Annals of Internal Medicine ORIGINAL RESEARCH

Safety and Efficacy of Combination SARS-CoV-2 Neutralizing Monoclonal Antibodies Amubarvimab Plus Romlusevimab in Nonhospitalized Patients With COVID-19

Teresa H. Evering, MD, MS*; Kara W. Chew, MD, MS*; Mark J. Giganti, PhD; Carlee Moser, PhD; Mauricio Pinilla, MS; David Alain Wohl, MD; Judith S. Currier, MD, MSc; Joseph J. Eron, MD; Arzhang Cyrus Javan, MD, MPH, DTM&H; Rachel Bender Ignacio, MD, MPH; David Margolis, MD, MPH; Qing Zhu, PhD; Ji Ma, PhD; Lijie Zhong, PhD, MBA; Li Yan, MD, PhD; Ulises D'Andrea Nores, MD; Keila Hoover, MD; Bharat Mocherla, MD; Manish C. Choudhary, PhD; Rinki Deo, PhD; Justin Ritz, MS; William A. Fischer, MD; Courtney V. Fletcher, PharmD; Jonathan Z. Li, MD, MMSc; Michael D. Hughes, PhD; Davey Smith, MD*; and Eric S. Daar, MD*; for the ACTIV-2/A5401 Study Team†

Background: Development of safe and effective SARS-CoV-2 therapeutics is a high priority. Amubarvimab and romlusevimab are noncompeting anti–SARS-CoV-2 monoclonal antibodies with an extended half-life.

Objective: To assess the safety and efficacy of amubarvimab plus romlusevimab.

Design: Randomized, placebo-controlled, phase 2 and 3 platform trial. (ClinicalTrials.gov: NCT04518410)

Setting: Nonhospitalized patients with COVID-19 in the United States, Brazil, South Africa, Mexico, Argentina, and the Philippines.

Patients: Adults within 10 days onset of symptomatic SARS-CoV-2 infection who are at high risk for clinical progression.

Intervention: Combination of monoclonal antibodies amubarvimab plus romlusevimab or placebo.

Measurements: Nasopharyngeal and anterior nasal swabs for SARS-CoV-2, COVID-19 symptoms, safety, and progression to hospitalization or death.

Results: Eight-hundred and seven participants who initiated the study intervention were included in the phase 3 analysis. Median age was 49 years (quartiles, 39 to 58); 51% were female, 18% were Black, and 50% were Hispanic or Latino. Median time from symptom onset at study entry was 6 days (quartiles, 4 to 7). Hospitalizations and/or death occurred in 9 (2.3%) participants in the amubarvimab plus romlusevimab group compared with 44 (10.7%) in the placebo group, with an estimated 79% reduction in events ($P < 0.001$). This reduction was similar between participants with 5 or less and more than 5 days of symptoms at study entry. Grade 3 or higher treatment-emergent adverse events through day 28 were seen less frequently among participants randomly assigned to amubarvimab plus romlusevimab (7.3%) than placebo (16.1%) ($P < 0.001$), with no severe infusion reactions or drug-related serious adverse events.

Limitation: The study population was mostly unvaccinated against COVID-19 and enrolled before the spread of Omicron variants and subvariants.

Conclusion: Amubarvimab plus romlusevimab was safe and significantly reduced the risk for hospitalization and/or death among nonhospitalized adults with mild to moderate SARS-CoV-2 infection at high risk for progression to severe disease.

Primary Funding Source: National Institute of Allergy and Infectious Diseases of the National Institutes of Health.

Ann Intern Med. doi:10.7326/M22-3428 **Annals.org**
For author, article, and disclosure information, see end of text.
This article was published at Annals.org on 18 April 2023.
* Drs. Evering, Chew, Smith, and Daar contributed equally to this work.
† For members of the ACTIV-2/A5401 Study Team, see the **Supplement** (available at Annals.org).

The COVID-19 pandemic caused by SARS-CoV-2 is ongoing, and the emergence of new variants has affected the activity of monoclonal antibody (mAb) regimens (1). Research evaluating safe and effective treatments to prevent progression to hospitalization and/or death has resulted in U.S. Food and Drug Administration (FDA) emergency use authorization (EUA) for several mAbs and direct-acting antivirals (2–8). However, 4 mAb EUAs have been withdrawn or limited because of reduced in vitro susceptibility to new variants (2, 9–11).

Amubarvimab (BRII-196) and romlusevimab (BRII-198) are recombinant human IgG1 mAbs derived from convalesced patients who had COVID-19 (Brii Biosciences, Tsinghua University, and Third People's Hospital of Shenzhen) (12, 13). They are directed against conserved, nonoverlapping epitopes in receptor-binding domain of SARS-CoV-2 spike protein with complementary neutralizing effects in vitro (12, 13). Activity against the Omicron variant (B.1.1.529) is predicted by in vitro studies (14), with live virus data suggesting efficacy against subvariants BA.4 and BA.5 (15). Both mAbs have a triple amino acid substitution, M257Y/S259T/T261E, in the fragment crystallizable region to prolong the half-life (16, 17) and reduce binding activity against Fcγ receptors, potentially minimizing risk for antibody-dependent enhancement (12, 13). Phase 1 studies investigating the safety, tolerability, and pharmacokinetics of intravenous amubarvimab (NCT04479631) and romlusevimab (NCT04479644) (12, 13) supported further clinical evaluation (18). We report the results of a phase 2 and 3 trial of amubarvimab plus

See also:

Web-Only
Supplement

romlusevimab in nonhospitalized persons with mild to moderate COVID-19 at high risk for progression to severe disease.

METHODS

Trial Design and Oversight

ACTIV-2/A5401 (Adaptive Platform Treatment Trial for Outpatients With COVID-19) is an ongoing, multinational, randomized controlled, blinded platform trial designed to evaluate safety and efficacy of investigational agents for treatment of nonhospitalized adults with mild to moderate COVID-19. The protocol was approved by a central institutional review board, Advarra (Pro00045266) for U.S. sites (with additional local institutional review board approval as required), and by local ethics committees for non-U.S. sites. All participants provided written informed consent before undergoing study procedures.

The study included a phase 2 evaluation with prespecified "graduation analysis" to determine if investigational agents would proceed to phase 3 (details provided in the protocol, available at Annals.org). An independent data safety and monitoring board (DSMB) reviewed the study during both phase 2 and 3. For the phase 3 portion of the trial, unless otherwise recommended by the DSMB, 3 interim reviews were planned to occur after 25%, 50%, and 75% of the planned enrollment had completed 28 days of follow-up. The O'Brien and Fleming stopping guideline for efficacy and the gamma (-2) spending function for evaluating futility were implemented using the Lan–DeMets spending function approach to allow for flexibility in the timing or number of interim analyses (19). Additional details regarding stopping guidelines for efficacy and timing of interim efficacy analyses are included in section 10 of the protocol and the statistical analysis plan (available at Annals.org). The first 2 interim analyses occurred as planned. However, there was a surge in enrollment such that the second review occurred after the planned enrollment for the study had been met. On request of the DSMB, the third DSMB interim review occurred 2 weeks later. At this review, the DSMB concluded that there was overwhelming evidence of benefit and recommended early release of results while continuing blinded follow-up of all participants.

Participants and Procedures

Participants were nonhospitalized adults, aged 18 years or older, and at high risk for progression to severe COVID-19 (defined in the **Supplement**, available at Annals.org). All participants had a positive molecular or antigen SARS-CoV-2 test result from the upper respiratory tract, and with 1 exception, were randomly assigned within 10 days of symptom onset. Inclusion and exclusion criteria are in the **Supplement** and protocol.

Participants were randomly assigned 1:1 to amubarvimab plus romlusevimab or placebo in both phase 2 and 3 portions of the study, with phase 2 participants included in the phase 3 study population. In this platform trial, phase 2 included the possibility of the control group including placebos for other agents concurrently studied in phase 2 (that is, pooled or shared placebo). Randomization was stratified by time from symptom onset (≤5 or >5 days). Details about randomization are in the **Supplement**.

The study intervention was administered as sequential intravenous infusions of 1000 mg of amubarvimab followed by 1000 mg of romlusevimab, or equivalent volumes of saline placebo (or pooled placebo for other agents), each infused over at least 25 minutes each on study day 0. Participants were monitored for 2 hours after infusion. A detailed schedule of assessments for phase 2 and 3 portions of trial are described in the protocol.

Study Objectives and Outcome Measures

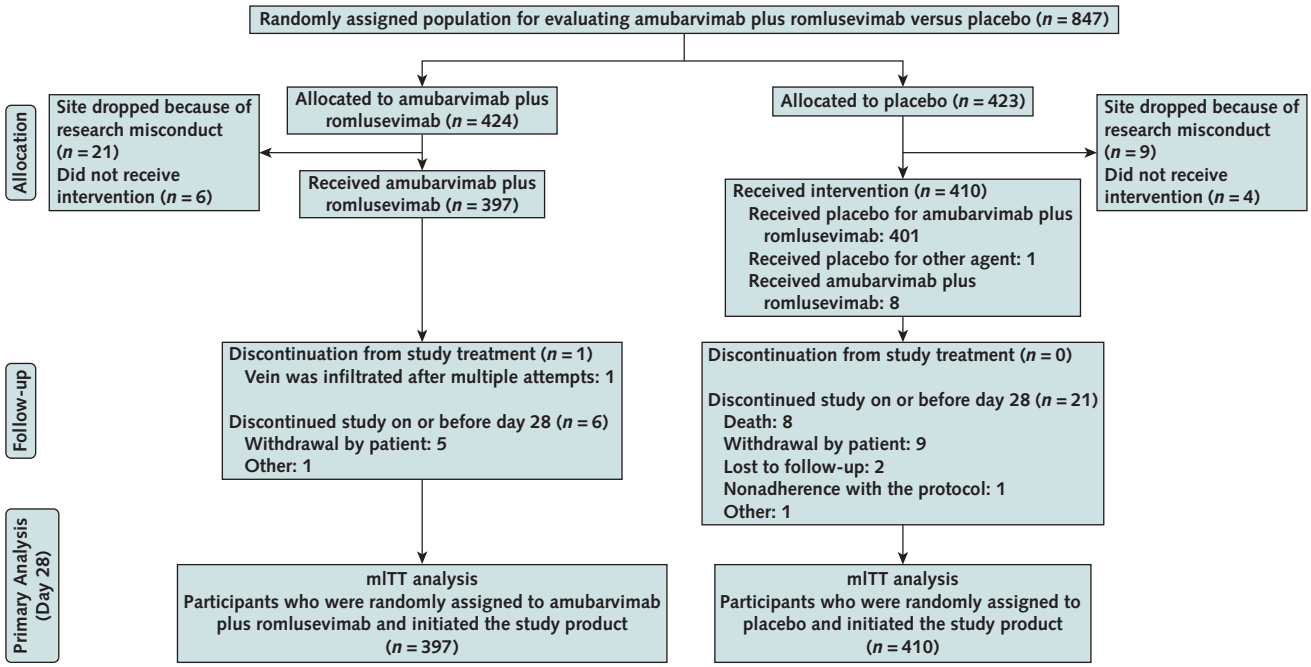
The primary outcomes for the phase 3 portion of the trial were all-cause hospitalization and/or death through study day 28 and grade 3 or higher treatment-emergent adverse events (TEAEs). Treatment-emergent adverse events of special interest included infusion reactions or allergic reactions occurring within 12 hours of infusion. Secondary symptom-related outcome measures included time to sustained symptom improvement (defined both as days from study entry to the first of 2 consecutive days with all symptoms improved or resolved and as the first of 4 consecutive days when all symptoms are scored as absent); time to self-reported return to usual health (defined as the number of days from start of investigational agents until the first of 2 consecutive days that a participant reported return to usual "pre–COVID-19" health); severity ranking (based on time-averaged total symptom scores through day 28); and progression through day 28 of 1 or more COVID-19–associated symptoms to a worse status than recorded in the study diary at study entry, before the start of the investigational agent or comparator intervention. All measures were based on a daily symptom diary completed by participants through day 28. Other key secondary outcomes were proportion of participants with SARS-CoV-2 RNA below the lower limit of quantification (LLoQ), quantitative SARS CoV-2 RNA levels and area under curve (AUC) of anterior nasal swabs collected by participants at days 0, 3, 7, 14, and 28. Methods for quantitative SARS-CoV-2 RNA measurement, SARS-CoV-2 variant determination, and symptom diary assessments are provided in the **Supplement**. Similar virologic outcomes were assessed from site-collected nasopharyngeal swabs during the phase 2 portion of the study.

Statistical Analysis

Analyses were restricted to the modified intention-to-treat population, defined as participants who initiated the study intervention. Except for descriptive safety summaries, participants were summarized according to the treatment to which they were randomly assigned. All analyses were done on data entered by time of data freeze on 2 June 2022.

The primary composite clinical end point of hospitalization and/or death during the first 28 days of follow-up was estimated for each randomized group using Kaplan–Meier methods. The difference between groups in estimated log cumulative proportion was calculated, and variance for this difference was obtained using the Greenwood formula (20). Two-sided 95% CIs and associated *P* value for the test of no difference between groups were obtained.

Figure 1. CONSORT flow diagram.



In this platform trial, participants randomly assigned to a placebo for other agents in phase 2 evaluation may be included in the control group for evaluating amubarvimab plus romlusevimab during phase 2. For amubarvimab plus romlusevimab, there was only 1 participant in the randomized population who received placebo corresponding to a different agent. The safety analysis population included 405 participants who initiated amubarvimab plus romlusevimab (including 8 randomly assigned to placebo) and 402 who initiated placebo. Details of the screened population are not shown in the CONSORT diagram, as screening was broad for evaluating multiple investigational agents in parallel and not specific to each agent. CONSORT = Consolidated Standards of Reporting Trials; mITT = modified intention to treat.

The primary safety end point was the proportion experiencing a grade 3 or higher TEAE by study day 28 between randomized groups using log-binomial regression and summarized with a risk ratio, corresponding 95% CI, and *P* value based on the Wald test. A descriptive comparison between study groups (defined by actual treatment received) of all TEAEs through day 28 was also done.

The time to sustained symptom improvement and return to usual health were compared between groups using the Gehan–Wilcoxon test. Symptom severity ranking and risk for symptom progression were compared between groups using a Wilcoxon test and a χ^2 test, respectively.

The proportion of participants with SARS-CoV-2 RNA below LLoQ was compared between groups across study visits using Poisson regression with robust variance adjusted for baseline (day 0) $\log_{10}$ transformed SARS-CoV-2 RNA level and summarized with a risk ratio and 95% CI at each study visit, and a Wald test across the multiple times. Quantitative SARS-CoV-2 RNA levels were compared between groups using Wilcoxon rank-sum tests, separately at each post-entry study visit, without adjustment for baseline value. Participant-specific AUCs were compared between groups using a Wilcoxon test.

All statistical tests used a 2-sided 5% significance level. Statistical analyses were done with SAS, version 9.4 (SAS Institute). The complete ACTIV-2 statistical analysis plan is provided.

Role of the Funding Source

The funding source had representatives on the study team and were involved in protocol development, study conduct, and analysis of the data.

RESULTS

Study Population

A total of 847 participants were randomly assigned between January and July 2021, after which enrollment was stopped due to meeting the target. The exclusion of 30 participants from 2 sites with data integrity issues and 10 who did not receive the study intervention resulted in 807 who received the intervention and were included in the modified intention-to-treat analysis (**Figure 1**). Participants were enrolled from 6 countries; 397 were randomly assigned to amubarvimab plus romlusevimab and 410 to placebo (including 1 who received placebo for another agent). Eight participants randomly assigned to placebo received amubarvimab plus romlusevimab, and 7 randomly assigned to study drugs and 21 to placebo stopped treatment or discontinued study on or before day 28.

The phase 3 population included 221 participants enrolled in the phase 2 portion of the trial, all in the United States (**Appendix Table 1**, available at Annals.org). Baseline characteristics of phase 3 participants are described in **Table 1**. Median age of participants was

Table 1. Phase 3 Baseline Characteristics (Modified Intention-to-Treat Analysis Group)

Characteristic	Amubarvimab Plus Romlusevimab (*n* = 397)	Placebo (*n* = 410)	Total (*n* = 807)
Median age (Q1–Q3), *y*	48 (39–58)	50 (39–59)	49 (39–58)
Age category, *n* (%)			
<60 y	313 (78.8)	314 (76.6)	627 (77.7)
≥60 y	84 (21.2)	96 (23.4)	180 (22.3)
Country, *n* (%)			
Argentina	49 (12.3)	49 (12.0)	98 (12.1)
Brazil	15 (3.8)	18 (4.4)	33 (4.1)
Mexico	3 (0.8)	2 (0.5)	5 (0.6)
Philippines	0	1 (0.2)	1 (0.1)
South Africa	72 (18.1)	59 (14.4)	131 (16.2)
United States	258 (65.0)	281 (68.5)	539 (66.8)
Sex at birth, *n* (%)			
Male	198 (49.9)	200 (48.8)	398 (49.3)
Female	199 (50.1)	210 (51.2)	409 (50.7)
Gender identity, *n* (%)			
Male	198 (49.9)	199 (48.5)	397 (49.2)
Female	199 (50.1)	209 (51.0)	408 (50.6)
Transgender male	0	1 (0.2)	1 (0.1)
Transgender female	0	1 (0.2)	1 (0.1)
Race, *n* (%)			
Asian	15 (3.8)	22 (5.4)	37 (4.6)
American Indian	0	1 (0.2)	1 (0.1)
Black/African American	79 (19.9)	62 (15.1)	141 (17.5)
Multiple	4 (1.0)	2 (0.5)	6 (0.7)
Native Hawaiian or Pacific Islander	1 (0.3)	1 (0.2)	2 (0.2)
White	284 (71.5)	307 (74.9)	591 (73.2)
Other	14 (3.5)	15 (3.7)	29 (3.6)
Ethnicity, *n* (%)			
Hispanic or Latino	200 (50.4)	204 (49.8)	404 (50.1)
Not Hispanic or Latino	197 (49.6)	206 (50.2)	403 (49.9)
Median baseline body mass index (Q1–Q3), *kg/m²**	29.5 (25.8–35.2)	30.0 (26.1–36.1)	29.7 (26.0–35.7)
Time from symptom onset			
≤5 d, *n* (%)	195 (49.1)	200 (48.8)	395 (48.9)
>5 d, *n* (%)	202 (50.9)	210 (51.2)	412 (51.1)
Median (Q1–Q3)	6.0 (4.0–7.0)	6.0 (4.0–7.0)	6.0 (4.0–7.0)
Risk factors for progression, *n* (%)			
Hypertension	148 (37.3)	140 (34.1)	288 (35.7)
Current smoker	123 (31.0)	127 (31.0)	250 (31.0)
Obesity (body mass index >35 kg/m^2)	98 (24.7)	113 (27.6)	211 (26.1)
Age ≥60 y†	72 (18.1)	75 (18.3)	147 (18.2)
Diabetes mellitus	57 (14.4)	53 (12.9)	110 (13.6)
Chronic lung disease	43 (10.8)	59 (14.4)	102 (12.6)
Cardiovascular disease	11 (2.8)	21 (5.1)	32 (4.0)
Immunosuppressed‡	9 (2.3)	6 (1.5)	15 (1.9)
Active cancer (other than localized skin)	3 (0.8)	6 (1.5)	9 (1.1)
History of cirrhosis	3 (0.8)	0	3 (0.4)
Chronic kidney disease	1 (0.3)	1 (0.2)	2 (0.2)
Moderate to severe asthma	0	0	0
COVID-19 vaccination, *n* (%)	28 (7.1)	38 (9.3)	66 (8.2)
U.S. participants with variant data, *n*	190	211	401
Delta, *n* (%)	37 (19.5)	52 (24.6)	89 (22.2)
Non-Delta, *n* (%)§	153 (80.5)	159 (75.4)	312 (77.8)

Continued on following page

Table 1–Continued

Characteristic	Amubarvimab Plus Romlusevimab (*n* = 397)	Placebo (*n* = 410)	Total (*n* = 807)
Participants with antinucleocapsid data, *n*	369	370	739
Positive, *n* (%)	96 (26)	115 (31)	211 (29)
Participants with antispike data, *n*	370	372	742
Positive, *n* (%)	158 (43)	166 (45)	324 (44)

* Missing 6 amubarvimab plus romlusevimab and 2 placebo.
† Not all persons aged ≥60 y had this listed as a risk factor by sites, resulting in this number being lower than the total number of study participants in this age group.
‡ Exogenous or endogenous immunosuppression is defined as any of the following: HIV infection with CD4 count <0.2 × 10^9 cells/L, receiving corticosteroids equivalent to prednisone ≥20 mg daily for at least 14 consecutive days within 30 d before study entry, treatment with biologics (e.g., infliximab, abalizumab, ustekinumab, and so forth), immunomodulators (e.g., methotrexate, 6MP, azathioprine, and so forth), or cancer chemotherapy within 90 d before study entry.
§ This included a mix of Alpha, Beta, Gamma, Epsilon, Mu, Iota, Lambda, and other variants.

49 years, with 22% aged 60 years or older; 51% were women, 0.2% were transgender, 73% were White, and 50% were Hispanic. Fifty-one percent enrolled between 6 and 10 days of symptom onset (10% after day 8). Variant data were available for 401 of 539 participants enrolled in the United States, with 22.2% infected with Delta and the remainder with pre-Delta variants.

Clinical Efficacy

Of 807 participants in the modified intention-to-treat population, 53 were hospitalized and/or died through study day 28–nine randomly assigned to amubarvimab plus romlusevimab and 44 to placebo (Table 2 and Figure 2). The cumulative incidence of hospitalization and/or death through day 28 was 79% lower (ratio of proportions, 0.21 [95% CI, 0.10 to 0.43]; $P < 0.001$) among participants randomly assigned to amubarvimab plus romlusevimab (2.3%) compared with placebo (10.8%). In analyses of subgroups defined by time from symptom onset to study entry (≤5 vs. >5 days), cumulative incidence of hospitalization and/or death was lower in participants randomly assigned to amubarvimab plus romlusevimab compared with placebo regardless of timing of treatment, with hospitalization or death rates of 2.1% versus 11.0% among those enrolled within 5 days, and 2.5% versus 10.5% among those enrolled more than 5 days from symptom onset (Table 2). In sensitivity analyses, findings were similar when participants lost to follow-up before day 28 were counted as events (ratio of proportions, 0.23 [CI, 0.12 to 0.45]; $P < 0.001$). Through day 28 of follow-up, there were no deaths in the amubarvimab plus romlusevimab group and 8 (2.0%) in the placebo group ($P = 0.008$). In subgroup analysis of those with variant data available, efficacy was seen in those infected with Delta and non-Delta variants (Appendix Figure and Appendix Table 2, available at Annals.org).

Symptom outcomes are summarized in Appendix Table 3 (available at Annals.org). The time to sustained symptom improvement for 2 consecutive days was similar between groups and similar for participants treated within 5 days versus more than 5 days after symptom onset. The median time to absence of symptoms for 4 consecutive days was also similar between groups. There was a trend toward a difference in median time to self-reported return to usual pre–COVID-19 health for 2 consecutive days between the amubarvimab plus romlusevimab (16 days [quartiles, 8 to >27]) and placebo (20 days [quartiles, 10 to >27]) ($P = 0.059$) groups. This difference was statistically significant for participants treated within 5 days but not those with greater than 5 days of symptoms at enrollment. Comparison of symptom severity rankings through day 28 showed statistically significant differences in AUC of total symptom score between groups, with a median of 2.41 (quartiles, 1.27 to 4.95) in the amubarvimab plus romlusevimab group versus 3.09 (quartiles, 1.29 to 6.46) in the placebo group ($P = 0.005$). Finally, the percentage of participants with progression of COVID-19 associated symptoms through day 28 was similar between groups.

Safety Analysis

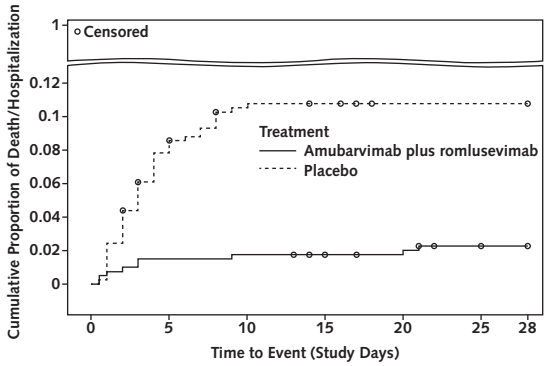
The primary safety end point involved a comparison of grade 3 or higher TEAEs through day 28 by randomized group. The event rate was significantly lower in the amubarvimab plus romlusevimab group compared with

Table 2. Death and/or Hospitalization Through Day 28 (Modified Intention to Treat)

Clinical Events	Amubarvimab Plus Romlusevimab	Placebo	Total
Hospitalizations and/or death, *n/total n* (%)*	9/397 (2.3)	44/410 (10.7)	53/807 (6.6)
Enrolled ≤5 d from symptom onset	4/195 (2.1)	22/200 (11.0)	26/395 (6.6)
Enrolled >5 d from symptom onset	5/202 (2.5)	22/210 (10.5)	27/412 (6.6)
Cumulative probability of hospitalization/death (SE)†	0.023 (0.0075)	0.108 (0.0154)	–
Ratio of proportions (95% CI)	–	–	0.21 (0.10–0.43); $P < 0.001$

* All events were hospitalizations. After hospitalization and through day 28 of follow-up, there were 8 deaths, all in the placebo-treated study group.
† Cumulative proportion of hospitalization or death (from any cause) estimated by Kaplan–Meier method with corresponding SEs calculated by the Greenwood method.

Figure 2. Cumulative proportion of death or hospitalizations through day 28.



At risk, *n*							
Amubarvimab plus romlusevimab	397	391	390	388	386	382	381
Placebo	410	374	361	359	355	355	355

Cumulative proportion of death or hospitalization is estimated by the Kaplan–Meier method. The first occurrence of either death or hospitalization is considered as the event. Hospitalization is defined as ≥24 h of acute care, in a hospital or similar acute care facility, including emergency rooms or temporary facilities instituted to address medical needs of those with severe COVID-19 during the COVID-19 pandemic, through day 28. Deaths from any cause through day 28 are included.

the placebo group: 7.3% versus 16.1% (risk ratio, 0.45 [CI, 0.30 to 0.69]; $P < 0.001$).

Treatment-emergent adverse events through day 28 by actual treatment received is summarized in **Table 3**. There were fewer TEAEs and grade 3 or higher TEAEs reported in the amubarvimab plus romlusevimab group than in the placebo group (35.8% vs. 39.6% and 7.4% vs. 16.2%, respectively). The groups had similar frequencies of study drug–related TEAEs and TEAEs of special interest (4.2% vs. 4.0% and 1.2% vs. 1.0%, respectively, for amubarvimab plus romlusevimab compared with placebo). There were no anaphylaxis-like reactions in either group.

Virologic Outcomes

Virologic outcomes for the phase 3 portion of the trial are summarized in **Table 4** and **Appendix Table 4** (available at Annals.org). The proportion of participants with anterior nasal SARS-CoV-2 RNA levels below LLoQ was significantly higher across all post-entry time points in the amubarvimab plus romlusevimab group compared with the placebo group (overall Wald test $P = 0.004$, adjusted for day 0 levels). In sensitivity analyses, this finding remained significant when participants with baseline levels below LLoQ were excluded ($P = 0.001$). When stratified by time from symptom onset (≤5 or >5 days), the proportion of participants with anterior nasal SARS-CoV-2 RNA levels below LLoQ was significantly higher across all post-entry time points in the amubarvimab plus romlusevimab group compared with the placebo group in those enrolled within 5 days ($P = 0.006$) but not those enrolled more than 5 days from onset of symptoms ($P = 0.27$).

Quantitative anterior nasal SARS-CoV-2 RNA levels were significantly lower in the amubarvimab plus romlusevimab group at days 3 and 7 in the overall population ($P = 0.001$ and 0.003, respectively) and the subset enrolled within 5 days from symptom onset ($P = 0.001$ and $P < 0.001$, respectively), with similar findings seen in a sensitivity analysis excluding those below LLoQ at day 0 ($P < 0.001$). There was also significantly lower viral AUC for amubarvimab plus romlusevimab versus placebo, with median of 3.90 (quartiles, 0.00 to 11.70) versus 6.15 (quartiles, 0.00 to 21.18) $\log_{10}$ copies/mL × days, respectively ($P = 0.002$).

Virologic outcomes on nasopharyngeal swabs in the smaller phase 2 population showed numerical differences favoring the amubarvimab plus romlusevimab group but no statistically significant difference in the proportion with RNA levels below LLoQ (overall Wald test $P = 0.60$, adjusted for day 0 levels) (**Appendix Table 5**, available at Annals.org). Nasopharyngeal SARS-CoV-2 RNA levels were lower for the amubarvimab plus romlusevimab group versus placebo at each time point, but a statistically significant difference was seen only at day 14 ($P = 0.008$) (**Appendix Table 5**). There was no statistically significant difference in the AUC of SARS-CoV-2 RNA levels between study groups ($P = 0.55$).

DISCUSSION

The ACTIV-2/A5401 trial demonstrated the safety and efficacy of amubarvimab plus romlusevimab for treatment of COVID-19 in nonhospitalized persons at higher risk for progression to severe COVID-19. The treatment was safe, and there was a 79% reduction in progression to hospitalization and/or death, with no deaths in the amubarvimab plus romlusevimab group compared with 8 in the placebo group through day 28. The clinical benefit was similar regardless of whether therapy was given within 5 days or more than 5 days of symptom onset.

Significantly greater reductions in anterior nasal swab viral levels were seen with amubarvimab plus romlusevimab compared with placebo. However, statistically significant virologic response was only seen in those treated within 5 days from symptom onset, with attenuated differences in those treated later, and in nasopharyngeal swab data from those enrolled in the phase 2 portion of the trial. These data suggest limitations to using nasal virologic measures to predict clinical efficacy of novel compounds. Although there was no difference in time to improvement in daily tracked COVID-19 symptoms, those in the amubarvimab plus romlusevimab group did show a trend toward more rapid self-reported return to usual health, a difference driven by those enrolled within 5 days of symptom onset. Those in the amubarvimab plus romlusevimab group also reported significantly decreased symptom severity rankings over time when compared with placebo.

Four mAb regimens (bamlanivimab, bamlanivimab/etesevimab, casirivimab/imdevimab, and sotrovimab) were shown to reduce hospitalizations and/or death in nonhospitalized persons (3, 4, 7, 21) and initially received FDA EUA. In addition, bebtelovimab received FDA EUA on the basis of in vitro susceptibility (22). However, these agents are no longer available in the United States because of the emergence of resistant SARS-CoV-2 variants, including Omicron (9, 10). The current study is the first to show that

Table 3. Treatment Emergent Adverse Events Through Day 28 of Follow-up (Based on Treatment Received)*

Treatment Emergent Adverse Events	Amubarvimab Plus Romlusevimab (*n* = 405), *n* (%)	Placebo (*n* = 402), *n* (%)	Total (*n* = 807), *n* (%)
TEAE	145 (35.8)	159 (39.6)	304 (37.7)
Grade 3 or higher TEAE	30 (7.4)	65 (16.2)	95(11.8)
Serious TEAE	10 (2.5)	43 (10.7)	53 (6.6)
Study drug-related TEAE	17 (4.2)	16 (4.0)	33 (4.1)
TEAE leading to study drug withdrawal	0	0	0
TEAE leading to study discontinuation	0	8 (2.0)	8 (1.0)
TEAE with outcome of death†	0	8 (2.0)	8 (1.0)
TEAE of special interest‡	5 (1.2)	4 (1.0)	9 (1.1)

TEAE = treatment-emergent adverse event.
* Participants were summarized according to the treatment received, with 8 randomly assigned to placebo inadvertently receiving active drug.
† Deaths were from COVID-19 pneumonia (*n* = 4), bowel perforation, cardiorespiratory arrest associated with progression of COVID-19 pneumonia, multiple organ failure stated to be COVID-19 related, and stroke.
‡ Includes grade 1 or higher infusion reaction or allergic/hypersensitivity reactions occurring within 12 h of study drug administration (deemed related to study product by site investigator).

treatment with an anti–SARS-CoV-2 mAb therapy as late as 6 to 10 days after symptom onset significantly reduces hospitalizations and/or death. Such data should not be used to suggest that treatment can be delayed, but supports that it may be of value even up to 10 days from symptom onset. In addition, the long half-life of these antibodies raises the possibility that a single infusion may also prevent reinfections (23).

A major issue for anti–SARS-CoV-2 mAbs relates to the effect of emerging variants. During this study, the highly transmissible and pathogenic Delta variant emerged. This study showed that in a subset enrolled in the United

Table 4. Phase 3 SARS-CoV-2 Self-Collected Anterior Nasal Swab RNA Levels (log_{10} copies/mL)*

Study Day	Amubarvimab Plus Romlusevimab			Placebo		
	Total	≤5 Days Symptoms	>5 Days Symptoms	Total	≤5 Days Symptoms	>5 Days Symptoms
Day 0						
Patients, *n*	359	173	186	376	185	191
<LLoQ†, *n* (%)	113 (31.5)	48 (27.7)	65 (34.9)	115 (30.6)	48 (25.9)	67 (35.1)
Median (Q1–Q3)	3.63 (1.70–5.81)	4.46 (1.70–6.63)	3.07 (1.70–4.99)	3.88 (1.70–5.76)	4.80 (1.70–6.55)	3.23 (1.70–5.09)
Day 3						
Patients, *n*	351	176	175	348	177	171
<LLoQ†, *n* (%)	191 (54.4)	83 (47.2)	108 (61.7)	155 (44.5)	62 (35.0)	93 (54.4)
Median (Q1–Q3)	1.70 (0.70–3.39)‡	2.19 (0.70–4.09)§	1.70 (0.70–2.73)	2.45 (0.70–4.29)‡	3.46 (1.70–5.33)§	1.70 (0.70–3.06)
Day 7						
Patients, *n*	352	173	179	332	168	164
<LLoQ†, *n* (%)	279 (79.3)	129 (74.6)	150 (83.8)	234 (70.5)	97 (57.7)	137 (83.5)
Median (Q1–Q3)	0.70 (0.70–1.70)‖	1.70 (0.70–2.04)¶	0.70 (0.70–1.70)	1.70 (0.70–2.44)‖	1.70 (0.70–3.10)¶	0.70 (0.70–1.70)
Day 14						
Patients, *n*	342	168	174	311	161	150
<LLoQ†, *n* (%)	321 (93.9)	156 (92.9)	165 (94.8)	291 (93.6)	148 (91.9)	143 (95.3)
Day 28						
Patients, *n*	348	166	182	351	174	177
<LLoQ†, *n* (%)	345 (99.1)	164 (98.8)	181 (99.5)	344 (98.0)	172 (98.9)	172 (97.2)

LLoQ = lower limit of quantitation of assay.
* For summaries of quantitative RNA levels, values below the limit of detection were imputed as 0.7 log_{10} copies/mL (i.e., half the distance from 0 to the limit of detection), values above limit of detection but below the LLoQ were imputed as 1.7 log_{10} copies/mL (i.e., half the distance from the limit of detection to the LLoQ).
† The *P* values from the joint test (2-sided Wald) across post day 0 time points from a generalized estimating equations model fit comparing the risk for below LLoQ in the amubarvimab plus romlusevimab group versus the placebo group were 0.004 (all participants), 0.006 (≤5 d from onset of symptoms), and 0.27 (>5 d from onset of symptoms).
‡ The Wilcoxon rank-sum test *P* value comparing day 3 quantitative SARS-CoV-2 RNA levels for amubarvimab plus romlusevimab to placebo (all participants) was 0.001.
§ The Wilcoxon rank-sum test *P* value comparing day 3 quantitative SARS-CoV-2 RNA levels for amubarvimab plus romlusevimab to placebo (≤5 d from onset of symptoms participants only) was <0.001.
‖ The Wilcoxon rank-sum test *P* value comparing day 7 quantitative SARS-CoV-2 RNA levels for amubarvimab plus romlusevimab to placebo (all participants) was 0.003.
¶ The Wilcoxon rank-sum test *P* value comparing day 7 quantitative SARS-CoV-2 RNA levels for amubarvimab plus romlusevimab to placebo (≤5 d from onset of symptoms participants only) was <0.001.

States, clinical benefit was seen in those infected with the Delta variant, consistent with reported in vitro susceptibility (12, 13). Since the current study closed to enrollment, Omicron subvariants have emerged, with in vitro data showing a lack of susceptibility to mAbs that have previously received FDA EUA (1, 14). Although this trial enrolled participants in the pre-Omicron era, there are in vitro data suggesting that Omicron (B.1.1.529) is susceptible to amubarvimab plus romlusevimab (14). Shortly after the study ended, the predominant circulating Omicron subvariants were BA.4 and BA.5, which were susceptible in vitro using a live virus assay (15). At the observed fold-change, plasma drug levels were anticipated to exceed those required for neutralization for at least 4 weeks after infusion. However, the currently predominant variants—for example, BQ.1, BQ.1.1, and XBB—have markedly reduced susceptibility to amubarvimab and romlusevimab (24, 25). It remains unknown whether future variants will be susceptible to any of the previously proven efficacious monoclonal antibody products, including amubarvimab plus romlusevimab.

Study limitations include that few enrolled participants were immunosuppressed or had received COVID-19 vaccines. In addition, enrollment preceded widespread circulation of the Omicron subvariants, and that there are likely differences in viral dynamics in the nasopharyngeal space relative to the lower respiratory tract not measured in this study. The variant analysis is limited by only including participants in United States, and substantial missing data. This study also did not assess the effect of early treatment on transmission or on long-term clinical outcomes such as postacute sequelae of SARS-CoV-2 infection.

This study shows that amubarvimab plus romlusevimab is safe and effective in reducing hospitalizations and deaths among those with mild to moderate COVID-19 at high risk for clinical progression and acquired infection before emergence of Omicron variants. The study also shows clinical benefit of amubarvimab plus romlusevimab for up to 10 days from COVID-19 symptom onset. Although initially approved in China, its utility in the United States with currently circulating Omicron subvariants is likely to be limited, although available in the future if new variants were shown to have in vitro susceptibility.

From Weill Cornell Medicine, New York, New York (T.H.E.); David Geffen School of Medicine at UCLA, Los Angeles, California (K.W.C., J.S.C.); Harvard T.H. Chan School of Public Health, Boston, Massachusetts (M.J.G., C.M., M.P., J.R., M.D.H.); University of North Carolina, Chapel Hill, North Carolina (D.A.W., J.J.E., W.A.F.); National Institutes of Health, Bethesda, Maryland (A.C.J.); University of Washington, Seattle, Washington (R.B.); Brii Biosciences, Durham, North Carolina (D.M., Q.Z., J.M., L.Z., L.Y.); Instituto Medico Rio Cuarto, Cordoba, Argentina (U.D.N.); Miami Clinical Research, Miami, Florida (K.H.); Las Vegas Medical Research, Las Vegas, Nevada (B.M.); Brigham & Women's Hospital, Harvard Medical School, Boston, Massachusetts (M.C.C., R.D., J.Z.L.); University of Nebraska Medical Center, Omaha, Nebraska (C.V.F.); University of California, San Diego, San Diego, California (D.S.); and Lundquist Institute at Harbor-UCLA Medical Center, Torrance, California (E.S.D.).

Note: These findings were presented in part in abstract form at the virtual IDWeek 2021 Conference, 29 September to 3 October 2021.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Acknowledgment: The authors thank the study participants, site staff, site investigators, and the entire ACTIV-2/A5401 study team; the ACTIV-2 Community Advisory Board; the AIDS Clinical Trials Group, including Lara Hosey, Jhoanna Roa, and Nilam Patel; the Harvard Center for Biostatistics in AIDS Research (CBAR) and ACTG Statistical and Data Analysis Center (SDAC), the National Institute of Allergy and Infectious Diseases (NIAID)/Division of AIDS (DAIDS), including Peter Kim; Bill Erhardt; the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) partnership, including Stacey Adams; and PPD.

Financial Support: By the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under award number 3UM1AI068636-14S2, UM1AI068634, UM1AI068636, and UM1AI106701. Investigational agent was supplied by Brii Biosciences.

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M22-3428.

Data Sharing Statement: The next-generation sequencing data generated in this study have been deposited on the NCBI Short Read Archive (SRA) under accession number PRJNA865340. All other data are available under restricted access due to ethical restrictions, with trial conduct ongoing. Access can be requested by submitting a data request at https://submit.mis.s-3.net/ and will require the written agreement of the AIDS Clinical Trials Group (ACTG) and the manufacturer of the investigational product. Requests will be addressed as per ACTG standard operating procedures. Completion of an ACTG Data Use Agreement may be required.

Corresponding Author: Eric S. Daar, MD, Lundquist Institute at Harbor-UCLA Medical Center, 1124 West Carson Street, CDCRC 205, Torrance, CA 90502; e-mail, EDaar@Lundquist.org.

Author contributions are available at Annals.org.

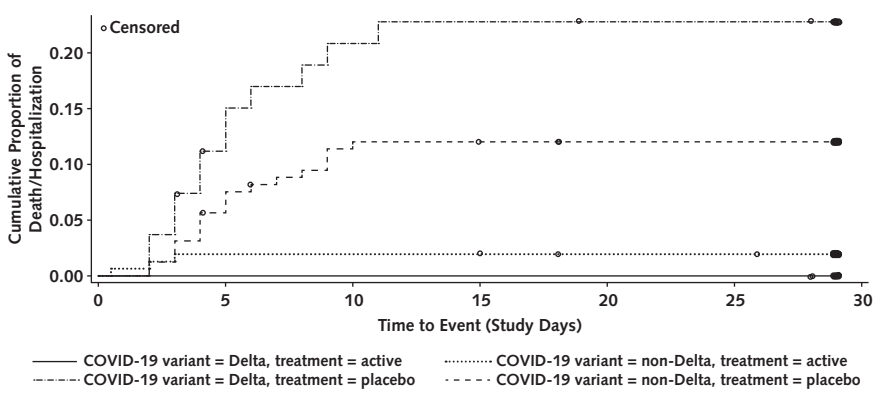
References

1. **National Center for Advancing Translational Sciences**. SARS-CoV-2 variants & therapeutics: therapeutic activity explorer. Accessed at https://opendata.ncats.nih.gov/variant/activity/singlemutationvariant on 6 February 2023.
2. **COVID-19 Treatment Guidelines Panel**. Coronavirus disease 2019 (COVID-19) treatment guidelines. National Institutes of Health. Accessed at www.covid19treatmentguidelines.nih.gov/ on 4 February 2023.
3. **Dougan M, Nirula A, Azizad M, et al.** Bamlanivimab plus etesevimab in mild or moderate COVID-19. N Engl J Med. 2021;385:1382-1392. [PMID: 34260849] doi:10.1056/NEJMoa2102685
4. **Gupta A, Gonzalez-Rojas Y, Juarez E, et al.** Early treatment for COVID-19 with SARS-CoV-2 neutralizing antibody sotrovimab.

N Engl J Med. 2021;385:1941-1950. [PMID: 34706189] doi:10.1056/NEJMoa2107934
5. **Hammond J, Leister-Tebbe H, Gardner A, et al.** Oral nirmatrelvir for high-risk, nonhospitalized adults with COVID-19. N Engl J Med. 2022;386:1387-1408. [PMID: 35172054] doi:10.1056/NEJMoa2118542
6. **Bernal AJ, Gomes da Silva MM, Musungaie DB, et al.** Molnupiravir for oral treatment of COVID-19 in nonhospitalized patients. N Engl J Med. 2022;386:509-520. [PMID: 34914868] doi:10.1056/NEJMoa2116044
7. **Weinreich DM, Sivapalasingam S, Norton T, et al; Trial Investigators.** REGN-COV2, a neutralizing antibody cocktail, in outpatients with COVID-19. N Engl J Med. 2021;384:238-251. [PMID: 33332778] doi:10.1056/NEJMoa2035002
8. **Weinreich DM, Sivapalasingam S, Norton T, et al.** REGEN-COV antibody combination and outcomes in outpatients with COVID-19. N Engl J Med. 2021;385:e81. [PMID: 34587383] doi:10.1056/NEJMoa2108163
9. **Administration for Strategic Preparedness & Response**. Bamlanivimab/etesevimab. Accessed at www.phe.gov/emergency/events/COVID19/investigation-MCM/bamlanivimab-etesevimab/Pages/default.aspx on 6 February 2023.
10. FDA revokes EUAs for two monoclonal antibodies shown to be ineffective against Omicron. Accessed at www.fdanews.com/articles/206320-fda-revokes-euas-for-two-monoclonal-antibodies-shown-to-be-ineffective-against-omicron on 6 February 2023.
11. **U.S. Food and Drug Administration.** FDA updates sotrovimab emergency use authorization. Accessed at www.fda.gov/drugs/drug-safety-and-availability/fda-updates-sotrovimab-emergency-use-authorization on 6 February 2023.
12. **Brii Biosciences**. BRII-196 investigator's brochure. Edition 3.0. Brii Biosciences; 2021.
13. **Brii Biosciences**. BRII-198 investigator's brochure. Edition 3.0. Brii Biosciences; 2021.
14. **Liu L, Iketani S, Guo Y, et al.** Striking antibody evasion manifested by the Omicron variant of SARS-CoV-2. Nature. 2022;602:676-681. [PMID: 35016198] doi:10.1038/s41586-021-04388-0
15. **Ji Y, Zhang Q, Cheng L, et al.** Preclinical characterization of amubarvimab and romlusevimab, a pair of non-competing neutralizing monoclonal antibody cocktail, against SARS-CoV-2. Front Immunol. 2022;13:980435. [PMID: 36189212] doi:10.3389/fimmu.2022.980435
16. **Robbie GJ, Criste R, Dall'acqua WF, et al.** A novel investigational Fc-modified humanized monoclonal antibody, motavizumab-YTE has an extended half-life in healthy adults. Antimicrob Agents Chemother. 2013;57:6147-6153. [PMID: 24080653] doi:10.1128/AAC.01285-13
17. **Saunders KO.** Conceptual approaches to modulating antibody effector functions and circulation half-life. Front Immunol. 2019;10:1296. [PMID: 31231397] doi:10.3389/fimmu.2019.01296
18. **Hao X, Zhang Z, Ma J, et al.** Randomized, placebo-controlled, single-blind phase 1 studies of the safety, tolerability, and pharmacokinetics of BRII-196 and BRII-198, SARS-CoV-2 spike-targeting monoclonal antibodies with an extended half-life in healthy adults. Front Pharmacol. 2022;13:983505. [PMID: 36147329] doi:10.3389/fphar.2022.983505
19. **Hwang IK, Shih WJ, De Cani JS.** Group sequential designs using a family of type I error probability spending functions. Stat Med. 1990;9:1439-1445. [PMID: 2281231] doi:10.1002/sim.4780091207
20. **Greenwood M**. A report on the natural duration of cancer. In: Ministry of Health, eds. Reports on Public Health and Medical Subjects. H.M.S.O.; 1926.
21. **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;384:229-237. [PMID: 33113295] doi:10.1056/NEJMoa2029849
22. **U.S. Food & Drug Administration**. Coronavirus (COVID-19) update: FDA authorizes new monoclonal antibody for treatment of COVID-19 that retains activity against Omicron variant. Accessed at www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-new-monoclonal-antibody-treatment-covid-19-retains on 6 February 2023.
23. **O'Brien MP, Forleo-Neto E, Musser BJ, et al.** Subcutaneous REGEN-COV antibody combination to prevent COVID-19. N Engl J Med. 2021;385:1184-1195. [PMID: 34347950] doi:10.1056/NEJMoa2109682
24. **Uraki R, Ito M, Kiso M, et al.** Antiviral and bivalent vaccine efficacy against an Omicron XBB.1.5 isolate. Lancet Infect Dis. 2023;23:402-403. [PMID: 36773622] doi:10.1016/S1473-3099(23)00070-1
25. **Cao J, Jian F, Wang J, et al.** Imprinted SARS-CoV-2 humoral immunity induces convergent Omicron RBD evolution. Nature. 2023;614:521-529. [PMID: 36535326] doi:10.1038/s41586-022-05644-7]

Author Contributions: Conception and design: R. Bender Ignacio, K.W. Chew, J.S. Currier, E.S. Daar, J.J. Eron, W.A. Fischer, C.V. Fletcher, M.D. Hughes, A.C. Javan, J.Z. Li, D. Margolis, C. Moser, D. Smith, D.A. Wohl, L. Yan.
Analysis and interpretation of the data: K.W. Chew, M.C. Choudhary, J.S. Currier, E.S. Daar, R. Deo, J.J. Eron, T.H. Evering, W.A. Fischer, C.V. Fletcher, M.J. Giganti, M.D. Hughes, J.Z. Li, D. Margolis, C. Moser, M. Pinilla, J. Ritz, D. Smith, L. Yan, L. Zhong.
Drafting of the article: E.S. Daar, T.H. Evering, C.V. Fletcher, C. Moser, M. Pinilla, J. Ritz, D.A. Wohl, L. Yan, Q. Zhu.
Critical revision of the article for important intellectual content: R. Bender Ignacio, K.W. Chew, J.S. Currier, E.S. Daar, J.J. Eron, W.A. Fischer, M.J. Giganti, M.D. Hughes, A.C. Javan, J.Z. Li, D. Margolis, C. Moser, D. Smith, L. Yan.
Final approval of the article: R. Bender Ignacio, K.W. Chew, M. C. Choudhary, J.S. Currier, E.S. Daar, U. D'Andrea Nores, R. Deo, J.J. Eron, T.H. Evering, W.A. Fischer, C.V. Fletcher, M.J. Giganti, K. Hoover, M.D. Hughes, A.C. Javan, J.Z. Li, J. Ma, D. Margolis, B. Mocherla, C. Moser, M. Pinilla, J. Ritz, D. Smith, D. A. Wohl, L. Yan, L. Zhong, Q. Zhu.
Provision of study materials or patients: R. Bender Ignacio, K.W. Chew, E.S. Daar, U. D'Andrea Nores, J.J. Eron, W.A. Fischer, B. Mocherla, D. Smith, D.A. Wohl, L. Yan, Q. Zhu.
Statistical expertise: M.J. Giganti, M.D. Hughes, C. Moser, M. Pinilla, J. Ritz, L. Zhong.
Obtaining of funding: K.W. Chew, J.S. Currier, E.S. Daar, M.D. Hughes, L. Yan.
Administrative, technical, or logistic support: K.W. Chew, J.S. Currier, A.C. Javan, J.Z. Li, J. Ma, D. Smith, L. Yan, Q. Zhu.
Collection and assembly of data: K.W. Chew, M.C. Choudhary, E.S. Daar, U. D'Andrea Nores, R. Deo, J.J. Eron, W.A. Fischer, D. Smith, L. Yan.

Appendix Figure. Death or hospitalization through day 28 by Delta versus non-Delta COVID-19 variant.



Analyses include modified intention to treat persons enrolled in U.S. sites only. Cumulative proportion of death or hospitalization is estimated by the Kaplan–Meier method. The first occurrence of either death or hospitalization is considered as the event. Hospitalization is defined as ≥24 h of acute care, in a hospital or similar acute care facility, including emergency rooms or temporary facilities instituted to address medical needs of those with severe COVID-19 during the COVID-19 pandemic, through day 28. Deaths from any cause through day 28 are included.

Appendix Table 1. Phase 2 Baseline Characteristics (Modified Intention To Treat Analysis Group)

Characteristic	Amubarvimab Plus Romlusevimab (*n* = 112)	Placebo (*n* = 109)	Total* (*n* = 221)
Median age (Q1–Q3), *y*	52 (41–61)	50 (41–61)	51 (41–61)
Age category, *n* (%)			
<60 y	78 (69.6)	76 (69.7)	154 (69.7)
≥60 y	34 (30.4)	33 (30.3)	67 (30.3)
Sex at birth, *n* (%)			
Male	58 (51.8)	58 (53.2)	116 (52.5)
Female	54 (48.2)	51 (46.8)	105 (47.5)
Race, *n* (%)			
Asian	2 (1.8)	5 (4.6)	7 (3.2)
American Indian	0	0	0
Black/African American	9 (8.0)	9 (8.3)	18 (8.1)
Multiple	2 (1.8)	2 (1.8)	4 (1.8)
Native Hawaiian or Pacific Islander	1 (0.9)	0	1 (0.5)
White	96 (85.7)	88 (80.7)	184 (83.3)
Other	2 (1.8)	5 (4.6)	7 (3.2)
Ethnicity, *n* (%)			
Hispanic or Latino	42 (37.5)	32 (29.4)	74 (33.5)
Not Hispanic or Latino	70 (62.5)	77 (70.6)	147 (66.5)
Median baseline body mass index, *kg/m²* (Q1–Q3)†	29.0 (25.8–36.1)	30.5 (26.3–36.0)	29.7 (26.0–36.0)
Time from symptom onset			
≤5 d, *n* (%)	42 (37.5)	37 (33.9)	79 (35.7)
>5 d, *n* (%)	70 (62.5)	72 (66.1)	142 (64.3)
Median (Q1–Q3)	6.0 (4.0–8.0)	6.0 (4.0–8.0)	6.0 (4.0–8.0)
Risk factors for progression, *n* (%)			
Hypertension	47 (42.0)	44 (40.4)	91 (41.2)
Current smoker	26 (23.2)	26 (23.9)	52 (23.5)
Obesity (body mass index >35 kg/m^2)	31 (27.7)	31 (28.4)	62 (28.1)
Age ≥60 y‡	34 (30.4)	31 (28.4)	65 (29.4)
Diabetes mellitus	14 (12.5)	14 (12.8)	28 (12.7)
Chronic lung disease	12 (10.7)	21 (19.3)	33 (14.9)
Cardiovascular disease	4 (3.6)	14 (12.8)	18 (8.1)
Immunosuppressed§	5 (4.5)	1 (0.9)	6 (2.7)
Active cancer (other than localized skin	0	1 (0.9)	1 (0.5)
History of cirrhosis	2 (1.8)	0	2 (0.9)
Chronic kidney disease	0	0	0
Moderate to severe asthma	0	0	0

* All phase 2 participants were enrolled in the United States.
† Missing 5 amubarvimab plus romlusevimab and 1 placebo.
‡ Not all persons aged ≥60 y had this listed as a risk factor by sites, resulting in this number being lower than the total number of study participants in this age group.
§ Exogenous or endogenous immunosuppression is defined as any of the following: HIV infection with CD4 count <0.2 × 10^9 cells/L, receiving corticosteroids equivalent to prednisone ≥20 mg daily for at least 14 consecutive days within 30 d before study entry, treatment with biologics (e.g., infliximab, abalizumab, ustekinumab, and so forth), immunomodulators (e.g., methotrexate, 6MP, azathioprine, and so forth), or cancer chemotherapy within 90 d before study entry.

Appendix Table 2. Death and/or Hospitalization Through Day 28 (Modified Intention to Treat) Among Those Enrolled at U.S. Sites With SARS-CoV-2 Variant Data Available

Variant	Amubarvimab Plus Romlusevimab (*n* = 190)	Placebo (*n* = 211)	Total (*n* = 401)
Delta, *n* (%)	37 (19.5)	52 (24.6)	89 (22.2)
Hospitalizations and/or death, *n* (%)*	0 (0.0)	12 (23.1)	12 (13.5)
P value		0.001†	
Non-Delta, *n* (%)	153 (80.5)	159 (75.4)	312 (77.8)
Hospitalizations and/or death, *n* (%)*	3 (2.0)	19 (11.9)	22 (7.1)
P value		<0.001†	

* All events were hospitalizations, and percentages are based on the events among the total Delta or non-Delta population in each study group.
† Because of the small number of hospitalizations for the variant subgroup comparisons, the proportion of hospitalizations was compared between groups using the Fisher exact test.

Appendix Table 3. Analysis of COVID-19–Associated Symptom Outcomes*

Symptom Outcome	Amubarvimab Plus Romlusevimab (*n* = 397)	Placebo (*n* = 410)	*P* Value
Median time to sustained COVID-19 improvement (Q1 to Q3), *d*	11 (6 to 26)	11 (6 to 27)	0.56
Enrolled ≤5 d from symptom onset	11 (6 to 23)	11 (5 to 25)	0.55
Enrolled >5 d from symptom onset	11 (6 to >27)	11 (6 to 27)	0.80
Median time to return to usual pre–COVID-19 health (Q1 to Q3), *d*	16 (8 to >27)	20 (10 to >27)	0.059
Enrolled ≤5 d from symptom onset	15 (8 to >27)	23 (10 to >27)	0.036
Enrolled >5 d from symptom onset	18 (8 to >27)	18 (9 to >27)	0.53
Median time to all targeted symptoms absent for 4 consecutive days (Q1 to Q3), *d*	18 (10 to >25)	22 (10 to >25)	0.58
Median time-averaged total symptoms score (Q1 to Q3)	2.41 (1.27 to 4.95)	3.10 (1.29 to 6.46)	0.005
Progression of ≥1 COVID-19–associated symptoms to a worse status than at day 0, *n* (%)	335 (84.4)	333 (81.2)	0.23

* Time to sustained COVID-19 improvement for 2 consecutive days, time to symptom absence for 4 consecutive days, and time to return to usual health for 2 consecutive days were compared using a Gehan–Wilcoxon test. The proportion of participants with symptom progression was compared between groups using a χ^2 test. The time-averaged total symptom score was compared between groups using a Wilcoxon test. All tests were 2-sided and used a 5% type I error rate.

Appendix Table 4. Analyses of Phase 3 Self-Collected Anterior Nasal Swab SARS-CoV-2 RNA <LLoQ by Visit*

Analysis Visit	Risk Ratio (95% CI)	*P* Value (Wald Test)
Primary		
Day 3	1.22 (1.06–1.40)	
Day 7	1.13 (1.04–1.22)	
Day 14	1.01 (0.96–1.06)	
Day 28	1.00 (0.97–1.04)	
Overall	–	0.004
Enrolled ≤5 d from symptom onset		
Day 3	1.34 (1.07–1.69)	
Day 7	1.29 (1.11–1.49)	
Day 14	0.99 (0.92–1.07)	
Day 28	0.98 (0.93–1.04)	
Overall	–	0.006
Enrolled >5 d from symptom onset		
Day 3	1.13 (0.96–1.34)	
Day 7	1.02 (0.93–1.11)	
Day 14	1.03 (0.97–1.09)	
Day 28	1.03 (0.98–1.07)	
Overall	–	0.27

LLoQ = lower limit of quantitation.
* Risk ratio (calculated as amubarvimab plus romlusevimab versus placebo) and 95% CI estimated from models fitted using generalized estimating equations with an independence working correlation structure and robust SEs. A joint test of all time points was assessed using a 2-sided Wald test. All analyses adjusted for baseline (day 0) $\log_{10}$ transformed SARS-CoV-2 RNA level.

Appendix Table 5. Phase 2 Nasopharyngeal Swab SARS-CoV-2 RNA Levels (log_{10} copies/mL)*

Study Day	Amubarvimab Plus Romlusevimab			Placebo		
	Total	≤5 Days Symptoms	>5 Days Symptoms	Total	≤5 Days Symptoms	>5 Days Symptoms
Day 0						
Patients, *n*	94	33	61	97	33	64
<LLoQ†, *n* (%)	15 (16.0)	3 (9.1)	12 (19.7)	27 (27.8)	7 (21.2)	20 (31.3)
Median (Q1-Q3)	4.86 (2.72–6.58)	5.87 (5.14–7.67)	3.86 (2.64–5.37)	4.53 (1.70–6.46)	5.79 (3.00–7.29)	4.34 (1.70–5.81)
Day 3						
Patients, *n*	100	37	63	92	31	61
<LLoQ†, *n* (%)	37 (37.0)	9 (24.3)	28 (44.4)	34 (37.0)	6 (19.4)	28 (45.9)
Median (Q1-Q3)	2.64 (1.70–4.21)	3.56 (2.28–5.06)	2.26 (1.70–3.30)	2.73 (1.70–4.53)	4.02 (2.43–6.28)	2.19 (1.70–3.58)
Day 7						
Patients, *n*	99	37	62	86	30	56
<LLoQ†, *n* (%)	72 (72.7)	29 (78.4)	43 (69.4)	55 (64.0)	13 (43.3)	42 (75.0)
Median (Q1-Q3)	1.70 (0.70–2.20)	1.70 (0.70–1.70)‡	1.70 (0.70–2.24)	1.70 (0.70–2.72)	2.36 (1.70–3.47)‡	1.70 (0.70–1.92)
Day 14						
Patients, *n*	92	32	60	79	25	54
<LLoQ†, *n* (%)	81 (88.0)	27 (84.4)	54 (90.0)	62 (78.5)	17 (68.0)	45 (83.3)
Median (Q1-Q3)	0.70 (0.70–1.70)§	0.70 (0.70–1.70)	0.70 (0.70–1.70)‖	1.70 (0.70–1.70)§	1.70 (0.70–2.23)	1.20 (0.70–1.70)‖
Day 28						
Patients, *n*	86	34	52	90	30	60
<LLoQ†, *n* (%)	82 (95.3)	34 (100)	48 (92.3)	86 (95.6)	28 (93.3)	58 (96.7)
Median (Q1-Q3)	0.70 (0.70–1.70)	0.70 (0.70–0.70)	0.70 (0.70–1.70)	0.70 (0.70–0.70)	0.70 (0.70–0.70)	0.70 (0.70–0.70)

LLoQ = lower limit of quantitation for nasopharyngeal swab SARS-CoV-2 RNA.

* For summaries of quantitative RNA levels, values below the limit of detection were imputed as 0.7 log_{10} copies/mL (i.e., half the distance from 0 to the limit of detection), values above limit of detection but below the LLoQ were imputed as 1.7 log_{10} copies/mL (i.e., half the distance from the limit of detection to the LLoQ).

† The *P* values from the joint test across post day 0 time points from a generalized estimating equations model fit comparing the risk for below LLoQ in the amubarvimab plus romlusevimab group versus the placebo group were 0.60 (all participants) and 0.045 (>5 d from onset of symptoms).

‡ The Wilcoxon rank-sum test *P* value comparing day 7 quantitative SARS-CoV-2 RNA levels for amubarvimab plus romlusevimab to placebo (≤5 d from onset of symptoms participants only) was 0.006.

§ The Wilcoxon rank-sum test *P* value comparing day 14 quantitative SARS-CoV-2 RNA levels for amubarvimab plus romlusevimab to placebo (all participants) was 0.008.

‖ The Wilcoxon rank-sum test *P* value comparing day 14 quantitative SARS-CoV-2 RNA levels for amubarvimab plus romlusevimab to placebo (>5 d from onset of symptoms participants only) was 0.027.