Sotrovimab was well tolerated and there was a low rate of adverse events. The results did not suggest antibody-dependent enhancement with sotrovimab because worsening of disease with sotrovimab vs placebo was not observed.[21]

In this final as-randomized analysis, hierarchical statistical testing was performed on the 5 key secondary outcomes. Four secondary outcomes were found to be statistically significant (Table 2). However, a formal analysis could not be performed for the fifth outcome, all-cause mortality through day 29, due to a lower number of anticipated deaths. Statistical testing of these secondary outcomes supports the findings previously published for the 3 clinical key secondary outcomes.[14] Specifically, no patients treated with sotrovimab required high-flow oxygen, oxygen via a nonrebreather mask, or mechanical ventilation through day 29. Among those who were hospitalized, no patients who received sotrovimab required admission to the intensive care unit compared with 9 patients who received placebo, raising a possibility that sotrovimab may prevent more severe complications of COVID-19 in addition to preventing the need for hospitalization.

Even though sotrovimab also significantly reduced viral load at day 8 (consistent with the drug's mode of action comprising virus neutralization and Fc-mediated effector function), the magnitude of these reductions was modest. These data suggest that nasopharyngeal viral load changes alone may

Table 4. Summary of Adverse Events for the As-Treated Population[a]

	No. (%)	
	Sotrovimab (n = 523)	Placebo (n = 526)
Any adverse event	114 (22)	123 (23)
Related to study treatment[b]	8 (2)	9 (2)
Leading to permanent discontinuation of study treatment	0	0
Leading to dose interruption or delay	2 (<1)[c]	0
Any systemic infusion-related reaction[d]	6 (1)	6 (1)
Related to study treatment[b]	0	3 (<1)
Leading to permanent discontinuation of study treatment	0	0
Leading to dose interruption or delay	0	0
Any grade 3 or 4 adverse event[e]	15 (3)	36 (7)
Any serious adverse event[f]	11 (2)	32 (6)
Related to study treatment[b]	0	2 (<1)
Fatal	0	4 (<1)[g]
Related to study treatment[b]	0	0
Most common adverse events (≥1% of patients in either group)		
Diarrhea	8 (2)	4 (<1)
COVID-19 pneumonia	5 (<1)	22 (4)
Nausea	5 (<1)	9 (2)
Headache	4 (<1)	11 (2)

[a] Includes all patients who received the study treatment and were analyzed according to the treatment received. One patient randomized to placebo received sotrovimab and was included in the sotrovimab group in the as-treated population but in the placebo group in the as-randomized population; this patient had no adverse events or hospitalizations. There was no imputation for missing data.

[b] Relatedness was determined by individual study investigators while blinded to study treatment.

[c] For both patients, the adverse event was infusion extravasation; both infusions were completed.

[d] Defined as adverse events that included the preferred terms of pyrexia, chills, dizziness, dyspnea, pruritus, rash, and infusion-related reaction within 24 hours of study drug administration.

[e] Determined using version 2.1 of the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. Severity grade was assessed on a scale of 1 to 4; with higher numbers indicating more serious events.

[f] Defined as any adverse event that resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, or resulted in persistent or significant disability or incapacity. In addition, there were possible Hy Law cases (alanine transaminase ≥3 times upper limit of normal or total bilirubin ≥2 times upper limit of normal) and patients with international normalized ratios greater than 1.5 considered to be serious adverse events.

[g] Two occurred prior to day 29 and 2 after day 29. Two of these deaths were classified as due to COVID-19 pneumonia, 1 as pneumonia, and 1 as respiratory failure.

not be a strong predictor of clinical disease course with sotrovimab treatment. This finding is consistent with the lack of evidence indicating that antiviral activity in the lung can be accurately measured with a nasopharyngeal RT-PCR test due to the anatomical site and the fact that viral RNA may persist in the absence of replication-competent virus.[22,23]

From the patient perspective, improvements in symptoms of COVID-19 were reported, with mean decreases in FLU-PRO Plus total score through day 7 that were significantly greater in the sotrovimab group compared with the placebo group. Together, the nonclinical secondary outcome results support the primary outcome results for hospitalization and death.

This trial was powered to evaluate the pandemic-relevant clinical outcome of COVID-19 progression in high-risk patients. Two or more risk factors for COVID-19 progression were present in 43% of patients, and viral load at baseline was consistent with previously reported data for other anti-SARS-CoV-2 monoclonal antibodies.[24,25] In addition, 65% of the patients in this trial identified themselves as Latinx, a population that has been disproportionately affected by COVID-19 and historically underrepresented in clinical trials.[26-29]

Limitations

This trial has several limitations. First, given the efficacy of sotrovimab, a small number of COVID-19 progression events for the primary and clinical secondary outcomes were reported in patients who were randomized to sotrovimab. As a result, it is challenging to determine the patient or disease characteristics associated with COVID-19 progression in sotrovimab-treated patients.

Second, the moderate size of the as-treated population limits the ability to detect rare adverse events.

Third, the study enrolled patients over approximately 6 months, representing a finite period of the pandemic. As a result, the complete picture of viral sequencing and clinical experience with sotrovimab for variants of concern is unknown. Despite this, sotrovimab targets a conserved viral epitope, and thus it is hypothesized that sotrovimab may remain effective against these variants.[12,30-32]

Conclusions

Among nonhospitalized patients with mild to moderate COVID-19 and at risk of disease progression, a single intravenous dose of sotrovimab, compared with placebo, significantly reduced the risk of a composite end point of all-cause hospitalization or death through day 29. The findings support sotrovimab as a treatment option for nonhospitalized, high-risk patients with mild to moderate COVID-19, although efficacy against SARS-CoV-2 variants that have emerged since the study was completed is unknown.

ARTICLE INFORMATION

Accepted for Publication: February 14, 2022.

Published Online: March 14, 2022. doi:10.1001/jama.2022.2832

Author Affiliations: Albion Finch Medical, William Osler Health Centre, Toronto, Ontario, Canada (Gupta); Optimus U Corp, Miami, Florida (Gonzalez-Rojas); Florida International Medical Research, Miami (Juarez); Álvaro Cunqueiro Hospital, IIS Galicia Sur, Vigo, Pontevedra, Spain (Crespo Casal); Pines Care Research Center, Pembroke Pines, Florida (Moya); Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil (Rodrigues Falci); Sarkis Clinical Trials, Gainesville, Florida (Sarkis); Centex Studies, McAllen, Texas (Solis); Vir Biotechnology Inc, San Francisco, California (Zheng, Cathcart, Parra, Sager, Alexander, Yeh, Aldinger); GlaxoSmithKline, Brentford, England (Scott, Austin); GlaxoSmithKline, Cambridge, Massachusetts (Peppercorn); Central Texas Clinical Research, Austin (Brinson); Departments of Global Health and Medicine, University of Washington, Seattle (Shapiro); Fred Hutchinson Cancer Research Center, Seattle, Washington (Shapiro).

Author Contributions: Dr Shapiro had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Sarkis, Zheng, Scott, Cathcart, Sager, Austin, Peppercorn, Alexander, Yeh, Aldinger.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Juarez, Rodrigues Falci, Sarkis, Zheng, Parra, Sager, Austin, Alexander, Yeh, Brinson, Shapiro.
Critical revision of the manuscript for important intellectual content: Gupta, Gonzalez-Rojas, Juarez, Crespo Casal, Moya, Rodrigues Falci, Sarkis, Solis, Zheng, Scott, Cathcart, Parra, Peppercorn, Alexander, Yeh, Aldinger, Shapiro.
Statistical analysis: Gupta, Gonzalez-Rojas, Moya, Zheng, Scott.
Administrative, technical, or material support: Cathcart, Austin, Yeh.
Supervision: Juarez, Crespo Casal, Sarkis, Solis, Alexander, Yeh, Aldinger, Shapiro.

Conflict of Interest Disclosures: Dr Gupta reported acting as a trial investigator for Vir Biotechnology and receiving nonfinancial support from Vir Biotechnology during the conduct of the study and serving as a consultant to GlaxoSmithKline, which co-funded the development of sotrovimab. Drs Gonzalez-Rojas, Juarez, Crespo Casal, Moya, and Solis reported acting as trial investigators for Vir Biotechnology and receiving nonfinancial support from Vir Biotechnology during the conduct of the study. Dr Rodrigues Falci reported receiving personal fees and nonfinancial support from Pfizer and United Medical; receiving nonfinancial support from Gilead Sciences and Merck Sharp & Dohme; and receiving personal fees from GlaxoSmithKline outside the submitted work. Dr Sarkis reported receiving research support from AbbVie, Eli Lilly, GlaxoSmithKline, Otsuka, Vir Biotechnology, Eisai, and Ironshore and serving on speaker bureaus for Janssen, Teva, and AbbVie. Drs Zheng, Parra, Sager, Alexander, Yeh, and Aldinger are employees of Vir Biotechnology and reported stock ownership in Vir Biotechnology and third-party funding from GlaxoSmithKline to Vir Biotechnology for the submitted work. Ms Scott and Drs Austin and Peppercorn are employees of GlaxoSmithKline and reported stock ownership in GlaxoSmithKline. Dr Cathcart is an employee of Vir Biotechnology; reported stock ownership in Vir Biotechnology and third-party funding from GlaxoSmithKline to Vir Biotechnology for the submitted work; and reported stock ownership in Gilead Sciences. Dr Brinson reported acting as a trial investigator for Vir Biotechnology and receiving nonfinancial support from Vir Biotechnology during the conduct of the study and receiving personal fees from Gilead Sciences and ViiV Healthcare for serving on advisory boards and speakers bureaus. Dr Shapiro reported acting as a trial investigator for Vir Biotechnology and receiving nonfinancial support from Vir Biotechnology during the conduct of the study and receiving grants from the National Institute of Allergy and Infectious Diseases. No other disclosures were reported.

Funding/Support: This study was sponsored by Vir Biotechnology Inc in collaboration with GlaxoSmithKline.

Role of the Funder/Sponsor: The sponsors designed the trial and were involved in the conduct of the trial, data collection, management, analysis, and interpretation; participated in the preparation and review of the manuscript; but did not have the right to veto publication. The authors selected the journal and made the decision to submit the manuscript for publication.

Group Information: A list of the COMET-ICE Investigators appears in Supplement 3.

Data Sharing Statement: See Supplement 4.

Additional Contributions: We thank Courtney St Amour, PhD (Cello Health Communications/SciFluent), for medical writing support, which was funded by Vir Biotechnology Inc and GlaxoSmithKline. We also thank Krystyna Grycz, BA, Jordan Clark, BS, and Minnie Kuo, MS (all 3 employed by Vir Biotechnology Inc), for clinical operations support. These individuals were compensated as part of their normal salaries.

REFERENCES

1. World Health Organization. WHO coronavirus (COVID-19) dashboard. Accessed January 3, 2022. https://covid19.who.int

2. SeyedAlinaghi S, Afsahi AM, MohsseniPour M, et al. Late complications of COVID-19; a systematic review of current evidence. *Arch Acad Emerg Med*. 2021;9(1):e14.

3. Gao Y-D, Ding M, Dong X, et al. Risk factors for severe and critically ill COVID-19 patients: a review. *Allergy*. 2021;76(2):428-455. doi:10.1111/all.14657

4. US Centers for Disease Control and Prevention. SARS-CoV-2 variant classifications and definitions. Accessed January 13, 2022. https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html

5. Lustig Y, Zuckerman N, Nemet I, et al. Neutralising capacity against Delta (B.1.617.2) and other variants of concern following Comirnaty (BNT162b2, BioNTech/Pfizer) vaccination in health care workers, Israel. *Euro Surveill*. 2021;26(26):2100557. doi:10.2807/1560-7917.ES.2021.26.26.2100557

6. National Institutes of Health. Coronavirus disease 2019 (COVID-19) treatment guidelines. Accessed January 28, 2022. https://www.covid19treatmentguidelines.nih.gov

7. Pinto D, Park YJ, Beltramello M, et al. Cross-neutralization of SARS-CoV-2 by a human monoclonal SARS-CoV antibody. *Nature*. 2020;583(7815):290-295. doi:10.1038/s41586-020-2349-y

8. Gaudinski MR, Coates EE, Houser KV, et al; VRC 606 Study Team. 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. doi:10.1371/journal.pmed.1002493

9. 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;31(6):e2231. doi:10.1002/rmv.2231

10. 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(4):100255. doi:10.1016/j.xcrm.2021.100255

11. Liu H, Wei P, Zhang Q, et al. 501Y.V2 and 501Y.V3 variants of SARS-CoV-2 lose binding to bamlanivimab in vitro. *MAbs*. 2021;13(1):1919285. doi:10.1080/19420862.2021.1919285

12. US Food and Drug Administration. Fact sheet for healthcare providers emergency use authorization (EUA) of sotrovimab. Accessed February 10, 2022. https://www.fda.gov/media/149534/download

13. Lempp FA, Soriaga LB, Montiel-Ruiz M, et al. Lectins enhance SARS-CoV-2 infection and influence neutralizing antibodies. *Nature*. 2021;598(7880):342-347. doi:10.1038/s41586-021-03925-1

14. Gupta A, Gonzalez-Rojas Y, Juarez E, et al; COMET-ICE Investigators. Early treatment for Covid-19 with SARS-CoV-2 neutralizing antibody sotrovimab. *N Engl J Med*. 2021;385(21):1941-1950. doi:10.1056/NEJMoa2107934

15. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D; Modification of Diet in Renal Disease Study Group. A more accurate method to estimate glomerular filtration rate from serum creatinine:

a new prediction equation. *Ann Intern Med*. 1999;130(6):461-470. doi:10.7326/0003-4819-130-6-199903160-00002

16. US Food and Drug Administration. COVID-19: developing drugs and biological products for treatment or prevention. Published February 2021. Accessed September 17, 2021. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/covid-19-developing-drugs-and-biological-products-treatment-or-prevention

17. Han A, Poon JL, Powers JH III, Leidy NK, Yu R, Memoli MJ. Using the Influenza Patient-Reported Outcome (FLU-PRO) diary to evaluate symptoms of influenza viral infection in a healthy human challenge model. *BMC Infect Dis*. 2018;18(1):353. doi:10.1186/s12879-018-3220-8

18. Stokes EK, Zambrano LD, Anderson KN, et al. Coronavirus disease 2019 case surveillance—United States, January 22-May 30, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(24):759-765. doi:10.15585/mmwr.mm6924e2

19. Lan KK, DeMets D. Discrete sequential boundaries for clinical trials. *Biometrika*. 1983;70(3):659-663. doi:10.2307/2336502

20. Hwang IK, Shih WJ, De Cani JS. Group sequential designs using a family of type I error probability spending functions. *Stat Med*. 1990;9(12):1439-1445. doi:10.1002/sim.4780091207

21. Arvin AM, Fink K, Schmid MA, et al. A perspective on potential antibody-dependent enhancement of SARS-CoV-2. *Nature*. 2020;584(7821):353-363. doi:10.1038/s41586-020-2538-8

22. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. *JAMA*. 2020;324(8):782-793. doi:10.1001/jama.2020.12839

23. Zheng S, Fan J, Yu F, et al. Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January-March 2020: retrospective cohort study. *BMJ*. 2020;369:m1443. doi:10.1136/bmj.m1443

24. Fajnzylber J, Regan J, Coxen K, et al; Massachusetts Consortium for Pathogen Readiness. SARS-CoV-2 viral load is associated with increased disease severity and mortality. *Nat Commun*. 2020;11(1):5493. doi:10.1038/s41467-020-19057-5

25. Chen P, Nirula A, Heller B, et al; BLAZE-1 Investigators. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with Covid-19. *N Engl J Med*. 2021;384(3):229-237. doi:10.1056/NEJMoa2029849

26. Riley AR, Chen YH, Matthay EC, et al. Excess mortality among Latino people in California during the COVID-19 pandemic. *SSM Popul Health*. 2021;15:100860. doi:10.1016/j.ssmph.2021.100860

27. Flores LE, Frontera WR, Andrasik MP, et al. Assessment of the inclusion of racial/ethnic minority, female, and older individuals in vaccine clinical trials. *JAMA Netw Open*. 2021;4(2):e2037640. doi:10.1001/jamanetworkopen.2020.37640

28. Craft JF, Travassos MA, Foppiano Palacios C, Openshaw JJ. Inadequate minority representation within SARS-CoV-2 vaccine trials. *Am J Trop Med Hyg*. 2021;104(1):32-34. doi:10.4269/ajtmh.20-1294

29. Cervantes L, Martin M, Frank MG, et al. Experiences of Latinx individuals hospitalized for COVID-19: a qualitative study. *JAMA Netw Open*. 2021;4(3):e210684. doi:10.1001/jamanetworkopen.2021.0684

30. National Institutes of Health. OpenData Portal: SARS-CoV-2 variants and therapeutics. Updated February 3, 2022. Accessed February 10, 2022. https://opendata.ncats.nih.gov/variant/activity

31. Cameroni E, Bowen JE, Rosen LE, et al. Broadly neutralizing antibodies overcome SARS-CoV-2 Omicron antigenic shift. *Nature*. Published online December 23, 2021. doi:10.1038/s41586-021-04386-2

32. VanBlargan LA, Errico JM, Halfmann PJ, et al. An infectious SARS-CoV-2 B.1.1.529 Omicron virus escapes neutralization by therapeutic monoclonal antibodies. *Nat Med*. Published online January 19, 2022. doi:10.1038/s41591-021-01678-y