Original Investigation

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Effect of Ivermectin vs Placebo on Time to Sustained Recovery in Outpatients With Mild to Moderate COVID-19

A Randomized Clinical Trial

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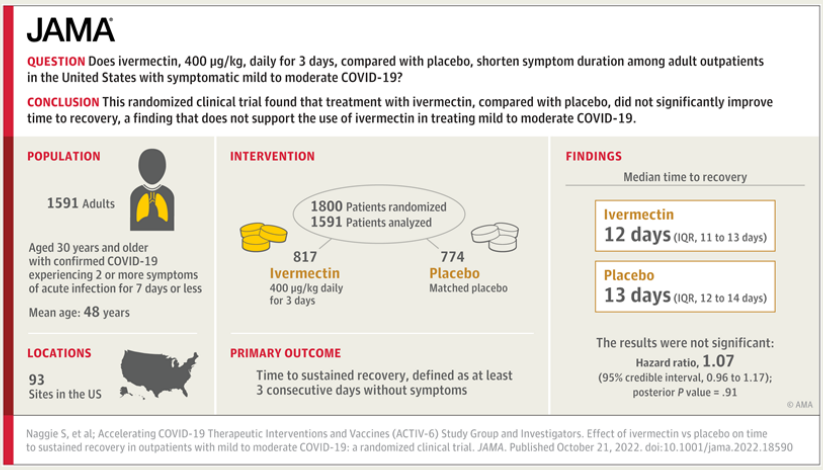

Key Points

Question Does ivermectin, 400 µg/kg, daily for 3 days, compared with placebo, shorten symptom duration among adult (≥30 years) outpatients in the US with symptomatic mild to moderate COVID-19?

Findings In this double-blinded, randomized, placebo-controlled platform trial conducted in the US during a period of Delta and Omicron variant predominance, and that included 1591 adult outpatients with COVID-19, the posterior probability of improvement in time to recovery in those treated with ivermectin vs placebo had a hazard ratio of 1.07, with a posterior probability of benefit of .91. This did not meet the prespecified threshold of posterior probability greater than .95.

Meaning These findings do not support the use of ivermectin in outpatients with mild to moderate COVID-19.

Abstract

Importance The effectiveness of ivermectin to shorten symptom duration or prevent hospitalization among outpatients in the US with mild to moderate symptomatic COVID-19 is unknown.

Objective To evaluate the efficacy of ivermectin, 400 µg/kg, daily for 3 days compared with placebo for the treatment of early mild to moderate COVID-19.

Design, Setting, and Participants ACTIV-6, an ongoing, decentralized, double-blind, randomized, placebo-controlled platform trial, was designed to evaluate repurposed therapies in outpatients with mild to moderate COVID-19. A total of 1591 participants aged 30 years and older with confirmed COVID-19, experiencing 2 or more symptoms of acute infection for 7 days or less, were enrolled from June 23, 2021, through February 4, 2022, with follow-up data through May 31, 2022, at 93 sites in the US.

Interventions Participants were randomized to receive ivermectin, 400 µg/kg (n=817), daily for 3 days or placebo (n=774).

Main Outcomes and Measures Time to sustained recovery, defined as at least 3 consecutive days without symptoms. There were 7 secondary outcomes, including a composite of hospitalization or death by day 28.

Results Among 1800 participants who were randomized (mean [SD] age, 48 [12] years; 932 women [58.6%]; 753 [47.3%] reported receiving at least 2 doses of a SARS-CoV-2 vaccine), 1591 completed the trial. The hazard ratio (HR) for improvement in time to recovery was 1.07 (95% credible interval [CrI], 0.96-1.17; posterior *P* value [HR >1]=.91). The median time to recovery was 12 days (IQR, 11-13) in the ivermectin group and 13 days (IQR, 12-14) in the placebo group. There were 10 hospitalizations or deaths in the ivermectin group and 9 in the placebo group (1.2% vs 1.2%; HR, 1.1 [95% CrI, 0.4-2.6]). The most common serious adverse events were COVID-19 pneumonia (ivermectin [n=5]; placebo [n=7]) and venous thromboembolism (ivermectin [n=1]; placebo [n=5]).

Conclusions and Relevance Among outpatients with mild to moderate COVID-19, treatment with ivermectin, compared with placebo, did not significantly improve time to recovery. These findings do not support the use of ivermectin in patients with mild to moderate COVID-19.

Trial Registration ClinicalTrials.gov Identifier: NCT04885530

Introduction

Despite advances in treatment of COVID-19, additional therapies are needed, particularly in the outpatient setting. Novel oral antivirals have been authorized for high-risk individuals in high-income countries[1,2]; however, efficacy of these drugs in vaccinated people is unclear and access globally is limited. For individuals in the US not considered at high risk, no COVID-19 therapy is currently recommended.

Numerous repurposed drugs have been investigated for COVID-19.[3-6] To date, the study of repurposed drugs has been largely in the inpatient setting for the treatment of severe COVID-19.[7-9] In the outpatient setting, repurposed drug studies have been challenged by small sample sizes, design limitations, and variable results, limiting the impact on clinical practice.

Ivermectin, an antiparasitic drug used worldwide for onchocerciasis and strongyloidiasis, emerged in 2020 as a potential repurposed drug for COVID-19 due to an in vitro study suggesting possible antiviral activity.[10] Numerous ivermectin studies have been completed across the spectrum of COVID-19 disease severity.[10] While early studies, particularly in the inpatient setting, suggested potential treatment effect, variability in dosing and overall study quality, followed by multiple article retractions, has resulted in controversy.[11-13] The largest randomized outpatient trial to date, TOGETHER, enrolled patients in Brazil with symptomatic mild to moderate COVID-19. No clinical benefit of ivermectin (400 µg/kg daily for 3 days) was observed for preventing disease progression.[14]

Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV-6) is an ongoing, fully remote (decentralized), double-blind, randomized, placebo-controlled, platform trial investigating repurposed drugs for the treatment of mild to moderate COVID-19 in the outpatient setting. This article reports the effect of ivermectin, 400 µg/kg, daily for 3 days, compared with placebo, for the treatment of early mild to moderate COVID-19.

Methods

Trial Design and Oversight

This double-blind, randomized, placebo-controlled platform protocol was designed to be flexible, allowing for use in a wide range of settings within health care systems and the community. The platform protocol enrolls outpatients with mild to moderate COVID-19 with a confirmed positive polymerase chain reaction or antigen test result for SARS-CoV-2, including home-based testing. Each repurposed medication (study drug group) is further described including drug-specific exclusion criteria in each drug-specific appendix. The trial protocol and statistical analysis plan are available in **Supplement 1** and **Supplement 2**, respectively.

A governing institutional review board for each site approved the protocol. Informed consent was obtained from each enrolled participant either via electronic consent or (in-person consent) written process. An independent data monitoring committee oversaw the monitoring of participant safety, efficacy, and trial conduct.

Participants

Recruitment into the platform trial opened on June 11, 2021, and is ongoing. Participants were enrolled in the ivermectin group or identical matched-placebo or contributing-placebo group from June 23, 2021, through February 4, 2022, at 93 sites in the US. The group was closed after meeting the prespecified accrual goal. Participants were either identified by sites or self-identified by contacting central study telephone hotline(s).

Sites verified eligibility criteria including age 30 years or older, confirmed SARS-CoV-2 infection within 10 days, and 2 or more symptoms of acute COVID-19 for 7 days or less from enrollment. Symptoms included fatigue, dyspnea, fever, cough, nausea, vomiting, diarrhea, body aches, chills, headache, sore throat, nasal symptoms, and loss of sense of taste or smell. Exclusion criteria included hospitalization, study drug use within 14 days, or known allergy or contraindication to study drug (**Supplement 1**). Vaccination was allowable, as were standard-of-care therapies for COVID-19.

Randomization

Participants were randomized, using a random number generator, in a 2-step process (**Figure 1**). First, participants were randomized with equal probability among the study drugs actively enrolling for which participants were eligible. Participants could choose to opt out of specific study drugs if they or the site investigator did not feel there was equipoise. After randomization among study drugs, participants were randomized to active agent or placebo in a ratio of *m*:1 where *m* is the number of study drugs for which the participant was eligible. The more study groups a participant was eligible for, the greater the chance of receiving an active study drug. Participants eligible for the ivermectin study drug group and another group(s) but randomized to placebo for a different study drug were included and contributed to the placebo group for ivermectin.

Interventions

A central pharmacy supplied ivermectin or placebo to participants via direct home delivery. Ivermectin was supplied as a bottle of 15 7-mg tablets. Participants were instructed to take a prespecified number of tablets for 3 consecutive days based on their weight for a daily dose of approximately 400 µg/kg (**Supplement 1**). Packaging for matched placebo was identical to that of ivermectin. Packaging for other contributing placebo was identical to that of the associated study drug.

Outcome Measures

The primary measure of effectiveness was based on time to sustained recovery, defined as achieving at least 3 consecutive days without symptoms; this was selected a priori from among the 2 co-primary end points that remained available to other study drugs in the platform (**Supplement 2**). Time to sustained recovery was the number of days between receipt of study drug and the third of 3 consecutive days without symptoms. Participants who died, by definition, did not recover regardless of reported symptom freedom. Time to recovery was administratively censored at 28 days. Secondary outcomes included the composite of hospitalization or death by day 28; the difference in mean time spent unwell estimated from a longitudinal ordinal model; the COVID Clinical Progression Scale on days 7, 14, and 28; mortality through day 28; and hospitalization, urgent care visit, or emergency department visit through day 28. The final secondary outcome per the statistical analysis plan, PROMIS-29, is planned to be assessed through day 90. Due to the longer 90-day follow-up, it is not reported in this article.

Trial Procedures

The study was designed as a fully remote, or decentralized, trial. Screening and eligibility confirmation were participant reported and site confirmed. A positive SARS-CoV-2 polymerase chain reaction or antigen test result was verified prior to randomization. At screening, participant-reported demographic information was collected and included race and ethnicity, eligibility criteria, medical history, concomitant medications, symptom reporting, and quality of life questionnaires. Participant-reported race and ethnicity were collected due to the disparity in the burden of COVID-19 infection carried by marginalized communities based on race and ethnicity. Participants were asked about ethnicity separately from race and were able to select any combination of race designations, including the option to not report any designation. While demographic data remained participant-reported, screening and enrollment could occur in person at sites and unplanned study visits could occur in person or remotely, as deemed appropriate by site investigators.

A central investigational pharmacy distributed the study drug. Shipping and delivery were tracked. Participants must have received the study drug to be included in the analysis; receipt of the study drug was defined as day 1 for this study.

Participants were asked to complete daily assessments and report adverse events via the study portal through day 14, then at other intervals through day 28, and at the final study visit at day 90. Assessments included symptoms and severity, health care visits, and medications. If participants were still reporting symptoms at day 14, they continued to be assessed until they experienced 3 consecutive days without symptoms or until day 28. At days 28 and 90, all participants completed assessments. Additional details are available in **Supplement 1**.

Statistical Analysis Plan

This ongoing platform trial was designed to be analyzed accepting the possibility of adding and dropping groups as the trial progresses. The general analytical approach was regression modeling. Proportional hazard regression was used for time-to-event analysis, and cumulative probability ordinal regression models were used for ordinal outcomes. In addition, mean time spent unwell was estimated using a longitudinal ordinal regression model as a quantification of benefit (**Supplement 2**).

The planned primary end point analysis was a bayesian proportional hazards model. The primary inferential (decision-making) quantity was the posterior distribution for the treatment assignment hazard ratio (HR), with HR >1 indicating benefit. If the posterior probability of benefit exceeded .95 at any of the interim or final analyses, the trial would conclude efficacy of the intervention. To preserve type I error less than .05, the prior for the treatment effect parameter (on the $\log_e$ relative hazard scale) was a normal distribution centered at 0 and scaled to an SD of 0.1. All other parameter priors were noninformative, using the software default of 2.5 times the ratio of the SD of the outcome divided by the SD of the predictor variable. The study design was estimated to have 80% power to detect an HR of 1.2 in the primary end point.

The primary end point model included the following predictor variables in addition to randomization assignment: age (as restricted cubic spline), sex, duration of symptoms prior to receipt of study drug, calendar time (as restricted cubic spline), vaccination status, geographic region (Northeast, Midwest, South, West), call center indicator, and baseline symptom severity. The proportional hazards assumption of the primary end point was evaluated by generating visual diagnostics such as the log-log plot and plots of time-dependent regression coefficients for each predictor in the model, a diagnostic that indicates deviations from proportionality if the time-dependent coefficients are not constant in time.

Secondary end points were analyzed with bayesian regression models (either proportional hazards or proportional odds). Noninformative priors were used for all parameters. Secondary end points were not used for formal decision-making, and no decision threshold was selected. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory. The same set of covariates used in the primary end point model was used in the analysis of secondary end points, provided the end point accrued enough events to be analyzed with covariate adjustment.

To achieve this sample size in an ongoing platform trial, once 1200 participants had been randomized to the study group or to matching placebo and had received study drug, enrollment into the study group was halted. Some participants had already consented to participate but had not received study drug, and these participants continued in their assigned study group.

As a platform trial, the primary analysis is implemented separately for each study drug, where the placebo group consists of contemporaneously randomized participants who meet the eligibility criteria for that study drug; this includes both matched and contributing placebo. From other remote trials,[3,6] it was recognized that medication delivery (placebo or active study drug) may not always occur (eg, failure of delivery, participant withdrawal, or interval hospitalization). For this trial, the full analysis set for the primary analyses included all participants who received study drug and participants were analyzed as assigned. All available data were used to compare each active study drug vs placebo control, regardless of postrandomization adherence to study protocols. In both the primary and secondary end point analyses, missing data among covariates were addressed with conditional mean imputation because the amount of missing covariate data was small (<4%).

A prespecified analysis tested for differential treatment effects as a function of preexisting participant characteristics. Analysis of heterogeneity of treatment effect included age, number of days of symptoms, body mass index, day 1 symptom severity, calendar time (surrogate for SARS-CoV-2 variant), sex, and vaccination status; continuous variables were modeled as such without creating subgroups.

Analyses were performed with R version 4.1 with the following primary packages: rstanarm, rmsb, and survival.[15]

Results

Study Population

Of the 3457 participants who met inclusion criteria and consented to be evaluated for inclusion in the ivermectin group, 1591 were eligible for this study group; randomized to ivermectin, 400 µg/kg (n = 817), or placebo (n = 774); and received study drug (**Figure 1**). Of participants receiving placebo, 545 (70%) received matching placebo and 229 (30%) received placebo as part of a concurrent study group and contributed to the pooled placebo group.

The mean (SD) age of the participants was 48 (12) years, and 43% were aged 50 years or older (**Table 1**). The population was 59% female, 7% identified as Black/African American, 81% identified as White, and 10% reported being of Latino/Hispanic ethnicity. Although not required for enrollment, high-risk comorbidities were prevalent, including body mass index (calculated as weight in kilograms divided by height in meters squared) greater than 30 (41%), diabetes (11.5%), hypertension (26%), asthma (15%), and chronic obstructive pulmonary disease (4%). Overall, 47% of participants reported receiving at least 2 doses of a COVID-19 vaccine. The median time from symptom onset to receipt of study drug was 6 days (IQR, 4-8). Baseline symptom prevalence and severity are described in eTable 1 in **Supplement 3**. Receipt of therapies available under US Food and Drug Administration approval or authorization was uncommon (remdesivir, 0.3%; monoclonal antibody, 3%; ritonavir-boosted nirmatrelvir, 0.1%).

Primary Outcome

In the full analysis population, the posterior probability of benefit on the primary outcome of time to recovery between the ivermectin and placebo groups was .91 (hazard ratio [HR], 1.07 [95% credible interval [CrI], 0.96-1.17) where an HR >1 is for faster symptom resolution in the active drug group (**Table 2**, **Figure 2**A). The median time to recovery was 12 days (IQR, 11-13) in the ivermectin group and 13 days (IQR, 12-14) in the placebo group. This posterior probability of the primary outcome was below the prespecified threshold of .95 (**Supplement 2**). Diagnostics did not indicate a violation of the proportional hazard assumption. Because the rate of enrollment was so rapid, it was not possible to complete the interim analyses. The analyses of the primary end point unadjusted for interim looks at the data resulted in similar point and interval estimates (noninformative prior, no prior) (**Table 2**). The unadjusted Kaplan-Meier analysis was consistent with the model-based inference (**Figure 3**).

Secondary Outcomes

Hospitalization or death were uncommon, occurring in 1.2% (10/817) in the ivermectin group and 1.2% (9/774) in the placebo group (HR, 1.1 [95% CrI, 0.4-2.6], where an HR >1 favors placebo); there was 1 death in the ivermectin group (**Table 2**; eFigure 1A in **Supplement 3**). The composite secondary outcome of urgent or emergency care visits, hospitalizations, or death was similar for ivermectin (3.9% [32/817]) compared with placebo (3.6% [28/774]) (HR, 1.2 [95% CrI, 0.6-1.8], where an HR >1 favors placebo) (**Table 2**, **Figure 2**B; eFigure 1B in **Supplement 3**). For the ordinal outcome at day 14, the difference in the amount of time spent feeling unwell with COVID-19 was estimated to be 0.49 days (95% CrI, 0.15-0.82 days) in favor of ivermectin. The posterior probability that this benefit exceeds 1 day was less than 0.01 (**Figure 2**C). The posterior probability of any benefit observed with the COVID Clinical Progression Scale at days 7, 14, and 28 was .88, .89, and .45, respectively (**Table 2**; eFigure 2 in **Supplement 3**). Because most participants were home (the lowest 2 levels of the scale), the model was approximately a logistic regression and questions of proportionality were moot.

Heterogeneity of Treatment Effect Analyses

Tests for heterogeneity of treatment effect showed no overall influence of the putative subgrouping variables on treatment effects. The overall effect of symptom severity at day 1 was not significant ($P = .12$) and all subgroup analyses across symptom severity were neither controlled nor adjusted for multiple comparisons (eFigure 3 in **Supplement 3**). There was no evidence of a different treatment effect with ivermectin compared with placebo for timing of symptom onset to receipt of study drug, body mass index, calendar time, or vaccination status.

Adverse Events

Adverse events were uncommon and similar in both groups (2.8% with ivermectin; 3.5% with placebo). All but 1 recorded event occurred in participants who confirmed taking their study drug; 1 participant who reported not taking the study drug experienced acute kidney injury. Ivermectin at 400 µg/kg was without additional serious adverse events compared with placebo (ivermectin [n = 10]; placebo [n = 9]) (eTable 2 in **Supplement 3**).

Discussion

Among outpatients with mild to moderate COVID-19, treatment with ivermectin, 400 µg/kg, daily for 3 days, compared with placebo, did not significantly improve time to recovery in this large trial that enrolled more than 1500 participants in the US. A lack of treatment effect was also seen for secondary clinical outcomes including hospitalization, death, or acute care visits. These findings do not support the use of ivermectin in patients with mild to moderate COVID-19.

Although there are numerous published studies reporting on the potential efficacy of ivermectin for the treatment of COVID-19, many are in the inpatient setting and the majority are small, variable in population and dosing, and some have been retracted.[11-13] In the outpatient setting, larger well-designed trials such as the current trial are emerging and do not support a clinical benefit of ivermectin when used at a dose of 400 µg/kg daily for 3 days.[14] Thus, this study adds to the growing evidence that there is not a clinically relevant treatment effect of ivermectin at this dose and duration.

This study has several strengths. This was a double-blind, randomized, placebo-controlled national study with enrolling sites in 28 states and a call center able to recruit participants from the remainder of the US. This ivermectin group of the platform trial enrolled rapidly due to the Delta and Omicron variant surges and included both vaccinated and unvaccinated patients, thus representing a highly relevant study population.

Limitations

This study has several limitations. First, the low mortality and hospitalization rates observed preclude drawing strict inferences on whether there are statistical differences in clinical event rates without much larger trials. Second, while the inclusion criteria allow for a broad study population, this study failed to achieve the level of representation desired for underrepresented populations in terms of racial and ethnic diversity. Third, ivermectin was dosed by weight to achieve a goal dose of 400 µg/kg, but the maximum dose of ivermectin provided by the study was 35 mg. While almost 42% of participants had a weight of more than 88 kg and thus did not achieve the goal dose, more than 75% of participants had a weight of less than 100 kg and so received at least 90% of the target dose. Fourth, due to the remote nature of the trial and constraints related to timing of randomization, the median time from start of symptoms to receipt of study drug was 6 days, which is later in the disease course than recent antiviral trials.[1,2] However, there was no evidence of a differential treatment effect based on the median time of symptom onset to receipt of study drug.

Conclusions

Among outpatients with mild to moderate COVID-19, treatment with ivermectin, compared with placebo, did not significantly improve time to recovery. These findings do not support the use of ivermectin in patients with mild to moderate COVID-19.

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Author Contributions: Drs Naggie and Hernandez had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Naggie, Boulware, Lindsell, Stewart, Gentile, Collins, McCarthy, Thicklin, Felker, Ginde, Gabriel, Dunsmore, Adam, Wilson, Hernandez.

Acquisition, analysis, or interpretation of data: Naggie, Boulware, Lindsell, Stewart, Gentile, Jayaweera, Castro, Sulkowski, McTigue, Felker, Bramante, Slandzicki, Shah, Lenert, Dunsmore, DeLong, Hanna, Remaly, Wilder, Shenkman, Hernandez.

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Other - clinical protocol development and protocol oversight: Gentile.

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Conflict of Interest Disclosures: Dr Naggie reported receiving grants from the National Institutes of Health (NIH) during the conduct of the study and grants from Gilead Sciences and AbbVie; personal fees from Pardes Biosciences, Personal Health Insights Inc, and Bristol Myers Squibb/PRA Health Services; and stock options from Vir Biotechnology as well as providing unpaid consultation to Silverback Therapeutics outside the submitted work. Dr Boulware reported receiving grants from the NIH during the conduct of the study. Dr Lindsell reported receiving grants from the National Center for Advancing Translational Sciences (NCATS) during the conduct of the study and grants from the NIH, Centers for Disease Control and Prevention, and Department of Defense to his institution and contracts to his institution for research services from Endpoint Health, bioMerieux, Entegrion Inc, AbbVie, and AstraZeneca outside the submitted work. In addition, Dr Lindsell had a patent for risk stratification in sepsis and septic shock issued to Cincinnati Children's Hospital Medical Center. Dr Stewart reported receiving grants from the NIH NCATS during the conduct of the study and grants from the NIH outside the submitted work. Dr Gentile reported receiving personal fees from Duke University during the conduct of the study and grants from the NIH outside the submitted work. Dr Collins reported receiving personal fees from Vir Biotechnology during the conduct of the study. Dr Jayaweera reported receiving grants from NCATS during the conduct of the study and grants from Gilead, Pfizer, Janssen, and ViiV and serving as a consultant for Theratechnologies outside the submitted work. Dr Castro reported receiving grants from the NIH, American Lung Association, Patient-Centered Outcomes Research Institute, AstraZeneca, GlaxoSmithKline, Novartis, Pulmatrix, Sanofi, and Shionogi and personal fees from Genentech, Teva, Sanofi, Merck, Novartis, Arrowhead, OM Pharma, Allakos, Amgen, AstraZeneca, GlaxoSmithKline, Regeneron, and Elsevier outside the submitted work. Dr Sulkowski reported receiving personal fees from AbbVie, Gilead, GlaxoSmithKline, Atea Pharmaceuticals, Antios Therapeutics, Precision BioSciences, Viiv, and Virion and grants from Janssen to Johns Hopkins University outside the submitted work. Dr McTigue reported receiving grants to her institution from the NIH during the conduct of the study and research contracts to her institution from Pfizer and Janssen outside the submitted work. Dr Felker reported receiving grants from the NIH during the conduct of the study and grants from Novartis outside the submitted work. Dr Ginde reported receiving grants from the NIH during the conduct of the study and grants from the NIH, Centers for Disease Control and Prevention, Department of Defense, AbbVie (investigator-initiated), and Faron Pharmaceuticals (investigator-initiated) outside the submitted work. Dr Adam reported receiving funding from the US government (funding through Operation Warp Speed) during the conduct of the study. Dr DeLong reported receiving grants from NCATS during the conduct of the study. Dr Hanna reported receiving grants from the US Biomedical Advanced Research and Development Authority during the conduct of the study and personal fees from Merck & Co and AbPro outside the submitted work. Dr Remaly reported receiving grants from NCATS during the conduct of the study. Dr Wilder reported receiving grants from NCATS during the conduct of the study. Dr Wilson reported receiving grants from NCATS during the conduct of the study. Dr Hernandez reported receiving grants from American Regent, Amgen, Boehringer Ingelheim, Merck, Verily, Somologic, and Pfizer, and personal fees from AstraZeneca, Boston Scientific, Bristol Myers Squibb, Cytokinetics, and Merck outside the submitted work. No other disclosures were reported.

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Group Information: The Accelerating Covid-19 Therapeutic Interventions and Vaccines (ACTIV-6) Study Group and Investigators are listed in **Supplement 4**.

Data Sharing Statement: See **Supplement 5**

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From: **Effect of Ivermectin vs Placebo on Time to Sustained Recovery in Outpatients With Mild to Moderate COVID-19: A Randomized Clinical Trial**

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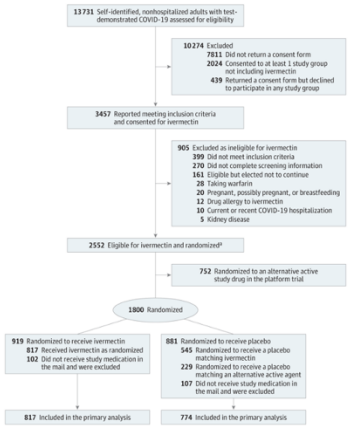

Figure Legend:

Flow Diagram of Participants in the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV-6) Trial[a]In this platform trial with multiple study drugs, participants were able to choose to which agents they were willing to be randomized. Participants were first randomized 1:m between placebo and study drug, where m was the number of study groups for which the participant was eligible and consented to participate. Then, participants were randomized with 1/m probability among the study drugs for which they were eligible.

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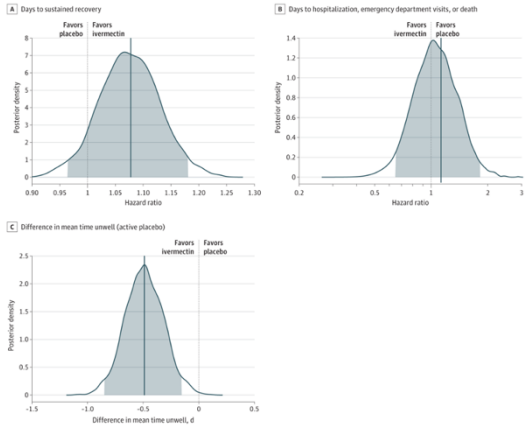

Figure Legend:

Posterior Distributions of Effects for (A) Time to Sustained Recovery (1257 Observed Events); (B) Hospitalization, Urgent Care Visits, Emergency Department Visits, or Death (60 Observed Events); and (C) Mean Time UnwellThick vertical lines denote the estimated mean of the posterior distribution. Density is the relative likelihood of posterior probability distribution. Outcomes with higher density are more likely than outcomes with lower density.

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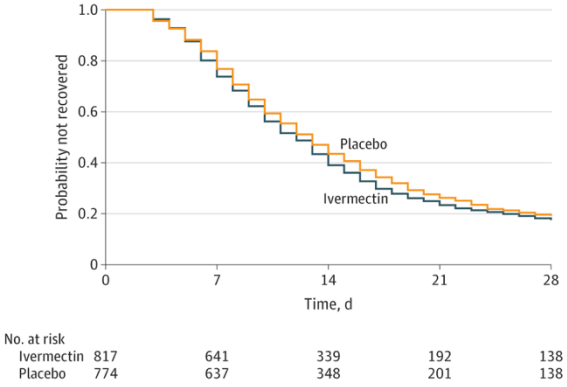

Figure Legend:

Kaplan-Meier Curve for Primary Outcome of Time to RecoveryRecovery occurs on the third of 3 consecutive days without symptoms. Sixty-six participants were censored for nonresponse, and all others were followed up until recovery, death, or the end of short-term 28-day follow-up.

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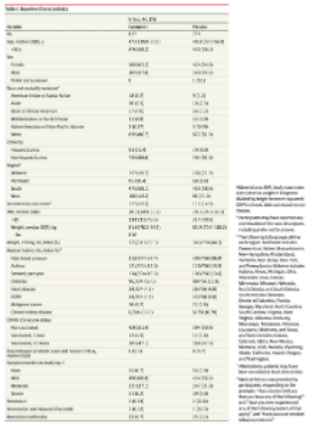

Table Title:

Baseline CharacteristicsAbbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COPD, chronic obstructive pulmonary disease.

[a] Participants may have selected any combination of the race descriptors, including prefer not to answer.

[b] The following state groups define each region: Northeast includes Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont, New Jersey, New York, and Pennsylvania; Midwest includes Indiana, Illinois, Michigan, Ohio, Wisconsin, Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, and South Dakota; South includes Delaware, District of Columbia, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, West Virginia, Alabama, Kentucky, Mississippi, Tennessee, Arkansas, Louisiana, Oklahoma, and Texas; and West includes Arizona, Colorado, Idaho, New Mexico, Montana, Utah, Neveda, Wyoming,

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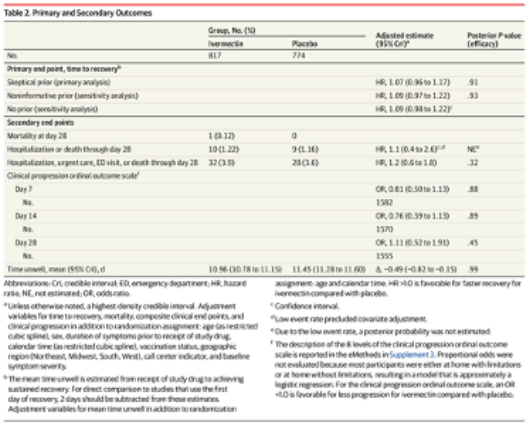

Table 2. Primary and Secondary Outcomes

	Group, No. (%)		Adjusted estimate (95% CrI)[a]	Posterior P value (efficacy)
	Ivermectin	Placebo		
No.	817	774		
Primary end point, time to recovery[b]				
Skeptical prior (primary analysis)			HR, 1.07 (0.96 to 1.17)	.91
Noninformative prior (sensitivity analysis)			HR, 1.05 (0.97 to 1.22)	.93
No prior (sensitivity analysis)			HR, 1.05 (0.98 to 1.22)[c]	
Secondary end points				
Mortality at day 28	1 (0.12)	0		
Hospitalization or death through day 28	10 (1.22)	9 (1.16)	HR, 1.1 (0.4 to 2.6)[c,d]	NE[e]
Hospitalization, urgent care, ED visit, or death through day 28	32 (3.9)	28 (3.6)	HR, 1.2 (0.6 to 1.8)	.32
Clinical progression ordinal outcome scale[f]				
Day 7			OR, 0.81 (0.50 to 1.13)	.88
No.			1582	
Day 14			OR, 0.76 (0.39 to 1.13)	.89
No.			1570	
Day 28			OR, 1.11 (0.52 to 1.91)	.45
No.			1555	
Time unwell, mean (95% CrI), d	10.96 (10.78 to 11.15)	11.45 (11.28 to 11.60)	Δ, −0.49 (−0.82 to −0.15)	.99

Abbreviations: CrI, credible interval; ED, emergency department; HR, hazard ratio; NE, not estimated; OR, odds ratio.

[a] Unless otherwise noted, a highest-density credible interval. Adjustment variables for time to recovery, mortality, composite clinical end points, and clinical progression in addition to randomization assignment: age (as restricted cubic spline), sex, duration of symptoms prior to receipt of study drug, calendar time (as restricted cubic spline), vaccination status, geographic region (Northeast, Midwest, South, West), call center indicator, and baseline symptom severity.

[b] The mean time unwell is estimated from receipt of study drug to achieving sustained recovery. For direct comparison to studies that use the first day of recovery, 2 days should be subtracted from these estimates. Adjustment variables for mean time unwell in addition to randomization assignment: age and calendar time. HR >1.0 is favorable for faster recovery for ivermectin compared with placebo.

[c] Confidence interval.

[d] Low event rate precluded covariate adjustment.

[e] Due to the low event rate, a posterior probability was not estimated.

[f] The description of the 8 levels of the clinical progression ordinal outcome scale is reported in the eMethods in Supplement 3. Proportional odds were not evaluated because most participants were either at home with limitations or at home without limitations, resulting in a model that is approximately a logistic regression. For the clinical progression ordinal outcome scale, an OR >1.0 is favorable for less progression for ivermectin compared with placebo.

Table Title:

Primary and Secondary OutcomesAbbreviations: CrI, credible interval; ED, emergency department; HR, hazard ratio; NE, not estimated; OR, odds ratio.

[a] Unless otherwise noted, a highest-density credible interval. Adjustment variables for time to recovery, mortality, composite clinical end points, and clinical progression in addition to randomization assignment: age (as restricted cubic spline), sex, duration of symptoms prior to receipt of study drug, calendar time (as restricted cubic spline), vaccination status, geographic region (Northeast, Midwest, South, West), call center indicator, and baseline symptom severity.

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