Outpatient treatment of Covid-19 and the development of Long Covid over 10 months: A multi-center, quadruple-blind, parallel group randomized phase 3 trial.

Carolyn T. Bramante, MD, MPH[1]; John B. Buse, MD, PhD[2]; David Liebovitz, MD[3]; Jacinda Nicklas, MD, MPH[4]; Michael A. Puskarich, MD[5]; Ken Cohen, MD[6]; Hrishikesh Belani, MD, MS[7]; Blake Anderson, MS[8]; Jared D. Huling, PhD[9]; Christopher Tignanelli, MD, MS[10]; Jennifer Thompson, MD, MPH[11]; Matthew Pullen, MD[12]; Esteban Lemus Wirtz, BS[9]; Lianne Siegel, PhD[9]; Jennifer Proper, PhD[9]; David J. Odde, PhD[13]; Nichole Klatt, PhD[10]; Nancy Sherwood, PhD[14]; Sarah Lindberg, MPH[9]; Amy Karger, MD, PhD[15]; Kenny Beckman, PhD[15]; Spencer Erickson, BA[1]; Sarah Fenno, MPH[1]; Katrina Hartman, BA[1]; Michael Rose, MD[16]; Tanvi Mehta, MS;[9] Barkha Patel, MS[1]; Gwendolyn Griffiths, BA[1]; Neeta Bhat, MPH[1]; Thomas A. Murray, PhD*[9]; David R. Boulware, MD, MPH[12]*

**contributed equally*

1. General Internal Medicine, University of Minnesota, Minneapolis, MN
2. Endocrinology, University of North Carolina, Chapel Hill, ND
3. General Internal Medicine, Northwestern University, Chicago, IL
4. General Internal Medicine, University of Colorado, Denver, CO
5. Emergency Medicine, Hennepin County Medical Center, Minneapolis, MD
6. UnitedHealth Group, Optum Labs, Minnetonka, MN
7. Department of Medicine, Olive View - University of California, Los Angeles, CA
8. Atlanta Veterans Affairs Medical Center, Atlanta, Georgia; Department of Medicine, Emory University School of Medicine, Atlanta, GA
9. Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis, MN
10. Department of Surgery, Medical School, University of Minnesota, Minneapolis, MN
11. Department of Obstetrics and Gynecology, Vanderbilt University Medical Center, Nashville, TN
12. Infectious Diseases, University of Minnesota Medical School, Minneapolis, MN
13. Department of Biomedical Engineering University of Minnesota, Minneapolis, MN
14. Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN
15. Department of Laboratory Medicine and Pathology, Medical School, University of Minnesota, Minneapolis, MN
16. Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD

Corresponding author:
Carolyn Bramante, MD MPH
Assistant Professor, Division of General Internal Medicine and Pediatrics
University of Minnesota
717 Delaware St SE, MMC 1932
Minneapolis, MN 55414
Email: bramante@umn.edu

Background: Post-acute sequelae of Covid, termed "Long Covid", is an emerging chronic illness potentially affecting ~10% of those with COVID-19. We sought to determine if outpatient treatment with metformin, ivermectin, or fluvoxamine could prevent Long Covid.

Methods: COVID-OUT (NCT04510194) was a decentralized, multi-site trial in the United States testing three medications (metformin, ivermectin, fluvoxamine) using a 2x3 parallel treatment factorial randomized assignment to efficiently share placebo controls. Participants, investigators, care providers, and outcomes assessors were masked to randomized treatment assignment. Inclusion criteria included: age 30 to 85 years with overweight or obesity, symptoms <7 days, enrolled within <=3 days of documented SARS-CoV-2 infection. Long Covid diagnosis from a medical provider was a pre-specified secondary outcome assessed by monthly surveys through 300 days after randomization and confirmed in medical records.

Findings: Of 1323 randomized trial participants, 1125 consented for long-term follow up, and 95.1% completed >9 months of follow up. The median age was 45 years (IQR, 37 to 54), and 56% were female (7% pregnant). The median BMI was 30 kg/m^2 (IQR, 27 to 34). Overall, 8.4% reported a medical provider diagnosed them with Long Covid; cumulative incidence: 6.3% with metformin and 10.6% with matched placebo. The hazard ratio (HR) for metformin preventing Long Covid was 0.58 (95%CI, 0.38 to 0.88; P=0·009) versus placebo. The metformin effect was consistent across subgroups, including viral variants. When metformin was started within <4 days of symptom onset, the HR for Long Covid was 0.37 (95%CI, 0.15 to 0.95). No statistical difference in Long Covid occurred in those randomized to either ivermectin (HR=0.99; 95%CI, 0.59 to 1.64) or fluvoxamine (HR=1.36; 95%CI, 0.78 to 2.34).

Interpretations: A 42% relative decrease and 4.3% absolute decrease in the Long Covid incidence occurred in participants who received early outpatient COVID-19 treatment with metformin compared to exact-matching placebo.

Background

Infection with severe-acute respiratory coronavirus 2 (SARS-CoV-2) has been observed to cause Post-Acute Sequelae of Covid (PASC), commonly referred to as "Long Covid."[1] The experience of Long Covid is heterogenous, ranging from a single symptom to serious multi-organ involvement, and from mild and short lived to chronically debilitating.[1,2] The Centers for Disease Control and Prevention (CDC) estimates that Long Covid disproportionately affects racial and ethnic minority populations, which makes understanding and reducing the incidence of Long Covid critically important.[1,3,4]

Cross-sectional studies estimate that 15% of adults in the US have symptoms after SARS-CoV-2 infection that correlate with a diagnosis of Long Covid.[5] One of the largest prospective cohorts to study persistent symptoms after Covid-19 suggests that somatic symptoms could be attributable to SARS-CoV-2 in approximately 12% of adults in the cohort.[6] An important gap in the literature is understanding the proportion of adults infected with SARS-CoV-2 who are diagnosed with Long Covid by medical providers. Previous efforts have tried to understand Long Covid using electronic health record data, but reliably capturing the condition is challenging.[7,8] A code in the International Classification of Diseases, 10th Edition, was not added until October 2021, and there are concerns about its sensitivity and specificity.[1,9,10]

COVID-OUT was a phase 3 randomized, quadruple-blinded placebo-controlled trial of early outpatient treatment of SARS-CoV-2 that used a 2 by 3 factorial design of parallel treatments to assess: metformin, ivermectin, and/or fluvoxamine as early outpatient treatments for Covid-19. The study included monthly follow-up for 300 days to test the prespecified secondary hypothesis that early treatment of Covid-19 with the study drugs would prevent Long Covid.[11]

Methods

Study Design

COVID-OUT was an investigator-initiated, multi-site, phase 3, randomized, quadruple-blinded placebo-controlled clinical trial (ClinicalTrials.gov: NCT04510194).[11] Those blinded included: participants, care providers, investigators, and outcomes assessors. The trial was

decentralized, with no in-person contact with participants. Informed consent was obtained from each participant via electronic consent, or written consent if they did not have an email address.

Institutional review boards at each site, and Advarra centrally, approved the protocol. An independent data safety monitoring board (DSMB) oversaw safety and efficacy monitoring, and an independent monitor oversaw study conduct in compliance with the Declaration of Helsinki, Good Clinical Practice Guidelines, and local requirements.[12]

Participants

Participants were recruited remotely with online advertising, patient portal messages, and health-system wide advertising at the six participating institutions. Eligibility criteria included: age 30 to 85 years with overweight or obesity by self-reported body mass index (BMI); documentation of confirmed SARS-CoV-2 infection; <7 days of symptoms; and no known prior infection with SARS-CoV-2. Participants had to provide consent within 3 days of their positive SARS-CoV-2 test. Participants were excluded if they were already taking one of the study medications or if they had already received an EUA-approved Covid-19 treatment. Home medications and treatments received after enrollment were recorded. Vaccination against SARS-CoV-2 was not an exclusion criterion.

Pregnant and lactating women were not excluded, which is important given that pregnant women are at risk for poor outcomes from Covid-19 and are excluded from 99% of non-obstetric clinical trials.[13,14] Pregnant and lactating women were randomized 1:1 to metformin or placebo, not fluvoxamine or ivermectin due to less established literature for safety during pregnancy and lactation for those medications, whereas a large body of literature supports the safety of metformin during pregnancy and lactation.[15,16]

The *a priori* primary sample population was a modified intention to treat (mITT) sample. Participants who did not receive the study medication; were hospitalized at the time of delivery; or reported not taking any study doses were excluded from the mITT.[11]

Randomization and Masking

The trial design simultaneously assessed three distinct oral medications (metformin, ivermectin, fluvoxamine) using a two by three parallel treatment factorial design to efficiently

share placebo controls in three separate trials. Participants were randomized with equal probability to each arm open at the time of enrollment. Randomization was stratified by study site and schedules were pre-generated using the mass-weighted urn design which limits deviations from the targeted equal allocation similar to permuted blocks.

The trial opened with a 1:1 randomization to metformin versus placebo on December 30, 2020. The factorial design opened May 21, 2021 at which point participants were randomized 1:1:1:1:1:1 to each study arm as described in a previous publication and shown in **Figure 1 and Figure S2**.[11] The fluvoxamine randomization was closed early on January 7, 2022 by the independent DSMB. Enrollment ended January 28, 2022 and all investigators except the unblinded statistician remained blinded to group-level results through February 14, 2022. The Day 300 follow-up ended Nov 27, 2022. All investigators, outcome assessors, treating clinicians, and participants remain blinded to individual treatment allocations.

Manufacturers provided exact-matching placebo pills. Because two of the arms had two active medications, each participant received two types of pills to maintain the blind in the factorial design: all participants received metformin or exact-matching metformin placebo; and a subset received fluvoxamine, ivermectin, or their exact-matching placebo.

Procedures

The medications were pre-packaged into pill boxes to speed delivery to participants and assure participants took the correct number of each type of pill. Study medication was sent via same-day courier or overnight shipping to participants which meant the average time from consent to ingestion of the first dose of study drug was <1 day.

The metformin dose was titrated over 6 days: 500mg on day 1; 500mg twice daily for 4 days; then 500mg mornings and 1000mg evening through 14 days. The ivermectin dose was 390-470 mcg/kg per day for 3 days (median 430 mcg/kg/day). Fluvoxamine was 50mg on Day 1 followed by 50mg twice daily through 14 days.

The active follow-up period for the trial was 28 days. Beginning at 60 days post randomization, surveys were sent every 30 days through 300 days (10 months) after randomization via automated email or other per patient preference. Ten-month follow-up for Long Covid was not in the original protocol as Long Covid was not a known entity in fall 2020. The pre-specified secondary endpoint on Long Covid was added to the protocol in April 2021,

and survey tools were IRB-approved in July 2021 (**Table S8).** Participants enrolled before the Long Covid surveys were approved were contacted for reconsent to receive the Long Covid survey assessment **(Figure 1).**

Outcomes

Understanding whether metformin, ivermectin, or fluvoxamine prevent the development of Long Covid was a separate question than whether they prevented severe Covid-19 in the first 14 days.[17] The primary method for ascertaining Long Covid was participant-reported receipt of a Long Covid diagnosis from a medical provider. Participants were asked whether a medical provider had given them a diagnosis of Long Covid, and if so when and what type of provider gave this diagnosis (Table S7). Participants consented for medical record review so these diagnoses could be confirmed in the electronic health record. This means of ascertaining Long Covid was chosen as an important balance of sensitivity and specifciity because the definition of Long Covid is rapidly changing, fluctuating symptoms are challenging to assess, and electronic health record codes lack specificity and sensitivity.[18,19]

Statistical Analysis

A factorial, 2 by 3 design of distinct, parallel treatments with exact-matching placebo pills allows the simultaneous conduct of three separate randomized trials that efficiently share concurrently randomized, blinded controls. Correcting for multiple comparisons for a factorial design of distinct parallel treatments is not indicated.[20,21] Accordingly, factorial design trials often present medications separately.[22-24] Because the overall structure of this 2 x 3 factorial design trial is that all participants received either metformin or metformin placebo, and only a subset received ivermectin, fluvoxamine, or their exact matching placebo **(Figure S1)**, we present the metformin trial in the main manuscript and the fluvoxamine and ivermecin trials in the supplement.

The comparison groups for each study drug consists of persons who were assigned the active version of the drug versus those who were at risk of being assigned to the active version of the drug but were assigned a blinded control instead (**Figure S1, Figure S2).** By design, the active and control comparison groups have balanced numbers of persons receiving active and placebo version of the other study drug.

Reports of Long Covid diagnosis by medical provider were analyzed using a time-to-event approach with time denoting the time from randomization. This approach appropriately accounts for participants who did not fill out all the potential Long Covid surveys, and thus were lost to follow up prior to Day 300. For persons who reported a Long Covid diagnosis, the date of their diagnosis was set to the 15th day of the earliest month in which they reported receiving the diagnosis. For persons who reported a Long Covid diagnosis but did not provide valid timing of diagnosis information (n=9), (i.e. they provided a month where the last day in that month occurred earlier than 15 days from their randomization) the date of their diagnosis was set to the study day of the earliest Long Covid survey on which they reported the diagnosis. Participants who did not report a Long Covid diagnosis were censored based on the study day of their latest Long Covid survey. A time-to-event approach also adds knowledge about this new disease state by reporting when individuals are receiving diagnoses of Long Covid.

Role of funding source

The trial was funded by the Parsemus Foundation, Rainwater Charitable Foundation, Fast Grants, and the UnitedHealth Group Foundation. The funders had no influence on the design or conduct of the trial and were not involved in data collection or analysis, writing of the manuscript, or decision to submit for publication. The authors assume responsibility for trial fidelity and the accuracy and completeness of the data and analyses.

Results

Study Participants

Of the original 1,323 randomized participants who received study medication, 1,125 consented for Long Covid follow-up and completed at least one survey on or after Day 180, 564 in the metformin group and 561 in the blinded control group. The median age was 45 years (IQR 37 to 54), 56% were female of whom 7% were pregnant. Overall, 2.0% identified as Native American; 3.7% as Asian; 7.4% as Black/African American; 82.8% as white; and 12.7% as Hispanic/Latino. The median BMI was 29.8 kg/m^2 (IQR 27.0 to 34.2), and 51% had a BMI >30kg/m^2. The median days from symptom onset to study drug initiation was 5 days (IQR 4 to 6), and 47% started study drug within 4 days or less of symptom onset. Overall, 55% (n=618) had received the primary Covid-19 vaccination series, including 5.1% (n=57) who received an initial booster, before enrollment (**Table 1)**.

Overall 95% (1070/1125) completed at least 9 months of follow up or reported a Long Covid diagnosis. The loss to follow-up before Day 270 was 5.1% (29/564) in the metformin group and 4.6% (26/561) in the placebo group.

Long Covid Diagnosis

Overall, 8.4% (94/1125) responded Yes to the question: "Has a medical provider told you that you have Long Covid?" Most of the Long Covid diagnoses were made by primary care providers, n=72 (73.4%); followed by a provider specializing in Long Covid, n=4 (4.3%); other specialists, n=8 (cardiology n=3, neurology n=1, infectious disease n=1, otolaryngologist n=1, pulmonologist n=1); emergency department n=3; in a hospital n=2; urgent care n=2; 1 by chiropractor; 1 other; 1 missing.

Among those randomized to metformin, the cumulative incidence for developing Long Covid was 6.3% (95% CI 4.2% to 8.2%) as compared with 10.6% (8.0% to 13.1) in the blinded, identical-matched placebo controls (**Figure 1, Table 2).** For metformin versus placebo, the hazard ratio for developing Long Covid was 0.58 (95% CI 0.38, to 0.88; P=0·009). The hazard ratio did not appreciably change when adjusting for vaccination and receipt of other study medicines in the factorial randomization (**Table 2**).

Heterogeneity of treatment effect was assessed for metformin across a priori subgroups of baseline risk factors (**Figure 3**). The effect of metformin for preventing Long Covid was consistent across subgroups, including across other study drugs and viral variants. When started within <4 days of symptom onset, the effect of metformin preventing Long Covid was potentially greater (Hazard Ratio = 0.37; 95% CI, 0.15 to 0.95) as compared with those who started metformin ≥4 days (Hazard Ratio = 0.64; 95% CI, 0.40 to 1.03).

Participants who reported receiving a provider-diagnosis of Long Covid were more likely to report having their work or leisure disrupted by ≥1 ongoing symptom after their Covid-19 infection **(Figure 4).**

Ivermectin and Fluvoxamine Randomization

Neither ivermectin or fluvoxamine had any benefit for prevention of Long Covid. For those participants randomized to ivermectin, the cumulative incidence of Long Covid was 8.0%

(95% CI 5.2% to 10.8%) as compared with 7.5% (95% CI 4.7% to 10.2%) in blinded, idenitical-matched placebo controls (**Table S4, Figure S4**). The hazard ratio for ivermectin versus control was 0.99 (95% CI, 0.59 to 1.64), and the ivermectin findings were consistent across apriori subgroups without any sign of preventative benefit in any subgroup (**Figure S5).** Among those randomized to fluvoxamine, the cumulative incidence of Long Covid was 10.1% (95% CI, 6.6% to 13.5%) as compared with 7.5% (95% CI 4.4% to 10.5% in the blinded, identical-matched placebo controls (**Table S5 and Figure S6**). The hazard ratio for fluvoxamine versus blinded control was 1.36 (95% CI, 0.79 to 2.39). The fluvoxamine findings were consistent across a priority subgroups (**Figure S7).** The HR's for ivermectin and fluvoxamine did not change when adjusting for vaccination and receipt of other study meds (**Tables S4 and S5**).

Risk Factors for Long Covid

Within this cohort, 11.1% (70/561) of female participants compared to the 4.9% (24/470) of male participants had a diagnosis of Long Covid. Second, those vaccinated with at least the primary SARS-CoV-2 vaccine series had a lower risk of developing Long Covid, 6.6% (41/618) as compared with 10.5% in those unvaccinated. Among the 57 participants who had received a booster vaccination prior to enrollment, only 1 (1.8%) participant developed Long Covid. Long Covid incidence did not differ across variant time periods (Range, 7.9% to 8.4%). **Table S6** shows proportion of participants who developed Long Covid and those who did not by baseline risk factors.

Discussion

COVID-OUT was an investigator-initiated, multi-site, phase 3, randomized, quadruple-blinded, placebo-controlled clinical trial of outpatient treatment of Covid-19 that followed participants for 10 months to assess whether early treatment prevented the development of Long Covid. Treatment with metformin during acute Covid-19 infection prevented over 40% of Long Covid cases, with 6.3% of participants in the metformin group and 10.6% in the placebo group receiving a diagnosis of Long Covid from a medical provider. Metform preventing over 40% of cases of Long Covid is consistent with the results for the acute Covid outcomes of the trial, in which metformin prevented over 40% of emergency department visits, hospitalizations, and

death due to Covid (OR 0.58, 95% CI 0.35 to 0.94) by Day 14.[11,25] By Day 28, those in the metformin group were also less likely to be hospitalized, 1.34% (8/596) versus 3.16% (19/601) of those receiving placebo. There was no decreased incidence of Long Covid attributable to ivermectin or fluvoxamine in this trial, and this is also consistent with the results for acute Covid outcomes for ivermectin and fluvoxamine.

A large recent observational analysis of electronic medical records reported that 12% of somatic symptoms could be attributed to infection with SARS-CoV-2.[6] This incidence of Long Covid is reasonably aligned with the findings in our trial, in which 8.4% of participants reported receiving a diagnosis of Long Covid from a provider, and approximately 5% who did not report a diagnosis of Long Covid did report that their work or leisure were affected by ongoing symptoms. Several factors could influence whether an individual receives a diagnosis of Long Covid from a medical provider within 10 months of infection, such as access to medical care, competing demands that prevent receiving medical care, willingness to seek medical care for post-Covid symptoms, and provider awareness of Long Covid as a diagnosis. Such factors would be expected to be equally distributed between treatment arms by the randomization in this clinical trial and should not influence our interpretation of treatment effects.

Metformin's prevention of over 40% severe Covid-19 in the Covid-Out trial is consistent with 2 other randomized trials that assessed metformin for prevention of Covid-19. The first trial assessed 1,500mg per day with no dose titration, which would be expected to cause side effects in a large number of individuals. Thus the per-protocol group may be particularly informative in that trial, and it showed a similar effect size (OR 0.61, 95% CI 0.27 to 1.38).[26] Another recent randomized trial suggested a similar effect, however the trial had only 20 participants.[27]

While the effect size for metformin preventing severe Covid-19 and Long Covid was similar, the number of cases of Long Covid was higher in our trial than the number of emergency department visits or hospitalizations for acute Covid-19. This supports the current understanding that Long Covid occurs in individuals who did not have severe Covid-19.[28] The exact pathophysiology of Long Covid is unknown but is likely multi-factorial, including the inflammatory cascade during acute infection and persistent viral replication.[29] Mechanistic in silico modeling predicts that translation of SARS-CoV-2 viral proteins is an especially sensitive

target for inhibition of viral replication,[30,31] and previous studies show metformin capable of suppressing protein translation via mTOR inhibition.[30,32]

Experimentally, metformin has *in vitro* activity at a physiologically relevant dose against SARS-CoV-2 in cell culture and in human lung tissue, *ex vivo*.[27,33-35] Larger effects for therapies started earlier in the course of infection support an anti-viral mechanism. Both the healthcare utilization component of the primary outcome and subsequent development of Long Covid were assessed by subgroup of initiation time from symptom onset. Those that started metformin in less than 4 days from symptom onset where compared to those starting metformin 4 or more days from symptom onset. The hazard ratios for outcomes were shifted further to the left when the study drug was started sooner, consistent with an anti-viral mechanism of action.

In addition to in vitro and in vivo activity against SARS-CoV-2, metformin has been extensively studied for actions relevant to oxidative stress and inflammation.[36] These actions have been studied in the setting of SARS-CoV-2 infection as well. In human bronchial and lung epithelial cell lines infected with SARS-CoV-2, metformin restored autophagic flux, inhibited cleavage of caspase-1 by non-structural protein 6 (NSP6), and inhibited maturation and release of interleukin-1β and interleukin-18.[37] Metformin also prevented a senescent phenotype induced by SARS-CoV-2 infection in dopaminergic neurons *in vitro,* which could be relevant to neurocognitive sequelae of infection seen in Long Covid.[38]

There were no issues with safety in this phase 3 trial of metformin in adults without diabetes.[11] Safety concerns for metformin have centered around a risk of lactic acidosis, but that historical concern was driven by experience with other biguanides. Several large studies and Cochrane reviews have demonstrated no increased risk of lactic acidosis, and in fact fewer cases of lactic acidosis, in persons on metformin.[39,40] This includes adults with heart failure.[41,42] Metformin is also safe in adults with kidney disease and should not be withheld from persons with glomerular filtration rates >30ml/min/1.73m^2, and perhaps even lower, because of associations with improved macrovascular outcomes in persons with chronic kidney disease.[36,39]

Metformin treats diabetes largely by preventing hepatic gluconeogenesis, not by lowering blood glucose levels, and thereby the risk of hypoglycemia is very low, including in persons without diabetes. Metformin's safety has also been demonstrated in children and during lactation

and pregnancy.[16,43-47] Guidelines recommend metformin should no longer be stopped upon hospital admission or for surgery.[48-51]

The Covid-Out trial does not indicate whether or not metformin would be effective at preventing Long Covid if started at the time of emergency department visit or hospitalization for Covid-19, nor whether metformin would be effective as treatment in persons who already have Long Covid. With the burden of Long Covid on society, confirmation is urgently needed in a trial that addresses our study's limitations in order to translate these results into practice and policy. The p-value (0.009) for metformin preventing Long Covid is low enough that it would still be less than 0.05 after applying a Bonferonni correction for the multiple testing of the primary and all four secondary clinical outcomes in this trial.[52] Further clinical trials could also assess whether there is synergy with other treatments, such as nirmatrelvir in vaccinated populations or in those with prior Covid-19.

Limitations

When the Long Covid assessment was added to the trial, little was known about the best assessment tool for incident Long Covid in clinical trial participants. The use of a Long Covid diagnosis based on the documented professional judgement of a medical provider, as well as the long duration of follow-up, would address some of the issues around the changing nature of this disease definition. Additionally, factors that may affect the receipt of a Long Covid diagnosis by a medical provider would be distributed between treatment arms in this randomized trial. The quadruple blinding also limits potential biases compared to observational cohorts or case-control studies that assess Long Covid.

This trial excluded low-risk individuals: those with a normal BMI and those younger than 30 years, and whether these findings would generalize to those populations is unknown. Additionally, it is unknown if these findings would generalize to early outpatient treatment of SARS-CoV-2 in someone who had previously been infected with SARS-CoV-2. The sample of participants in this trial was mostly white (82.8%), compared to 76% of the US population; and only 12.7% identified as Latino or Hispanic.[53] With 56% of trial participants being female, sex was well balanced. Of females, 7% in the trial were pregnant being one of few randomized trials of outpatient Covid-19 treatment to enroll pregnant women.[11,54]

Conclusions

Outpatient treatment with metformin at the time of SARS-CoV-2 infection decreased the development of Long Covid by 42% in a phase 3 randomized trial, and by over 50% when started less than 4 days from symptom onset. This finding is consistent with the 42% reduction in healthcare utilization for severe Covid-19 with metformin in the first 14 days of the trial. Fluvoxamine and ivermectin did not decrease the development of Long Covid, which is consistent with outcomes in the first 14 days of the trial. These results are highly relevant to the current state of the pandemic because the study sample was approximately half vaccinated, and despite the 10-month follow-up of these outcome, the trial enrolled during Omicron wave. Long Covid is a significant public health emergency that may have lasting health, mental health, and economic sequelae, especially in socioeconomically marginalized groups, and metformin is safe, low-cost, and widely available.

Research in context.

Evidence before this study

Few randomized trials of outpatient treatment of Covid-19 have followed participants for 10 months to assess the effect of early treatments on preventing Long Covid. Emerging clinical, observational, and pre-clinical data show metformin inhibits SARS-CoV-2 and prevents severe Covid-19.

Added value of this study

This is the first phase 3 randomized, placebo controlled, randomized clinical trial of an outpatient treatment that prevents the development of Long Covid by over 40%. Additionally, this is one of the few Covid-19 treatment trials to include pregnant women.[13,14] Metformin is safe, inexpensive, widely available, and has few contra-indications or medication interactions.

Implications of all the available evidence

According to workers compensation insurers, 71% of persons with Long Covid required either continuing medical treatment or were unable to work for six months or more.[55] Taking the necessary steps to understand metformin as an intervention to prevent Long Covid is an urgent public health need.

References

1. CDC. Post-Covid Conditions: Information for Healthcare Providers. 2022. https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-conditions.html (accessed 11 Dec 2022).
2. Yang C, Zhao H, Tebbutt SJ. A glimpse into long COVID and symptoms. *The Lancet Respiratory medicine* 2022; **10**(9): e81.
3. Cutler DM. The Costs of Long COVID. *JAMA Health Forum* 2022; **3**(5): e221809.
4. CDC. Long Covid. 2022. https://www.cdc.gov/nchs/covid19/pulse/long-covid.htm.
5. Perlis RH, Santillana M, Ognyanova K, et al. Prevalence and Correlates of Long COVID Symptoms Among US Adults. *JAMA Netw Open* 2022; **5**(10): e2238804.
6. Ballering AV, van Zon SKR, Olde Hartman TC, Rosmalen JGM. Persistence of somatic symptoms after COVID-19 in the Netherlands: an observational cohort study. *Lancet (London, England)* 2022; **400**(10350): 452-61.
7. Rando HM, Bennett TD, Byrd JB, et al. Challenges in defining Long COVID: Striking differences across literature, Electronic Health Records, and patient-reported information. *medRxiv* 2021; **doi**: 10.1101/2021.03.20.21253896.
8. Pfaff ER, Girvin AT, Bennett TD, et al. Identifying who has long COVID in the USA: a machine learning approach using N3C data. *Lancet Digit Health* 2022; **4**(7): e532-e41.
9. McGrath LJ, Scott AM, Surinach A, Chambers R, Benigno M, Malhotra D. Use of the Postacute Sequelae of COVID-19 Diagnosis Code in Routine Clinical Practice in the US. *JAMA network open* 2022; **5**(10): e2235089.
10. Pfaff ER, Girvin AT, Bennett TD, et al. Identifying who has long COVID in the USA: a machine learning approach using N3C data. *The Lancet Digital Health* 2022; **4**(7): e532-e41.

11. Bramante CT, Huling JD, Tignanelli CJ, et al. Randomized Trial of Metformin, Ivermectin, and Fluvoxamine for Covid-19. *The New England journal of medicine* 2022; **387**(7): 599-610.
12. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013; **310**(20): 2191-4.
13. Jorgensen SCJ, Miljanic S, Tabbara N, et al. Inclusion of pregnant and breastfeeding women in nonobstetrical randomized controlled trials. *American Journal of Obstetrics & Gynecology MFM* 2022; **4**(6): 100700.
14. Villar J, Soto Conti CP, Gunier RB, et al. Pregnancy outcomes and vaccine effectiveness during the period of omicron as the variant of concern, INTERCOVID-2022: a multinational, observational study. *The Lancet* 2023; **401**(10375): 447-57.
15. Drugs and Lactation Database (LactMed®) [Internet]. National Institute of Child Health and Human Development, 2006.
16. Kalafat E, Sukur YE, Abdi A, Thilaganathan B, Khalil A. Metformin for prevention of hypertensive disorders of pregnancy in women with gestational diabetes or obesity: systematic review and meta-analysis of randomized trials. *Ultrasound Obstet Gynecol* 2018; **52**(6): 706-14.
17. Higgins AM, Berry LR, Lorenzi E, et al. Long-term (180-Day) Outcomes in Critically Ill Patients With COVID-19 in the REMAP-CAP Randomized Clinical Trial. *Jama* 2023; **329**(1): 39-51.
18. Holmes C, Brown M, Hilaire DS, Wright A. Healthcare provider attitudes towards the problem list in an electronic health record: a mixed-methods qualitative study. *BMC Med Inform Decis Mak* 2012; **12**: 127.
19. Davis HE, Assaf GS, McCorkell L, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *eClinicalMedicine* 2021; **38**.
20. Molloy SF, White IR, Nunn AJ, Hayes R, Wang D, Harrison TS. Multiplicity adjustments in parallel-group multi-arm trials sharing a control group: Clear guidance is needed. *Contemp Clin Trials* 2022; **113**: 106656.
21. Parker RA, Weir CJ. Non-adjustment for multiple testing in multi-arm trials of distinct treatments: Rationale and justification. *Clin Trials* 2020; **17**(5): 562-6.
22. Manson JE, Cook NR, Lee I-M, et al. Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease. *New England Journal of Medicine* 2018; **380**(1): 33-44.
23. Manson JE, Cook NR, Lee IM, et al. Marine n−3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer. *New England Journal of Medicine* 2018; **380**(1): 23-32.
24. Declercq J, Van Damme KFA, De Leeuw E, et al. Effect of anti-interleukin drugs in patients with COVID-19 and signs of cytokine release syndrome (COV-AID): a factorial, randomised, controlled trial. *Lancet Respir Med* 2021; **9**(12): 1427-38.
25. Pocock SJ, Stone GW. The Primary Outcome Fails — What Next? *New England Journal of Medicine* 2016; **375**(9): 861-70.
26. Reis G, dos Santos Moreira Silva EA, Medeiros Silva DC, et al. Effect of early treatment with metformin on risk of emergency care and hospitalization among patients with COVID-19: The TOGETHER randomized platform clinical trial. *The Lancet Regional Health – Americas* 2022; **6**.
27. Ventura-López C, Cervantes-Luevano K, Aguirre-Sánchez JS, et al. Treatment with metformin glycinate reduces SARS-CoV-2 viral load: An in vitro model and randomized, double-blind, Phase IIb clinical trial. *Biomed Pharmacother* 2022; **152**: 113223.

28. Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. *Nature Reviews Microbiology* 2023; **21**(3): 133-46.
29. Mantovani A, Morrone MC, Patrono C, et al. Long Covid: where we stand and challenges ahead. *Cell Death Differ* 2022; **29**(10): 1891-900.
30. Castle BT, Dock C, Hemmat M, et al. Biophysical modeling of the SARS-CoV-2 viral cycle reveals ideal antiviral targets. *bioRxiv* 2020: 2020.05.22.111237.
31. Gordon DE, Jang GM, Bouhaddou M, et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature* 2020; **583**(7816): 459-68.
32. Karam BS, Morris RS, Bramante CT, et al. mTOR inhibition in COVID-19: A commentary and review of efficacy in RNA viruses. *Journal of medical virology* 2021; **93**(4): 1843-6.
33. Gordon DE, Jang GM, Bouhaddou M, et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature* 2020; **583**(7816): 459-68.
34. Parthasarathy H, Tandel D, Siddiqui AH, Harshan KH. Metformin suppresses SARS-CoV-2 in cell culture. *Virus research* 2022; **323**: 199010.
35. Schaller MA, Sharma Y, Dupee Z, et al. Ex vivo SARS-CoV-2 infection of human lung reveals heterogeneous host defense and therapeutic responses. *JCI Insight* 2021; **6**(18).
36. Sun T, Liu J, Xie C, Yang J, Zhao L, Yang J. Metformin attenuates diabetic renal injury via the AMPK-autophagy axis. *Exp Ther Med* 2021; **21**(6): 578.
37. Sun X, Liu Y, Huang Z, et al. SARS-CoV-2 non-structural protein 6 triggers NLRP3-dependent pyroptosis by targeting ATP6AP1. *Cell Death Differ* 2022; **29**(6): 1240-54.
38. Chen S, Han Y, Yang L, et al. SARS-CoV-2 Infection Causes Dopaminergic Neuron Senescence. *Res Sq* 2021.
39. Inzucchi SE, Lipska KJ, Mayo H, Bailey CJ, McGuire DK. Metformin in patients with type 2 diabetes and kidney disease: a systematic review. *JAMA* 2014; **312**(24): 2668-75.
40. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2010; **2010**(4): CD002967.
41. Eurich DT, Weir DL, Majumdar SR, et al. Comparative safety and effectiveness of metformin in patients with diabetes mellitus and heart failure: systematic review of observational studies involving 34,000 patients. *Circ Heart Fail* 2013; **6**(3): 395-402.
42. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016; **18**(8): 891-975.
43. Hyer S, Balani J, Shehata H. Metformin in Pregnancy: Mechanisms and Clinical Applications. *Int J Mol Sci* 2018; **19**(7).
44. Brand KMG, Saarelainen L, Sonajalg J, et al. Metformin in pregnancy and risk of adverse long-term outcomes: a register-based cohort study. *BMJ Open Diabetes Res Care* 2022; **10**(1): e002363.
45. Hosey CM, Halpin K, Yan Y. Considering metformin as a second-line treatment for children and adolescents with prediabetes. *Journal of pediatric endocrinology & metabolism : JPEM* 2022; **35**(6): 727-32.
46. Masarwa R, Brunetti VC, Aloe S, Henderson M, Platt RW, Filion KB. Efficacy and Safety of Metformin for Obesity: A Systematic Review. *Pediatrics* 2021; **147**(3).

47. Warnakulasuriya LS, Fernando MMA, Adikaram AVN, et al. Metformin in the Management of Childhood Obesity: A Randomized Control Trial. *Child Obes* 2018; **14**(8): 553-65.
48. Pasquel FJ, Umpierrez GE. Web Exclusive. Annals for Hospitalists Inpatient Notes - How We Treat Hyperglycemia in the Hospital. *Annals of internal medicine* 2021; **174**(8): Ho2-ho4.
49. Chang LL, Umpierrez GE, Inzucchi SE. Management of Hyperglycemia in Hospitalized, Non-Critically Ill Adults. *The New England journal of medicine* 2022; **387**(11): 1040-2.
50. Haltmeier T, Benjamin E, Beale E, Inaba K, Demetriades D. Insulin-Treated Patients with Diabetes Mellitus Undergoing Emergency Abdominal Surgery Have Worse Outcomes than Patients Treated with Oral Agents. *World J Surg* 2016; **40**(7): 1575-82.
51. Reitz KM, Marroquin OC, Zenati MS, et al. Association Between Preoperative Metformin Exposure and Postoperative Outcomes in Adults With Type 2 Diabetes. *JAMA Surg* 2020; **155**(6): e200416.
52. Gates S. Statistical significance and clinical evidence. *The Lancet Oncology* 2020; **21**(3): e118.
53. Census. https://www.census.gov/quickfacts/fact/table/US/PST045221.
54. Skipper CP, Pastick KA, Engen NW, et al. Hydroxychloroquine in Nonhospitalized Adults With Early COVID-19 : A Randomized Trial. *Annals of internal medicine* 2020; **173**(8): 623-31.
55. NYSIF. NYSIF Releases Report on Long-Term Impacts of Covid-19. 2023. https://ww3.nysif.com/en/FooterPages/Column1/AboutNYSIF/NYSIF_News/2023/20230124LongCovid.

Funding

Dr. Bramante was supported by grants (KL2TR002492 and UL1TR002494) from the National Center for Advancing Translational Sciences (NCATS) of the National Institutes of Health (NIH) and by a grant (K23 DK124654–01-A1) from the National Institute of Diabetes and Digestive and Kidney Diseases of the NIH. Dr. Buse was supported by a grant (UL1TR002489) from NCATS. Dr. Nicklas was supported by a grant (K23HL133604) from the National Heart, Lung, and Blood Institute of the NIH. Dr. Odde was supported by the Institute for Engineering in Medicine, the Earl E. Bakken Professorship for Engineering in Medicine, and by grants (U54 CA210190 and P01 CA254849) from the National Cancer Institute of the NIH. Dr. Murray was supported in part by the Medtronic Faculty Fellowship.

The fluvoxamine placebo tablets were donated by the Apotex pharmacy. The ivermectin placebo and active tablets were donated by the Edenbridge pharmacy. The trial was funded by the Parsemus Foundation, Rainwater Charitable Foundation, Fast Grants, and the UnitedHealth Group Foundation. The funders had no influence on the design or conduct of the trial and were not involved in data collection or analysis, writing of the manuscript, or decision to submit for publication. The authors assume responsibility for trial fidelity and the accuracy and completeness of the data and analyses.

Acknowledgements

We thank the participants in the trial. We would also like to thank many others who made this trial possible, including: The M Health Fairview Obesity Medicine Research Advisory Panel, particularly Stacy Dean and Yelena Kibasova. The numerous volunteers who helped fold and tape boxes and place labels so that the study team could focus on enrollment and follow-up. Volunteers include: Stacy Washington, Ben Tsech, Sasha Fraser, Evan Fraser, Piotr Bednarski, Paloma Good, Josie June Veit.

University of Minnesota, M Health Fairview: Program in Health Disparities Research; Clinical and Translational Science Institute's (CTSI) Best Practices Integrated Informatics Core (BPIC); Medical School Communications; M Health Fairview Recruiting Office; Department of Surgery Clinical Trials Office; Fairview Investigational Drug Services Pharmacy; Sponsored Projects Administration; Advanced Research and Diagnostic Laboratory; Center for Pediatric Obesity Medicine; UMN Institute for Engineering in Medicine; CTSI Regulatory support; Department of Medicine Research Operations and Division of General internal Medicine, especially Jill Charles, Manuria Yang, and Kate Brekke.

Dr. Bramante thanks her KL2 and K23 mentors for their continued career mentorship and support: Anne Joseph, MD, MPH; Aaron Kelly, PhD; Claudia Fox, MD, MPH; and Kimberly Gudzune, MD, MPH.

Dr. Bramante thanks the M Health Fairview Learning Health Systems career development program and mentors Genevieve Melton-Meaux, MD, PhD and Bradley Benson, MD; and Fairview Research Services, especially Andrew Snyder and Jill Cordes. Dr. Bramante also thanks other colleagues and mentors who contributed to considerations for the protocol: Eric Lenze, MD; Angela Reiersen, MD; David Haynes, PhD; Carlos Chaccour, MD; Ildilko Linvay, MD; Ana Palacio, MD; Leonardo Tamariz, MD, MPH; Ananth Shalev, MD; Erik Anderson, MD; and Jeanne M. Clark, MD, MPH.

Disclosures

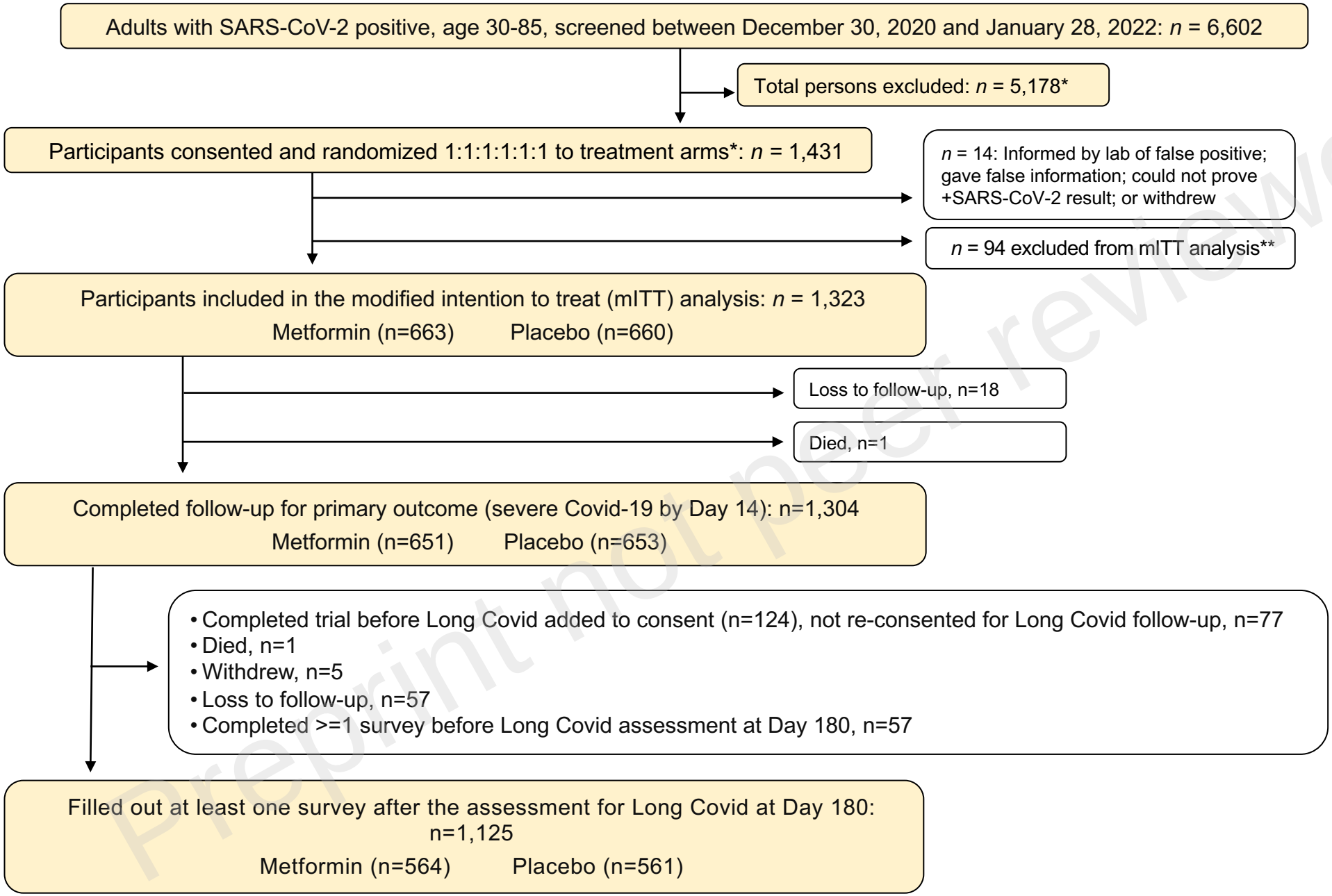
JBB reports contracted fees and travel support for contracted activities for consulting work paid to the University of North Carolina by Novo Nordisk; grant support by Dexcom, NovaTarg, Novo Nordisk, Sanofi, Tolerion and vTv Therapeutics; personal compensation for consultation from Alkahest, Altimmune, Anji, AstraZeneca, Bayer, Biomea Fusion Inc, Boehringer-Ingelheim, CeQur, Cirius Therapeutics Inc, Corcept Therapeutics, Eli Lilly, Fortress Biotech, GentiBio, Glycadia, Glyscend, Janssen, MannKind, Mellitus Health, Moderna, Pendulum Therapeutics, Praetego, Sanofi, Stability Health, Terns Inc, Valo and Zealand Pharma; and stock/options in Glyscend, Mellitus Health, Pendulum Therapeutics, PhaseBio, Praetego, and Stability Health.

Figure 1. Consort diagram. Overview of factorial design groups. Participants were randomized to equal allocation to one of the 6 arms above. They were compared to concurrently randomized controls from the groups outlined above. Every participant in the trial received a pill that looked like metformin – either active metformin or exact matching metformin placebo.

Figure 2. Cumulative incidence curve of Long Covid diagnoses over 10 months after randomization. The Y axis represents the cumulative incidence and the X axis represents days since randomization. Below the curve, a table is shown with the number at risk at each time point, and the number censored.

Figure 3. Assessment of heterogeneity of treatment effect of metformin compared to placebo across a priori subgroups of baseline characteristics. This is a forest plot of hazard ratios (HR) with 95% confidence intervals, and the vertical line represents an HR of 1.0. HR's to the left of 1.0 indicate that metformin was protective compared to exact-matching placebo. The top row is the hazard ratio for the whole sample, and rows below that are a-priori subgroups of baseline characteristics.

Figure 4. Proportion of participants who have at least one symptom that affects their work or leisure activities. The Y axis represents the proportion of participants. The Y axis represents the days since randomization. The blue line is the proportion of those who reported receiving a Long Covid diagnosis by a medical provider who had at least 1 persistent symptom affecting work or leisure. The red line is the proportion of participants who reported not having received a diagnosis of Long Covid by a medical provider who had at least 1 persistent symptom affecting work or leisure.



*Detail on the 2x3 factorial design and number excluded for each reason are outlined in the Supplementary Appendix.

**Excluded from mITT analysis: did not receive kit (n=9); confirmed taking zero doses (n=77); hospitalized before received study medications (n=8).

Table 1: Baseline characteristics.

Demographics		Metformin n=564	Placebo n=561
Age in years, median (IQR)		46 (37 to 54)	45 (37 to 54)
Female*		305 (54.1)	326 (58.1)
	Native American	9 (1.6)	15 (2.7)
	Asian	21 (3.7)	21 (3.7)
Race	Black	43 (7.6)	40 (7.1)
	White	469 (83.2)	463 (82.5)
	Other & unknown	40 (7.2)	37 (6.6)
Hispanic or Latino**		66 (11.8)	76 (13.7)
Medical history			
BMI, Median (IQR) kg/m^2		29.7 (27 to 34)	30.0 (27 to 34)
BMI $\geq$ 30 kg/m^2		266 (47.2)	282 (50.3)
Cardiovascular disease		147 (26.1)	138 (24.6)
Diabetes		6 (1.1)	11 (2.0)
SARS-CoV-2 Primary vaccine		326 (57.8)	292 (52.0)
First vaccine booster		30 (5.3)	27 (4.8)
Days from symptom onset to study drug initiation			
Median (IQR)		5 (4 to 6)	5 (3 to 6)
Percent started in <4 days		130 (23.3)	143 (26.0)
SARS-CoV-2 Variant period			
Alpha (pre-June 19, 2021)		34 (6.0)	29 (5.2)
Delta (June 19 – Dec 12, 2021)		399 (70.7)	401 (71.5)
Omicron (post-Dec 12, 2021)		131 (23.2)	131 (23.4)
Healthcare Insurance			
Private		358 (64.4)	345 (62.5)
Public Medicare		41 (7.4)	38 (6.9)
Public Medicaid		75 (13.5)	97 (17.6)
No insurance		82 (14.7)	72 (13.0)

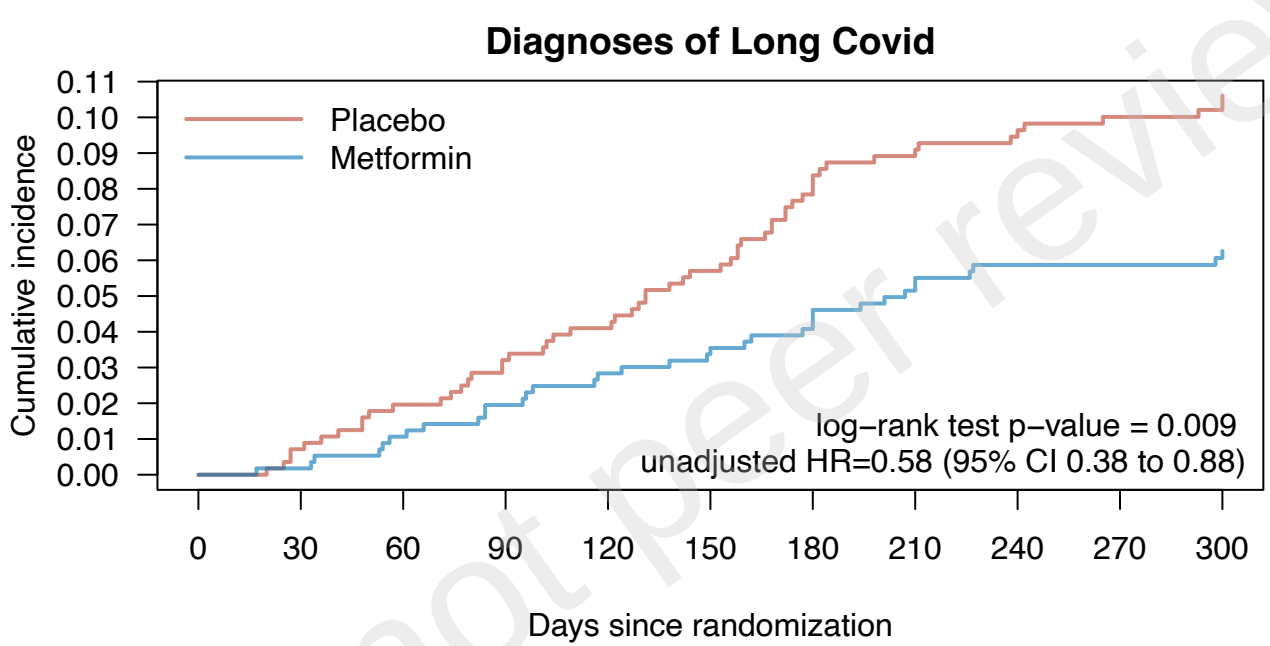
Values are n (%) unless specified.
Abbreviations: BMI = body mass index; IQR=inter-quartile range; SD = standard deviation.
Cardiovascular disease defined as: hypertension, hyperlipidemia, coronary artery disease, past myocardial infarction, congestive heart failure, pacemaker, arrhythmias, or pulmonary hypertension.
* 7% of Females were pregnant. **missing n=9

Table 2. Cumulative incidence and absolute risk reduction for metformin compared to placebo, percentages with 95% confidence intervals.

Study Day	Metformin 35/564 (6.2%)	Placebo 59/561 (10.5%)	Absolute Risk Reduction
60	1.1% (0.2% to 1.9%)	2.0% (0.8% to 3.1%)	0.9% (2.3% to -0.5%)
120	2.8% (1.5% to 4.2%)	4.1% (2.4% to 5.7%)	1.3% (3.4% to -0.9%)
180	4.6% (2.9% to 6.3%)	8.4% (6.1% to 10.6%)	3.8% (6.6% to 0.9%)
240	5.9% (3.9% to 7.8%)	9.6% (7.2% to 12.1%)	3.8% (6.9% to 0.6%)
300	6.3% (4.2% to 8.2%)	10.6% (8.0% to 13.1%)	4.3% (7.6% to 1.1%)

Unadjusted Hazard Ratio for Long Covid in the metformin group: 0.576 (95% CI 0.379 to 0.875).

Adjusted Hazard Ratio for Long Covid in the metformin group: 0.588 (95% CI 0.387 to 0.894) when adjusted via a Cox regression model for other study drugs in the factorial randomization, primary vaccination and booster vaccination status at baseline.



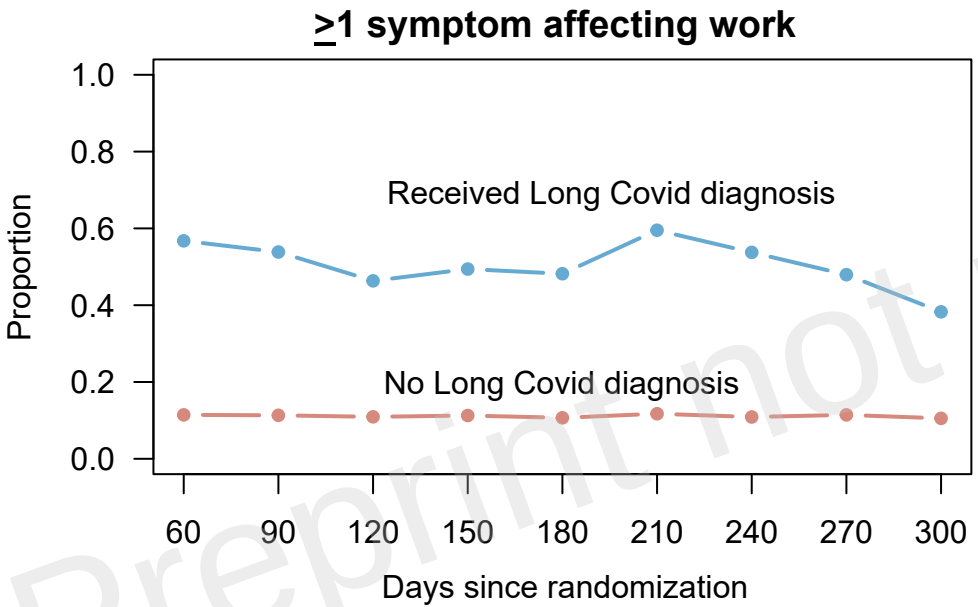
Number at risk

Placebo	561	557	550	543	538	529	517	506	497	479	455
Metformin	564	563	558	553	548	545	540	529	517	502	483

Number censored

Placebo	0	0	0	0	0	0	0	5	11	26	49
Metformin	0	0	0	0	0	0	1	6	14	29	47

Subgroup	Metformin	Placebo	Hazard Ratio (95% CI)
All Participants	35/564 (6.2%)	59/561 (10.5%)	0.58 (0.38 to 0.88)
Assessment of treatment effect across a priori subgroups of pre-randomization baseline risk factors:			
Biologic sex			
Female	24/305 (7.9%)	46/326 (14.1%)	0.54 (0.33 to 0.89)
Male	11/259 (4.2%)	13/235 (5.5%)	0.76 (0.34 to 1.70)
BMI			
<30 kg/m2	20/298 (6.7%)	23/279 (8.2%)	0.80 (0.44 to 1.46)
>=30 kg/m2	15/266 (5.6%)	36/282 (12.8%)	0.43 (0.23 to 0.78)
Days since symptom onset			
< 4 days	6/130 (4.6%)	17/143 (11.9%)	0.37 (0.15 to 0.95)
>=4 days	29/427 (6.8%)	42/407 (10.3%)	0.64 (0.40 to 1.03)
Age			
<45 years	13/265 (4.9%)	33/272 (12.1%)	0.39 (0.20 to 0.73)
>=45 years	22/299 (7.4%)	26/289 (9.0%)	0.82 (0.46 to 1.44)
Dominant variant			
Alpha	1/34 (2.9%)	4/29 (13.8%)	0.21 (0.02 to 1.87)
Delta	27/399 (6.8%)	40/401 (10.0%)	0.67 (0.41 to 1.08)
Omicron	7/131 (5.3%)	15/131 (11.5%)	0.45 (0.18 to 1.11)
Vaccination status			
Not Vaccinated	15/238 (6.3%)	38/269 (14.1%)	0.43 (0.23 to 0.78)
Vaccinated	20/326 (6.1%)	21/292 (7.2%)	0.85 (0.46 to 1.56)
Additional study drug			
Nothing/Placebo	11/221 (5.0%)	23/229 (10.0%)	0.48 (0.23 to 0.98)
Ivermectin	11/189 (5.8%)	19/188 (10.1%)	0.56 (0.27 to 1.18)
Fluvoxamine	13/154 (8.4%)	17/144 (11.8%)	0.72 (0.35 to 1.48)



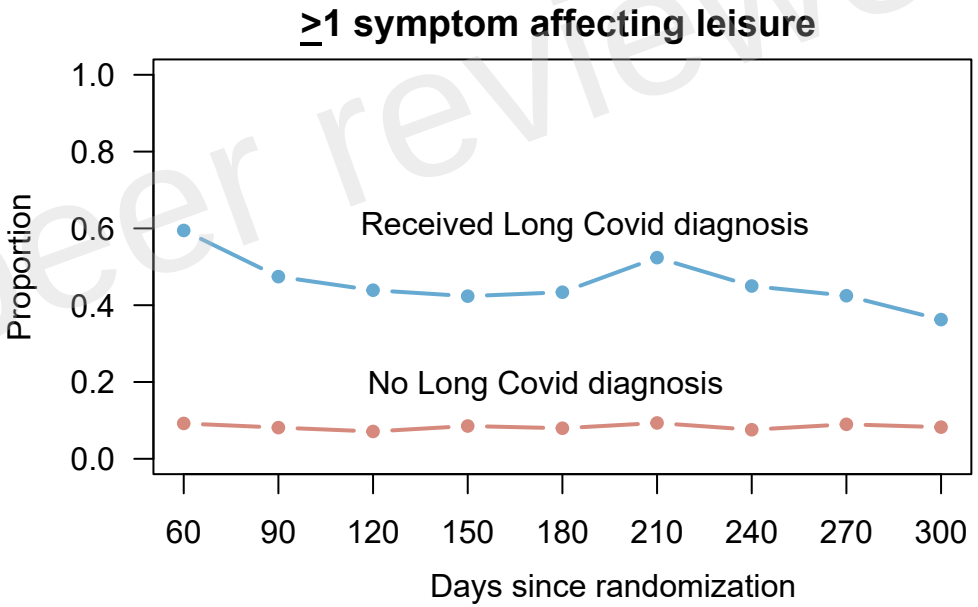


Table of Contents.

Table S1. COVID-OUT Study Team

Name	Institute	Location
Blake Anderson	Emory	Atlanta, GA
Riannon C Atwater	University of Colorado	Aurora, CO
Nandini Avula	University of Minnesota	Minneapolis, MN
Kenny B Beckman	University of Minnesota	Minneapolis, MN
Hrishikesh K Belani	Olive View - UCLA	Sylmar, CA
David R Boulware	University of Minnesota	Minneapolis, MN
Carolyn T Bramante	University of Minnesota	Minneapolis, MN
Jannis Brea	Northwestern University	Chicago, IL
Courtney A Broedlow	University of Minnesota	Minneapolis, MN
John B Buse	University of North Carolina	Chapel Hill, NC
Paula Campora	University of Minnesota	Minneapolis, MN
Anup Challa	Vanderbilt University	Nashville, TN
Jill Charles	University of Minnesota	Minneapolis, MN
Grace Christensen	University of Minnesota	Minneapolis, MN
Theresa Christiansen	M Health Fairview	Minneapolis, MN
Ken Cohen	Optum	Minnetonka, MN
Bo Connelly	University of Minnesota	Minneapolis, MN
Srijani Datta	University of Minnesota	Minneapolis, MN
Nikita Deng	University of Colorado	Aurora, CO
Alex T Dunn	Hennepin Healthcare	Minneapolis, MN
Spencer M Erickson	University of Minnesota	Minneapolis, MN
Faith M Fairbairn	University of Minnesota	Minneapolis, MN
Sarah L Fenno	University of Minnesota	Minneapolis, MN
Daniel J Fraser	University of Minnesota	Minneapolis, MN
Regina D Fricton	Feinberg School of Medicine, Northwestern	Chicago, IL
Gwen Griffiths	University of Minnesota	Minneapolis, MN
Aubrey A Hagen	University of Minnesota	Minneapolis, MN
Katrina M Hartman	University of Minnesota	Minneapolis, MN
Audrey F Hendrickson	Hennepin Healthcare	Minneapolis, MN
Jared D Huling	University of Minnesota	Minneapolis, MN
Nicholas E Ingraham	University of Minnesota	Minneapolis, MN
Arthur C Jeng	Olive View - UCLA	Sylmar, CA
Darrell M Johnson	University of Minnesota	Minneapolis, MN
Amy B Karger	University of Minnesota	Minneapolis, MN
Nichole R Klatt	University of Minnesota	Minneapolis, MN
Erik A Kuehl	M Health Fairview	Minneapolis, MN
Derek D LaBar	M Health Fairview	Minneapolis, MN

Samuel Lee	Feinberg School of Medicine, Northwestern	Chicago, IL
David M Liebovitz	Feinberg School of Medicine, Northwestern	Chicago, IL
Sarah Lindberg	University of Minnesota	Minneapolis, MN
Darlette G Luke	M Health Fairview	Minneapolis, MN
Rosario Machicado	Olive View - UCLA	Sylmar, CA
Zeinab Mohamud	University of Minnesota	Minneapolis, MN
Thomas A Murray	University of Minnesota	Minneapolis, MN
Rumbidzai Ngonyama	University of Minnesota	Minneapolis, MN
Jacinda M Nicklas	University of Colorado	Aurora, CO
David J Odde	University of Minnesota	Minneapolis, MN
Elliott Parrens	M Health Fairview	Minneapolis, MN
Daniela Parra	University of Minnesota	Minneapolis, MN
Barkha Patel	University of Minnesota	Minneapolis, MN
Jennifer L Proper	University of Minnesota	Minneapolis, MN
Matthew F Pullen	University of Minnesota	Minneapolis, MN
Michael A Puskarich	Hennepin Healthcare	Minneapolis, MN
Via Rao	University of Minnesota	Minneapolis, MN
Neha V Reddy	University of Minnesota	Minneapolis, MN
Naveen Reddy	Northwestern University	Chicago, IL
Katelyn J Rypka	University of Minnesota	Minneapolis, MN
Hanna G Saveraid	University of Minnesota	Minneapolis, MN
Paula Seloadji	Olive View - UCLA	Sylmar, CA
Arman Shahriar	University of Minnesota	Minneapolis, MN
Nancy Sherwood	University of Minnesota	Minneapolis, MN
Jamie L Siegart	University of Colorado	Aurora, CO
Lianne K Siegel	University of Minnesota	Minneapolis, MN
Lucas Simmons	University of Minnesota	Minneapolis, MN
Isabella Sinelli	University of Colorado	Aurora, CO
Palak Singh	University of Minnesota	Minneapolis, MN
Andrew Snyder	M Health Fairview	Minneapolis, MN
Maxwell T Stauffer	St. Olaf College	Northfield, MN
Jennifer Thompson	Vanderbilt University	Nashville, TN
Christopher J Tignanelli	University of Minnesota	Minneapolis, MN
Tannon L Tople	University of Minnesota	Minneapolis, MN
Walker J Tordsen	Hennepin Healthcare	Minneapolis, MN
Ray HB Watson	University of Minnesota	Minneapolis, MN
Beiqing Wu	University of Minnesota	Minneapolis, MN
Adnin Zaman	University of Colorado	Aurora, CO
Madeline R Zolik	M Health Fairview	Minneapolis, MN
Lena Zinkl	M Health Fairview	Minneapolis, MN

Back to Top

Figure S1. Overview of factorial design groups.

	Metformin	Metformin Placebo
Ivermectin	**1:** Metformin + Ivermectin	**4:** Metformin Placebo + Ivermectin
Fluvoxamine	**2:** Metformin + Fluvoxamine	**5:** Metformin Placebo + Fluvoxamine
Placebo (Ivermectin or Fluvoxamine)	**3:** Metformin + Placebo	**6:** Metformin Placebo + Placebo

Metformin trial: 1 + 2 + 3 vs 4 + 5 + 6

Ivermectin trial: 2 + 5 vs 3 + 6

Fluvoxamine trial: 1 + 4 vs 3 + 6

In this 2x3 factorial design randomized trial, each participant received two types of study pills to maintain the blind because two of the groups had two active medications (groups 1 and 2).

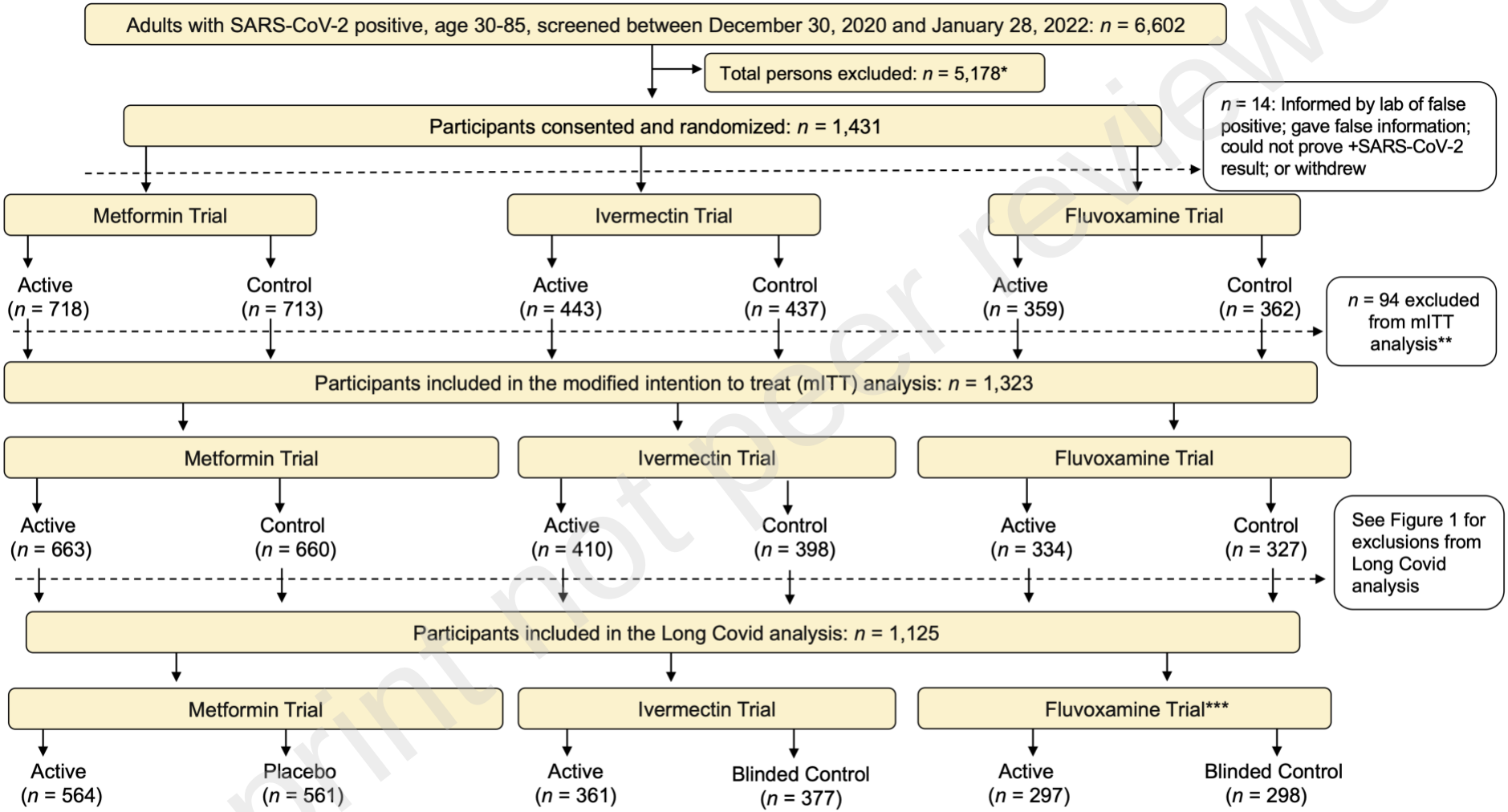
Every participant in the trial received a pill that looked like metformin – either active metformin or exact-matching metformin placebo.

The second pill was either ivermectin or exact-matching ivermectin placebo; or fluvoxamine or exact-matching fluvoxamine placebo. A small subset of the control group for fluvoxamine received ivermectin placebo, and a small subset of the control group for ivermectin received the fluvoxamine placebo, because of shipping and supply chain issues. For that reason, the control groups for fluvoxamine and ivermectin are referred to as “Blinded Control” (Figure S2).

Pills were dispensed in pre-filled pill boxes to assure the right number of each pill was taken.

Back to Top

Figure S2. Consort diagram. Overview of factorial design groups. Participants were randomized with equal allocation to 1 of 6 arms. Active drug groups were compared to concurrently randomized controls from the arms outlined above. Every participant in the trial received a pill that looked like metformin – either active metformin or exact matching metformin placebo



*Detail on the number excluded for each reason are outlined in the Supplementary Appendix Table 2.
**Excluded from mITT analysis: did not receive kit (n=9); confirmed taking zero doses (n=77); hospitalized before received study medications (n=8). These 94 participants are included in the intention to treat analysis of the primary outcome paper.
***The fluvoxamine arm was closed on January 7th, 2022 by the independent data and safety monitoring board.

Back to Top

Table S2. Reasons for exclusion from enrollment.

Total Persons excluded (*n* = 5,178)

- Body mass index <25 kg/m^2 (*n* = 769)
- *Current medication exclusion (*n* = 594)
- Symptoms started >7 days ago (*n* = 593)
- More than 3 days since positive SARS-CoV-2 test (*n* = 589)
- Currently admitted to hospital (*n* = 427)
- Previously tested positive for SARS-CoV-2 in prior illness (*n* = 413)
- Spoken language not available in translated materials (*n* = 199)
- Immunocompromised (*n* = 145)
- Chronic Kidney Disease with GFR <45 mL/min/1.73m^2 within last 2 months (*n* = 79)
- Incarcerated (*n* = 77)
- Alcohol use disorder (*n* = 32)
- Already enrolled in another clinical trial for Covid-19 treatment (*n* = 16)
- At an inpatient rehab center (*n* = 14)
- Severe liver disease with GFR <45 mL/min/1.73m^2 within last 2 months (*n* = 11)
- Stage 3-4 heart failure with GFR <45 mL/min/1.73m^2 within last 2 months (*n* = 8)
- Previous allergic reaction to one of the study drugs (*n* = 3)
- Other (*n* = 1209)

Abbreviation: GFR=glomerular filtration rate

*Medication exclusion list: metformin, insulin, cimetidine, hydroxychloroquine, sulfonylurea, dolutegravir, patiromir, ranolazine, tafenoquine., ivermectin, sodium picosulfate, lithium, valproate, fluvoxamine, rasagiline, selegiline, MAOis, linezolid, duloxetine, methylene blue, tizanidine, ramelteon, alosetron, agomelatine, bromopride, dapoxetine, tamsimelteon, thioridazine, urokinase, pimozide.

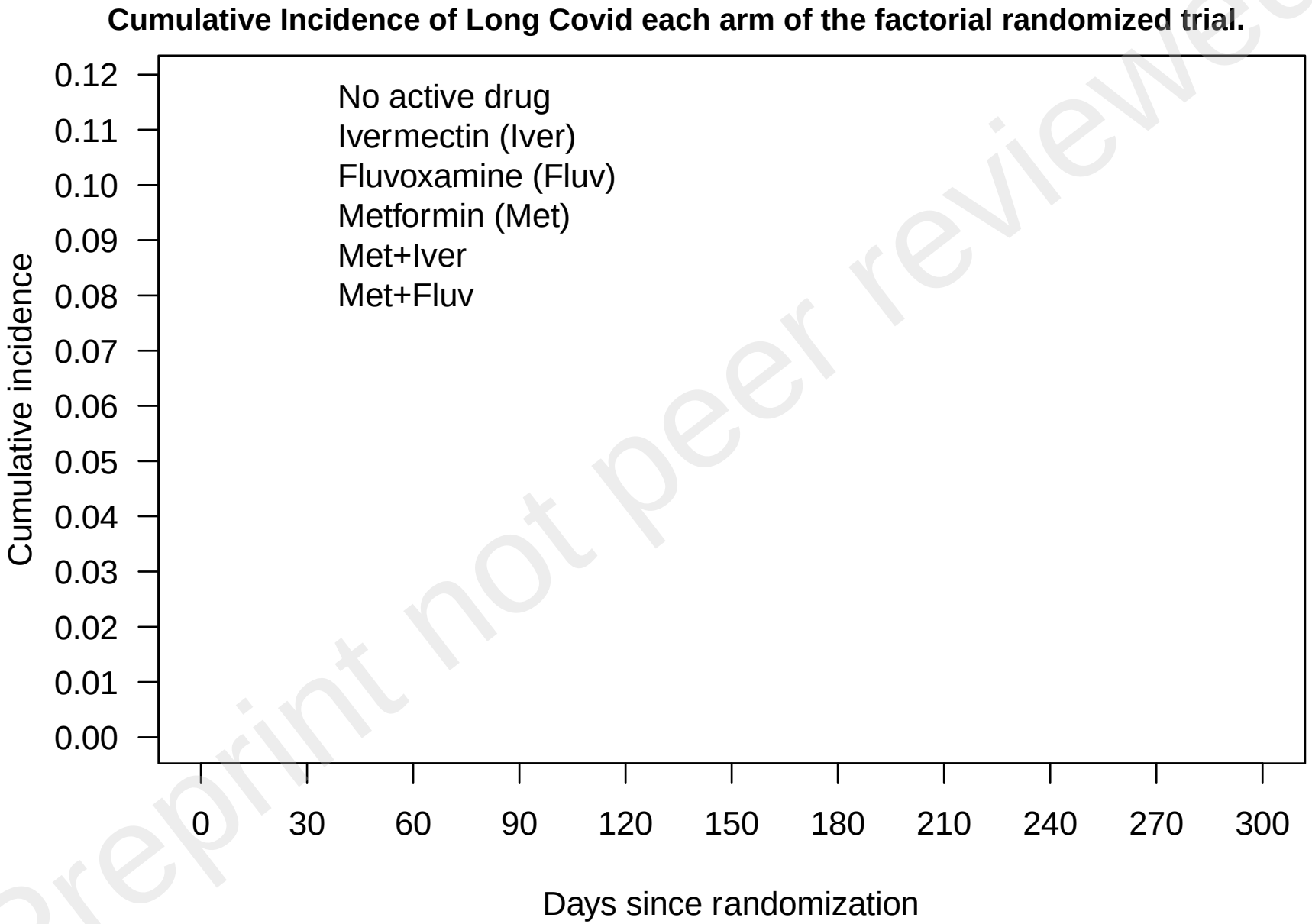
Dose-dependent: SSRI, SNRI, tricyclic antidepressant, alprazolam, diazepam, theophylline, clozapine, olazapine, NSAIDS, aspirin, warfarin, phenytoin, clopidogrel, St. John's wort, or high dose antipsychotic.

Table S3. Baseline characteristics of those in the ivermectin and fluvoxamine randomized groups.

Demographics		Ivermectin Trial		Fluvoxamine Trial	
		Ivermectin n=361	Blinded placebo n=377	Fluvoxamine n=297	Blinded placebo n=298
Age, median (IQR)		45 (37 to 55)	47 (39 to 55)	43 (37 to 52)	46.5 (38 to 53)
Female, 7% were pregnant		208 (57.6)	198 (52.5)	173 (58.2)	153 (51.3)
Race	Native American	9 (2.5)	7 (1.9)	9 (3.0)	8 (2.7)
	Asian	15 (4.2)	19 (5.0)	10 (3.4)	5 (1.7)
	Black	28 (7.8)	26 (6.9)	22 (7.4)	22 (7.4)
	White	291 (80.6)	311 (82.5)	241 (81.1)	252 (84.6)
	Other & unknown*	30 (8.3)	25 (6.6)	25 (8.4)	17 (5.7)
Hispanic or Latino*		53 (14.9)	37 (9.9)	43 (14.8)	38 (12.8)
Medical history					
BMI, median (IQR)		29.6 (27 to 34)	29.5 (27 to 34)	29.6 (27 to 34)	29.5 (27 to 34)
BMI >= 30 kg/m^2		172 (47.6)	177 (46.9)	144 (48.5)	141 (47.3)
Cardiovascular disease		83 (23.0)	88 (23.3)	71 (23.9)	93 (31.2)
Diabetes		5 (1.4)	7 (1.9)	3 (1.0)	3 (1.0)
Primary vaccine		211 (58.4)	206 (54.6)	174 (58.6)	165 (55.4)
Vaccine booster		22 (6.1)	15 (4.0)	18 (6.1)	12 (4.0)
Days of symptoms before study drug initiation, missing n=18					
Days, median (IQR)		5 (4 to 6)	5 (3 to 6)	5 (4 to 6)	5 (4 to 6)
Started in <4 days		157 (44.4)	186 (49.9)	158 (54.1)	131 (44.4)
SARS-CoV-2 Variant period					
Alpha (pre Jun 19, 2021)		8 (2.2)	10 (2.7)	8 (2.7)	9 (3.0)
Delta (Jun 19 – Dec 12, 2021		252 (69.8)	258 (68.4)	252 (84.8)	249 (83.6)
Omicron (post Dec 12, 2021)		101 (28.0)	109 (28.9)	37 (12.5)	40 (13.4)
Insurance					
Private		215 (61.3)	238 (63.8)	184 (63.9)	188 (63.5)
Medicare		28 (8.0)	24 (6.4)	18 (6.2)	22 (7.4)
Medicaid		54 (15.4)	63 (16.9)	39 (13.5)	37 (12.5)
No insurance		54 (15.4)	48 (12.9)	47 (16.3)	49 (16.6)

Values are n (%) unless specified. Abbreviations: BMI = body mass index; IQR=inter-quartile range; SD = standard deviation. Cardiovascular disease defined as: hypertension, hyperlipidemia, coronary artery disease, past myocardial infarction, congestive heart failure, pacemaker, arrhythmias, or pulmonary hypertension. *Includes Hawaiian / Pacific Islander. Fluvoxamine enrollment halted on January 7, 2022 by the independent data safety monitoring board.

Figure S3.



Back to Top

Table S4. Cumulative Incidence and Hazard Ratio for Long Covid for Ivermectin versus control, percent with 95% confidence intervals.			
Study Day	Blinded Control 29/361 (8.0%)	Ivermectin 30/377 (8.0%)	Absolute Risk Reduction
60	1.9% (0.5% to 3.4%)	1.3% (0.2% to 2.5%)	0.6% (2.4% to -1.2%)
120	3.9% (1.9% to 5.8%)	3.4% (1.6% to 5.3%)	0.4% (3.1% to -2.3%)
180	5.6% (3.2% to 7.9%)	6.1% (3.7% to 8.5%)	-0.5% (2.8% to -3.9%)
240	7.5% (4.8% to 10.2%)	7.2% (4.5% to 9.8%)	0.3% (4.1% to -3.4%)
300	8.2% (5.3% to 11.0%)	8.0% (5.2% to 10.7%)	0.1% (4.1% to -3.8%)
Unadjusted Hazard Ratio. 0.985 (0.591 to 1.641)			
Adjusted Hazard Ratio 0.952 (0.571 to 1.587)			

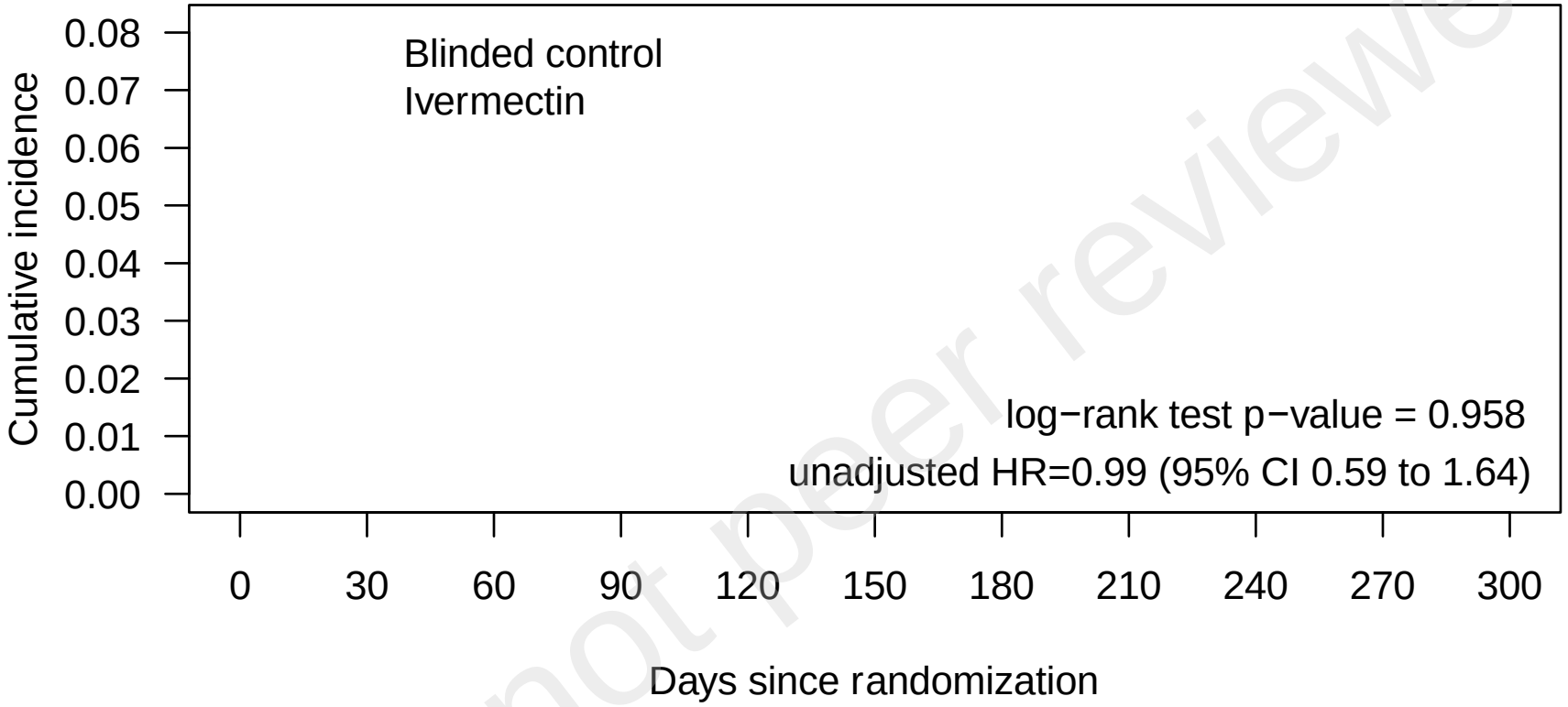
*Adjusted HR reflects a Cox model adjusted for other study drugs in the factorial randomization, primary vaccination and booster vaccination prior to baseline.

Table S5. Cumulative Incidence and Hazard Ratio for Long Covid for Fluvoxamine versus control, percent with 95% confidence intervals.			
Study Day	Blinded Control 22/297 (7.4%)	Fluvoxamine 30/298 (10.1%)	Absolute Risk Reduction
60	1.7% (0.2% to 3.1%)	1.0% (0.0% to 2.1%)	0.7% (2.5% to -1.2%)
120	4.0% (1.8% to 6.3%)	3.0% (1.1% to 4.9%)	1.0% (4.0% to -1.9%)
180	5.4% (2.8% to 7.9%)	8.7% (5.5% to 11.9%)	-3.3% (0.8% to -7.4%)
240	7.1% (4.1% to 10.0%)	9.4% (6.0% to 12.7%)	-2.3% (2.1% to -6.7%)
300	7.5% (4.4% to 10.5%)	10.1% (6.6% to 13.5%)	-2.6% (1.9% to -7.2%)
Unadjusted Hazard Ratio 1.359 (0.784 to 2.355)			
Adjusted Hazard Ratio 1.346 (0.776 to 2.335)			

*Adjusted HR reflects a Cox model adjusted for other study drugs in the factorial randomization, primary vaccination and booster vaccination prior to baseline.

Back to Top

Figure S4. Cumulative incidence of Long Covid for ivermectin versus identical matched placebo control.



Number at risk

Control	361	359	354	350	347	345	343	332	321	305	293
Ivermectin	377	376	372	367	364	361	355	347	341	331	314

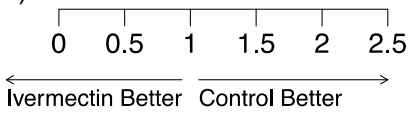
Number censored

Control	0	0	0	0	0	0	1	6	13	29	40
Ivermectin	0	0	0	0	0	0	0	5	9	17	33

Back to Top

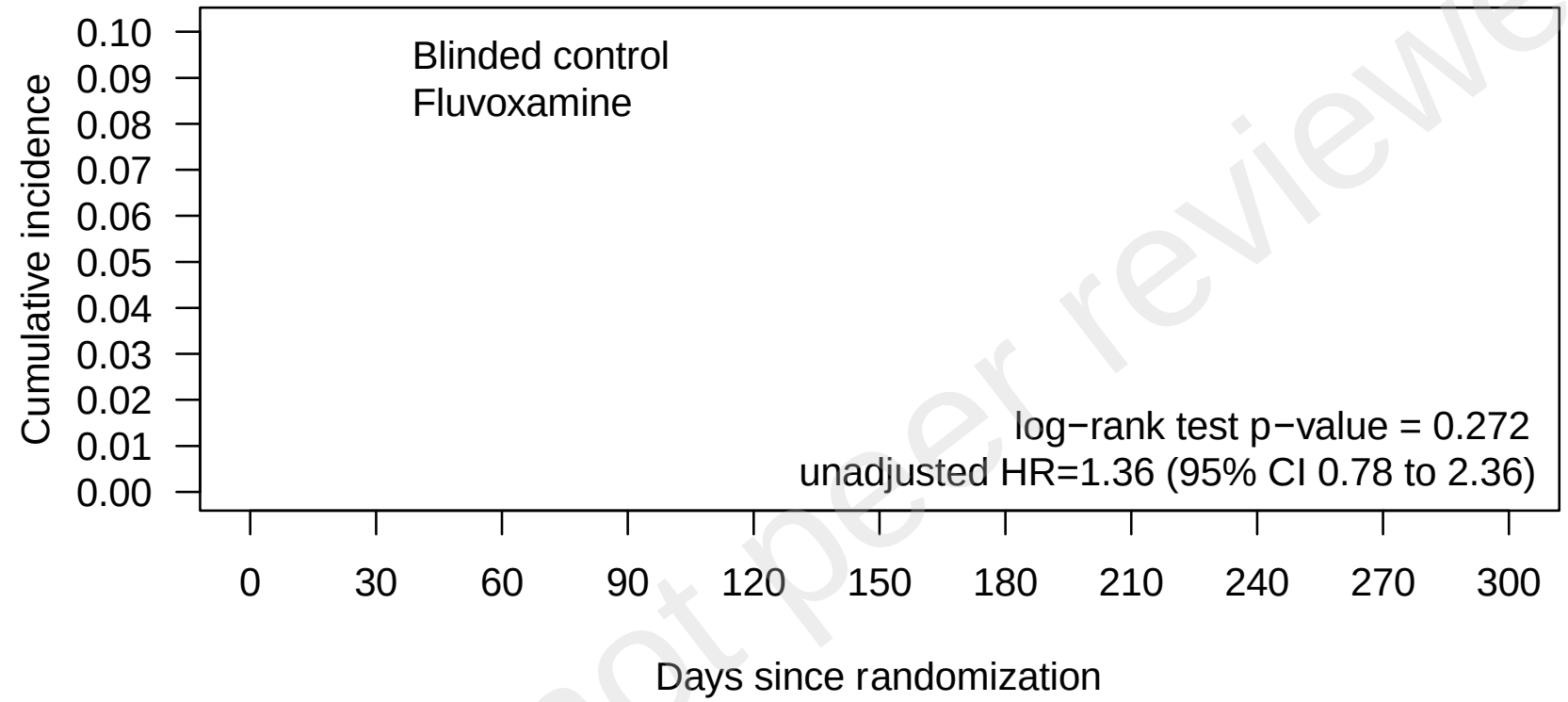
Figure S5. Heterogeneity of Ivermectin treatment effect for preventing Long Covid.

Subgroup	Ivermectin	Blinded Control	Hazard Ratio (95% CI)
All Participants	30/377 (8.0%)	29/361 (8.0%)	0.99 (0.59 to 1.64)
Assessment of treatment effect across a priori subgroups of pre-randomization baseline variables:			
Biologic sex			
Female	23/198 (11.6%)	22/208 (10.6%)	1.10 (0.61 to 1.97)
Male	7/179 (3.9%)	7/153 (4.6%)	0.85 (0.30 to 2.42)
BMI			
<30 kg/m2	15/200 (7.5%)	13/189 (6.9%)	1.08 (0.51 to 2.27)
>=30 kg/m2	15/177 (8.5%)	16/172 (9.3%)	0.91 (0.45 to 1.84)
Days since symptom onset			
<=3 days	8/102 (7.8%)	8/82 (9.8%)	0.80 (0.30 to 2.13)
>=4 days	22/271 (8.1%)	21/272 (7.7%)	1.05 (0.58 to 1.90)
Age			
<45 years	16/163 (9.8%)	17/176 (9.7%)	1.00 (0.50 to 1.97)
>=45 years	14/214 (6.5%)	12/185 (6.5%)	1.01 (0.47 to 2.19)
Dominant variant			
Alpha	0/10 (0.0%)	2/8 (25.0%)	0.00 (0.00 to Inf)
Delta	24/258 (9.3%)	18/252 (7.1%)	1.31 (0.71 to 2.42)
Omicron	6/109 (5.5%)	9/101 (8.9%)	0.60 (0.22 to 1.70)
Vaccination status			
Not Vaccinated	21/171 (12.3%)	15/150 (10.0%)	1.24 (0.64 to 2.41)
Vaccinated	9/206 (4.4%)	14/211 (6.6%)	0.65 (0.28 to 1.50)
Additional study drug			
Placebo	19/188 (10.1%)	19/185 (10.3%)	0.98 (0.52 to 1.84)
Metformin	11/189 (5.8%)	10/176 (5.7%)	1.03 (0.44 to 2.42)



Back to Top

Figure S6. Cumulative incidence of Long Covid, fluvoxamine versus identical matched placebo control.



Number at risk

Control	297	296	292	288	285	283	281	272	264	254	246
Fluvoxamine	298	297	295	292	289	283	274	271	268	262	252

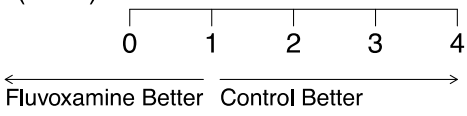
Number censored

Control	0	0	0	0	0	0	1	6	12	22	29
Fluvoxamine	0	0	0	0	0	0	0	0	3	8	18

Back to Top

Figure S7. Heterogeneity of Fluvoxamine treatment effect for preventing Long Covid.

Subgroup	Fluvoxamine	Blinded Control	Hazard Ratio (95% CI)
All Participants	30/298 (10.1%)	22/297 (7.4%)	1.36 (0.78 to 2.36)
Assessment of treatment effect across a priori subgroups of pre-randomization baseline variables:			
Biologic sex			
Female	21/153 (13.7%)	17/173 (9.8%)	1.41 (0.74 to 2.67)
Male	9/145 (6.2%)	5/124 (4.0%)	1.54 (0.51 to 4.58)
BMI			
<30 kg/m2	14/157 (8.9%)	9/153 (5.9%)	1.52 (0.66 to 3.50)
>=30 kg/m2	16/141 (11.3%)	13/144 (9.0%)	1.26 (0.60 to 2.61)
Days since symptom onset			
<=3 days	6/71 (8.5%)	4/69 (5.8%)	1.47 (0.41 to 5.20)
>=4 days	24/224 (10.7%)	18/223 (8.1%)	1.33 (0.72 to 2.44)
Age			
<45 years	9/132 (6.8%)	12/160 (7.5%)	0.88 (0.37 to 2.09)
>=45 years	21/166 (12.7%)	10/137 (7.3%)	1.77 (0.84 to 3.77)
Dominant variant			
Alpha	1/9 (11.1%)	2/8 (25.0%)	0.42 (0.04 to 4.67)
Delta	24/249 (9.6%)	18/252 (7.1%)	1.35 (0.73 to 2.49)
Omicron	5/40 (12.5%)	2/37 (5.4%)	2.32 (0.45 to 11.94)
Vaccination status			
Not Vaccinated	13/133 (9.8%)	10/123 (8.1%)	1.18 (0.52 to 2.70)
Vaccinated	17/165 (10.3%)	12/174 (6.9%)	1.51 (0.72 to 3.16)
Additional study drug			
Placebo	17/144 (11.8%)	14/152 (9.2%)	1.26 (0.62 to 2.56)
Metformin	13/154 (8.4%)	8/145 (5.5%)	1.55 (0.64 to 3.74)



Back to Top

Supplemental Table S6: Baseline characteristics between those who reported receiving a diagnosis of Long Covid and those who reported no diagnosis of Long Covid.

	Overall n=1,125	No Long Covid n=1031 (91.6%)	Long Covid n=94 (8.4%)
Age, median (IQR)	45.0 (37.0 to 54.0)	45.0 (37.0 to 55.0)	45.0 (38.0 to 51.0)
Female	631 (56.1)	561 (54.4)	70 (74.5)
Pregnant	44 (3.9)	41 (4.0)	3 (3.2)
Race Native American	24 (2.1)	21 (2.0)	3 (3.2)
Race Asian	42 (3.7)	39 (3.8)	3 (3.2)
Race Hawaiian / Pacific Islander	7 (0.6)	6 (0.6)	1 (1.1)
Race Black	83 (7.4)	72 (7.0)	11 (11.7)
Race White	932 (82.8)	855 (82.9)	77 (81.9)
Race Other and unknown	70 (6.2)	68 (6.6)	2 (2.1)
Hispanic or Latino *	142 (12.7)	133 (13.0)	9 (9.7)
Medical history			
BMI, median (IQR)	29.8 (27.0 to 34.2)	29.7 (26.8 to 33.9)	31.0 (27.5 to 36.0)
BMI >= 30 kg/m^2	548 (48.7)	497 (48.2)	51 (54.3)
Cardiovascular Disease	285 (25.3)	263 (25.5)	22 (23.4)
Diabetes	17 (1.5)	17 (1.6)	0 (0.0)
Primary vaccine before enrollment	618 (54.9)	577 (56.0)	41 (43.6)
Vaccine booster before enrollment	57 (5.1)	56 (5.4)	1 (1.1)
Any Vaccine after enrollment	160 (14.2)	144 (14.0)	16 (17.0)
Days of symptoms before study drug initiation, median (IQR)*	5 (4 to 6)	5 (4 to 6)	5 (4 to 6)
<=3 Days with Symptoms*	518 (46.8)	480 (47.4)	38 (40.4)
Variant period			
Alpha (before June 19, 2021)	63 (5.6)	58 (5.6)	5 (5.3)
Delta (June 19 – Dec 12, 2021)	800 (71.1)	733 (71.1)	67 (71.3)
Omicron (after Dec 12, 2021)	262 (23.3)	240 (23.3)	22 (23.4)
Insurance status			
Private	703 (63.4)	651 (64.1)	52 (55.9)
Medicare	79 (7.1)	70 (6.9)	9 (9.7)
Medicaid	172 (15.5)	152 (15.0)	20 (21.5)
No insurance	154 (13.9)	142 (14.0)	12 (12.9)
Randomized to metformin	564 (50.1)	529 (51.3)	35 (37.2)
Randomized to ivermectin	377 (33.5)	347 (33.7)	30 (31.9)
Randomized to fluvoxamine	298 (26.5)	268 (26.0)	30 (31.9)

Values are n (%), median (interquartile range), or mean (±Standard Deviation).
Abbreviations: BMI = body mass index; IQR=inter-quartile range;
Cardiovascular disease defined as: hypertension, hyperlipidemia, coronary artery disease, past myocardial infarction, congestive heart failure, pacemaker, arrhythmias, or pulmonary hypertension.
*missing n=18 for symptom duration; missing n=9 of Hispanic ethnicity

Top of the Document

Supplemental Table S7.

Outcome Ascertainment

If answered "Yes," then branching logic asked when the diagnosis occurred and by what type of provider.

1) Has a medical provider told you that you have "Long Covid" Yes/No

– If yes: "Approximately when? _____(month)"
– If yes: "Who Told you?"
- My primary care provider;
- A provider who specializes in Long Covid;
- A specialist; then branching logic for: cardiologist; neurologist; pulmonologist; other:_____
- A chiropractor;
- Other:_____

Back to Top

Supplemental Table 8.

Overview of changes to the Protocol for adding assessments of Long Covid

The protocol version dates on the front page of each protocol.
Only the first and final protocols were published with the first outcomes paper.
We submit links to each version of the protocol after Long Covid was added:

- **April, 2021,** Version 3.1: Long Covid / PASC was added as an outcome (section 3.1), initially under primary outcomes.
- **July, 2021,** Version 3.2: Long Covid / PASC questionnaire was added as a protocol addendum
- **Sept, 2021,** Version 3.3**:** small protocol changes, not related to PASC
- **Dec 8, 2021**, Version 3.4: moved PASC down to secondary outcomes. This final version of the protocol was published on clinicaltrials.gov in January 20, 2022 while enrollment was still ongoing.
    - **Text in protocol version 3.4:**
        - "Portion of participants with Post-Acute Sequelae of SARS-CoV-2 Infection (PASC)
        - a. PASC assessment monthly after enrollment for 6 months to 12 months with the "Questionnaire to characterize long COVID." (Appendix G).[62]"

Statistical Analysis Plan

- No changes to the Statistical Analysis Plan have been made since unblinding.
- The SAP was emailed to the DSMB on Feb 14, 2022, before unblinding to the primary outcome on Feb 15, 2022.
- The outcome assessors, patients, care providers and all investigators except the unblinded statistician and graduate student assistant still remain blinded to individual treatment allocation
- PASC is listed as an efficacy outcome in the SAP in section 5.1
- Section 6.4 gives details about how PASC will be analyzed

Overview changes regarding Long Covid or PASC on Clinical Trials.gov:

1. On clinicaltrials.gov on May 3, 2021, this had been added to the study description:
"5. To understand if any of the active treatment arms prevent long-covid syndrome, PASC (post-acute sequelae of SARS-CoV-2 infection)."

2. On clinicaltrials.gov on May 17, 2021 it had been added under primary outcome measures:
"Post-Acute Sequelae of SARS-CoV-2 Infection (PASC) Questionnaire
[Time Frame: 6 and 12 months]
PASC assessment will be conducted monthly after enrollment for 6 months to 12 months with the Questionnaire to characterize long COVID. Outcome is reported as the percent of participants who report PASC any symptoms."

Back to Top

3. On clinical trials.gov on Sept 30, 2021, it had been moved down to secondary outcome measures:

"Post-Acute Sequelae of SARS-CoV-2 Infection (PASC) Questionnaire
[Time Frame: 6 and 12 months]
PASC assessment will be conducted monthly after enrollment for 6 months to 12 months with the Questionnaire to characterize long COVID. Outcome is reported as the percent of participants who report PASC any symptoms."

4. On Clinical trials.gov on Jan 20, 2022 (before enrollment finished), it was still in the study description and still a secondary outcome. The protocol was also uploaded to clinicaltrials.gov in Jan 2022 before enrollment was complete:

"Portion of participants with Post-Acute Sequelae of SARS-CoV-2 infection (PASC)
[Time Frame: 6 and 12 months]
PASC assessment will be conducted monthly after enrollment for approximately 9 months with the Questionnaire to characterize long COVID."

Back to Top