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Effect of Higher-Dose Ivermectin for 6 Days vs Placebo on Time to Sustained Recovery in Outpatients With COVID-19
A Randomized Clinical Trial

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IMPORTANCE It is unknown whether ivermectin, with a maximum targeted dose of 600 µg/kg, shortens symptom duration or prevents hospitalization among outpatients with mild to moderate COVID-19.

OBJECTIVE To evaluate the effectiveness of ivermectin at a maximum targeted dose of 600 µg/kg daily for 6 days, compared with placebo, for the treatment of early mild to moderate COVID-19.

DESIGN, SETTING, AND PARTICIPANTS The ongoing Accelerating COVID-19 Therapeutic Interventions and Vaccines 6 (ACTIV-6) platform randomized clinical trial was designed to evaluate repurposed therapies among outpatients with mild to moderate COVID-19. A total of 1206 participants older than 30 years with confirmed COVID-19 experiencing at least 2 symptoms of acute infection for less than or equal to 7 days were enrolled at 93 sites in the US from February 16, 2022, through July 22, 2022, with follow-up data through November 10, 2022.

INTERVENTIONS Participants were randomly assigned to receive ivermectin, with a maximum targeted dose of 600 µg/kg (n = 602) daily, or placebo (n = 604) for 6 days.

MAIN OUTCOMES AND MEASURES The primary outcome was time to sustained recovery, defined as at least 3 consecutive days without symptoms. The 7 secondary outcomes included a composite of hospitalization, death, or urgent/emergent care utilization by day 28.

RESULTS Among 1206 randomized participants who received study medication or placebo, the median (IQR) age was 48 (38-58) years, 713 (59.1%) were women, and 1008 (83.5%) reported receiving at least 2 SARS-CoV-2 vaccine doses. The median (IQR) time to sustained recovery was 11 (11-12) days in the ivermectin group and 11 (11-12) days in the placebo group. The hazard ratio (posterior probability of benefit) for improvement in time to recovery was 1.02 (95% credible interval, 0.92-1.13; $P = .68$). Among those receiving ivermectin, 34 (5.7%) were hospitalized, died, or had urgent or emergency care visits compared with 36 (6.0%) receiving placebo (hazard ratio, 1.0 [95% credible interval, 0.6-1.5]; $P = .53$). In the ivermectin group, 1 participant died and 4 were hospitalized (0.8%); 2 participants (0.3%) were hospitalized in the placebo group and there were no deaths. Adverse events were uncommon in both groups.

CONCLUSIONS AND RELEVANCE Among outpatients with mild to moderate COVID-19, treatment with ivermectin, with a maximum targeted dose of 600 µg/kg daily for 6 days, compared with placebo did not improve time to sustained recovery. These findings do not support the use of ivermectin in patients with mild to moderate COVID-19.

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Visual Abstract
Editorial and Editor's Note
Supplemental content

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Group Information: A complete list of the members of the Accelerating Covid-19 Therapeutic Interventions and Vaccines (ACTIV)-6 Study Group and Investigators appears in Supplement 4.

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Despite treatment advances for COVID-19, the evolution of SARS-CoV-2 variants and subvariants has shifted therapeutic options, including the recent loss of effectiveness of monoclonal antibodies. Novel oral antivirals have been authorized for high-risk individuals in high-income countries.[1,2] However, efficacy of these antivirals in those vaccinated or with prior SARS-CoV-2 infection remains unclear. Interest remains for the potential of repurposed drugs to improve symptoms and clinical outcomes among patients with COVID-19.

Numerous repurposed drugs have been investigated for COVID-19 management, with several large randomized outpatient trials published.[3-5] Trial results have been mixed. Trials of some drugs suggest possible benefit by reducing emergency department (ED) visits or hospitalizations, including fluvoxamine dosed at 100 mg twice daily[3] and immediate-release metformin.[6] Others have failed to show a reduction in ED visits or hospitalizations, such as fluvoxamine 50 mg twice daily.[6,7] Although recently completed trials benefit from the increasing representation of vaccinated people, which is more relevant to the pandemic's current state, the results have not affected treatment guidelines largely due to study design limitations, including definitions of outcomes that were of unclear significance in the US health care setting.[8-10]

Ivermectin, an antiparasitic drug used worldwide for onchocerciasis and strongyloidiasis, emerged in 2020 as a potential repurposed drug for COVID-19 initially informed by an in vitro study suggesting possible antiviral activity.[11] The interest for ivermectin as a therapy for COVID-19 has remained high and, although there have been numerous ivermectin studies, its use has become controversial due to a lack of high-quality adequately powered randomized trials and article retractions of some of the earlier and most positive studies.[12-15] Three large randomized outpatient trials of people with symptomatic mild or moderate COVID-19 failed to identify a clinical benefit of ivermectin when dosed at 400 µg/kg daily for 3 days.[16-18] One possibility is that the dose and duration studied were too low and too short, missing the therapeutic window for ivermectin. A combination of modeling studies and a proof-of-concept clinical study have suggested doses up to 600 µg/kg daily may achieve system levels sufficient for in vitro antiviral activity.[18,19] For this reason we tested ivermectin, with a maximum targeted dose of 600 µg/kg daily, for 6 days from February 16, 2022, through July 22, 2022. This report describes the effectiveness of this dose and duration of ivermectin compared with placebo for the treatment of early mild to moderate COVID-19. The primary outcome was time to sustained recovery, defined as at least 3 consecutive days without symptoms, and secondary outcomes included a composite of hospitalization, death, or urgent/emergent care utilization by day 28.

Key Points

Question Does ivermectin, with a maximum targeted dose of 600 µg/kg daily for 6 days, compared with placebo, shorten symptom duration among adult (≥30 years) outpatients with symptomatic mild to moderate COVID-19?

Findings In this double-blind, randomized, placebo-controlled platform trial including 1206 US adults with COVID-19 during February 2022 to July 2022, the median time to sustained recovery was 11 days in the ivermectin group and 11 days in the placebo group. In this largely vaccinated (84%) population, the posterior probability that ivermectin reduced symptom duration by more than 1 day was less than 0.1%.

Meaning These findings do not support the use of ivermectin among outpatients with COVID-19.

Methods

Trial Design and Oversight

Accelerating COVID-19 Therapeutic Interventions and Vaccines 6 (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. The platform protocol is designed to be flexible, allowing enrollment across a wide range of settings within health care systems and the community, as well as virtually. The platform enrolls outpatients with mild to moderate COVID-19 with a confirmed positive SARS-CoV-2 test result. The full trial protocol and statistical analysis plan are available in Supplement 1 and Supplement 2.

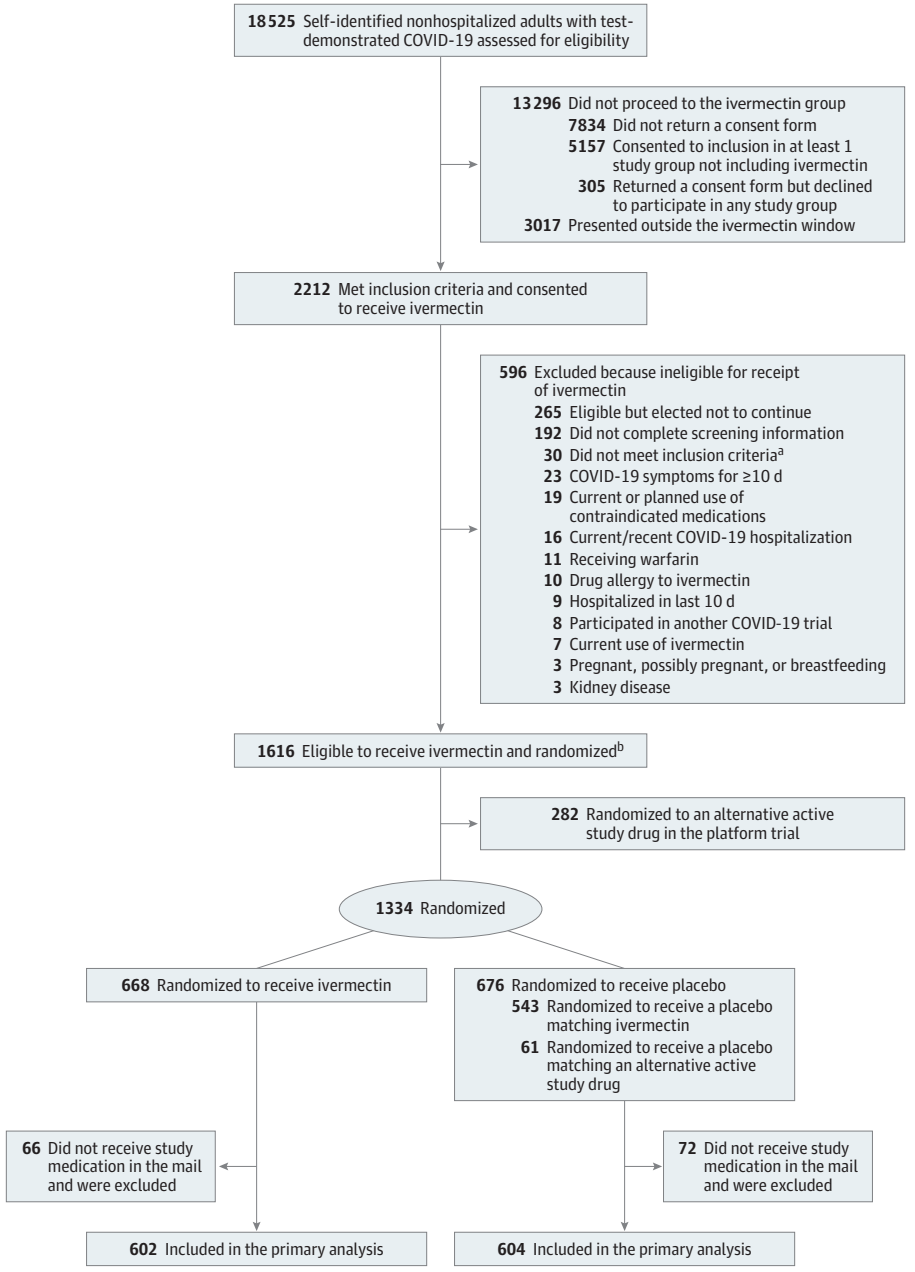
The trial protocol was approved by each site's institutional review board. Participants provided informed consent either via written consent or an electronic consent process. An independent data monitoring committee oversaw participant safety and trial conduct.

Participants

Recruitment into the platform trial opened on June 11, 2021, and ivermectin 600 µg/kg was included on the platform beginning on February 16, 2022. Enrollment into the ivermectin 600 µg/kg group was stopped on July 22, 2022, when 1206 participants had received their study drug, identical matched placebo, or contributing placebo. Participants were either identified by sites or self-identified by contacting a central study telephone hotline or website.

Study staff verified eligibility criteria including age of 30 years or older, SARS-CoV-2 infection within 10 days (positive polymerase chain reaction or antigen test result, including home-based tests), and experiencing at least 2 symptoms of acute COVID-19 for no more than 7 days from enrollment. The protocol defined "mild to moderate" as having symptoms as noted above self-reported at the time of enrollment, and symptoms were graded by participants as none, mild, moderate, or severe. Symptoms included fatigue, dyspnea, fever, cough, nausea, vomiting, diarrhea, body aches, chills, headache, sore throat, nasal symptoms, and new loss of sense of taste or smell. Exclusion criteria included hospitalization, ivermectin use within 14 days, and known allergy or contraindication to the study drug (Supplement 1). Vaccination against SARS-CoV-2 was allowable, as was concurrent use of standard therapies for COVID-19 available under US Food and Drug Administration Emergency Use Authorization or approval.

Figure 1. Participant Flow in a Trial of Higher-Dose Ivermectin for Mild to Moderate COVID-19



[a] After consent, test results, birth date and pre-enrollment symptoms were reviewed. Patients whose test result date was found to be 10 days prior, who had less than 2 symptoms, whose date of symptom onset was more than 7 days prior, or who was younger than 30 years did not proceed because they did not meet baseline inclusion criteria.

[b] In this platform trial with multiple study drugs, participants were able to choose what agents they were willing to be randomized to receive. Participants were first randomized in a ratio of *m*:1, where *m* is the number of study drugs for which the participant was eligible. After randomization to receive an active agent vs placebo, participants were randomized with equal probability among the study drugs for which they were eligible.

Randomization

Participants were randomized using a random number generator in a 2-step process (**Figure 1**). First, participants were randomized to receive an 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 other study drug under investigation during this period was fluvoxamine 50 mg twice daily for 10 days. Participants could choose to opt out of specific study drug groups during the consent process if they or the site investigator did not feel there was equipoise or if there was a contraindication to any study drug on the platform. After randomization to receive an active agent vs placebo, participants were randomized with equal probability among the study drugs for which they were eligible. The more study drugs a participant was eligible for, the greater the chance of receiving an active agent. Participants who were eligible to receive both ivermectin and fluvoxamine 50 mg but were randomized to the fluvoxamine-matched placebo group were included in 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 7-mg tablets. Participants were instructed to take

a prespecified number of tablets for 6 consecutive days based on their weight for a maximum targeted daily dose of approximately 600 µg/kg. The dosing schedule was based on weight ranges as follows: those weighing 35 to 52 kg received a 21-mg daily dose; 53 to 69 kg, 28-mg daily dose; 70 to 89 kg, 42-mg daily dose; 90 to 109 kg, 49-mg daily dose; 110 to 129 kg, 56-mg daily dose; and more than 129 kg, 70-mg daily dose. This schedule resulted in a range of doses from 400 to 600 µg/kg (eFigure 1 in Supplement 3) and a median (IQR) dose of 498 (465-532) µg/kg per day. The median daily dose was calculated among participants randomized to receive ivermectin. Packaging for the matched placebo was identical to ivermectin and packaging for the contributing placebos was identical to that of the associated study drug, which in this case was fluvoxamine 50 mg twice daily.

Outcome Measures

The primary measure of effectiveness was time to sustained recovery, defined as the number of days between study drug receipt and the third of 3 consecutive days without symptoms. This outcome was selected a priori from among the 2 co-primary end points that remain available to other study drugs in the platform (Supplement 2). The key secondary outcome was the composite of hospitalization or death by day 28. Other secondary outcomes included mean time unwell, estimated from a longitudinal ordinal model; COVID-19 Clinical Progression Scale score on days 7, 14, and 28; mortality through day 28; and the composite of urgent or emergency care visits, hospitalizations, or death through day 28. The final secondary outcome, the Patient-Reported Outcomes Measurement Information System 29 profile, was to be assessed through day 90 and is not reported in this article because of the longer follow-up.

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 via uploading into the participant portal and reviewal by the site. 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.

A central investigational pharmacy distributed the study drug (either active or placebo) using a next-day priority shipping service. Delivery was tracked and participants needed to have received the study drug within 7 days of enrollment to be included. Confirmation that the study drug was delivered to the participant's address was required for the participant to be included in the analysis. Receipt of study drug was defined as study day 1.

Participants were asked to complete daily assessments and report adverse events through day 14. Assessments included symptoms and severity, health care visits, and medications. If symptoms were still ongoing at day 14, daily surveys continued until participants experienced 3 consecutive days without symptoms or until day 28. At days 28 and 90, all participants completed assessments. Supplement 1 presents survey details. Additional details of participant monitoring during follow-up are available in Supplement 3.

Statistical Analysis Plan

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

The complete statistical analysis plan is provided in Supplement 2. Briefly, the planned primary end point analysis was a bayesian proportional hazards model for time to sustained recovery. The primary inferential (decision-making) quantity was the posterior distribution for the treatment assignment hazard ratio (HR), with HR greater than 1 indicating faster recovery. Decision thresholds and modeling parameters are as previously described[16] and provided in Supplement 2. The study design was estimated to have 80% power to detect an HR of 1.2 in the primary end point with approximately 1200 participants. To achieve this sample size in an ongoing platform trial, once 1200 participants had been randomized to the study group or matching placebo and had received the study drug, the study group became unavailable for new participants expressing interest in the platform. Some participants had already consented to participate but had not yet been randomized or received the study drug at the time of group closure, and these participants were allowed to continue as assigned.

The primary end point-adjusted model included the following predictor variables in addition to randomization assignment: age (as restricted cubic spline), sex, duration of symptoms at study drug receipt, calendar time (as restricted cubic spline, surrogate for SARS-CoV-2 variant/subvariant), vaccination status (no vaccination vs ≥1 dose), geographic region (Northeast, Midwest, South, West), call center indicator, and day 1 symptom severity. This adjusted model was prespecified. 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) using noninformative priors for all parameters. Secondary end points were not used for formal decision-making, and no decision threshold was selected. Due to an increased potential for type I error due to multiple comparisons, secondary end points should be interpreted as exploratory. The same covariates used in the primary end point model were used in the adjusted analysis of secondary end points, provided that the end point accrued enough events to be analyzed with covariate adjustment.

As a platform trial, the primary analysis is implemented separately for each study drug, where the placebo group

Table 1. Baseline Characteristics in a Trial of Higher-Dose Ivermectin for Mild to Moderate COVID-19

Variable	No. (%) Ivermectin (n = 602)	Placebo (n = 604)
Age, median (IQR), y	47.0 (38.0-58.0)	48.0 (39.0-58.0)
>50 y	272 (45.2)	279 (46.2)
Sex[a]		
Women	350 (58.1)	363 (60.1)
Men	249 (41.4)	240 (39.7)
Undifferentiated	3 (0.5)	0
Prefer not to answer	0	1 (0.2)
Race (not mutually exclusive)[b]		
American Indian or Alaska Native	9 (1.5)	11 (1.8)
Asian	52 (8.6)	44 (7.3)
Black or African American	45 (7.5)	48 (8.0)
Middle Eastern or North African	14 (2.3)	15 (2.5)
Native Hawaiian or Other Pacific Islander	2 (0.3)	6 (1.0)
White	448 (74.4)	461 (76.3)
None of the above	31 (5.2)	22 (3.6)
Prefer not to answer	14 (2.3)	14 (2.3)
Ethnicity		
Hispanic/Latino	136 (22.6)	124 (20.5)
Not Hispanic/Latino	466 (77.4)	480 (79.5)
Region[c]		
Midwest	112 (18.6)	111 (18.4)
Northeast	56 (9.3)	49 (8.1)
South	285 (47.3)	297 (49.2)
West	149 (24.8)	147 (24.3)
Recruited via call center[d]	61 (10.1)	42 (7.0)
BMI, median (IQR)	28.4 (24.5-32.8)	28.2 (24.9-32.5)
>30	236 (39.2)	223 (36.9)
Weight, median (IQR), kg	81.6 (70.3-97.5)	80.7 (69.4-93.0)
>88 kg	233 (38.7)	212 (35.1)
Medical history, No./total No. (%)[e]		
Hypertension	150/593 (25.3)	167/591 (28.3)
Smoking (past year)	89/593 (15.0)	69/591 (11.7)
Asthma	77/593 (13.0)	94/591 (15.9)
Diabetes	56/593 (9.4)	53/591 (9.0)
Heart disease	27/593 (4.6)	20/591 (3.4)
COPD	13/593 (2.2)	13/591 (2.2)
Cancer	11/588 (1.9)	13/589 (2.2)
Chronic kidney disease	5/593 (0.8)	6/591 (1.0)
COVID-19 vaccine status		
Vaccinated		
≥2 doses	499 (82.9)	509 (84.3)
1 dose	3 (0.5)	3 (0.5)
Not vaccinated	100 (16.6)	92 (15.2)
Time between symptom onset and receipt of drug, median (IQR), d	5 (3-7) [n = 600]	5 (3-7) [n = 603]
Time between symptom onset and enrollment, median (IQR), d	3 (2-5) [n = 599]	3 (2-5) [n = 602]
Symptom burden on study day 1[f]	n = 584	n = 593
No symptoms	37 (6.3)	32 (5.4)
Mild	362 (62.0)	341 (57.5)
Moderate	170 (29.1)	210 (35.4)
Severe	15 (2.6)	10 (1.7)
Allowable COVID-19 medications		
Monoclonal antibodies	25 (4.2)	22 (3.6)
Nirmatrelvir and ritonavir (Paxlovid)	15 (2.5)	26 (4.3)
Molnupiravir	1 (0.2)	5 (0.8)
Remdesivir	0	0

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

[a] Participants also had the option to select "unknown," although no participant selected this option.

[b] Participants may have selected any combination of the race descriptors, including "prefer not to answer." Consequently, the sum of counts over all race categories will not match the column total.

[c] 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, Nevada, Wyoming, Alaska, California, Hawaii, Oregon, and Washington.

[d] Patients may have alternatively been recruited at local clinical sites.

[e] Medical history was provided by participants responding to the following prompts: "Has a doctor told you that you have any of the following?" and "Have you ever experienced any of the following (select all that apply)" and "Have you ever smoked tobacco products?"

[f] Each day, participants were asked to "Please choose the response that best describes the severity of your COVID-19 symptoms today" with the response options being "no symptoms," "mild," "moderate," and "severe."

consists of contemporaneously randomized participants who met the eligibility criteria for that study drug; this includes both matched and contributing placebo. For this trial, the modified intention-to-treat analysis set for the primary analyses included all participants who received the study drug, and participants were analyzed as assigned. All available data were used to compare ivermectin vs placebo, regardless of postrandomization study drug treatment adherence. In both the primary and secondary end point analyses, missing data among covariates used for adjustment were addressed with conditional mean imputation because the amount of missing covariate data was minimal (<4%).

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

Table 2. Primary and Secondary Outcomes in a Trial of Higher-Dose Ivermectin for Mild to Moderate COVID-19

End point	No. (%)		Adjusted HR (95% CrI)[a]	Posterior *P* value (efficacy)
	Ivermectin (n = 602)	Placebo (n = 604)		
Primary				
Time to recovery[b]				
Skeptical prior (primary analysis)			1.02 (0.92 to 1.13)	.68
Skeptical prior (matched/unmatched placebos)			1.03 (0.93 to 1.14)	.70
Noninformative prior (sensitivity analysis)			1.03 (0.91 to 1.17)	.69
No prior (sensitivity analysis)			1.03 (0.91 to 1.17)	NE[c]
Secondary				
Mortality at day 28	1 (0.17)	0		
Hospitalization or death through day 28	5 (0.83)	2 (0.33)	2.51 (0.49 to 12.96)[c]	
Hospitalization, urgent care, ED visit, or death through day 28	34 (5.65)	36 (5.96)	1.0 (0.6 to 1.5)	.53
Clinical progression ordinal outcome scale[d]				
Day 7 (n = 1206)			OR, 1.61 (0.87 to 2.46)	.04
Day 14 (n = 1175)			OR, 2.14 (0.87 to 3.77)	.03
Day 28 (n = 1206)			OR, 2.61 (0.77 to 4.80)	.02
Time unwell, mean (95% CrI), d[e]	11.21 (11.01 to 11.41)	11.35 (11.16 to 11.54)	Difference, −0.14 (−0.51 to 0.24)	.77
Days of benefit, mean (95% CrI), d[f]	3.42 (3.18 to 3.64)	3.26 (3.03 to 3.48)	Difference, 0.16 (−0.28 to 0.61)	.77

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

[a] Unless otherwise noted, a highest-density credible interval. Adjustment variables for time to recovery, mortality, composite clinical endpoints, 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. For time to recovery, HR >1 is favorable for faster recovery for ivermectin compared with placebo. For the secondary end points, HR <1, OR <1, and difference <0 indicate favorability for ivermectin.

[b] Time to recovery is from receipt of study drug to achieving the third of 3 days of recovery. HR >1.0 is favorable for faster recovery for ivermectin compared with placebo.

[c] CI rather than CrI because low event rate precluded covariate adjustment.

[d] The description of the 8 levels of the clinical progression ordinal outcome scale is reported in Supplement 3. Proportional odds was not evaluated because the vast majority of participants were either at home with limitations or at home without limitations, resulting in a model that is approximately a logistic regression.

[e] Adjustment variables for mean time unwell in addition to randomization assignment include age and calendar time.

[f] $P(Y_A \text{ better } Y_B|$ day i) is the probability of a better outcome in the treatment A group on follow-up day i. The days benefit of A is the sum of $P(Y_A \text{ better } Y_B|$ day i) over each day of follow-up. For example, if the probability that outcomes in treatment group A were better than treatment group B was 0.8 for each day of follow-up (eg, 10 days), the days of benefit would be 0.8 × 10 = 8 days. Continuing the example, if the probability that outcomes in group B were better was 0.1 for each day of follow-up, the days of benefit of B would be 1 day. The difference in days of benefit is the days of benefit of A minus the days benefit of B. Using the values from the example, the difference in days of benefit (A minus B) would be 8 − 1 = 7 days.

Analyses were performed with R, version 4.1 (R Foundation for Statistical Computing) with primary packages of rstanarm, rmsb, and survival.[20] Additional details are available in Supplement 3.

Results

Study Population

Of the 2212 participants who consented for inclusion in the ivermectin group, 1334 were eligible to receive ivermectin and randomized to receive either ivermectin or placebo and 1206 were included in the modified intention-to-treat analysis because they received the study drug.

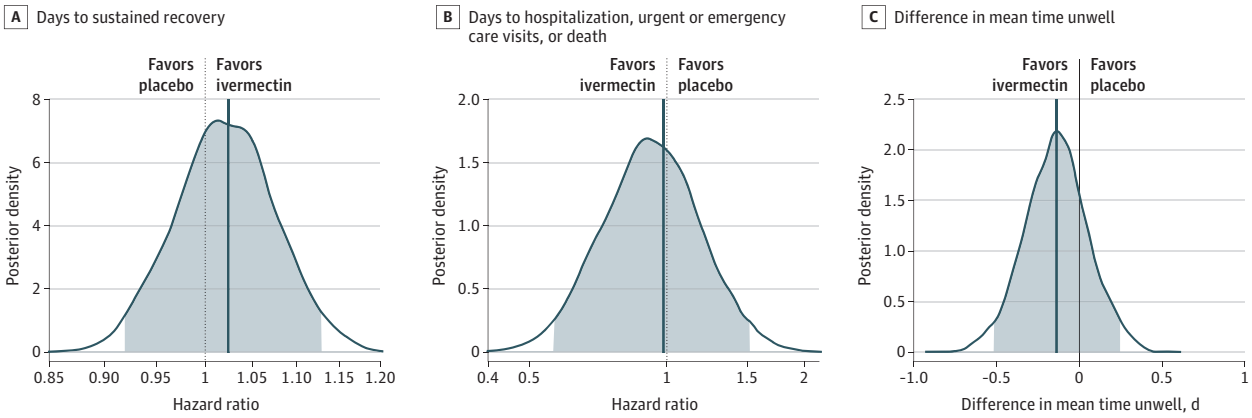
Those randomized to receive the active agent in the ivermectin group received the active study drug with a targeted maximum dose of 600 µg/kg (n = 602); the median (IQR) dose of ivermectin was 498 (465-532) µg/kg (eFigure 1 in Supplement 3). Of participants receiving placebo, 543 (90%) received matching placebo and 61 (10%) received placebo as part of the contributing placebo group (Figure 1).

The median (IQR) age of the participants was 48 (38-58) years and 551 (45.7%) were 50 years or older (**Table 1**). The population included 713 (59.1%) women and 93 participants (7.7%) identified as Black or African American, 96 (8.0%) identified as Asian, and 260 (21.6%) reported being of Latino/Hispanic ethnicity. Although not required for enrollment, high-risk comorbidities included BMI greater than 30 (38.1%), diabetes (9.2%), hypertension (26.8%), asthma (14.4%), and chronic obstructive pulmonary disease (2.2%). Overall, 1008 participants (83.6%) reported receiving at least 2 COVID-19 vaccine doses. Median (IQR) time from symptom onset to enrollment was 3 (2-5) days and to study drug receipt was 5 (3-7) days, with 60% receiving the study drug within 5 days of symptom onset (eFigure 2 in Supplement 3). eTable 1 in Supplement 3 presents baseline symptom prevalence and severity.

Primary Outcome

The median (IQR) time to recovery was 11 (11-12) days in the ivermectin group and 11 (11-12) days in the placebo group. The posterior probability for benefit was .68 for the primary outcome of time to recovery, with an HR of 1.02 (95% credible

Figure 2. Time to Sustained Recovery, Hospitalization, Urgent or Emergency Care Visits, or Death, and Mean Time Unwell



Thick 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.

interval [CrI], 0.92-1.13), where HR greater than 1 indicates faster symptom resolution with ivermectin (**Table 2** and **Figure 2**A). This posterior probability was below the prespecified threshold of .95 (Supplement 2). The data do not provide evidence of a conclusive treatment benefit when using a bayesian noninformative prior, no prior, with various approaches to imputing missing symptom data, or when restricting the analysis to participants who received the drug within 2 or 3 days of symptom onset and across severity of symptoms reported on day 1 (Table 2, **Figure 3**, and eFigures 3 and 4 in Supplement 3). The probability that ivermectin reduced symptom duration by 24 hours was less than 0.1%.

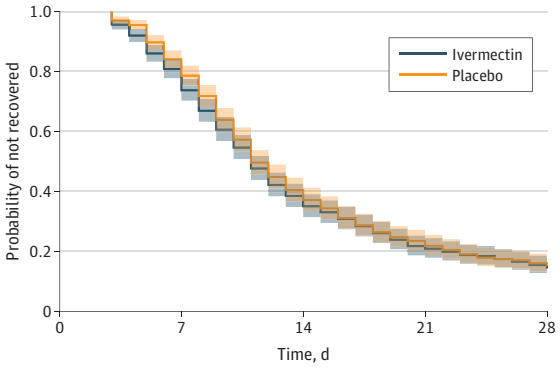
Secondary Outcomes

Hospitalizations and deaths were uncommon, with 5 events (including 1 death not attributable to COVID-19 or treatment) in the ivermectin group and 2 events (no deaths) in the placebo group (eFigure 5A in Supplement 3). Statistical comparisons were uninformative due to the few events. The composite secondary outcome of urgent care or ED visits, hospitalizations, or death was not shown to differ with ivermectin compared with placebo (5.6% [34/602] vs 6.0% [36/604]; HR, 1.0 [95% CrI, 0.6-1.5]; $P = .53$) (Table 2, Figure 2B, and eFigure 5B in Supplement 3). The difference in the amount of time spent feeling unwell with COVID-19 was estimated as 3 hours and 20 minutes faster with ivermectin (95% CrI, 12 hours better to 6 hours worse) than placebo (Figure 2C). The COVID Clinical Progression Scale scores at days 7, 14, and 28 did not meet prespecified thresholds for beneficial treatment effect (Supplement 3). For example, by day 7, a total of 532 of 602 participants (88%) in the ivermectin group and 549 of 604 (91%) in the placebo group were not hospitalized and did not report limitation of activities (eFigure 6 in Supplement 3).

Heterogeneity of Treatment Effect Analyses

Interaction tests for heterogeneity of treatment effect showed no overall influence of the putative treatment effect modifiers, even when all subgroup analyses across symptom severity were not adjusted for multiple comparisons (eFigure 7 in Supplement 3). The overall effect of timing from symptom onset to receipt of the study drug was not significant ($P = .15$ for heterogeneity). Similarly, no evidence existed for a different treatment effect of ivermectin compared with placebo for severity of symptoms, sex, age, BMI, calendar time, or vaccination status (eFigure 8 in Supplement 3).

Figure 3. Primary Outcome of Time to Sustained Recovery



No. of patients at risk

Ivermectin	602	487	232	131	92
Placebo	604	508	244	142	95

Recovery was defined as the third of 3 consecutive days without symptoms. Four participants were censored for nonresponse and all others were followed up until recovery, death, or the end of short-term 28-day follow-up. Median (IQR) time to recovery was 11 (11-12) days in the ivermectin group and 11 (11-12) days in the placebo group. Shaded regions denote the pointwise 95% CIs.

Adverse Events

Among participants who reported taking the study drug at least once, adverse events were similar in both groups (52/566 [9.2%] in the ivermectin group and 41/576 [7.1%] in the placebo group with adverse events) (eTable 2 in Supplement 3). Adverse events reported more than twice, only in the ivermectin group, included cognitive impairment (n = 4), blurred vision (n = 5),

light sensitivity to eye (n = 5), photophobia (n = 4), dizziness (n = 5), and asthma (n = 3). Serious adverse events were rare, with 5 in the ivermectin group and 3 in the placebo group. The death in the ivermectin group was reported to be an accident and not attributable to the study drug or COVID-19.

Discussion

Among a largely vaccinated outpatient population with mild to moderate COVID-19, treatment with ivermectin, with a targeted maximum dose of 600 µg/kg daily for 6 days, compared with placebo was not shown to improve time to recovery in more than 1200 participants in the US during a period of Omicron variant/subvariant circulation. No evidence of benefit was observed for secondary clinical outcomes, including the composite of hospitalization, death, or acute care visits. Hospitalization and death were uncommon in this largely vaccinated population. These findings do not support the use of ivermectin in outpatients with COVID-19.

Multiple large double-blind randomized clinical trials have failed to identify a clinically meaningful benefit of ivermectin when used at a targeted dose of 400 µg/kg daily for 3 days.[6,17] This large clinical trial addresses a potential gap in knowledge by testing (1) a higher daily dose (targeted maximum dose of 600 µg/kg) and (2) a longer (6-day) duration of ivermectin. Due to the lack of early-phase studies or animal-model studies to determine optimal dosing for a therapeutic drug, the appropriate dosing of ivermectin for COVID-19 was never determined. Modeling studies and a proof-of-concept clinical study have suggested that doses up to 600 µg/kg daily may achieve levels sufficient for in vitro antiviral activity[18,19]; however, a phase 2 trial testing ivermectin, 600 µg/kg daily for 7 days, and assessing a virologic end point of oropharyngeal SARS-CoV-2 polymerase chain reaction test result did not show measurable antiviral activity and was stopped for futility.[21] With weight-based dosing, there is additional variability in the range for dosing and, in this study, the dosing per weight strata was targeted to a maximum dose of 600 µg/kg; thus, the median dose across the study population of approximately 500 µg/kg is meaningfully higher than that achieved in studies that targeted a maximum dose of 400 µg/kg. For example, a previous study from the current platform trial that had a maximum targeted dose of ivermectin 400 µg/kg achieved a median dose of 343 µg/kg. The 600-µg/kg dose was safe and generally well tolerated, with a higher prevalence of the known self-resolving visual disturbances in the intervention group previously reported with similar doses of ivermectin for parasitic infections.[18,19]

The notable difference in baseline characteristics between these 2 cohorts is the completed vaccination rate, which was 84% for this study and 47% for the prior ivermectin 400 µg/kg group.[16] Hospitalizations and COVID-19–related clinical events were less common in this largely vaccinated cohort. The incidence of acute care visits, hospitalizations, or death was similar with ivermectin (5.7%) and placebo (6.0%), which was a result also observed in the 2 previous randomized trials of ivermectin 400 µg/kg in the US.[6,16]

This trial has several strengths. This was a double-blind, randomized, placebo-controlled nationwide trial with 93 enrolling sites and a call center that recruited participants from all 50 US states. The ivermectin 600 µg/kg group of the platform trial enrolled rapidly due to ongoing Omicron variant/subvariant surges and largely included vaccinated people, thus representing a highly relevant study population that also addresses a weakness of many other studies that excluded vaccinated people. Furthermore, standard-of-care therapies were allowable in this study, although utilization was low.

Limitations

This study has limitations. Due to infrequent hospitalization, this study cannot assess the effect of the intervention on this clinical outcome. Also, due to the remote nature of the trial, 60% of participants received the study drug within 5 days of symptom onset. Most outpatient COVID-19 antiviral trials have limited enrollment to participants within 5 days of symptom onset.[1,2] In this trial, no evidence of a differential treatment effect was observed based on shorter time to study drug receipt. Lastly, the primary end point–adjusted model did not include underlying comorbidities. Treatment effect was putatively expected to differ based on age and BMI, and these were included as covariates and evaluated for heterogeneity of treatment effect.

Conclusions

Among outpatients with mild or moderate COVID-19, treatment with ivermectin, with a targeted maximum dose of 600 µg/kg daily for 6 days, was not shown to improve time to sustained recovery compared with placebo. These findings do not support the use of ivermectin in outpatients with COVID-19.

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