Supplementary Appendix

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This appendix has been provided by the authors to give readers additional information about the work.

Supplementary Appendix, COVID-OUT Study

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1 List of Investigators

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
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

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2 Supplementary Methods

The Covid-Out trial was performed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice (GCP) standards as an FDA Investigational New Drug (IND) registered trial.

2.1 Full Inclusion and Exclusion Criteria

2.1.1 Inclusion Criteria

- Positive laboratory test for active SARS-CoV-2 viral infection based on local laboratory standard (e.g. PCR, rapid antigen test) within 3 days of randomization. Result must be verifiable.
- No known previous history of confirmed SARS-CoV-2 infection
- Age ≥30 years and < 85 years
- Body Mass Index (BMI) ≥ 25 kg/m^2 by self-report height/weight or ≥ 23 kg/m^2 in persons with Asian or Latinx background [1-3]
- Has an address and electronic device for communication
- Estimated Glomerular Filtration Rate (eGFR) >45ml/min/1.73m^2 within 2 weeks for patients >75 years old, or with history of heart, kidney, or liver failure.*

  *If eGFR not available in electronic health record within 2 weeks, eGFR was tested via self-collected capillary blood sample into a microtainer or mobile phlebotomy where available. Participants were allowed to start study drug while the sample was processed by the study lab as it was deemed low risk to take low-dose metformin for 1 to 5 days while this processing occurred. If eGFR resulted as less than 45ml/min/1.73m^2, participants were instructed to discontinue study medicines and were considered as a screen failure.

2.1.2 Exclusion Criteria

- Hospitalized, for COVID-19 or other reasons.
- Symptom onset greater than 7 days before randomization (symptoms not required for inclusion).
- Immunocompromised (e.g. solid organ transplant, bone marrow transplant, AIDS, on chronic high dose steroids).
- Hepatic impairment (Child-Pugh B and C)
- Inability to obtain informed consent
- Enrollment in another blinded COVID-19 randomized trial
- Already received an effective (FDA approved/EUA*) therapy for COVID-19 BEFORE randomization (e.g. SARS-CoV-2 monoclonal antibody)
- Alcohol use disorder
- Other unstable medical condition or combination of home medications that in the view of the investigator make it unsafe for the individual to participate
- History of severe kidney disease:
  - Stage 4-5 chronic kidney disease or eGFR of <45ml/min/ 1.73 m^2*
  - Other kidney disease that in the opinion of the investigator would affect clearance of metformin
- Unstable heart failure (Stage 3 or 4 heart failure)
- Current use of or past allergy to metformin, fluvoxamine, or ivermectin
- Bipolar disease: individuals who report they have bipolar disorder or are taking medication for bipolar disorder (lithium, valproate, high-dose antipsychotic), unless the investigator concludes that the risk for mania is unlikely (i.e. it is doubtful that the patient actually has bipolar disorder).
- Current Loa Loa or onchocerciasis infection
- Typhoid, Bacillus Calmette–Guérin (BCG), or cholera vaccination within 14-days.

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- Concomitant medication exclusion, as below.

Medication Exclusions:

- cimetidine, hydroxychloroquine, insulin, sulfonylurea, dolutegravir, patiromer, ranolazine, tafenoquine.
- rasagiline, selegiline, or monoamine oxidase inhibitors, linezolid, methadone
- duloxetine, methylene blue
- tizanidine, ramelteon, sodium picosulfate
- alosetron, agomelatine, bromopride, dapoxetine, tamsimelteon, thioridazine, urokinase, pimozide

The following medications may not need to be excluded when dose for that individual is considered alongside the low dose of fluvoxamine being used and other medications being used. The PI or site PI may review and decide if the patient should be excluded from the fluvoxamine arms as these are all *Risk C, monitor therapy*:

a. Taking SSRIs, SNRIs, or tricyclic antidepressants, unless these are at a low dose such that a study investigator concludes that a clinically significant interaction with fluvoxamine (ie either serotonin syndrome or TCA overdose) is unlikely (examples: participant takes escitalopram but only at 10mg daily; that dose plus 100mg fluvoxamine would be insufficient to cause serotonin syndrome; or, participant takes amitriptyline but only at 25mg nightly; even if fluvoxamine inhibits its metabolism, it would be an insufficient dose to cause QTc prolongation or problematic side effects).

b. Individuals who take alprazolam or diazepam and are unwilling to cut the medication by 20% (rationale: fluvoxamine modestly inhibits the metabolism of these drugs).

c. Participants taking theophylline, clozapine, or olanzapine (drugs with a narrow therapeutic index that are primarily metabolized by CYP 1A2, which is inhibited by fluvoxamine) will be reviewed with a study investigator and excluded unless the investigator concludes that the risk to the participant is low (this would be unlikely; example: participant takes clozapine only as needed and is willing to avoid it for the 14 days of the study).

d. Patients will be advised that there is a small risk that the following substances will be affected by fluvoxamine, but that significant effects are not likely at the low dose being used of: caffeine, nicotine, melatonin.

e. Taking warfarin-also known as Coumadin, NSAIDs, and Aspirin (rationale: increased risk of bleeding), phenytoin (rationale: fluvoxamine inhibits its metabolism), clopidogrel (rationale: fluvoxamine inhibits its metabolism from pro-drug to active drug which raises risk of cardiovascular events), and St John's wort (rationale: fluvoxamine + St John's wort are considered contraindicated because of the risk of serotonin syndrome).

2.2 Reasons for Trial Exclusion

- Total Persons excluded (*n* = 5,178)
- BMI <25 kg/m^2, or <23 kg/m^2 for those who identify as Asian or Latinx background (*n* = 769)
- 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 eGFR <45 mL/min/1.73m^2 within last 2 months (*n* = 90) Back to Top

- 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)
- Stage 4 heart failure within last 2 months (*n* = 8)
- Previous allergic reaction to one of the study drugs (*n* = 3)
- Other (*n* = 1209, the most common reason was no interest in participating in the research study)

2.3 Randomization Details

- The statistician pre-generated allocation sequences for each study site using the mass weighted urn design,[4] which restricts deviations from the targeted equal allocation similar to randomly permuted blocks but with fewer deterministic assignments on average. Schedules for the 1:1 metformin versus placebo allocation used a total urn mass of alpha = 3, which is similar to randomly permuted blocks of size 6. Schedules for the 6 arms used a total urn mass of alpha = 6, which is similar to randomly permuted blocks of size 12. After the two fluvoxamine arms were stopped early for futility, the unused assignments for the fluvoxamine arms were skipped over (or deleted) from the pre-generated 6 arm allocation schedules.
- Assignments were drawn sequentially from the pre-generated schedules using a password protected Shiny application that required research coordinators to provide participant weight (because of ivermectin's weight-based dosing) and study site. The application would provide the research coordinator with a packet ID containing study drug at the appropriate weight-based dosage corresponding to the assigned arm. Pharmacists with the University of Minnesota Investigational Drug Service worked with the study statistician to create study packets with these unique identifiers. The assigned packet was then distributed to the study subject.
- Metformin randomization began December 30, 2020. Ivermectin and fluvoxamine arms opened on May 21, 2021, and thereafter every participant received two blinded study medicines, pre-packed by pharmacists into a pillbox to assure they took the correct number of each study medicine. Refer to **Supplemental Figure S9** for images of the pillboxes.
- For the analysis, the metformin group consists of participants who received metformin alone or metformin in combination with either fluvoxamine or ivermectin. The metformin control group consists of participants who received placebo, fluvoxamine alone, or ivermectin alone. The fluvoxamine group consists of participants who received fluvoxamine alone or fluvoxamine in combination with metformin. The fluvoxamine control group consists of participants who enrolled when fluvoxamine was available but who were randomized to either placebo or metformin alone. The ivermectin and ivermectin control groups were constructed similarly (**Figure 1)**. Only concurrently randomized controls were used.
- As pictured in **Figure 1**, the concurrent control group for each study drug consists of participants who were eligible to be randomized to a condition with the active version of the study drug, but who were randomized to a control condition instead. Specifically, the metformin active group includes persons randomized to metformin alone, metformin + ivermectin, or metformin + fluvoxamine, whereas the metformin control arm includes persons randomized to metformin matched placebo, ivermectin alone, or fluvoxamine alone.
- The control group for ivermectin includes persons randomized to placebo or metformin alone, but who were eligible to be randomized to a regimen with ivermectin, and similarly for fluvoxamine. In particular, the control arms for ivermectin and fluvoxamine do not include any persons randomized to placebo

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during the initial study period where metformin was the only active drug available. The primary statistical analysis estimates the main effect of each study drug controlling for baseline vaccination status and the other study drug(s).

2.4 Sample Size Considerations

The a priori assumptions in designing the trial included were:

- A hypothesized rate of the primary composite endpoint would be 20% in the placebo arm and 11% in each monotherapy arm, which corresponds to a relative risk reduction of 45%.
- Assuming additive effects on the log-odds scale, the hypothesized rate of the primary composite endpoint in the combination therapy arms is 6%.
- Under equal allocation to the 6 arms, this leads to hypothesized rates of 14% = (0.2 + 0.11 + 0.11)/3 versus 7.7% = (0.11 + 0.06 + 0.06)/3 in the metformin control and active arms, respectively, which corresponds to a relative risk reduction of 45%.
- To detect this effect with 90% power using a marginal test two-sample binomial proportion test with 5% two-sided type I error requires 1,008 total participants contributing data, equating to 169 participants per arm.
- The fluvoxamine and ivermectin comparisons have lower power as these arms include participants assigned to 4 of the 6 arms.
- The a priori assumption was of 10% withdrawal and/or lost to follow up not contributing outcome data
- To account for the interim analysis plan and losses to follow-up, the original plan was for enrollment of 1,124 total participants (account for up to 10% withdrawal).

Sample Size Re-estimation

At time of the second interim analysis, a planned sample size re-estimation occurred which incorporated the current (lower than expected) lost to follow up rate, the projected proportion of participants vaccinated (which was increasing over time), the actual event rate in the placebo arm by vaccination status, as well as external data on possible effect sizes of fluvoxamine motivating detection of a relative risk reduction of 35% with at least 80% power.

On 24 November 2021, motivated by lack of certainty in the placebo control event rate and external data indicating that fluvoxamine may provide a ~33% relative risk reduction,[5] the unblinded statistician carried out a pre-specified sample size re-estimation procedure based on interim outcome data to revise the target enrollment to 1,350 participants. This revised target would provide 90% power for the main effect of metformin, and 80% power for the main effects of fluvoxamine and ivermectin, assuming multiplicative 35% relative risk reductions of each study drug and a projected estimate of the event rate in the placebo arm that accounted for the vaccination rates of recent enrollees.

On 7 January 2022, the DSMB conducted a third interim analysis of futility and efficacy, after enrollment of approximately 1,100 participants. At that time, the DSMB recommended stopping fluvoxamine for futility with a conditional power of less than 3%. The final sample size was reduced by the number of participants who would have been allocated to fluvoxamine in remaining study period for a total enrollment goal of 1,290 participants.

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2.5 Outcome Assessments

Pulse Oximetry

Pulse oximetry was assessed using a home finger pulse oximeter, "Zacurate, 500DL Pro Series" Distributed by Einstein Associates LLC; 10101 Stafford Centre Dr, Ste B, Stafford TX 77477. Designed in the USA, Made in China. This pulse oximeter provides oxygen saturation and heart rate. The manufacturer's stated accuracy of is within ±2% for oximetry readings between 70% to 99%.

The threshold of ≤93% for hypoxemia was defined as per FDA definition for severe Covid-19.[6]

Participants were instructed to take daily pulse oximetry measurements and record these on a daily symptom diary. Additionally, participants were instructed that if they had a pulse oximetry level below 94%, they should sit-up straight, make sure their hands are warm, and retake their pulse oximetry. Many participants recorded multiple readings per day. Research staff were not in communication with participants on each day of their involvement (unless the participant desired/needed daily communication), so oxygen readings were reviewed after the daily symptom diaries were returned by US postal mail. This delayed review of pulse oximetry data prevented clarity on values written down in the daily diary that did not appear to be pulse oxygen measurements.

Sources of bias for the oxygen readings are outlined below. Hypoxemia likely added noise as a component of the 4-party binary composite primary outcome.[8]

1) **Measurement error:** While instructions were given to minimize measurement error, values may have been falsely low due to measurement techniques (i.e. having cold hands; or having the oximeter on a finger with the thickest skin).
    a. Also, the devices may not fit all individuals' fingers the same, causing measurement error.

2) **Inherent error in the device**: On February 21, 2021, the FDA issued a safety communication with concerns expressed over the accuracy of home pulse oximeters.[7] We did not use prescription oximeters, but rather over-the-counter oximeters due to cost limitations. For prescription oximeters, 66% of readings will fall within 2-3% of arterial blood gas. Additionally, analyses have found that color of skin can affect the accuracy of pulse oximetry.[9]

3) **Misclassification bias:** The protocol did not specify movement before measurements, nor time between measurements, as we did not want to overwhelm participants. The values were collected on paper logs, which created a lag time to analysis of the written values.
    a. Some low values may represent transient lower oxygen saturation that does not represent true hypoxemia (i.e. atelectasis because they had not coughed, stood up, or walked in some time).

4) **Selection bias:** Instructions to participants did not specify a certain number of times that each person had to measure their oxygen each day, nor that participants should always record their highest value.
    a. Some individuals may have entered their lowest number.
    b. Some entered many readings per day, while others entered only one.

Emergency Department Visits, Hospitalizations, and Death

Primary outcome events that occurred between enrollment and taking the first dose of study drug were not included as outcomes in the modified intent-to-treat analysis. These outcomes are included in the intent-to-treat analysis.

Participants provided informed consent to review medical records in order to verify the occurrence of emergency room visits, hospitalizations, and death as needed. Emergency department visits and hospitalizations were adjudicated as Covid-19 related or not, and all investigators remain blinded to randomized study arm for individual participants. Only one hospitalization was adjudicated as non-Covid-related of a bacterial abscess on the leg.

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2.6 Handling of Missing Data

Overall, 18 participants (1.36%) were missing one or more components of the day 14 composite outcome and were unresponsive to attempts at follow up. Overall, 10 had unknown vital status of whom none had an online obituary that we could find, or deactivated email account as of 12 May 2022. The a priori approach as specified in the Statistical Analysis Plan was to multiply impute missing data.

Descriptive statistics regarding the incomplete aspects of the primary endpoint.							
	Overall	**Metformin**		**Ivermectin**		**Fluvoxamine**	
		Active	Control	Active	Control	Active	Control
Missing Participant - Reported Component	18/1323 (1%)	11/663 (2%)	7/660 (1%)	3/410 (1%)	7/398 (2%)	5/334 (1%)	6/327 (2%)
Hypoxemia or Supplemental O_2	18/1323 (1%)	11/663 (2%)	7/660 (1%)	3/410 (1%)	7/398 (2%)	5/334 (1%)	6/327 (2%)
Emergency Dept Visit	15/1323 (1%)	10/663 (2%)	5/660 (1%)	3/410 (1%)	4/398 (1%)	5/334 (1%)	3/327 (1%)
Hospitalization	14/1323 (1%)	9/663 (1%)	5/660 (1%)	3/410 (1%)	4/398 (1%)	5/334 (1%)	3/327 (1%)
Death	10/1323 (1%)	5/663 (1%)	5/660 (1%)	2/410 (0%)	2/398 (1%)	0/334 (0%)	0/327 (0%)
Incomplete or missing SpO_2 Daily Log Data (<14 Days)	371/1323 (28%)	199/663 (30%)	172/660 (26%)	100/410 (24%)	111/398 (28%)	99/334 (30%)	89/327 (27%)
0 Days with Data	250/1323 (19%)	134/663 (20%)	116/660 (18%)	69/410 (17%)	77/398 (19%)	68/334 (20%)	63/327 (19%)
1 - 7 Days with Data	29/1323 (2%)	14/663 (2%)	15/660 (2%)	5/410 (1%)	13/398 (3%)	6/334 (2%)	7/327 (2%)
8 - 13 Days with Data	92/1323 (7%)	51/663 (8%)	41/660 (6%)	26/410 (6%)	21/398 (5%)	25/334 (7%)	19/327 (6%)

Our primary approach to handling missing primary outcome data on Day 14 was to conduct our analysis using multiple imputation. Specifically, we used predictive mean matching to multiply impute missing outcomes and vaccination status. Missing covariate information were jointly imputed along with missing outcomes using multiple imputation with chained equations and predictive mean matching for the univariate imputation models; along with outcome and vaccination status information, imputation models were informed by sex, BMI, symptom duration, race, baseline comorbidities, and maximum daily SpO_2 from the logs, per the guidelines of Sterne, et al (2009) as well as self-reported outcomes.[10]

Further guidance on choice of imputation model is described in the Statistical Analysis Plan. Imputation regression models were developed based on all available data, i.e. patients who have completed the requisite follow-up time of 14 days for the primary outcome. Imputation was carried out using the mice R package version 3.14.0.[11] Imputation was carried out using 50 imputed datasets, each with at least 40 iterations of the mice algorithm.[11] We assessed convergence diagnostics to verify convergence of the imputations per Section 6.5 of Van Buuren et al.[12] The primary analysis utilized a multiply-imputed likelihood ratio test that tests the effect of the treatment by comparing nested logistic regression models.[13] Odds ratios and confidence intervals are constructed by combining results across imputed datasets via Rubin's rules.[14]

Additionally, as a sensitivity analysis, we performed a complete case analysis without any imputation, thereby excluding participants missing day 14 outcome data or SARS-CoV-2 vaccination status. Vaccination status was adjusted for in the regression model as in the primary analysis. Results are not

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appreciably changed. This complete case analysis is presented in **Table S4**. The same approach was used for the intent-to-treat analyses.

2.7 Study Medication Dosing (and for exact-matching placebo)

2.7.1 Metformin

Metformin immediate release was given via a dose titration with:

Day 1: 500mg once
Day 2-5: 500mg twice daily
Day 6-14: 500mg in the morning and 1,000mg in the evening

A maximum dose of 1,500mg was used because the risk of side effects is greatest at doses of 2,000mg per day,[15] which is the goal dose for diabetes treatment but titration to this dose is typically done over several weeks.

2.7.2 Ivermectin Dosing

Ivermectin and matched placebo were kindly provided as 7 and 14mg tablets by Edenbridge Pharmaceuticals (Parsippany-Troy Hills, New Jersey, USA). Ivermectin or matching placebo was given for 3 days with weight-based dosing with an objective to achieve at least approximately 400 mcg/kg/day dosing. This dose was chosen as it was higher than what was done in other trials at the time, but still well within the range of safe doses. As per the U.S. FDA Investigational New Drug (IND) procedures, FDA had to approve the dosing as safe. The weight-based dosing was:

Less than 74kg	28 mg once daily (2 x 14mg)
74 to < 88kg	35mg once daily (2 x 14mg + 7mg)
88 to < 106kg	42mg once daily (3 x 14)
106 to < 124kg	49mg once daily (3 x 14mg + 7mg)
124kg to < 160kg	56mg once daily (4 x 14mg)
≥ 160 kg	63mg once daily (4 x 14mg + 7mg)

Overall, 90% (369 of 411) of participants received doses between 390 to 470 mcg/kg/day with 17 (4.1%) participants having received less than 390 mcg/kg/day, and 25 (6.1%) having received greater than 470 mcg/kg/day. The median dose received was 430 mcg/kg/day.

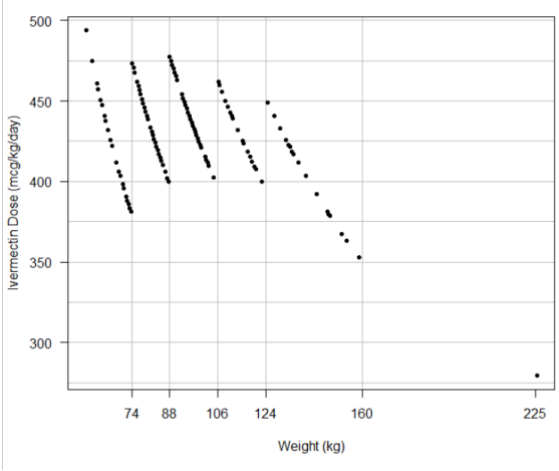

Figure 2.7.2 Distribution of weight-based dosing.

2.7.3 Fluvoxamine Dosing

Fluvoxamine was given 1 dose on Day 1, then 50mg twice daily for days 2-14.
Fluvoxamine and identically matched placebo were kindly provided by Apotex Pharmaceuticals (Toronto, Ontario, Canada).

Refer to **Supplement Figure S9** for pictures of the study medicine and exact-matching placebo.

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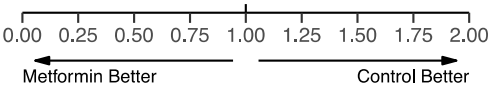
3 Supplementary Figures

3.1 Figure S1A. Effect of metformin vs. control for the primary outcome, overall and by subgroups.

Subgroup	Metformin	Control	Adjusted Odds Ratio (95% CI)
	n events /	n (n missing)	
All Participants	154/652 (11)	179/653 (7)	0.84 (0.66 to 1.09)
Sex			
Female	78/352 (7)	107/378 (4)	0.73 (0.52 to 1.02)
Male	76/300 (4)	72/275 (3)	1.04 (0.71 to 1.52)
Body Mass Index (BMI)			
< 30 kg/m^2	80/344 (3)	78/326 (4)	1.01 (0.70 to 1.45)
≥ 30 kg/m^2	74/308 (8)	101/327 (3)	0.71 (0.50 to 1.01)
Symptom onset to drug initiation			
< 4 days	63/290 (6)	73/298 (5)	0.90 (0.61 to 1.32)
≥ 4 days	85/352 (5)	103/337 (2)	0.74 (0.53 to 1.04)
Unknown	6/10 (0)	3/18 (0)	
Age			
< 45 years	53/303 (5)	61/309 (4)	0.93 (0.61 to 1.42)
≥ 45 years	101/349 (6)	118/344 (3)	0.78 (0.56 to 1.08)
Covid−19 Variant Time Period			
Alpha	27/78 (1)	35/80 (0)	0.66 (0.34 to 1.28)
Delta	101/434 (6)	113/426 (5)	0.87 (0.63 to 1.19)
Omicron	26/140 (4)	31/147 (2)	0.87 (0.48 to 1.57)
Vaccinated, primary series			
No	87/293 (8)	112/322 (5)	0.80 (0.57 to 1.12)
Yes	67/357 (2)	67/329 (2)	0.90 (0.62 to 1.32)
Unknown	0/2 (1)	0/2 (0)	
Pregnant			
Not Pregnant	151/630 (10)	175/630 (6)	0.84 (0.65 to 1.09)
Pregnant	3/22 (1)	4/23 (1)	0.77 (0.14 to 4.21)
Combo/Monotherapy Subgroups			
Metformin only vs. Placebo	70/278 (6)	79/291 (4)	0.91 (0.62 to 1.33)
Met+Ivermectin vs. Ivermectin	50/201 (3)	55/206 (0)	0.92 (0.58 to 1.44)
Met+Fluvox vs. Fluvoxamine	34/173 (2)	45/156 (3)	0.65 (0.39 to 1.09)



This forest plot shows a priori subgroups analyses of the primary composite endpoint showing odds ratios with 95% confidence intervals, adjusted for vaccination status. The 95% confidence intervals are not adjusted for multiplicity. If vaccination status was unknown, the value was multiply-imputed when used as a controlling variable. Hypoxemia is defined as oxygen saturation ≤93% or supplemental oxygen to maintain an oxygen saturation ≥ 94% on day 2 or later. Participants who only have an oxygen saturation ≤93% on Day 1 and not after are not counted as having achieved this endpoint. The number in parentheses for each subgroup stratum is the number of persons within that stratum that had any component of the primary outcome missing (Hypoxemia, emergency department visits, hospitalization, or death). A body mass index (BMI) cut-off of 30 kg/m^2 was used to compare those with overweight versus obesity. Variant periods were defined by epidemiologic data, Alpha: before June 19, 2021; Delta: June 19-December 12, 2021; Omicron: after December 12, 2021 through end of enrollment on January 28, 2022. The top row is all participants, subsequent rows are sub-groups. Abbreviations: Met = metformin, Fluvox = fluvoxamine.

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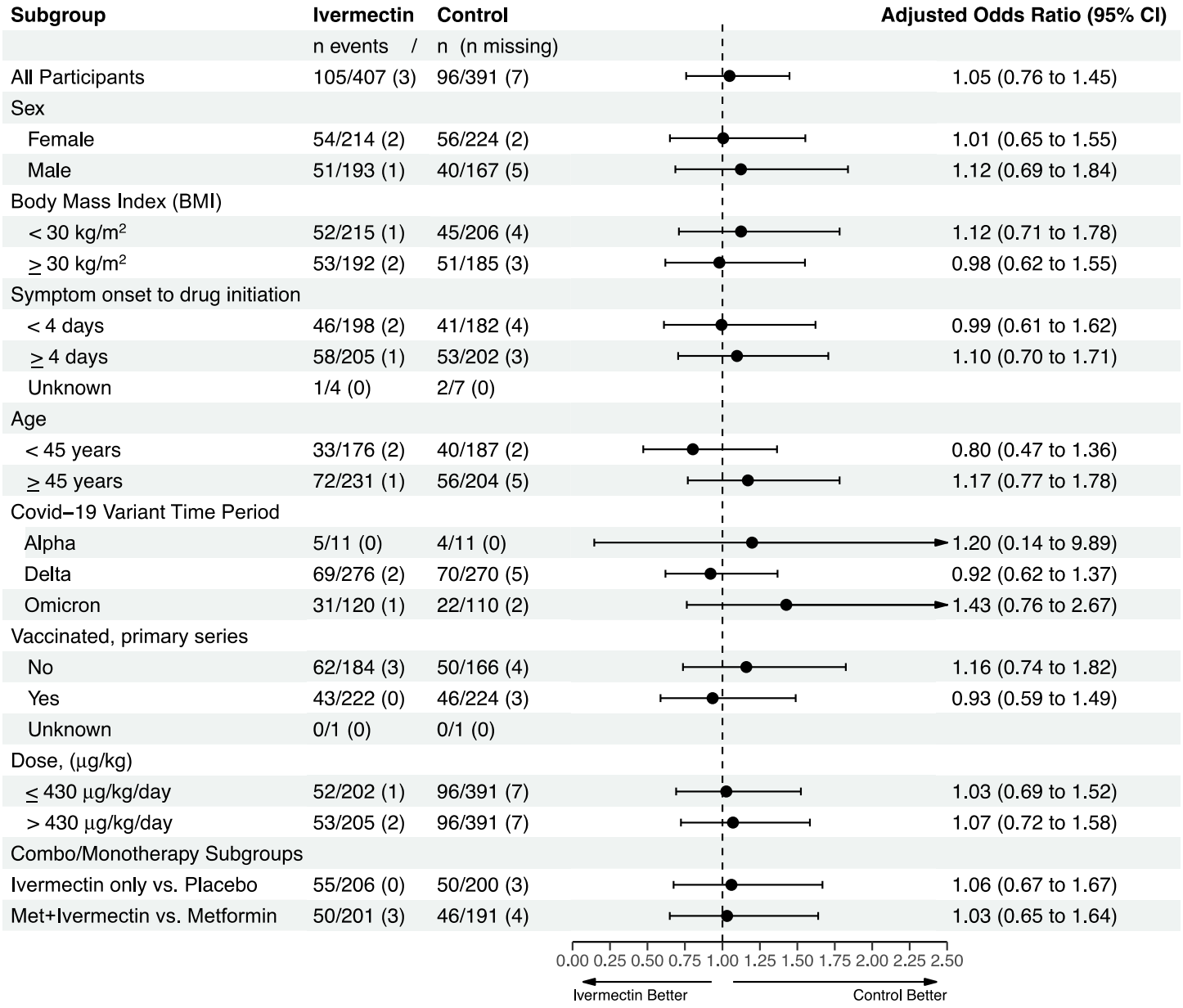
3.2 Figure S1B. Effect of ivermectin vs. control for the primary outcome, overall and by subgroups.



This forest plot shows a priori subgroups analyses of the primary composite endpoint showing odds ratios with 95% confidence intervals, adjusted for vaccination status and not adjusted for multiplicity. If vaccination status was unknown, the value was multiply-imputed when used as a controlling variable. Hypoxemia is defined as oxygen saturation ≤93% or supplemental oxygen to maintain an oxygen saturation ≥ 94% on day 2 or later. Participants who only have an oxygen saturation ≤93% on Day 1 and not after are not counted as having achieved this endpoint. The number in parentheses for each subgroup stratum is the number of persons within that stratum that had any component of the primary outcome missing (hypoxemia, emergency department visits, hospitalization, or death). A body mass index (BMI) cut-off of 30 kg/m^2 was used to compare those with overweight versus obesity. The top row is all participants, subsequent rows are sub-groups.
Abbreviations: Met = metformin.

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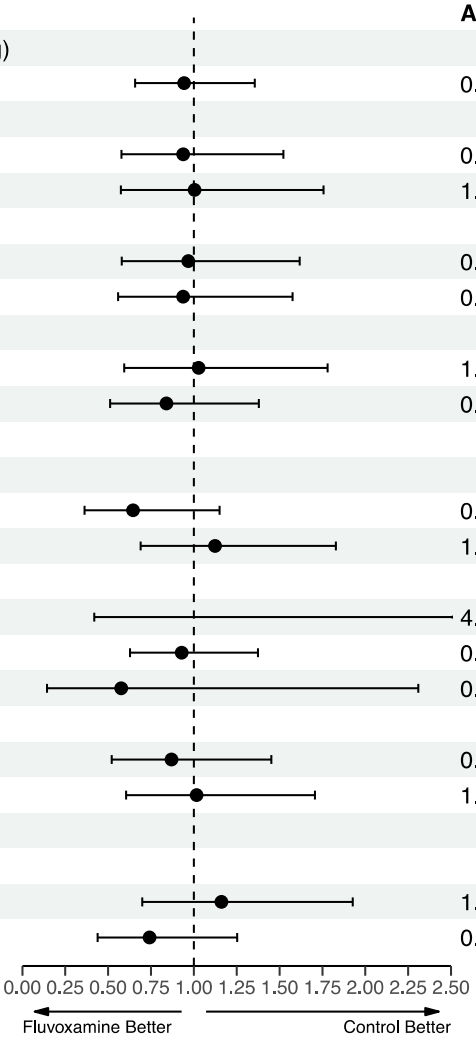
3.3 Figure S1C. Effect of fluvoxamine vs. control for the primary outcome, overall and by subgroups.

Subgroup	Fluvoxamine	Control	Adjusted Odds Ratio (95% CI)
	n events /	n (n missing)	
All Patients	79/329 (5)	80/321 (6)	0.94 (0.66 to 1.35)
Sex			
Female	42/166 (4)	49/187 (1)	0.94 (0.58 to 1.52)
Male	37/163 (1)	31/134 (5)	1.00 (0.57 to 1.76)
Body Mass Index (BMI)			
<30kg/m^2	39/179 (1)	37/167 (3)	0.97 (0.58 to 1.62)
>=30kg/m^2	40/150 (4)	43/154 (3)	0.94 (0.56 to 1.58)
Symptom onset to drug initiation			
< 4 days	35/145 (4)	34/150 (3)	1.03 (0.59 to 1.78)
>= 4 days	42/180 (1)	45/166 (3)	0.84 (0.51 to 1.38)
Unknown	2/4 (0)	1/5 (0)	
Age			
<45 years	23/150 (3)	38/170 (2)	0.65 (0.36 to 1.15)
>=45 years	56/179 (2)	42/151 (4)	1.12 (0.69 to 1.83)
Covid−19 Variant Time Period			
Alpha	7/12 (0)	4/11 (0)	4.14 (0.42 to 40.87)
Delta	68/274 (3)	70/270 (5)	0.93 (0.63 to 1.37)
Omicron	4/43 (2)	6/40 (1)	0.58 (0.14 to 2.31)
Vaccinated			
No	43/143 (4)	44/135 (4)	0.87 (0.52 to 1.45)
Yes	36/184 (1)	36/185 (2)	1.02 (0.60 to 1.71)
Unknown	0/2 (0)	0/1 (0)	
Combo/Monotherapy Subgroups			
Fluv only vs. Placebo	45/156 (3)	40/163 (3)	1.16 (0.70 to 1.93)
Met+Fluv vs. Met	34/173 (2)	40/158 (3)	0.74 (0.44 to 1.25)



This forest plot shows for fluvoxamine the a priori subgroups analyses of the primary composite endpoint showing odds ratios with 95% confidence intervals, adjusted for vaccination status and not adjusted for multiplicity. If vaccination status was unknown, the value was multiply-imputed when used as a controlling variable. Hypoxemia is defined as oxygen saturation ≤93% or supplemental oxygen to maintain an oxygen saturation ≥ 94% on day 2 or later. Participants who only have an oxygen saturation ≤93% on Day 1 and not after are not counted as having achieved this endpoint. The number in parentheses for each subgroup stratum is the number of persons within that stratum that had any component of the primary outcome missing (hypoxemia, emergency department visits, hospitalization, or death). A body mass index (BMI) cut-off of 30 kg/m^2 was used to compare those with overweight versus obesity. The top row is all participants, subsequent rows are sub-groups. Abbreviations: Met = metformin.

Enrollment in the fluvoxamine arm was stopped on January 7, 2022 by the DSMB, thus this arm has a higher proportion of persons enrolled during the SARS-CoV-2 delta variant time period.

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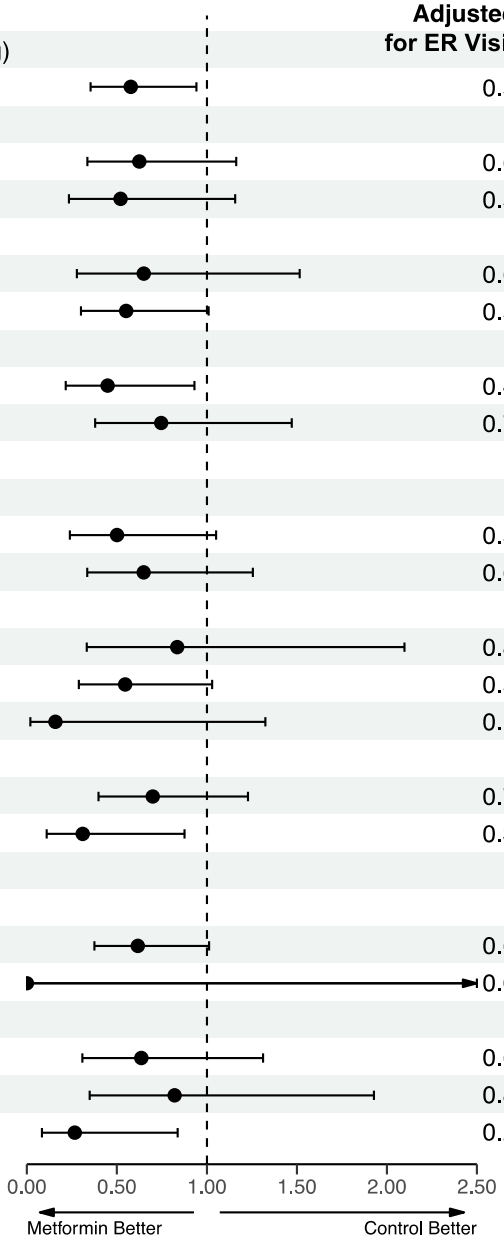
3.4 Figure S2A. Effect of metformin vs. control for healthcare utilization, overall and by subgroups.

Subgroup	Metformin	Control	Adjusted Odds Ratio (95% CI) for ER Visit, Hospitalization, Death
	n events /	n (n missing)	
All Participants	27/652 (11)	48/655 (5)	0.58 (0.35 to 0.94)
Sex			
Female	17/351 (8)	29/378 (4)	0.62 (0.34 to 1.16)
Male	10/301 (3)	19/277 (1)	0.52 (0.23 to 1.16)
Body Mass Index (BMI)			
< 30 kg/m^2	9/343 (4)	15/327 (3)	0.65 (0.28 to 1.51)
≥ 30 kg/m^2	18/309 (7)	33/328 (2)	0.55 (0.30 to 1.01)
Symptom onset to drug initiation			
< 4 days	11/290 (6)	26/299 (4)	0.45 (0.22 to 0.93)
≥ 4 days	16/352 (5)	21/338 (1)	0.75 (0.38 to 1.47)
Unknown	0/10 (0)	1/18 (0)	
Age			
< 45 years	11/303 (5)	24/309 (4)	0.50 (0.24 to 1.05)
≥ 45 years	16/349 (6)	24/346 (1)	0.65 (0.34 to 1.25)
Covid−19 Variant Time Period			
Alpha	10/77 (2)	12/80 (0)	0.84 (0.33 to 2.10)
Delta	16/435 (5)	29/427 (4)	0.55 (0.29 to 1.03)
Omicron	1/140 (4)	7/148 (1)	0.16 (0.02 to 1.32)
Vaccinated, primary series			
No	22/292 (9)	34/323 (4)	0.70 (0.40 to 1.23)
Yes	5/358 (1)	14/330 (1)	0.31 (0.11 to 0.88)
Unknown	0/2 (1)	0/2 (0)	
Pregnant			
Not Pregnant	27/630 (10)	45/632 (4)	0.62 (0.38 to 1.01)
Pregnant	0/22 (1)	3/23 (1)	0.00 (0.00 to Inf)
Combo/Monotherapy Subgroups			
Metformin only vs. Placebo	13/279 (5)	21/293 (2)	0.64 (0.31 to 1.31)
Met+Ivermectin vs. Ivermectin	10/200 (4)	13/206 (0)	0.82 (0.35 to 1.93)
Met+Fluv vs. Fluvoxamine	4/173 (2)	14/156 (3)	0.27 (0.08 to 0.84)



This forest plot presents the a priori subgroup analysis of the primary composite endpoint, with exclusion of the hypoxemia component – thereby presenting the odds of emergency department visit, hospitalization, or death due to Covid-19. The forest plot shows the adjusted odds ratios with 95% confidence intervals, which is adjusted for SARS-CoV-2 vaccination status and other medicines in the factorial trial design and not adjusted for multiplicity. If vaccination status was unknown, the value was multiply-imputed when used as a controlling variable. The number in parentheses for each subgroup stratum is the number of persons within that stratum that had any component of the primary outcome missing (emergency department visits, hospitalization, or death). A body mass index (BMI) cut-off of 30 kg/m^{2}was used to compare those with overweight versus obesity. The top row is all participants, subsequent rows are sub-groups. Abbreviations: Met = metformin; Fluvox = fluvoxamine.

Previous research suggesting that metformin enhances T cell response may support a potential synergistic effect in those who had been vaccinated.[16, 17]

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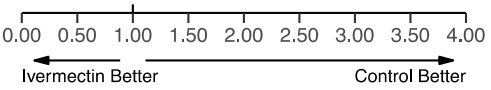
3.5 Figure S2B. Effect of ivermectin vs control for healthcare utilization, overall and by subgroups.

Subgroup	Ivermectin n events / n (n missing)	Control n events / n (n missing)	Adjusted Odds Ratio (95% CI) for ER Visit, Hospitalization, Death
All Patients	23/406 (4)	16/394 (4)	1.39 (0.72 to 2.69)
Sex			
Female	14/213 (3)	10/224 (2)	1.50 (0.65 to 3.47)
Male	9/193 (1)	6/170 (2)	1.27 (0.43 to 3.74)
BMI			
<30kg/m^2	6/214 (2)	5/207 (3)	1.17 (0.35 to 3.94)
>=30kg/m^2	17/192 (2)	11/187 (1)	1.50 (0.68 to 3.34)
Symptom onset to drug initiation			
< 4 days	11/197 (3)	10/184 (2)	0.99 (0.40 to 2.40)
>= 4 days	12/205 (1)	6/203 (2)	2.07 (0.75 to 5.69)
Unknown	0/4 (0)	0/7 (0)	
Age			
<45 years	10/175 (3)	12/188 (1)	0.91 (0.38 to 2.20)
>=45 years	13/231 (1)	4/206 (3)	2.78 (0.88 to 8.73)
Covid–19 Variant Time Period			
Alpha	2/10 (1)	2/11 (0)	1.10 (0.09 to 13.12)
Delta	16/276 (2)	12/272 (3)	1.29 (0.59 to 2.82)
Omicron	5/120 (1)	2/111 (1)	2.51 (0.47 to 13.56)
Vaccinated			
No	15/183 (4)	12/167 (3)	1.16 (0.52 to 2.56)
Yes	8/222 (0)	4/226 (1)	2.10 (0.62 to 7.12)
Unknown	0/1 (0)	0/1 (0)	
Dose (µg/kg)			
<= 430 µg/kg/day	9/201 (2)	16/394 (4)	1.09 (0.47 to 2.54)
> 430 µg/kg/day	14/205 (2)	16/394 (4)	1.73 (0.81 to 3.66)
Combo/Monotherapy Subgroups			
Iver only vs. Placebo	13/206 (0)	12/202 (1)	1.03 (0.45 to 2.33)
Met+Iver vs. Met	10/200 (4)	4/192 (3)	2.43 (0.75 to 7.93)



This forest plot presents the a priori subgroup analysis of the primary composite endpoint, with exclusion of the hypoxemia component – thereby presenting the odds of emergency department visit, hospitalization, or death. The forest plot shows the adjusted odds ratios with 95% confidence intervals, which is adjusted for vaccination status and other medicines in the factorial trial design and not adjusted for multiplicity. If vaccination status was unknown, the value was multiply-imputed when used as a controlling variable. The number in parentheses for each subgroup stratum is the number of persons within that stratum that had any component of the primary outcome missing (emergency department visits, hospitalization, or death). A Body mass index (BMI) cut-off of 30 kg/m^{2}was used to compare those with overweight versus obesity. The top row is all participants, subsequent rows are sub-groups. Abbreviation: Met = metformin.

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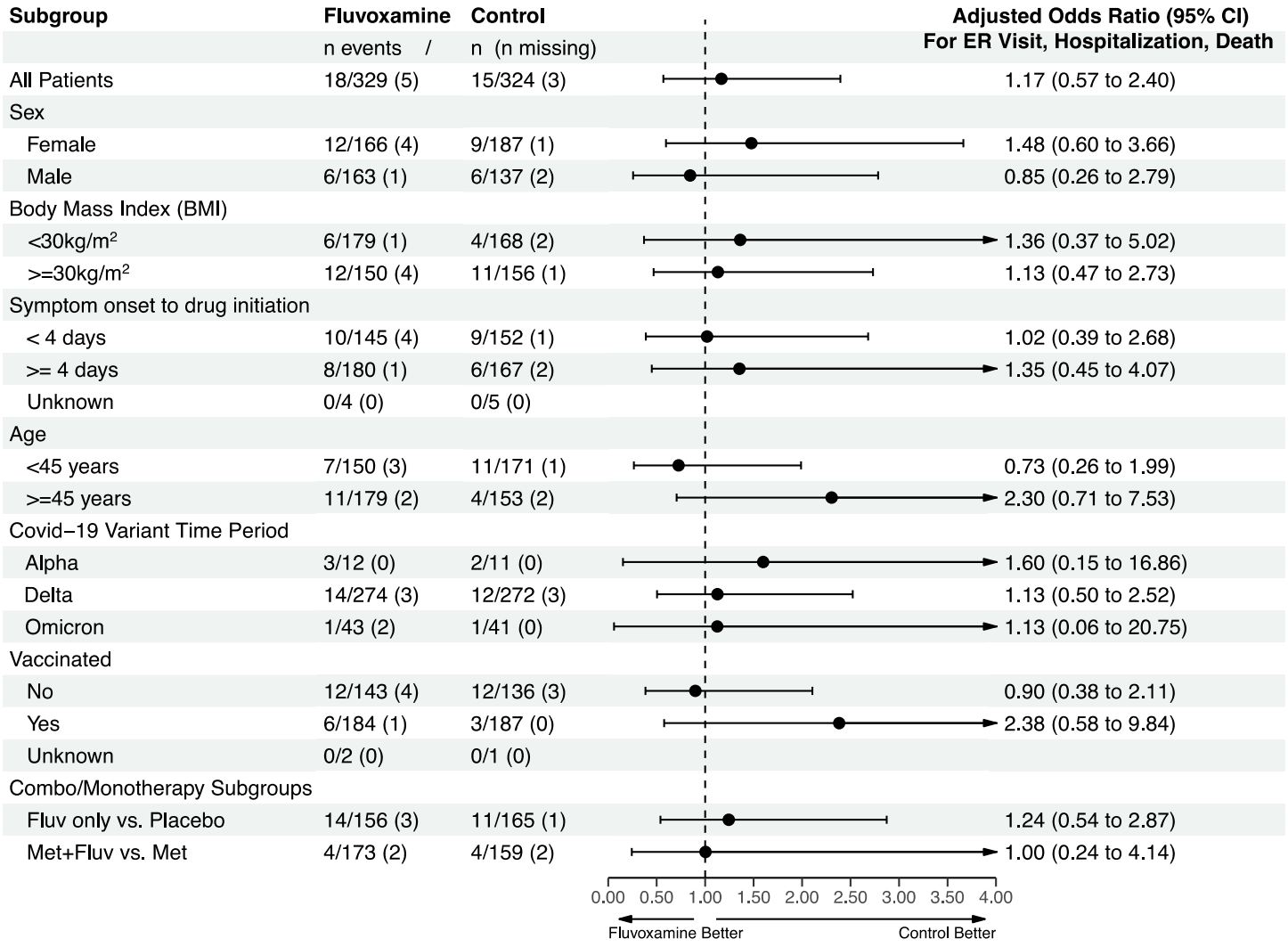
3.6 Figure S2C. Effect of fluvoxamine vs. control for healthcare utilization, overall and by subgroups.



This forest plot presents the a priori subgroup analysis of the primary composite endpoint, with exclusion of the hypoxemia component – thereby presenting the odds of emergency department visit, hospitalization, or death. The forest plot shows the adjusted odds ratios with 95% confidence intervals, which is adjusted for vaccination status and other medicines in the factorial trial design and not adjusted for multiplicity. If vaccination status was unknown, the value was multiply-imputed when used as a controlling variable. The number in parentheses for each subgroup stratum is the number of persons within that stratum that had any component of the primary outcome missing (emergency department visits, hospitalization, or death). A Body mass index (BMI) cut-off of 30 kg/m^2 was used to compare those with overweight versus obesity. The top row is all participants, subsequent rows are sub-groups. Abbreviations: Met = metformin.

Enrollment in the fluvoxamine arm was stopped on January 7, 2022 by the DSMB, thus this arm has a higher proportion of persons enrolled during delta variant time period.

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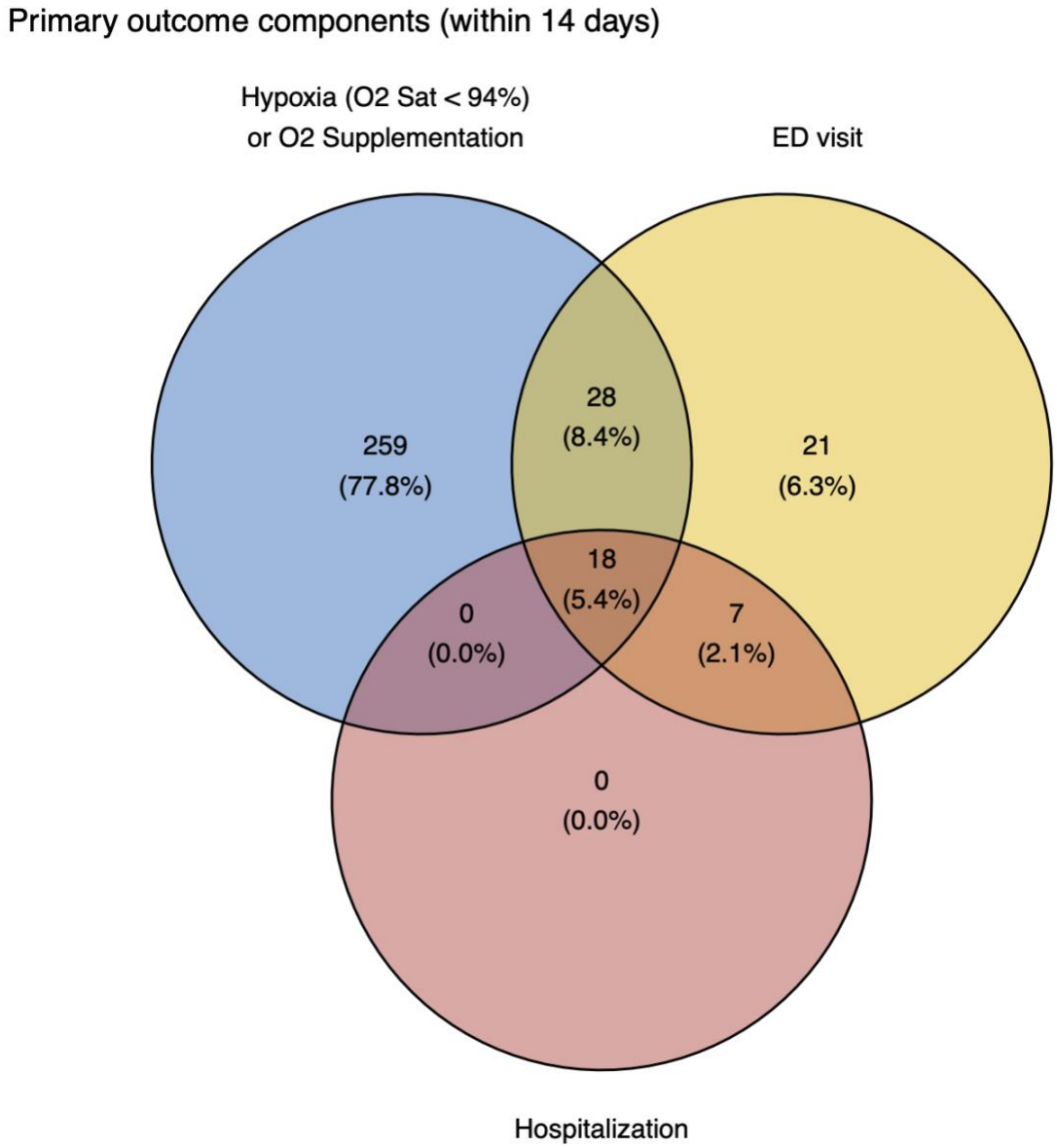
3.7 Figure S3. Venn Diagram of Components of Primary Composite Endpoint



This is a Venn diagram of the components of the composite primary outcome: the blue circle is the hypoxemia; the yellow circle is emergency department visit; and the red circle is hospitalization. Of note, the one death did not have a preceding hospitalization or ED visit. As noted in the methods, participants recorded pulse oximetry readings on a daily symptom diary or reported via interview with research personnel, or both. The number with hypoxemia reflects those reporting any pulse oximetry reading ≤93% during the 14-day study period. The investigators later had concerns on the accuracy of self-reported oximetry readings after numerous participants recorded apparent spurious, transient readings which likely could reflect measurement error. Participants recorded a variable number of readings each day, thus causing a potential selection bias if averaging of readings were performed.

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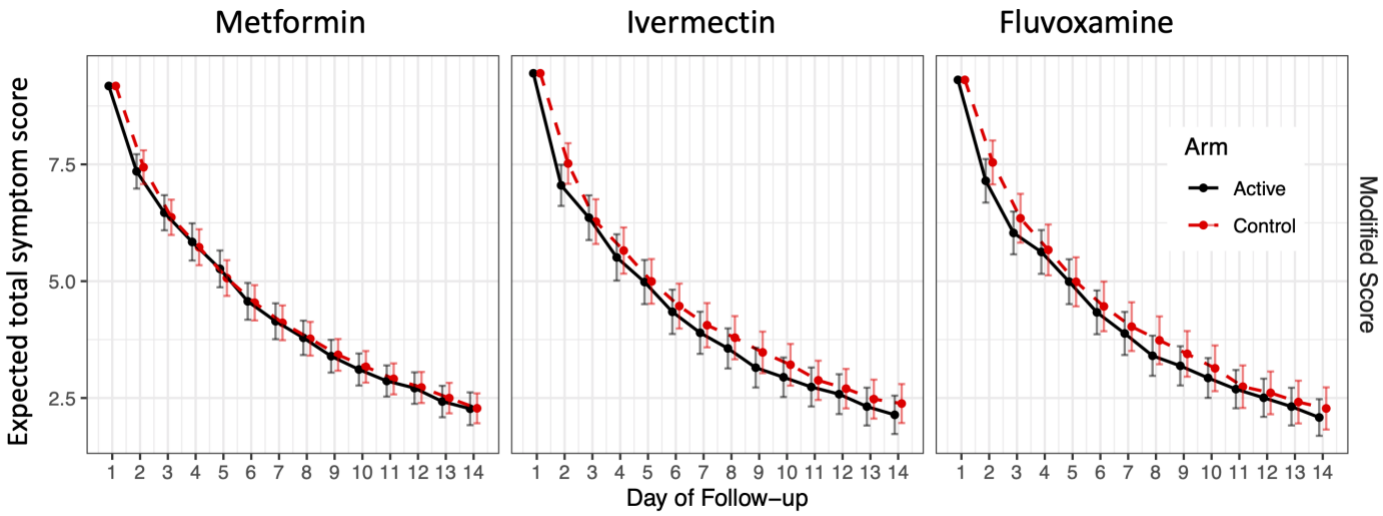
3.8 Figure S4. Covid-19 Specific Symptoms over Time by Study Medicine



This line graph presents the composite Covid-specific symptom score, with active treatment group in black and the control group in red, compared using a generalized estimating equation adjusted for baseline score, vaccination status, and other study medications. The y-axis is the expected symptom severity score, and the x-axis is the number of days since randomization. The trajectories reflect the expected score over time conditional on the baseline mean score in the pooled analysis cohort, being unvaccinated, and not taking any other study medications.

Symptoms are graded as none (0), mild (1), moderate (2), or severe (3). Eight symptoms comprise the composite score based on COVID-19 symptoms are those present in the U.S. Council of State and Territorial Epidemiologists clinical case definition of: cough, shortness of breath, subjective fever, fatigue, myalgia, sore throat, chills, and headache as used in recent FDA emergency use authorizations. Lack of taste or lack of smell are not included in this composite as these were measured on a different 0, 1, 2 scale, and may have a different time to resolution. Refer to Supplemental Figure 5 for plots of individual symptoms.

These symptoms were recorded on a daily symptom log, and 78% (1033/1,323) of participants returned their logs by U.S. postal mail. The missingness of symptom information averaged 25% per day (Range 21-25% by day).

3.8.1 Data Table for Manuscript Figure 2, the Mean (±SD) total symptom severity score

	Metformin		**Ivermectin**		**Fluvoxamine**	
	Active	*Control*	*Active*	*Control*	*Active*	*Control*
Day 1	12.43 (6.18)	12.98 (6.45)	12.73 (6.52)	13.13 (6.03)	12.48 (5.97)	13.30 (6.02)
Day 7	6.48 (4.85)	6.57 (5.42)	6.35 (5.08)	6.57 (5.14)	6.49 (5.15)	6.72 (5.25)
Day 14	3.48 (4.00)	3.73 (4.29)	3.45 (4.12)	3.85 (4.28)	3.53 (4.24)	3.96 (4.46)

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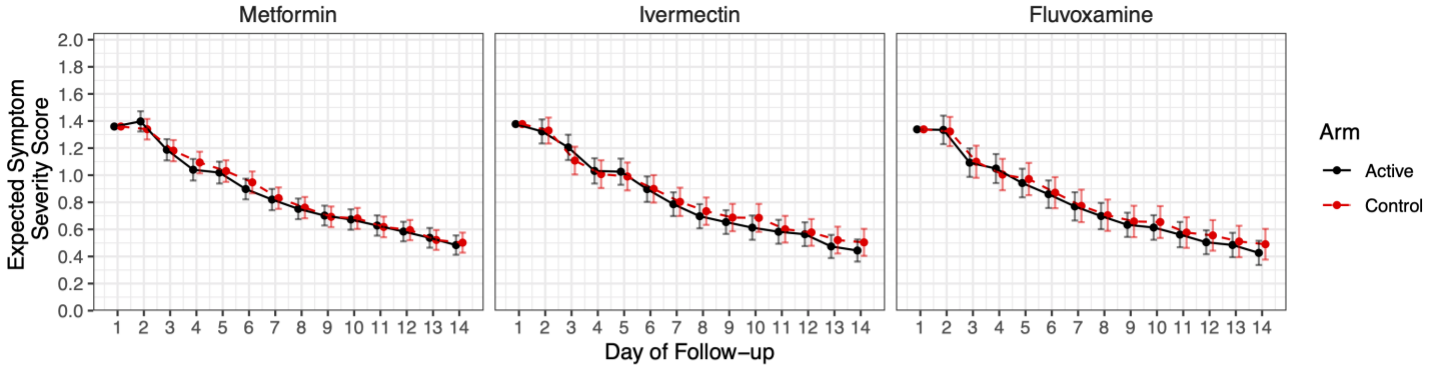
3.9 Figures S5. Individual Symptom Severity over time

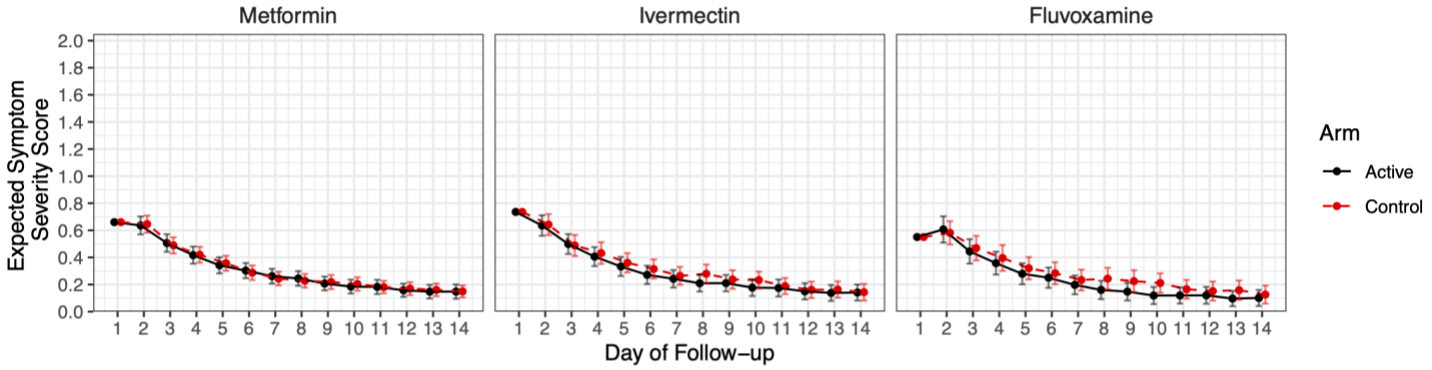
Each row represents a different symptom, and the columns represent each medication. Symptoms (A) through (J) were self-graded as none (0), mild (1), moderate (2), or severe (3).

3.9.1 Figures S5.A-D. Symptoms over Time: Rhinorrhea, Sore Throat, Dyspnea, Cough

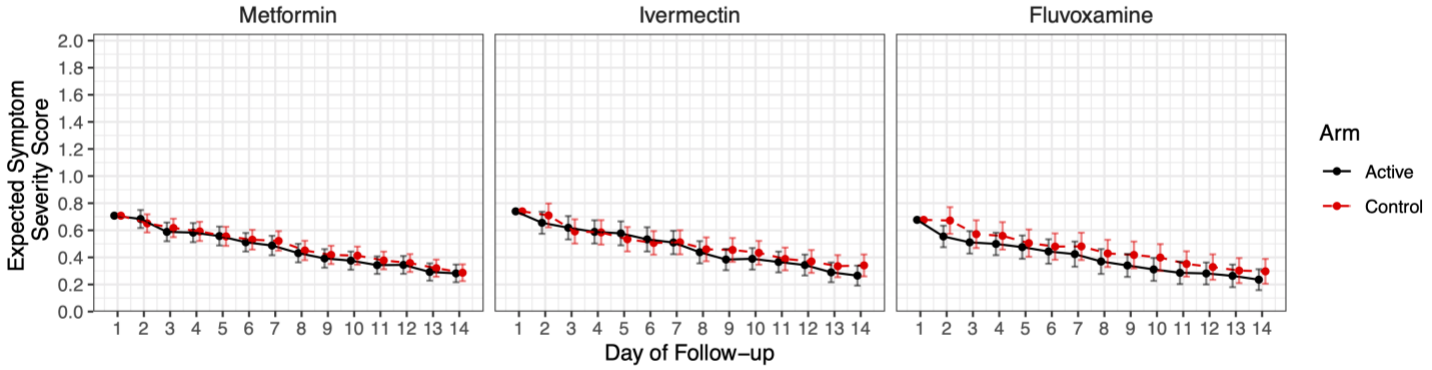
(A) Nasal Congestion or Rhinorrhea



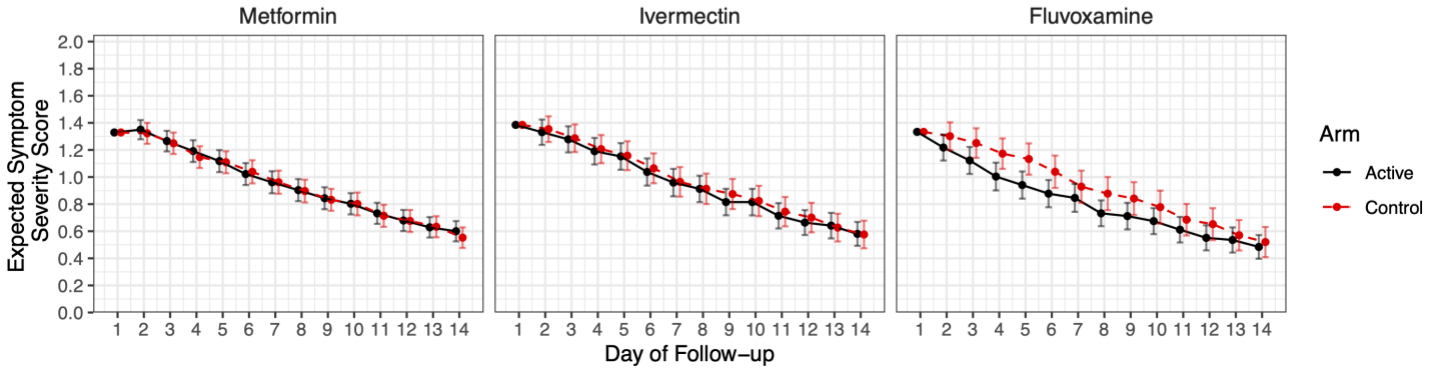
(B) Sore Throat



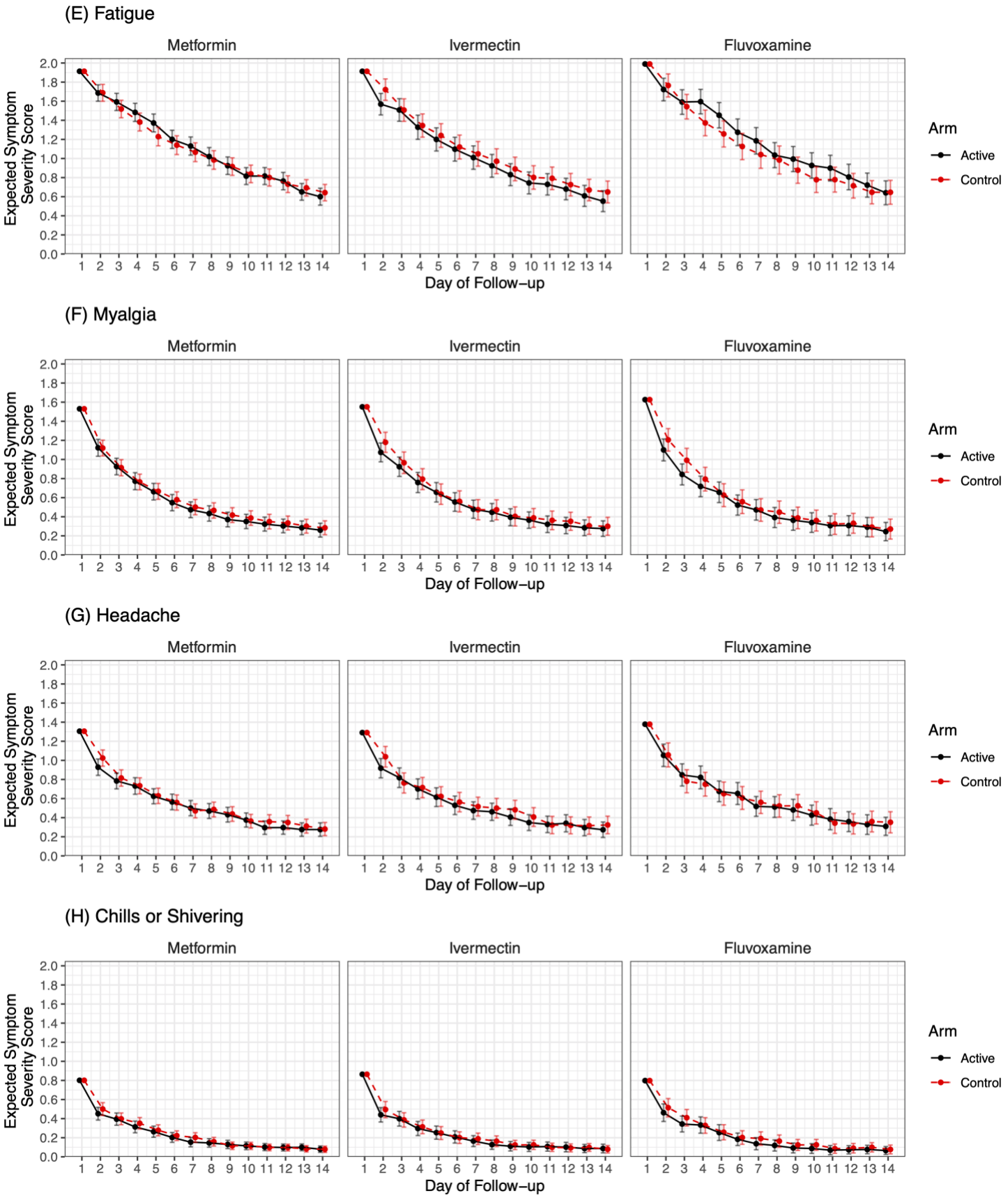
(C) Shortness of Breath or Difficulty Breathing



(D) Cough

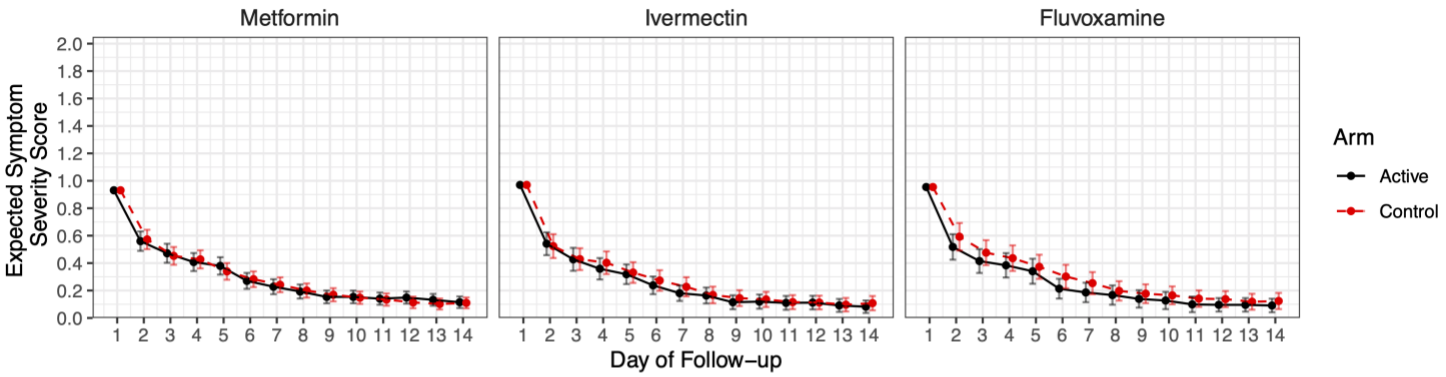


3.9.2 Figures S5.E-H. Symptoms over time: Fatigue, Myalgia, Headache, Chills

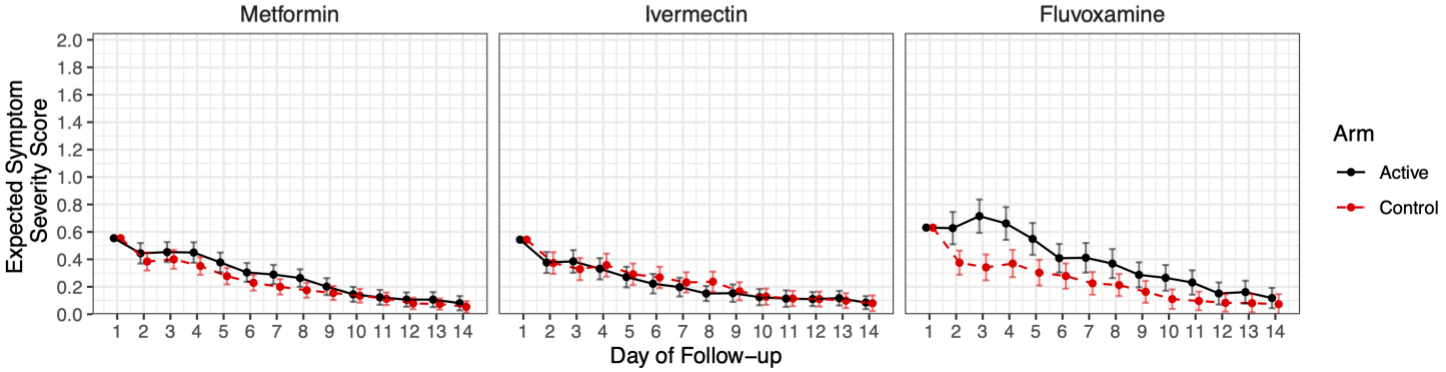


3.9.3 Figures S5.I-L. Symptoms over time: Fever, Nausea, Vomiting, Diarrhea

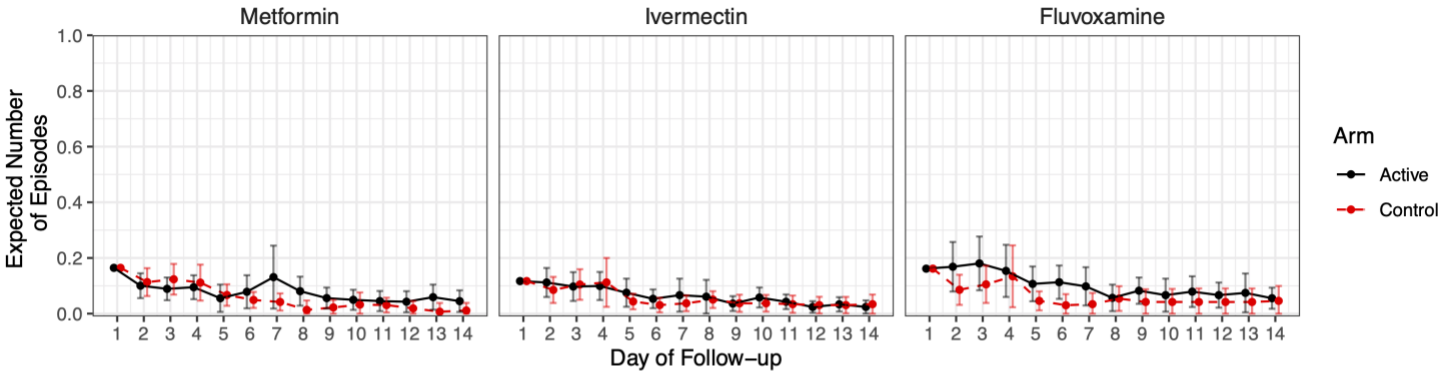
(I) Subjective Fever



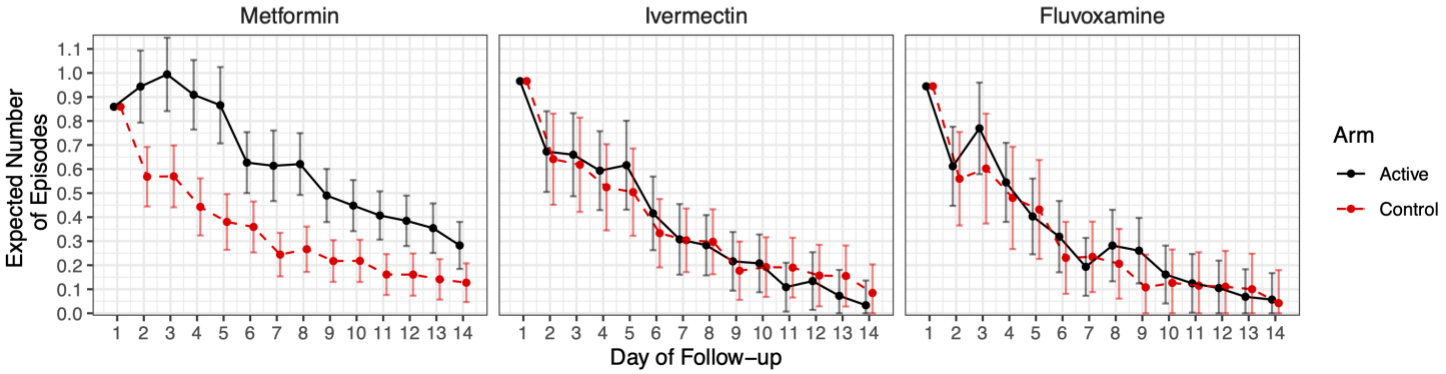
(J) Nausea



(K) Vomiting



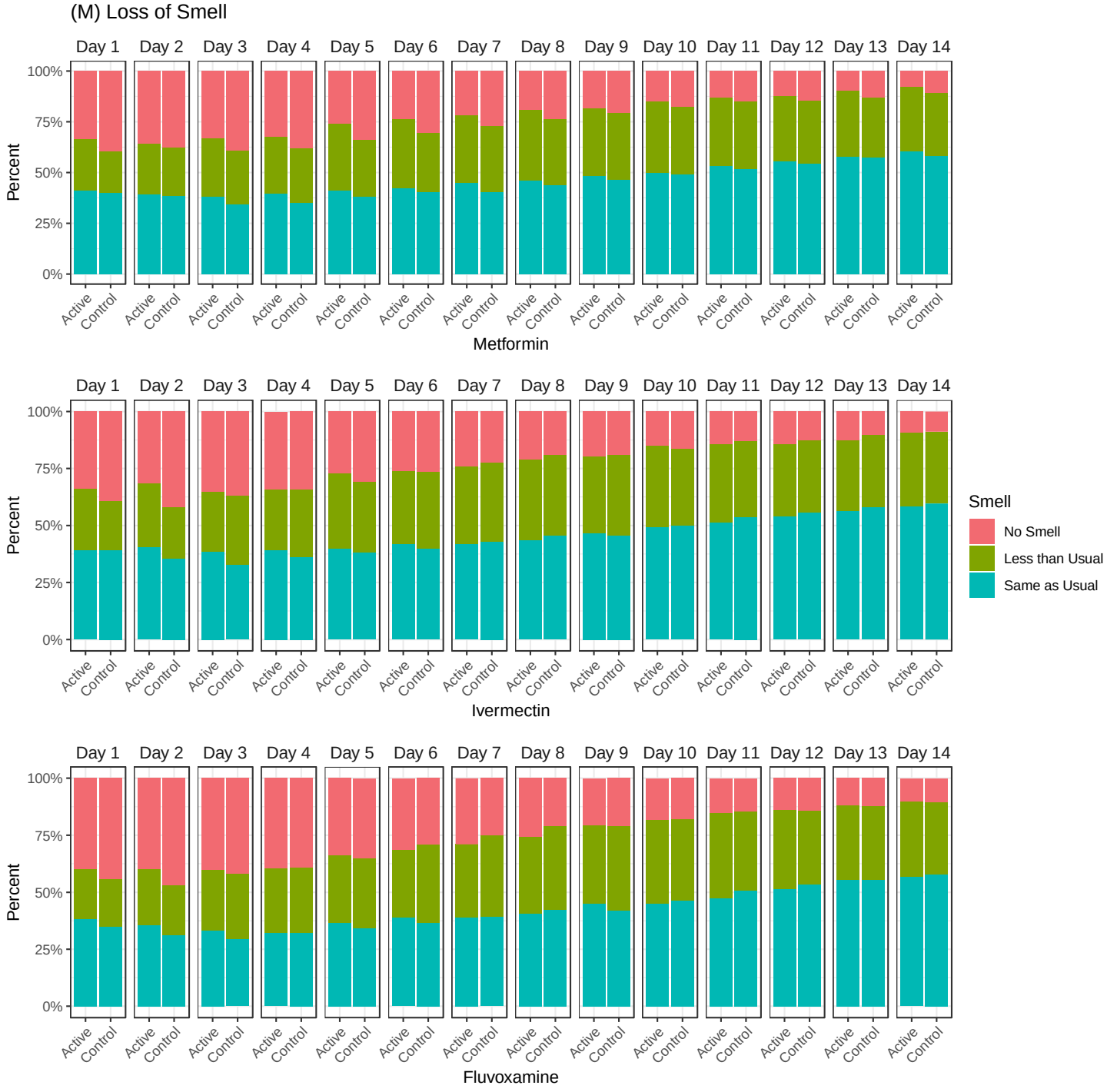
(L) Diarrhea



Vomiting and diarrhea were graded on a daily basis as none (0 points), 1-2 times (1 point), 3-4 times (2 points), and ≥5 times (3 points).

3.9.4 Figure S5.M. Symptoms over time: Loss of Smell

Loss of Smell is represented by stacked bar plots that show the percentage of individuals with the following responses: (0) = Same as Usual, (1) = Less than Usual, (2) = No Smell.



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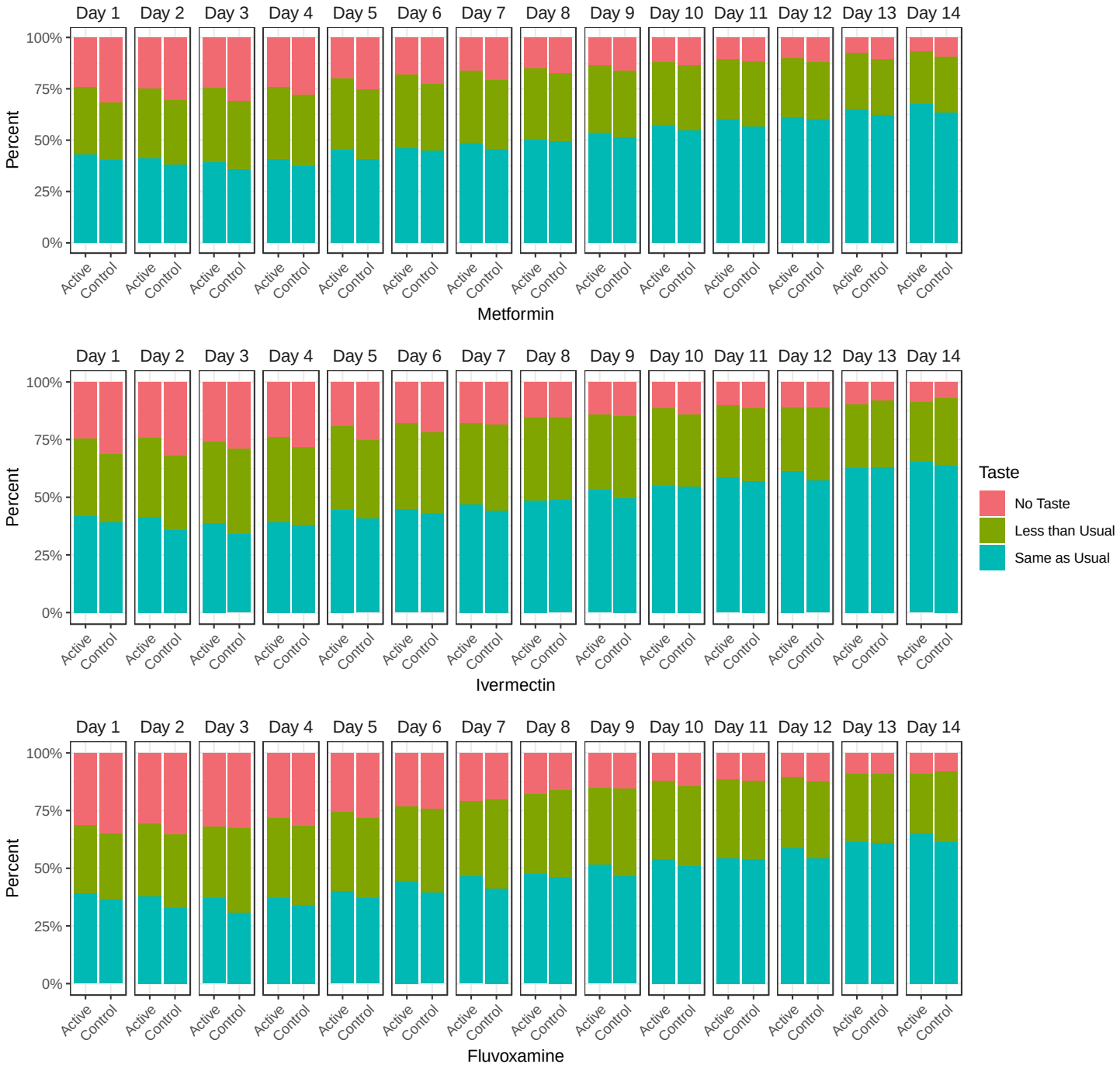
3.9.5 Figure S5.N. Symptoms over time: Loss of Taste

Loss of Taste is represented by stacked bar plots that show the percentage of individuals with the following responses: (0) = Same as Usual, (1) = Less than Usual, (2) = No Taste.

(N) Loss of Taste



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3.10 Figure S6. Factorial Interaction of Combination Therapy

Arm	Active	Control	Adjusted Odds Ratio (95% CI)
	n events / n (n missing)		
Metformin + Ivermectin	50/201 (3)	50/200 (3)	0.98 (0.62 to 1.54)
Metformin + Fluvoxamine	34/173 (2)	40/163 (3)	0.76 (0.45 to 1.29)
Metformin Alone	70/278 (6)	79/291 (4)	0.91 (0.62 to 1.33)
Ivermectin Alone	55/206 (0)	50/200 (3)	1.06 (0.67 to 1.67)
Fluvoxamine Alone	45/156 (3)	40/163 (3)	1.16 (0.70 to 1.93)

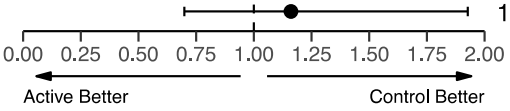

Figure S6a. The above is for the primary composite endpoint of hypoxemia ≤93%, emergency department visit, hospitalization, or death. Comparisons are against concurrent placebo controls only. The trial was not powered for these comparisons. Vertical comparison of the rows is not valid.

Arm	Active	Control	Adjusted Odds Ratio (95% CI)
	n events / n (n missing)		
Metformin + Ivermectin	10/200 (4)	12/202 (1)	0.83 (0.34 to 1.98)
Metformin + Fluvoxamine	4/173 (2)	11/165 (1)	0.34 (0.10 to 1.12)
Metformin Alone	13/279 (5)	21/293 (2)	0.64 (0.31 to 1.31)
Ivermectin Alone	13/206 (0)	12/202 (1)	1.03 (0.45 to 2.33)
Fluvoxamine Alone	14/156 (3)	11/165 (1)	1.24 (0.54 to 2.87)

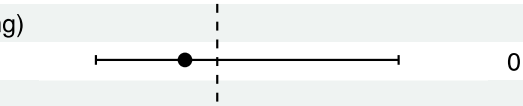

Figure S6b. The above is for the healthcare utilization components of the primary composite endpoint: emergency department visit, hospitalization, or death. Comparisons are against concurrent placebo controls only. The trial was not powered for these comparisons. Vertical comparison of the rows is not valid.

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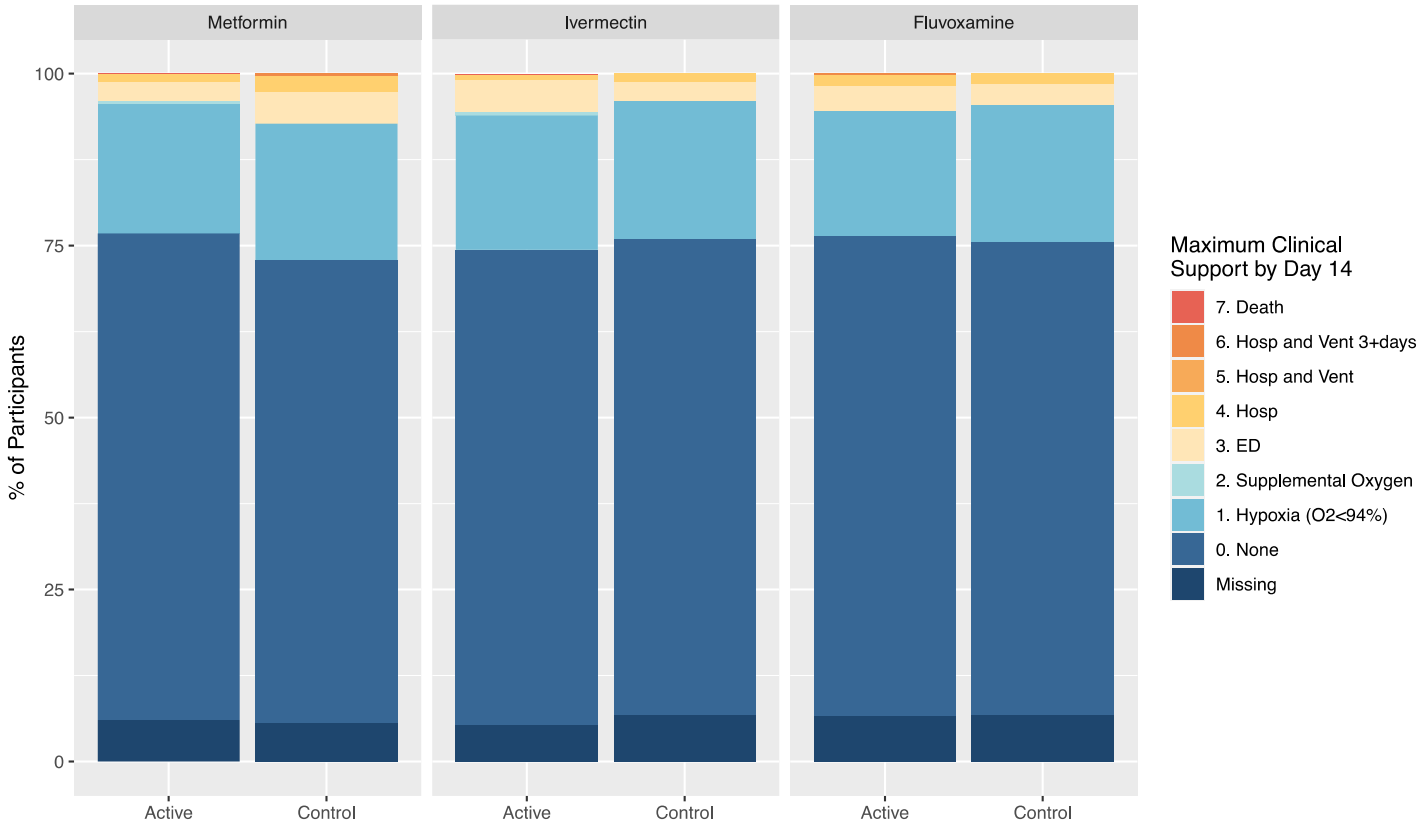
3.11 Figure S7. Maximum Clinical Support over 14-days in ordinal scale



3.12
Figure S7 Data Table of Maximal Clinical Progression through Day 14:

	Metformin # (% | Cumulative %)		**Ivermectin # (% | Cumulative %)**		**Fluvoxamine # (% | Cumulative %)**	
	Active	Control	Active	Control	Active	Control
7. Death	1 (0.2% | 0.2%)	0 (0% | 0%)	1 (0.3% | 0.3%)	0 (0% | 0%)	0 (0% | 0%)	0 (0% | 0%)
6. Hosp & Vent ≥3 days	0 (0% | 0.2%)	2 (0.3% | 0.3%)	0 (0% | 0.3%)	0 (0% | 0%)	1 (0.3% | 0.3%)	0 (0% | 0%)
5. Hosp & Vent	0 (0% | 0.2%)	0 (0% | 0.3%)	0 (0% | 0.3%)	0 (0% | 0%)	0 (0% | 0.3%)	0 (0% | 0%)
4. Hospital	7 (1.1% | 1.3%)	16 (2.6% | 2.9%)	3 (0.8% | 1%)	5 (1.3% | 1.3%)	5 (1.6% | 1.9%)	5 (1.6% | 1.6%)
3. Emergency Dept. Visit	19 (3% | 4.3%)	30 (4.8% | 7.7%)	19 (4.9% | 5.9%)	11 (3% | 4.3%)	12 (3.8% | 5.8%)	10 (3.3% | 4.9%)
2. Supplemental Oxygen	2 (0.3% | 4.7%)	0 (0% | 7.7%)	2 (0.5% | 6.4%)	0 (0% | 4.3%)	0 (0% | 5.8%)	0 (0% | 4.9%)
1. Hypoxemia (O_2 ≤93%)	125 (20.1% | 24.7%)	131 (21% | 28.7%)	80 (20.6% | 27.1%)	80 (21.6% | 25.9%)	61 (19.6% | 25.3%)	65 (21.3% | 26.2%)
0. None	469 (75.3% | 100%)	444 (71.3% | 100%)	283 (72.9% | 100%)	275 (74.1% | 100%)	233 (74.7% | 100%)	225 (73.8% | 100%)
Missing	40	37	22	27	22	22
Adjusted Odds Ratio (95%CI)	0.793 (0.617 - 1.019)		1.032 (0.749 - 1.423)		0.965 (0.675 - 1.381)	

Complete case analysis adjusted odds ratio estimate for worst clinical outcome through Day 14 from a proportional odds model adjusted for vaccination status and other study drugs within the factorial randomization on the modified intention to treat cohort who received study medicines.

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3.13 Figure S8. Maximum Clinical Support over 28-days in ordinal scale

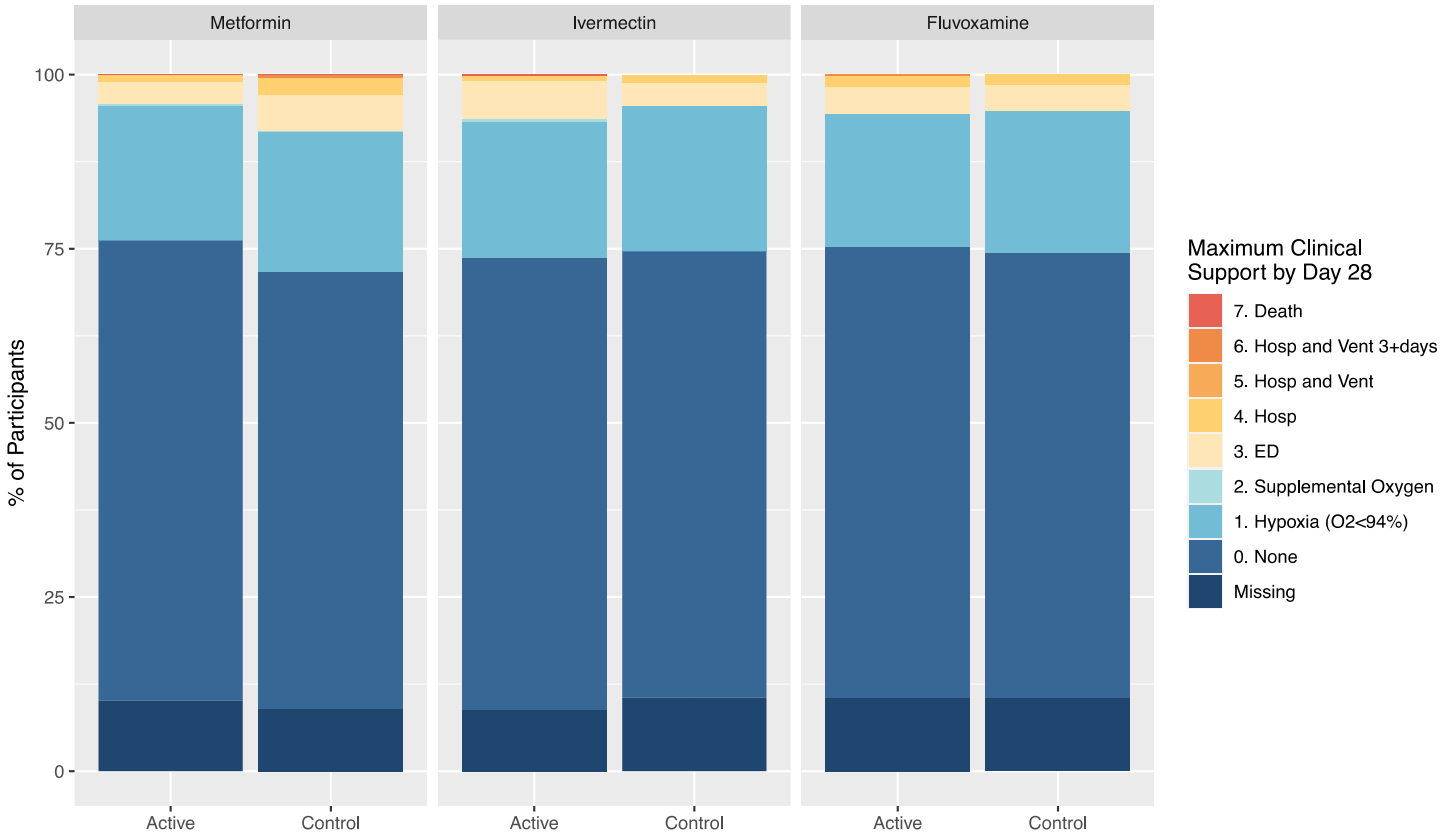

Figure S8 Data Table of Maximal Clinical Progression through Day 28:

	Metformin # (% | Cumulative %)		**Ivermectin # (% | Cumulative %)**		**Fluvoxamine # (% | Cumulative %)**	
	Active	Control	Active	Active	Control	Active
7. Death	1 (0.2% | 0.2%)	1 (0.2% | 0.2%)	1 (0.3% | 0.3%)	0 (0% | 0%)	0 (0% | 0%)	0 (0% | 0%)
6. Hosp and Vent ≥3 days	0 (0% | 0.2%)	2 (0.3% | 0.5%)	0 (0% | 0.3%)	0 (0% | 0%)	1 (0.3% | 0.3%)	0 (0% | 0%)
5. Hosp & Vent	0 (0% | 0.2%)	0 (0% | 0.5%)	0 (0% | 0.3%)	0 (0% | 0%)	0 (0% | 0.3%)	0 (0% | 0%)
4. Hospital	7 (1.2% | 1.3%)	16 (2.7% | 3.2%)	3 (0.8% | 1.1%)	5 (1.4% | 1.4%)	5 (1.7% | 2%)	5 (1.7% | 1.7%)
3. Emergency Dept. Visit	20 (3.4% | 4.7%)	35 (5.8% | 9%)	22 (5.9% | 7%)	13 (3.7% | 5.1%)	13 (4.3% | 6.4%)	12 (4.1% | 5.8%)
2. Supplemental Oxygen	2 (0.3% | 5%)	1 (0.2% | 9.2%)	2 (0.5% | 7.5%)	0 (0% | 5.1%)	0 (0% | 6.4%)	0 (0% | 5.8%)
1. Hypoxemia (O_2 ≤93%)	128 (21.5% | 26.5%)	132 (22% | 31.1%)	80 (21.4% | 28.9%)	83 (23.3% | 28.4%)	64 (21.4% | 27.8%)	67 (22.9% | 28.7%)
0. None	438 (73.5% | 100%)	414 (68.9% | 100%)	266 (71.1% | 100%)	255 (71.6% | 100%)	216 (72.2% | 100%)	209 (71.3% | 100%)
Missing	67	59	36	42	35	34
Adjusted Odds Ratio (95% CI)	0.817 (0.635 - 1.051)		1.069 (0.774 - 1.476)		0.969 (0.674 - 1.391)	

Complete case analysis adjusted odds ratio estimate for worst clinical outcome through Day 28 from a proportional odds model adjusted for vaccination status and other study drugs within the factorial randomization on the modified intention to treat cohort who received study medicines. By day 28, 1.34% (8/596) of those receiving metformin were hospitalized or died compared to 3.16% (19/601) of controls.

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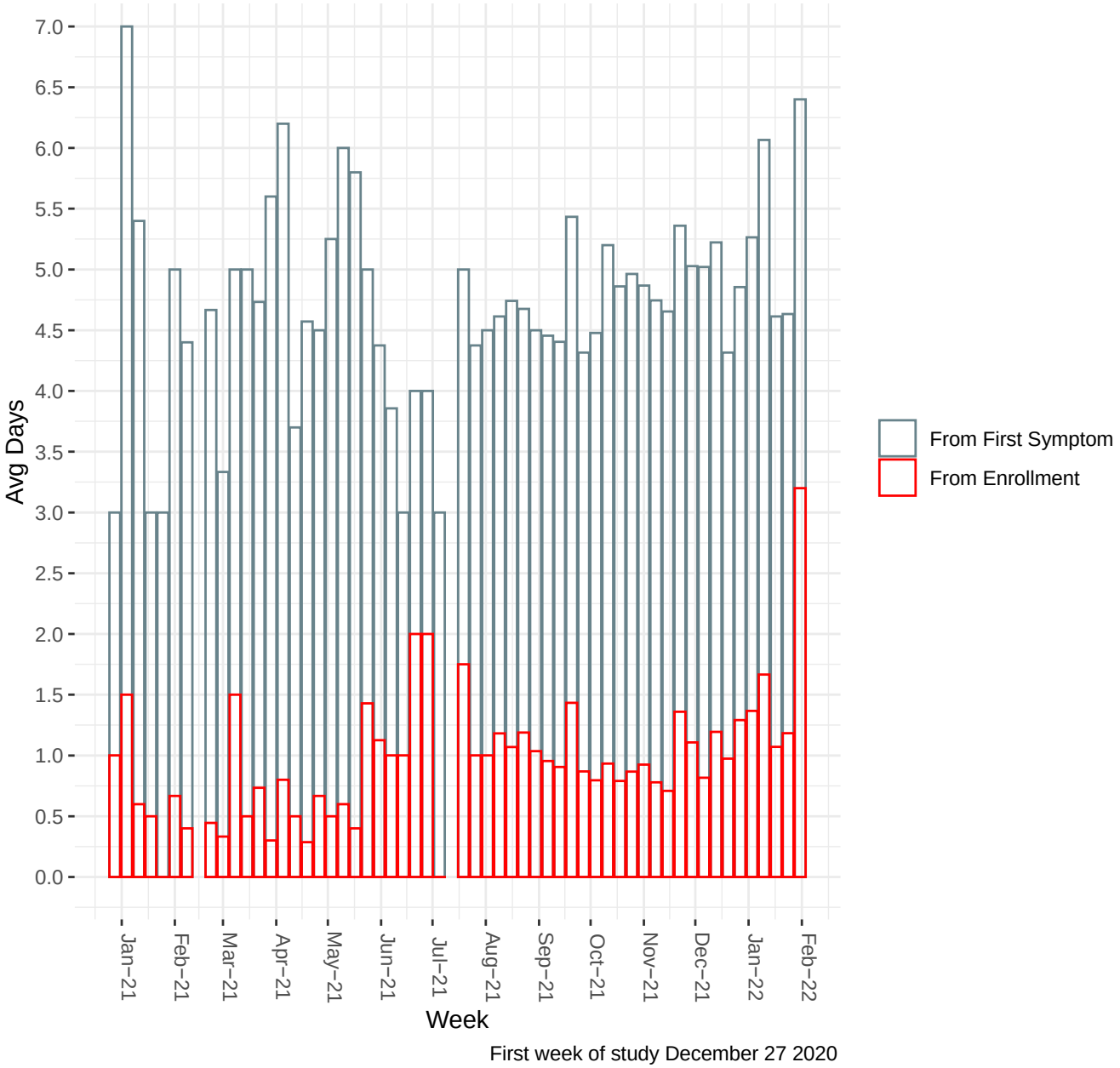
3.14 Figure S8. Time to Study Drug Initiation over Time

This is a stacked bar graph showing the mean days from symptom onset to initiation of study drug (total column height), with the lower part of each bar showing the time from randomization to initiation of study drug (subset of total column height). The y axis represents mean days, the x axis represents the week of enrollment. Factors like holidays, blizzards, and surges were noted to affect these times because of both limitations in testing and shipping during those times. Couriers were utilized for medicine delivery which in some locales allowed for same day study drug initiation. Enrollment and shipping generally occurred 7 days per week. The mean time from enrollment to study drug initiation was 0.998 (± 0.95) days.

Average Days of Symptoms to Study Drug Initiation across weeks of the trial



First week of study December 27 2020

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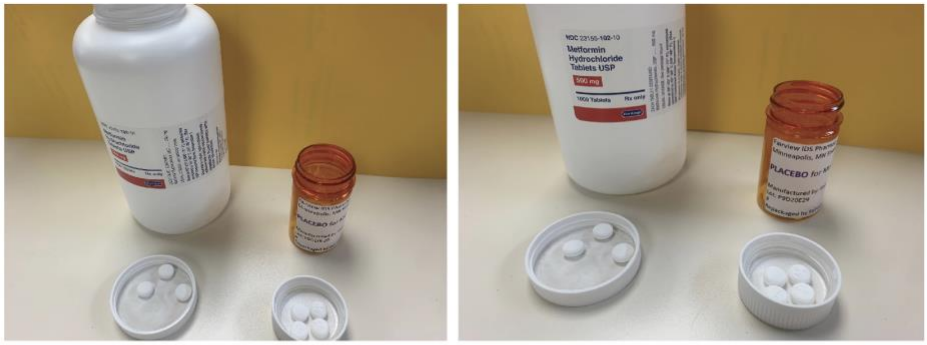
3.15 Figure S9. Pictures of Study Medicine and Matched Placebo

This is a picture of the medications and their exact-matching placebo tablets. The top row is metformin, the middle row is ivermectin, and the third row is fluvoxamine. Medicines were dispensed in pill boxes.

Metformin and Metformin placebo, 2 views



Ivermectin and ivermectin placebo, 7mg on the Left and 14mg on the Right

Fluvoxamine and fluvoxamine placebo, 2 views

Pill boxes (week 2 on the top, week 1 on the bottom)

The days of the week were covered with stickers denoting the day of the study invovlement (because not all started the study on a Monday)

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4 Supplementary Tables

4.1 Table S1. Study Medication Adherence

Adherence	Overall N = 1,323	Metformin N = 284	Metformin+ Ivermectin N = 204	Metformin+ Fluvoxamine N = 175	Ivermectin N = 206	Fluvoxamine N = 159	Placebo N = 295
70-100%	1,015 (77)	208 (73)	165 (81)	116 (66)	175 (85)	121 (76)	230 (78)
35-70%	102 (7.7)	20 (7.0)	20 (9.8)	17 (9.7)	11 (5.3)	16 (10)	18 (6.1)
0-35%	139 (11)	36 (13)	9 (4.4)	33 (19)	14 (6.8)	16 (10)	31 (11)
Missing Adherence	67 (5.1)	20 (7.0)	10 (4.9)	9 (5.1)	6 (2.9)	6 (3.8)	16 (5.4)

Data represent n (%).

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4.2 Table S2. Study Medication Interruption, Missed Doses, and/or Discontinuation

Reason, n (%)	Overall n = 1323	Metformin n = 284	Ivermectin n = 206	Fluvoxamine n = 159	Metformin+ Ivermectin n = 204	Metformin+ Fluvoxamine n = 175	Placebo n = 295
Total Interruption or Discontinuation	365(28)	81 (29)	41 (20)	48 (30)	51 (25)	69 (40)	75 (25)
Restart after interruption, n (%) of those who interrupted	116 (32)	25 (31)	15 (37)	13 (27)	19 (37)	16 (23)	28 (37)
Resolution of symptoms	36 (3)	7 (3)	3 (2)	6 (4)	7 (3)	5 (3)	8 (3)
ER visit, not hospitalized	6 (1)	1 (0)	3 (2)	1 (1)	1 (1)	0 (0)	0 (0)
Hospitalization	18 (1)	5 (2)	0 (0)	2 (1)	2 (1)	0 (0)	9 (3)
Physician prescribed alternate therapy or advised against	4 (0)	0 (0)	1 (1)	0 (0)	1 (1)	0 (0)	2 (1)
Receipt of FDA EUA therapy	5 (0)	1 (0)	1 (1)	0 (0)	0 (0)	1 (1)	2 (1)
Allergic reaction (rash, hives)	4 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (1)
Forgetting or lost study medicine	48 (4)	9 (3)	8 (4)	5 (3)	8 (4)	6 (3)	12 (4)
Nausea	90 (7)	18 (6)	7 (3)	15 (9)	9 (4)	27 (15)	14 (5)
Vomiting	23 (2)	6 (2)	1 (1)	3 (2)	6 (3)	4 (2)	3 (1)
Diarrhea	78 (6)	23 (8)	7 (3)	7 (4)	11 (5)	21 (12)	9 (3)
Stomach upset / gastritis	88 (7)	19 (7)	3 (2)	16 (10)	16 (8)	20 (11)	14 (5)
Bloating	10 (1)	2 (1)	1 (1)	3 (2)	1 (1)	2 (1)	1 (0)
Constipation	4 (0)	1 (0)	0 (0)	1 (1)	2 (1)	0 (0)	0 (0)
Abdominal pain	5 (0)	0 (0)	0 (0)	2 (1)	1 (1)	1 (1)	1 (0)
Loss of appetite	3 (0)	0 (0)	0 (0)	1 (1)	0 (0)	2 (1)	0 (0)
Headache	31 (2)	7 (3)	3 (2)	7 (4)	4 (2)	7 (4)	3 (1)
Dizziness, vertigo, or tinnitus	15 (1)	4 (1)	0 (0)	4 (3)	1 (1)	4 (2)	2 (1)
Insomnia	13 (1)	0 (0)	1 (1)	5 (3)	0 (0)	5 (3)	2 (1)
Fear of side effects or stigma	10 (1)	4 (1)	2 (1)	0 (0)	2 (1)	1 (1)	1 (0)
Anxiety, mood swings, brain fog, feeling jittery, tremors	20 (2)	1 (0)	2 (1)	7 (4)	1 (1)	9 (5)	0 (0)
Feeling too ill, fatigued or too overwhelmed to continue	29 (2)	11 (4)	2 (1)	5 (3)	1 (1)	6 (3)	4 (1)
Menstrual effects	2 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)
Symptoms worsening	15 (1)	5 (2)	4 (2)	2 (1)	2 (1)	0 (0)	2 (1)
Impacts return to work, lifestyle	8 (1)	1 (0)	0 (0)	3 (1)	1 (1)	3 (2)	1 (0)
Dry mouth	4 (0)	0 (0)	0 (0)	2 (1)	1 (1)	1 (1)	0 (0)
Loss of taste/smell or developing foul taste/smell	5 (0)	0 (0)	0 (0)	1 (1)	2 (1)	2 (1)	0 (0)
Eye or vision issues	4 (0)	0 (0)	2 (1)	0 (0)	1 (1)	1 (1)	0 (0)
Other stated reasons	257 (19)	58 (20)	30 (15)	38 (24)	33 (16)	41 (23)	57 (19)
Unknown reason	44 (3)	10 (4)	8 (4)	4 (3)	7 (3)	5 (3)	10 (3)

4.3 Table S3. Additional Open-label Therapeutics Utilized after Randomization

Variable	Overall n = 1,323	Metformin n = 284	Metformin+ Ivermectin n = 204	Metformin+ Fluvoxamine n = 175	Ivermectin n = 206	Fluvoxamine n = 159	Placebo n = 295
Monoclonal Antibody	55 (4.2)	13 (4.6)	9 (4.4)	8 (4.6)	6 (2.9)	7 (4.4)	12 (4.1)
Ivermectin	8 (0.6)	3 (1.1)	1 (0.5)	0 (0)	2 (1.0)	0 (0)	2 (0.7)
Inhaler	30 (2.3)	8 (2.8)	4 (2.0)	3 (1.7)	2 (1.0)	2 (1.3)	11 (3.7)
Anti-coagulants	19 (1.4)	7 (2.5)	1 (0.5)	1 (0.6)	1 (0.5)	4 (2.5)	5 (1.7)
Outpatient Steroids	20 (1.5)	3 (1.1)	5 (2.5)	2 (1.1)	2 (1.0)	5 (3.1)	3 (1.0)
Other*	165 (12)	36 (13)	31 (15)	11 (6.3)	27 (13)	20 (13)	40 (14)
Sertraline †	35 (2.6)	12 (4.2)	2 (1.0)	3 (1.7)	5 (2.4)	2 (1.3)	11 (3.7)

Values are n (%).

* Other includes a wide variety of non-FDA EUA therapies.

† Sertraline is an antagonist to sigma-1 receptors, whereas fluvoxamine is an agonist.[18]

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4.4 Table S4. Complete Case Analysis of the primary outcome in the modified intention to treat population.

Metformin						
Outcome	**Metformin (n=663)**	**%**	**Control (n=660)**	**%**	**Adjusted Odds Ratio**	**95% CI**
Primary Composite	154/650	23.7	179/651	27.5	0.841	(0.653 - 1.082)
Hypoxemia ≤93% only	147/648	22.7	158/649	24.3	0.940	(0.725 - 1.218)
Emergency Dept visit, hospitalization, or death	27/650	4.2	48/653	7.4	0.570	(0.35 - 0.929)
Hospitalization or death	8/649	1.2	18/653	2.8	0.463	(0.199 - 1.078)
Death	1/654	0.2	0/653	0.0		
Ivermectin						
Outcome	**Ivermectin (n=410)**	**%**	**Control (n=398)**	**%**	**Adjusted Odds Ratio**	**95% CI**
Primary Composite	105/406	25.9	96/390	24.6	1.051	(0.761 - 1.452)
Hypoxemia ≤93% only	96/405	23.7	88/389	22.6	1.044	(0.748 - 1.457)
Emergency Dept visit, hospitalization, or death	23/405	5.7	16/393	4.1	1.382	(0.715 - 2.673)
Hospitalization or death	4/405	1.0	5/393	1.3	0.737	(0.195 - 2.784)
Death	1/407	0.2	0/395	0.0		
Fluvoxamine						
Outcome	**Fluvoxamine (n=334)**	**%**	**Control (n=327)**	**%**	**Adjusted Odds Ratio**	**95% CI**
Primary Composite	79/327	24.2	80/320	25.0	0.949	(0.661 - 1.363)
Hypoxemia ≤93% only	71/326	21.8	73/319	22.9	0.930	(0.64 - 1.351)
Emergency Dept visit, hospitalization, or death	18/327	5.5	15/323	4.6	1.169	(0.571 - 2.394)
Hospitalization or death	6/327	1.8	5/323	1.5	1.12	(0.332 - 3.778)
Death	0/328	0.0	0/324	0.0		

† Odds ratio reflects outcome defined as the corresponding component or worse, adjusted for vaccination status and the factorial design.

Figures reflect the # with event / # with complete data in the modified intention to treat cohort. The number with incomplete data reflects the number of people with a missing outcome or unknown vaccination status (n=5). Additionally, results are also consistent when not excluding the participants with a missing vaccination status and treating them as unvaccinated (data not shown).

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4.5 Table S5. Comparison of Background Information on race, ethnicity, age, sex of the broader population affected by SARS-CoV-2 based on CDC data.

	COVID-19 Cases		U.S. General Population
	U.S. CDC Data	Covid-Out Participants	
Female %	53%	54%	51%
Age, years (median)	36-41	46	38.1
Race (%)			
Native American	1.1%	2.2%	0.7%
Asian	3.8%	3.8%	5.6%
Hawaiian, Pacific Islander	0.3%	0.6%	0.2%
Black	12.3%	7.3%	12.5%
White	54%	82%	60.1%
Ethnicity (%)			
Latino	25%	11%	18.5%

Overall representativeness of the trial: The COVID-OUT population had the expected percentage of females and a slightly older age than the general U.S. COVID-19 case population, likely due to the minimum age requirement of 30 years. The overall population of the COVID-OUT trial was similar in respect to the USA population and current COVID-19 population for persons self-identifying the following backgrounds: Native American, Asian, Hawaiian, Pacific Islander. The COVID-OUT population had a higher portion of individuals self-identifying as White and lower portions identifying as Black and Latino than both the US population and Covid-19 case population in the US. The COVID-OUT trial under-represents individuals identifying as Black and Latino.

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5 Intention to treat (ITT) analyses

Participants who were randomized (i.e. intent-to-treat analysis), but who did not receive or start study medicine were not included in the modified intent to treat analysis.

5.1 Table S6. Baseline characteristics of participants who were randomized but not included in the modified intention to treat analysis

Baseline Characteristics	Overall n=1,323	ITT and not MITT N=94	Metformin		Ivermectin		Fluvoxamine	
			Active n=48	Control n=46	Active n=28	Control n=36	Active n=23	Control n=32
Age, median (IQR)	46 (37, 55)	46 (37, 55)	45 (37, 55)	48 (40, 56)	44 (38, 55)	50 (37, 56)	46 (38, 54)	48 (36, 55)
Female, % (n)	56% (741)	47% (44)	42% (20)	52% (24)	57% (16)	42% (15)	48% (11)	41% (13)
Race, % (n)								
Native American	2.0% (27)	5.3% (5)	6.2% (3)	4.3% (2)	0% (0)	5.6% (2)	13% (3)	6.2% (2)
Asian	3.9% (51)	2.1% (2)	2.1% (1)	2.2% (1)	0% (0)	2.8% (1)	4.3% (1)	3.1% (1)
Hawaiian/Pacific Isl.	0.7% (9)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)
Black	7.6% (100)	8.5% (8)	10% (5)	6.5% (3)	3.6% (1)	5.6% (2)	13% (3)	6.2% (2)
White	82%(1,091)	70% (66)	67%(32)	74%(34)	89%(25)	67%(24)	57% (13)	62% (20)
Other / Declined	6.1% (80)	16.5%(15)	16.2%(6)	15.2%(7)	7.2% (2)	19.3% (7)	21.3%(5)	21.5%(7)
Ethnicity, n (%) Latinx	12% (160)	12% (11)	8.3% (4)	15% (7)	7.1% (2)	14% (5)	13% (3)	12% (4)
Medical history, insurance status								
BMI, median (IQR)	29.8 (27, 34)	30.2 (27, 34)	28.2 (27, 32)	31.0 (28, 35)	30.1 (27, 34)	29.6 (28, 37)	30.4 (26, 33)	29.6 (28, 37)
BMI $\geq$ 30 kg/m^2	49% (646)	53% (50)	44% (21)	63% (29)	54% (15)	50% (18)	57% (13)	50% (16)
Cardiovascular disease*	27% (353)	28% (26)	33% (16)	22% (10)	25% (7)	22% (8)	30% (7)	19% (6)
Diabetes	2.0% (26)	2.1% (2)	2.1% (1)	2.2% (1)	3.6% (1)	0% (0)	4.3% (1)	0% (0)
Vaccinated, primary series	52% (690)	46% (43)	48% (23)	43% (20)	36% (10)	61% (22)	35% (8)	59% (19)
Symptom Days, mean ($\pm$SD)	4.8 ($\pm$1.9)	4.9 (1.8)	4.4 (1.8)	5.3 (1.8)	4.3 (1.5)	4.9 (1.9)	5.4 (2.1)	5.0 (2.0)
Symptoms $\leq$4 days	47% (603)	42% (36)	53% (24)	29% (12)	54% (14)	40% (14)	29% (6)	35% (11)
Variant Period: Alpha	12% (159)	11% (10)	8.3% (4)	13% (6)	7.1% (2)	5.6% (2)	4.3% (1)	6.2% (2)
Variant Period: Delta	66% (871)	65% (61)	67% (32)	63% (29)	54% (15)	72% (26)	83% (19)	81% (26)
Variant Period: Omicron	22% (293)	24% (23)	25% (12)	24% (11)	39% (11)	22% (8)	13% (3)	12% (4)
Medicaid	15% (200)	16% (15)	21% (10)	11% (5)	14% (4)	14% (5)	17% (4)	16% (5)
Medicare	7.6% (100)	9.6% (9)	6.2% (3)	13% (6)	11% (3)	5.6% (2)	13% (3)	6.2% (2)
Private	62% (823)	51% (48)	52% (25)	50% (23)	57% (16)	61% (22)	30% (7)	59% (19)
No insurance	13% (178)	22% (21)	21% (10)	24% (11)	18% (5)	17% (6)	39% (9)	16% (5)

Values are n (%), median (interquartile range), or mean ($\pm$SD).
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.

5.2 Table S7: Intent-to-Treat (ITT) analysis of the primary outcome with imputation.

	Metformin			Ivermectin			Fluvoxamine		
	Active (n=711)	Control (n=706	Adj. Odds Ratio (95% CI)	Active (n=438)	Control (n=434)	Adj. Odds Ratio (95% CI)	Active (n=357)	Control (n=359)	Adj. Odds Ratio (95% CI)
Primary Outcome	161/673 (23.9)	188/674 (27.9)	0.838 (0.655 - 1.073)	109/416 (26.2)	101/410 (24.6)	1.049 (0.763 - 1.443)	86/342 (25.1)	83/337 (24.3)	1.007 (0.709 - 1.429)
Hypoxemia ≤93% Only	153/670 (22.8)	162/667 (24.3)	0.930 (0.721 - 1.200)	99/414 (23.9)	90/406 (22.2)	1.047 (0.753 - 1.457)	76/339 (22.4)	74/334 (22.2)	0.994 (0.693 - 1.427)
Emergency dept visit, hospitalization, or death	31/678 (4.6)	54/682 (7.9)	0.586 (0.372 - 0.925)	27/420 (6.4)	20/417 (4.8)	1.287 (0.705 - 2.350)	20/342 (5.8)	18/343 (5.8)	1.048 (0.537 - 2.048)
Hospitalization or death	11/678 (1.6)	24/682 (3.5)	0.479 (0.231 - 0.993)	8/420 (1.9)	8/417 (1.9)	0.897 (0.326 - 2.470)	8/342 (2.3)	8/343 (2.3)	0.898 (0.327 - 2.467)
Death	1/686 (0.1)	0/679 (0.0)		1/422 (0.2)	0/419 (0.0)		0/342 (0.0)	0/344 (0.0)	

† Outcome reflects outcome defined as the corresponding component or worse.
Figures reflect # with event / # with known outcome (%) in ITT cohort. Adjusted Odds Ratio and 95% CI are based on a logistic regression model adjusted for baseline vaccination and other study drugs. Missing outcomes are multiply imputed. Abbreviation: Adj=adjusted

Table S8: Complete case Intent-to-Treat analysis of the primary outcome without imputation.

	Metformin			Ivermectin			Fluvoxamine		
	Active (n=711)	Control (n=706)	Adj. Odds Ratio (95% CI)	Active (n=438)	Control (n=434)	Adj. Odds Ratio (95% CI)	Active (n=357)	Control (n=359)	Adj. Odds Ratio (95% CI)
Primary Outcome	161/671 (24.0)	188/672 (28.0)	0.838 (0.654 - 1.073)	109/415 (26.3)	101/409 (24.7)	1.061 (0.773 - 1.457)	86/340 (25.3)	83/336 (24.7)	1.013 (0.712 - 1.442)
Hypoxemia ≤93% Only	153/668 (22.9)	162/665 (24.4)	0.953 (0.737 - 1.231)	99/413 (24.0)	90/405 (22.2)	1.079 (0.776 - 1.499)	76/337 (22.6)	74/333 (22.2)	1.001 (0.694 - 1.445)
Emergency dept visit, hospitalization, or death	31/676 (4.6)	54/680 (7.9)	0.586 (0.37 - 0.928)	27/419 (6.4)	20/416 (4.8)	1.305 (0.716 - 2.38)	20/340 (5.9)	18/342 (5.3)	1.062 (0.543 - 2.078)
Hospitalization or death	11/675 (1.6)	24/680 (3.5)	0.482 (0.233 - 0.998)	8/419 (1.9)	8/416 (1.9)	0.923 (0.34 - 2.503)	8/340 (2.4)	8/342 (2.3)	0.912 (0.332 - 2.51)
Death	1/682 (0.1)	0/677 (0.0)		1/21 (0.2)	0/417 (0.0)		0/340 (0.0)	0/342 (0.0)	

†Outcome reflects outcome defined as the corresponding component or worse.
Figures reflect the # with event / # with complete data (%) in ITT cohort. The number with incomplete data reported in parentheses reflects the number of people with a missing outcome or an unknown vaccination status (n=8). Abbreviation: Adj. = Adjusted

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6 Data Safety Monitoring Board

a. **Catherine Benziger, MD, MPH**
    i. *Director of Research, Essentia Health Heart and Vascular Center.*
b. **Hsin-Chieh Yeh, PhD**
    i. *Associate Professor; Senior Epidemiologist of the Osler Housestaff Program; Director of General Internal Medicine - Welch Center Methods Core, Johns Hopkins University School of Medicine*
c. **Timothy Plante, MD, MHS**
    i. *Assistant Professor, General Internal Medicine; Bloomfield Early Career Professor in Cardiovascular Research at the University of Vermont's Larner College of Medicine.*
d. **Anika Hines, PhD**
    i. *Assistant Professor, Department of Health Behavior and Policy, Virginia Commonwealth University.*
e. **Eva Tseng, MD, MPH**
    i. *Assistant Professor, General Internal Medicine; Core Faculty in the Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins University School of Medicine*

External study monitor:

University of Minnesota Clinical & Translational Science Institute (CTSI) supported via NIH National Center for Advancing Translational Sciences (NCATS) UL1TR002494.

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7. Investigational Drug Services Datasheet

University of Minnesota Medical Center, Fairview
Department of Pharmaceutical Services

IDS# 5812
IRB# Advarra MET29324
IND# 152439

1. Drug Name: Metformin, Fluvoxamine, Ivermectin; COVID-OUT: Outpatient Treatment for SARS-CoV-2 Infection, a Factorial Randomized Clinical Trial.

2. Synonyms:
COVID-OUT Protocol version 3.1 dated 05 April 2021

3. Dosage Form(s) and Strength(s):
Metformin 500mg immediate release tablet and matching placebo
Fluvoxamine 50mg tablet and matching placebo
Ivermectin 7mg,14 mg tablets and matching placebo

4. Study Medication Description:
Metformin 500mg immediate release tablet and identical matching placebo
Fluvoxamine 50mg tablet and identical matching placebo
Ivermectin 7mg,14 mg tablets and identical matching placebo

5. Usual Therapeutic Dose: *All dosing will begin with the evening dose on Day 1.*
Subjects will be randomized 1:1:1:1:1:1 to one of the following six arms:

1) **Metformin** and placebo for ivermectin
2) **Metformin** and **Fluvoxamine**
3) **Metformin** and **Ivermectin**
4) **Fluvoxamine** and placebo for ivermectin
5) **Ivermectin** and placebo for fluvoxamine
6) Placebo for metformin and placebo for fluvoxamine

Metformin or matching placebo: 500mg once on Day 1, ideally in the PM; 500mg in the AM and PM of Days 2-5; and 500mg in the AM and 1,000mg in the PM of Days 6-14.

Fluvoxamine or matching placebo: 50mg twice per day, approximately every 12 hours, for 14 days.

Ivermectin or matching placebo: for 3 days

Less than 74kg	28 mg once daily (2 x 14mg)
74 to < 88kg	35mg once daily (2 x 14mg + 7mg)
88 to < 106kg	42mg once daily (3 x 14)
106 to < 124kg	49mg once daily (3 x 14mg + 7mg)
124kg to < 160kg	56mg once daily (4 x 14mg)
≥ 160 kg	63mg once daily (4 x 14mg + 7mg)

There is a pregnant women sub-study for subjects 18 years and older. There is a separate group of blinded study packs for pregnant women containing only metformin or placebo. This will be packaged in **prescription vials**, not in pill minders.

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6. **Usual Dosage Range:** If subjects experience moderate or moderate-substantial side effects that they find intolerable, they can break tablets in half. Communication with study team is required.

7. **Location of Drug Supply and Dose Preparation/Storage Conditions:**
IDS Pharmacy; store all agents at room temperature up to 30ºC.

8. **Temperature Excursion Management:** Handle study drugs as per the package insert for each commercial medication.

9. **Expected Therapeutic Effect(s):** The primary objectives of the trial are:
   1) To understand whether metformin vs fluvoxamine vs ivermectin vs metformin + fluvoxamine vs metformin + ivermectin are superior to placebo in non-hospitalized adults with SARS-CoV-2 infection for preventing COVID-19 disease progression.
   2) To understand if the active treatment arms are superior to placebo in improving viral load, serologic markers associated with Covid-19, and gut microbiome in non-hospitalized adults with SARS-CoV-2 infection.
   3) To understand if any of the active treatment arms prevent long-covid syndrome, PASC (post-acute sequelae of SARS-CoV-2 infection).

10. **Possible Adverse Effects:** per commercial literature

11. **Drug Interactions:** per commercial literature

12. **Reconstitution Directions:** not applicable

13. **Save used and partial vials (Method of Destruction):** Study subjects should report any unused drug to the study team. Nothing is returned to the pharmacy.

14. **Route and Rate of Administration:**
Ivermectin or matching placebo should be taken by mouth on an empty stomach with water. 1 hour before or 2 hours after a meal.
All other agents should be taken by mouth at the end of a balanced snack or small meal.

15. **Special Instructions:**
Fairview IDS Pharmacy will oversee the pre-packaging of the study drug into 2-week AM/PM pill packs. The pill packs will be placed in opaque packing so that the research study staff will remain blinded to the contents in the pill boxes. The pill packs will contain a unique identifier. Pill packs will expire 6 months from the date of preparation or the earliest expiration date of the ingredients, whichever is sooner.

IDS will provide these pre-packaged, uniquely identified study pill packs to and the local study team and participating sites.

Participants will be assigned a packet number according to the randomization. Packet numbers are coded by site (e.g. UMN site 01-XXX, Hennepin site 02-XXX, etc.). The

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pharmacy team involved will be unblinded to packet randomization. All other members of the clinical care team and the participants will be blinded to treatment allocation.

The research staff will select the pill pack based on the randomization code that preserves blinding, place the patient's name and study ID on the opaque packing, place it in the study kit for that patient and arrange for delivery of the kit.

Emergency unblinding plan

Each participating pharmacy team will hold the blind for their site. Each site will have 24-hour access to the blind. Each subject will be provided information as to whom to contact for unblinding information in the event of an emergency. There is one unblinded statistician with two unblinded supporting statisticians on the study team.
University of Minnesota IDS Pharmacy will also have an unblinding key available as a backup for other sites. Call xxx-xxx-xxxx to access unblinding information at the University of Minnesota.

16. **Medication Re-supply Information:**
IDS has purchased commercial metformin and fluvoxamine for study use.
Placebo for metformin has been prepared by Green Mountain Pharmacy.
Placebo for fluvoxamine will be provided by Apotex
Ivermectin and placebo will be provided by Edenbridge Pharma

17. **Principal Investigator/Telephone Number:** Dr. Carolyn Bramante

18. **Authorized Physicians/Telephone Number:** __

19. **Study Coordinator/Telephone Number:** __

20. **Date:** 21 April 2021
Update: 24 May 2021 (Section 5)

21. **Prepared/verified by:**_____
Updated by:_____

Prior to dispensing study medication pharmacists are responsible for information contained on the datasheet and must sign the training log.

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