REVIEW

Annals of Internal Medicine

Outpatient Treatment of Confirmed COVID-19: A Living, Rapid Review for the American College of Physicians

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Background: Clinicians and patients want to know the benefits and harms of outpatient treatment options for SARS-CoV-2 infection.

Purpose: To assess the benefits and harms of 12 different COVID-19 treatments in the outpatient setting.

Data Sources: Epistemonikos COVID-19 L·OVE Platform, searched on 4 April 2022.

Study Selection: Two reviewers independently screened abstracts and full texts against a priori–defined criteria. Randomized controlled trials (RCTs) that compared COVID-19 treatments in adult outpatients with confirmed SARS-CoV-2 infection were included.

Data Extraction: One reviewer extracted data and assessed risk of bias and certainty of evidence (COE). A second reviewer verified data abstraction and assessments.

Data Synthesis: The 26 included studies collected data before the emergence of the Omicron variant. Nirmatrelvir–ritonavir and casirivimab–imdevimab probably reduced hospitalizations (1% vs. 6% [1 RCT] and 1% vs. 4% [1 RCT], respectively; moderate COE). Nirmatrelvir–ritonavir probably reduced all-cause mortality (0% vs. 1% [1 RCT]; moderate COE), and regdanvimab probably improved recovery (87% vs. 72% [1 RCT]; moderate COE). Casirivimab–imdevimab reduced time to recovery by a median difference of 4 days (10 vs. 14 median days [1 RCT]; high COE). Molnupiravir may reduce all-cause mortality, sotrovimab may reduce hospitalization, and remdesivir may improve recovery (low COE). Lopinavir–ritonavir and azithromycin may have increased harms, and hydroxychloroquine may result in lower recovery rates (low COE). Other treatments had insufficient evidence or no statistical difference in efficacy and safety versus placebo.

Limitation: Many outcomes had few events and small samples.

Conclusion: Some antiviral medications and monoclonal antibodies may improve outcomes for outpatients with mild to moderate COVID-19. However, the generalizability of the findings to the currently dominant Omicron variant is limited.

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In the United States, COVID-19 has resulted in more than 1 million deaths (1) and led to a decrease in life expectancy of 1.87 years (2). Various pharmacologic therapies, including antiviral drugs, corticosteroids, and other repurposed medications, have emerged as treatment options for outpatients with COVID-19.

Several reviews have systematically assessed the efficacy and safety of these therapies (3–10). However, given the pace of the pandemic and the emerging evidence, without regular updates these reviews quickly become outdated. In addition, most included both inpatient and outpatient management and focused only on 1 specific COVID-19 treatment. The aim of this living, rapid review was to systematically collate and assess the evidence regarding the benefits and harms of COVID-19 treatments of interest to support the American College of Physicians (ACP) Scientific Medical Policy Committee (SMPC) in developing practice points on the use of COVID-19 treatments in adult outpatients.

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METHODS

We conducted this living, rapid review in accordance with the Cochrane Rapid Reviews Methods Group guidance (11). We registered our protocol in PROSPERO (CRD42022323440) and made no changes to it. Throughout this review, we adhered to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement (12).

Our methods differed from those of a systematic review in the following ways: We searched only 1 electronic database (the Epistemonikos COVID-19 L·OVE Platform [13]), and single reviewers extracted data and rated risk of bias and certainty of evidence (COE); a second, senior investigator verified data abstraction and assessments.

We plan to conduct monthly surveillance searches over a period of 1 year for new randomized controlled trials (RCTs). The study eligibility criteria might be revised if the treatments of interest change. The methodological approach will remain the same. The SMPC is planning to maintain this topic as living, rapid practice points with

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literature surveillance and periodic updating of the living, rapid review and SMPC practice points. Details of the practice points' living process, including signals for updating and retirement, can be found in ACP's methods articles (14).

Research Questions and Eligibility Criteria

We addressed the following key questions (KQs):

KQ: What are the benefits and harms of COVID-19 treatments in symptomatic and asymptomatic adult patients with a confirmed SARS-CoV-2 infection in the outpatient setting?

KQa: Do the benefits and harms vary by patient characteristics (age, gender, or comorbid conditions), type of SARS-CoV-2 variant, immunity status (prior SARS-CoV-2 infection, vaccination status, or time since infection or vaccination), symptom duration, or disease severity?

We considered RCTs that included adult outpatients with a confirmed diagnosis of SARS-CoV-2 infection and were published in English. Treatments of interest included antiviral drugs, neutralizing monoclonal antibodies, antibiotic or antiparasitic drugs, convalescent plasma, corticosteroids, and fluvoxamine. Comparators were placebo to determine treatment efficacy or standard of care if no placebo-controlled trials were available, which was not the case for any of the treatments of interest.

The ACP SMPC selected all-cause mortality, COVID-19–specific mortality, recovery, time to recovery, hospitalization due to COVID-19, and incidences of serious or any adverse events as critical outcomes for decision making. Supplement Table 1 (available at Annals.org) presents the a priori–specified inclusion and exclusion criteria.

Data Sources and Searches

An experienced information specialist (I.K.) searched Epistemonikos COVID-19 L·OVE, a free-access repository and classification platform for COVID-19 evidence (13), up to 4 April 2022 (Supplement Table 2, available at Annals.org). In addition, we searched the COVID-NMA initiative website, a living evidence database of COVID-19 trials (15). On 17 August 2022, a surveillance search was conducted to identify studies to be included in periodic updating of the living, rapid review and SMPC practice points.

Study Selection

Two trained reviewers (from among I.S., A.D., D.L., I.M., E.P., K.T., and G.G.) independently screened titles, abstracts, and relevant full-text articles against predefined eligibility criteria using DistillerSR (Evidence Partners). Conflicts were resolved by discussion or by consulting a third reviewer. All results were tracked in an EndNote 20 database (Clarivate).

Data Extraction and Quality Assessment

One reviewer (I.S., A.D., D.L., I.M., E.P., or K.T.) abstracted characteristics of the study populations, settings, interventions, comparators, methods, and results from each included study. A second reviewer (I.S., A.D., D.L., I.M., E.P., or K.T.) checked all data abstractions for completeness and accuracy.

A single investigator assessed the risk of bias of the included RCTs using the Cochrane Risk of Bias Tool 2.0 (16). We validated the ratings against the risk-of-bias assessments provided by COVID-NMA, which had applied the same tool (15). If the ratings differed, we involved a second investigator to resolve the discrepancy. For trials that were not included in the COVID-NMA database, we dually assessed the risk of bias. Supplement Figure 1 (available at Annals.org) presents the risk-of-bias assessments.

Data Synthesis and Analysis

If we found 2 or more similar studies for a comparison of interest, we conducted meta-analyses. We chose the Bayesian random-effects model because it allows us to update the analyses without concern for *P* value inflation (17, 18). We conducted all analyses with R, version 4.1.3 (19), using the bayesmeta (20) and metafor (21) packages. We chose noninformative priors for both the treatment effect (mean, 0; SD, 4) and the heterogeneity (half-normal with a scale of 0.5). The results were calculated as risk ratios (RRs) and presented as forest plots.

We determined the appropriateness of a meta-analysis by assessing the clinical and methodological heterogeneity following established guidance (22). Although we used an intention-to-treat-analysis for data we pooled in a meta-analysis, we relied on the data as reported in the individual studies for the narrative summary. When possible, we conducted sensitivity analysis to explore potential sources of heterogeneity. Although we had planned to perform subgroup analyses, we were unable to identify enough studies to do so.

Certainty of Evidence

We graded the COE on the basis of the guidance established by the GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group (23). A single investigator assessed the COE for each key outcome, and a second senior investigator checked this for plausibility and consistency.

Role of the Funding Source

This living, rapid review was funded by ACP, which assisted in the development of the KQs and study inclusion criteria and selection of the outcomes of interest. The ACP was not involved in data collection, analysis, or manuscript preparation.

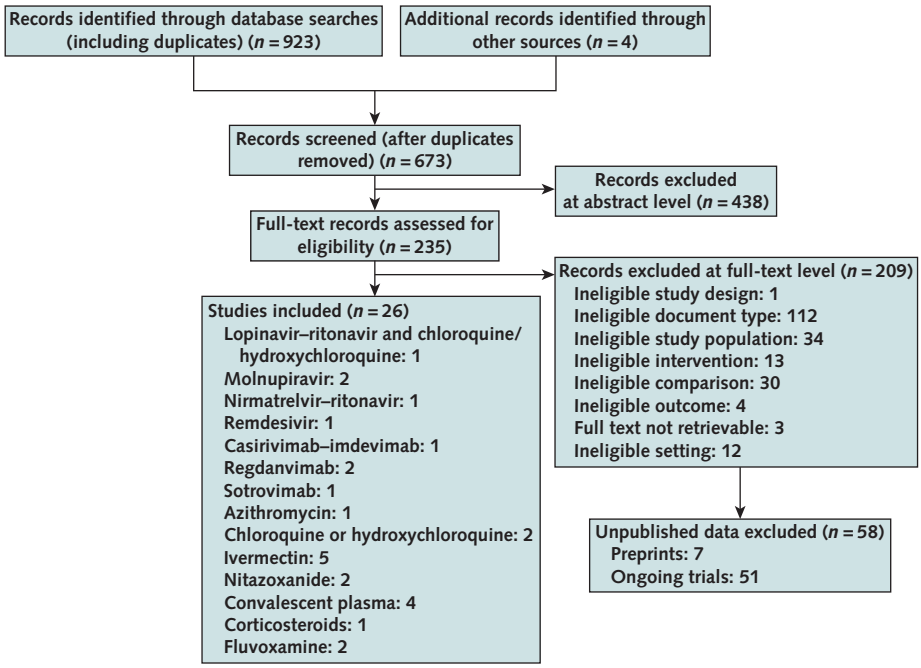
RESULTS

The searches yielded 679 references, from which we included 26 RCTs (24–49). Figure 1 shows the study selection process. Supplement Tables 3 to 5 (available at Annals.org) list eligible preprints, ongoing studies, and other excluded studies with the reasons for exclusion.

Study and Participant Characteristics

The number of participants in the included studies ranged from 18 to 5607. The median ages of participants varied from 26 to 77 years, and the proportion of females varied between 1% and 72%. Trials were conducted in the United States (31, 36, 40, 41, 43, 46), Canada (27,

Figure 1. PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flowchart.



45), Argentina (24, 47), Brazil (30, 32, 39, 49), Colombia (26), Spain (29, 37), Italy (48), the Middle East (28), or multiple countries (25, 33–35, 38, 42, 44). Out of 26 trials, 16 were funded with industry involvement (24, 25, 27, 31, 33–35, 37, 38, 41–46, 48). Among studies reporting vaccination status as an eligibility criterion, 11 studies (44%) (25, 28, 31, 33–37, 39, 44, 45) excluded vaccinated participants, and 4 studies (12%) included them (42, 43, 46, 49). Five studies excluded participants who had previously been diagnosed with COVID-19 (35, 37, 42, 43, 46); 1 study included them only if they had not been hospitalized or treated (44). All studies were conducted before the Omicron variant became the dominant strain.

Participants were symptomatic across studies except in 1 study that included both symptomatic and asymptomatic participants (41). Ten studies (24, 26, 30, 32, 34, 37, 39, 40, 42, 43) provided data on disease severity; in 6 of them, participants had only mild symptoms (24, 26, 30, 32, 39, 40, 42). In all studies, the SARS-CoV-2 infection status was confirmed by a diagnostic test, usually a reverse transcriptase polymerase chain reaction test; 7 studies (26, 34, 37, 38, 41, 46, 49) also accepted antigen tests. **Supplement Table 6** (available at Annals.org) presents the characteristics and results of the included studies; **Supplement Table 7** (available at Annals.org) lists the definitions of "recovery" that were used in the included studies.

We rated 9 studies as having low risk of bias (31, 33, 34, 37–39, 45–47), 16 as having some bias concerns (24–30, 32, 35, 36, 40–44, 49), and 1 as having high risk of bias (48). The risk-of-bias ratings of 8 studies differed from those in the COVID-NMA database (15) and required the involvement of a second reviewer. We dually assessed the risk of bias of 2 studies (42, 49) that were not available in the COVID-NMA database. Risk of bias included possible reporting bias, unclear blinding, lack of information on randomization and allocation concealment, or lack of an intention-to-treat analysis (**Supplement Figure** 1).

Efficacy and Risk for Harms of COVID-19 Treatments

Overall, only nirmatrelvir–ritonavir, casirivimab–imdevimab, and sotrovimab reduced hospitalizations due to COVID-19 compared with placebo (**Figure 2**). Lopinavir–ritonavir and azithromycin led to higher incidence of adverse events than placebo (**Figure 3**). Molnupiravir and nirmatrelvir–ritonavir reduced all-cause mortality (**Supplement Figure 2**, available at Annals.org). Nirmatrelvir–ritonavir, remdesivir, casirivimab–imdevimab, and sotrovimab reduced the incidence of serious adverse events (**Supplement Figure 3**, available at Annals.org).

The **Table** summarizes results and COE ratings for each treatment versus placebo. **Supplement Figures 4** to **19** (available at Annals.org) display meta-analyses, and **Supplement Table 8** (available at Annals.org) presents summary-of-findings tables.

Antiviral Drugs

Lopinavir–Ritonavir. One RCT (n = 471; some risk of bias) assessed 800 mg of lopinavir and 200 mg of ritonavir at the first 2 intakes, followed by 400 mg of lopinavir and 100 mg of ritonavir for the next 9 days, compared with placebo (30). Lopinavir–ritonavir may have no effect on hospitalization due to COVID-19 (5.6% vs. 4.8%; hazard ratio, 1.16 [95% confidence interval {CI}, 0.53 to 2.56]; low COE) but may increase the incidence of adverse events

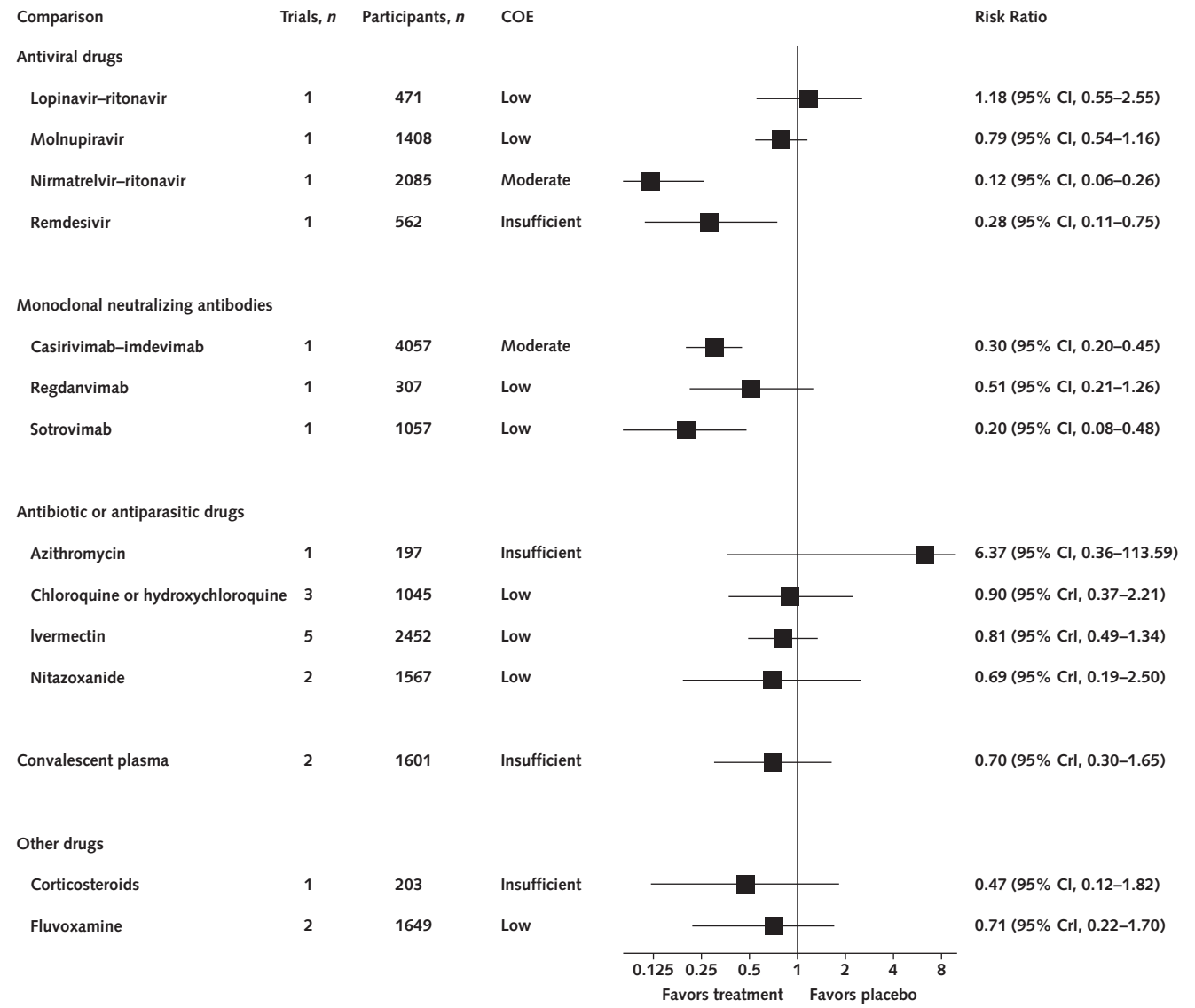
(39.7% vs. 20.9%; RR, 1.90 [CI, 1.40 to 2.57]; low COE). Although larger, the difference in serious adverse events between lopinavir–ritonavir and placebo was not statistically significant (8.6% vs. 5.5%; RR, 1.58 [CI, 0.79 to 3.16]; low COE). The evidence for all-cause mortality was insufficient to draw conclusions.

Molnupiravir. Two RCTs (n = 1637; low risk of bias) assessed molnupiravir, 800 mg (31, 33) or 200 to 800 mg (31), compared with placebo.

The MOVe-OUT study (33) reported a reduction in all-cause mortality (which corresponded to COVID-19–related mortality as all deaths were due to COVID-19) (<0.1% vs. 1.3%; RR, 0.11 [CI, 0.01 to 0.86]; low COE) with molnupiravir and no effect on hospitalization due to COVID-19 (6.2% vs. 7.9%; RR, 0.79 [CI, 0.54 to 1.16]; low COE). Molnupiravir at doses of 200, 400, or 800 mg probably results in similar recovery (48.4% vs. 48.3%; odds ratio, 1.04 [CI, 0.84 to 1.29]; 1 RCT; moderate COE) (31, 33) and time to recovery (median, 5.5 to 9.0 vs. 8.5 days; 1 RCT; low COE) compared with placebo (31, 33). The proportion of participants affected by serious or any adverse events in the 2 studies did not differ statistically between groups (serious adverse events: 6.1% vs. 8.7%; RR, 0.77 [95% credible interval {CrI}, 0.32 to 2.03]; low COE [**Supplement Figure 4**]; any adverse events: 30.1% vs. 32.0%; RR, 0.96 [CrI, 0.55 to 1.73]; moderate COE [**Supplement Figure 5**]).

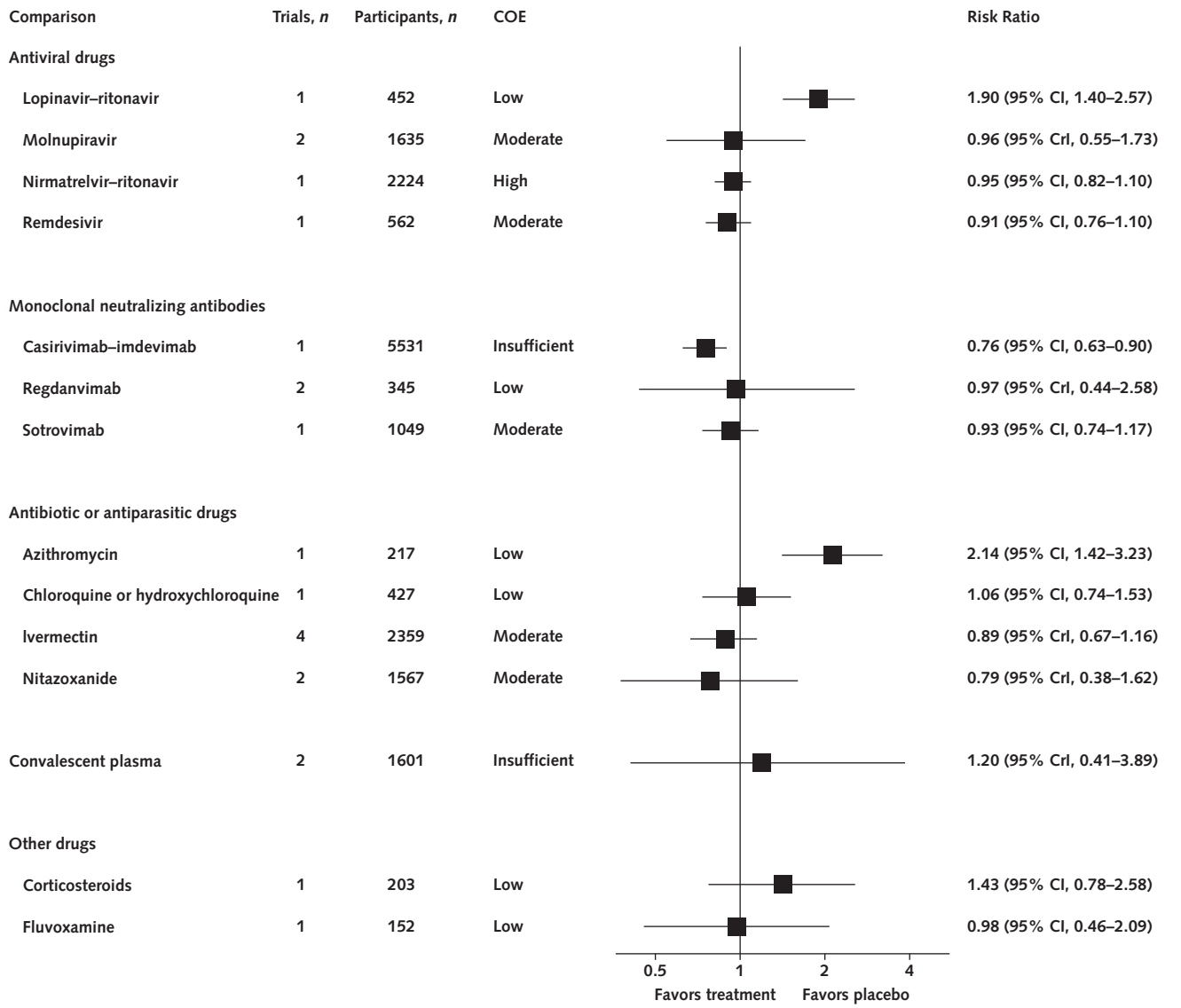
Nirmatrelvir–Ritonavir. One RCT (n = 2246; some risk of bias) assessed nirmatrelvir–ritonavir (300 and 100 mg) every 12 hours for 5 days compared with placebo (35).

Figure 2. Summary plot of hospitalization due to COVID-19.



The risk ratios were self-calculated. CI = confidence interval; COE = certainty of evidence; CrI = credible interval.

Figure 3. Summary plot of incidence of adverse events.



The risk ratios were self-calculated. CI = confidence interval; COE = certainty of evidence; CrI = credible interval.

Nirmatrelvir–ritonavir probably reduced all-cause mortality (0% vs. 1.1%; RR, 0.04 [CI, 0.002 to 0.68]; moderate COE) and hospitalization due to COVID-19 for patients with 5 or fewer days of symptoms (0.7% vs. 6.2%; RR, 0.12 [CI, 0.06 to 0.26]; moderate COE). The incidence of any adverse events did not statistically differ compared with placebo (22.6% vs. 23.9%; RR, 0.95 [CI, 0.82 to 1.10]; high COE).

Remdesivir. One RCT (n = 584; some risk of bias) assessed remdesivir, 200 mg on day 1 and 100 mg on days 2 and 3, compared with placebo (44).

Remdesivir may improve recovery between days 1 and 14 (36.1% vs. 20.0%; rate ratio, 1.92 [CI, 1.26 to 2.94]; low COE). There was no statistical difference in incidence of any adverse events (42.3% vs. 46.3%; RR, 0.91 [CI, 0.76 to 1.10]; moderate COE). Evidence was insufficient to draw conclusions about other outcomes.

Monoclonal Neutralizing Antibodies

We identified studies for 3 out of 5 monoclonal neutralizing antibodies approved by the U.S. Food and Drug Administration or the European Medicines Agency at the date of our search (4 April 2022).

Casirivimab–Imdevimab. One RCT (n = 4057; some risk of bias) assessed casirivimab–imdevimab, 1200 to 8000 mg, compared with placebo (25). Casirivimab–imdevimab reduced time to recovery (10 vs. 14 median days; high COE) and probably decreased hospitalizations due to COVID-19 (1.3% vs. 4.4%; RR, 0.30 [CI, 0.20 to 0.45]; moderate COE). Evidence was insufficient to draw conclusions about other outcomes.

Table. Results and COE Ratings for Each Treatment Versus Placebo

Treatment	All-Cause Mortality	COVID-19–Specific Mortality	Recovery	Time to Recovery	Hospitalization Due to COVID-19	Serious Adverse Events	Adverse Events
Antiviral drugs							
Lopinavir–ritonavir vs. placebo (30)	Studies: 1 Participants: 471 Study duration: 90 d Treatment effect: 1% vs. 0.4%; RR, 1.86 (95% CI, 0.17 to 20.38)* Insufficient COE	No evidence	No evidence	No evidence	Studies: 1 Participants: 471 Study duration: 90 d Treatment effect: 6% vs. 5%; HR, 1.16 (95% CI, 0.53 to 2.56) Low COE for non-statistically different effect	Studies: 1 Participants: 452 Study duration: 90 d Treatment effect: 9% vs. 6%; RR, 1.58 (95% CI, 0.79 to 3.16)* Low COE for non-statistically different effect	Studies: 1 Participants: 452 Study duration: 90 d Treatment effect: 40% vs. 21%; RR, 1.90 (95% CI, 1.40 to 2.57)* Low COE for higher risk with lopinavir–ritonavir
Molnupiravir vs. placebo (31, 33)	Studies: 1 Participants: 1433 Study duration: 29 d Treatment effect: 0.1% vs. 1%; RR, 0.11 (95% CI, 0.01 to 0.86)* Low COE for lower risk with molnupiravir	Studies: 1 Participants: 1433 Study duration: 29 d Treatment effect: 0% vs. 1%; RR, 0.11 (95% CI, 0.01 to 0.86)* Low COE for lower risk with molnupiravir	Studies: 1 Participants: 1295 Study duration: 29 d Treatment effect: 48% vs. 48%; OR, 1.04 (95% CI, 0.84 to 1.29) Moderate COE for non-statistically different effect	Studies: 1 Participants: 202 Study duration: 28 d Treatment effect: molnupiravir, 5.5 to 9 d; placebo, 8.5 d Low COE for similar effect with molnupiravir	Studies: 1 Participants: 1408 Study duration: 29 d Treatment effect: 6% vs. 8%; RR, 0.79 (95% CI, 0.54 to 1.16)* Low COE for non-statistically different effect	Studies: 2 Participants: 1635 Study duration: 28 to 29 d Treatment effect: 6% vs. 9%; RR, 0.77 (95% CI, 0.32 to 2.03)* Low COE for non-statistically different effect	Studies: 2 Participants: 1635 Study duration: 28 to 29 d Treatment effect: 30% vs. 32%; RR, 0.96 (95% CrI, 0.55 to 1.73)* Moderate COE for non-statistically different effect
Nirmatrelvir–ritonavir vs. placebo (35)	Studies: 1 Participants: 2085 Study duration: 28 d Treatment effect: 0% vs. 1%; RR, 0.04 (95% CI, 0.002 to 0.68)* Moderate COE for lower risk with nirmatrelvir–ritonavir	No evidence	No evidence	No evidence	Studies: 1 Participants: 2085 Study duration: 28 d Treatment effect: 1% vs. 6%; RR, 0.12 (95% CI, 0.06 to 0.26)* Moderate COE for lower risk with nirmatrelvir–ritonavir	Studies: 1 Participants: 2224 Study duration: 34 d Treatment effect: 2% vs. 7%; RR, 0.25 (95% CI, 0.16 to 0.38)* Insufficient COE	Studies: 1 Participants: 2224 Study duration: 34 d Treatment effect: 23% vs. 24%; RR, 0.95 (95% CI, 0.82 to 1.10)* High COE for non-statistically different effect
Remdesivir vs. placebo (44)	Studies: 1 Participants: 562 Study duration: 28 d Treatment effect: 0% vs. 0%; RR not estimable Insufficient COE	No evidence	Studies: 1 Participants: 334 Study duration: 14 d Treatment effect: 36% vs. 20%; rate ratio, 1.92 (95% CI, 1.26 to 2.94) Low COE for greater effect with remdesivir	No evidence	Studies: 1 Participants: 562 Study duration: 28 d Treatment effect: 2% vs. 6%; HR, 0.28 (95% CI, 0.10 to 0.75) Insufficient COE	Studies: 1 Participants: 562 Study duration: 28 d Treatment effect: 2% vs. 7%; RR, 0.27 (95% CI, 0.10 to 0.70) Insufficient COE	Studies: 1 Participants: 562 Study duration: 28 d Treatment effect: 42% vs. 46%; RR, 0.91 (95% CI, 0.76 to 1.10) Moderate COE for non-statistically different effect
Monoclonal neutralizing antibodies							
Casirivimab–imdevimab vs. placebo (25)	Studies: 1 Participants: 4057 Study duration: 29 d Treatment effect: 0.1% vs. 0.2%; RR, 0.33 (95% CI, 0.06 to 1.97) Insufficient COE	No evidence	No evidence	Studies: 1 Participants: 3432 Study duration: 29 d Treatment effect: 10 vs. 14 d; P = 0.0001 High COE for greater effect with casirivimab–imdevimab	Studies: 1 Participants: 4057 Study duration: 29 d Treatment effect: 1% vs. 4%; RR, 0.30 (95% CI, 0.20 to 0.45) Moderate COE for lower risk with casirivimab–imdevimab	Studies: 1 Participants: 5531 Study duration: 45 d Treatment effect: 1% vs. 4%; RR, 0.34 (95% CI, 0.24 to 0.48) Insufficient COE	Studies: 1 Participants: 5531 Study duration: 45 d Treatment effect: 8% vs. 3%; RR, 0.76 (95% CI, 0.63 to 0.90) Insufficient COE
Regdanvimab vs. placebo (34, 42)	Studies: 1 Participants: 325 Study duration: 28 d Treatment effect: 0% vs. 0%; RR not estimable Insufficient COE	No evidence	Studies: 1 Participants: 285 Study duration: 28 d Treatment effect: 87% vs. 72%; RR, 1.21 (95% CI, 1.05 to 1.38) Moderate COE for greater effect with regdanvimab	Studies: 2 Participants: 303 Study duration: 14 to 28 d Treatment effect: regdanvimab, 5.5 to 9 d; placebo, 8.0 to 8.5 d Low COE for non-statistically different effect	Studies: 1 Participants: 307 Study duration: 28 d Treatment effect: 4% vs. 9%; RR, 0.51 (95% CI, 0.21 to 1.26) Low COE for non-statistically different effect	Studies: 2 Participants: 345 Study duration: 14 to 28 d Treatment effect: 0% vs. 0%; RR not estimable Insufficient COE	Studies: 2 Participants: 345 Study duration: 14 to 28 d Treatment effect: 29% vs. 31%; RR, 0.97 (95% CrI, 0.44 to 2.58) Low COE for non-statistically different effect

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Treatment	All-Cause Mortality	COVID-19-Specific Mortality	Recovery	Time to Recovery	Hospitalization Due to COVID-19	Serious Adverse Events	Adverse Events
Sotrovimab vs. placebo (38)	Studies: 1 Participants: 1057 Study duration: 29 d Treatment effect: 0% vs. 0.4%; RR, 0.20 (95% CI, 0.01 to 4.12) Insufficient COE	No evidence	No evidence	No evidence	Studies: 1 Participants: 1057 Study duration: 29 d Treatment effect: 1% vs. 6%; RR, 0.20 (95% CI, 0.08 to 0.48) Low COE for lower risk with sotrovimab	Studies: 1 Participants: 1049 Study duration: 29 d Treatment effect: 2% vs. 6%; RR, 0.3 (95% CI, 0.18 to 0.68) Insufficient COE	Studies: 1 Participants: 1049 Study duration: 29 d Treatment effect: 22% vs. 23%; RR, 0.93 (95% CI, 0.74 to 1.17) Moderate COE for non-statistically different effect
Antibiotic or antiparasitic drugs							
Azithromycin vs. placebo (41)	Studies: 1 Participants: 197 Study duration: 21 d Treatment effect: 0% vs. 0%; RR not estimable Insufficient COE	No evidence	Studies: 1 Participants: 201 Study duration: 14 d Treatment effect: 50% vs. 50%; RR, 1.02 (95% CI, 0.91 to 1.13) Low COE for non-statistically different effect	No evidence	Studies: 1 Participants: 197 Study duration: 21 d Treatment effect: 4% vs. 0%; RR, 6.37 (95% CI, 0.36 to 113.59) Insufficient COE	Studies: 1 Participants: 217 Study duration: 21 d Treatment effect: 0% vs. 0%; RR not estimable Insufficient COE	Studies: 1 Participants: 217 Study duration: 3 d Treatment effect: 57% vs. 26%; RR, 2.14 (95% CI, 1.42 to 3.23) Low COE for higher risk with azithromycin
Chloroquine or hydroxychloroquine vs. placebo (27, 28, 30)	Studies: 3 Participants: 1045 Study duration: 21 to 90 d Treatment effect: 0% vs. 0.2%; RR, 0.41 (95% CI, 0.05 to 3.31)* Insufficient COE	Studies: 2 Participants: 604 Study duration: 21 to 30 d Treatment effect: 0% vs. 0%; RR not estimable Insufficient COE	Studies: 1 Participants: 147 Study duration: 30 d Treatment effect: 61% vs. 78%; RR, 0.78 (95% CI, 0.62 to 0.97)* Low COE for lower effect with chloroquine/hydroxychloroquine	Studies: 1 Participants: 148 Study duration: 30 d Treatment effect: 14 vs. 12 d Low COE for non-statistically different effect	Studies: 3 Participants: 1045 Study duration: 21 to 90 d Treatment effect: 3% vs. 4%; RR, 0.90 (95% CrI, 0.37 to 2.21)* Low COE for non-statistically different effect	Studies: 3 Participants: 1045 Study duration: 21 to 90 d Treatment effect: 2% vs. 3%; RR, 1.02 (95% CrI, 0.36 to 2.96)* Low COE for non-statistically different effect	Studies: 1 Participants: 427 Study duration: 90 d Treatment effect: 22% vs. 21%; RR, 1.06 (95% CI, 0.74 to 1.53) Low COE for non-statistically different effect
Ivermectin vs. placebo (26, 29, 47–49)	Studies: 5 Participants: 2452 Study duration: 21 to 30 d Treatment effect: 2% vs. 2%; RR, 0.89 (95% CrI, 0.42 to 1.91) Low COE for non-statistically different effect	Studies: 3 Participants: 593 Study duration: 21 to 30 d Treatment effect: 0% vs. 0.4%; RR, 0.55 (95% CI, 0.07 to 4.37) Insufficient COE	Studies: 2 Participants: 569 Study duration: 21 to 30 d Treatment effect: 68% vs. 66%; RR, 1.04 (95% CrI, 0.61 to 1.72)* Moderate COE for non-statistically different effect	Studies: 3 Participants: 1836 Study duration: 21 to 30 d Treatment effect: ivermectin, 10 to 29 d; placebo, 12 to 14 d Insufficient COE	Studies: 5 Participants: 2452 Study duration: 21 to 30 d Treatment effect: 8% vs. 10%; RR, 0.81 (95% CI, 0.49 to 1.34) Low COE for non-statistically different effect	Studies: 5 Participants: 2452 Study duration: 21 to 30 d Treatment effect: 2% vs. 2%; RR, 1.06 (95% CI, 0.47 to 2.5) Insufficient COE	Studies: 4 Participants: 2359 Study duration: 21 to 30 d Treatment effect: 28% vs. 32%; RR, 0.89 (95% CrI, 0.67 to 1.16) Moderate COE for non-statistically different effect
Nitazoxanide vs. placebo (32, 43)	Studies: 2 Participants: 1567 Study duration: 14 to 28 d Treatment effect: 0.2% vs. 0%; RR, 2.08 (95% CI, 0.19 to 22.35) Insufficient COE	Studies: 1 Participants: 1092 Study duration: 28 d Treatment effect: 0.2% vs. 0%; RR, 2.68 (95% CI, 0.13 to 55.74) Insufficient COE	Studies: 1 Participants: 392 Study duration: mean, 5 d Treatment effect: 70% vs. 74%; RR, 0.94 (95% CI, 0.83 to 1.07) Moderate COE for non-statistically different effect	Studies: 1 Participants: 379 Treatment effect: median days, 13.3 (IQR, 6.3 to 21) vs. 12.4 (IQR, 7.2 to 21) Moderate COE for non-statistically different effect	Studies: 2 Participants: 1567 Study duration: 5 to 28 d Treatment effect: 1% vs. 1%; RR, 0.69 (95% CrI, 0.19 to 2.5) Low COE for non-statistically different effect	Studies: 2 Participants: 1567 Study duration: 5 to 28 d Treatment effect: 0.3% vs. 1%; RR, 0.33 (95% CrI, 0.07 to 1.56) Low COE for non-statistically different effect	Studies: 2 Participants: 1567 Study duration: 5 to 28 d Treatment effect: 14% vs. 19%; RR, 0.79 (95% CrI, 0.38 to 1.62) Moderate COE for non-statistically different effect
Convalescent plasma							
Convalescent plasma vs. placebo (24, 36, 37, 46)	Studies: 4 Participants: 2272 Study duration: 15 to 28 d	Studies: 2 Participants: 1385 Study duration: 15 to 28 d	No evidence	Studies: 1 Participants: 376 Study duration: 30 d Treatment effect: 12	Studies: 2 Participants: 1601 Study duration: 28 d	Studies: 4 Participants: 2272 Study duration: 15 to 28 d	Studies: 2 Participants: 1601 Study duration: 28 d

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Treatment	All-Cause Mortality	COVID-19-Specific Mortality	Recovery	Time to Recovery	Hospitalization Due to COVID-19	Serious Adverse Events	Adverse Events
	Treatment effect: 1% vs. 1%; RR, 0.68 (95% CrI, 0.20 to 2.34) Low COE for non–statistically different effect	Treatment effect: 0.3% vs. 1%; RR, 0.37 (95% CI, 0.08 to 1.84) Insufficient COE		vs. 12 d; HR, 1.05 (95% CI, 0.85 to 1.30) Low COE for non–statistically different effect	Treatment effect: 5% vs. 7%; RR, 0.70 (95% CI, 0.30 to 1.65) Insufficient COE	Treatment effect: 1% vs. 1%; RR, 1.09 (95% CrI, 0.38 to 3.78) Low COE for non–statistically different effect	Treatment effect: 7% vs. 8%; RR, 1.2 (95% CI, 0.41 to 3.89) Insufficient COE
Other drugs							
Ciclesonide vs. placebo (45)	Studies: 1 Participants: 203 Study duration: 14 d Treatment effect: 0% vs. 0%; RR not estimable Insufficient COE	Studies: 1 Participants: 215 Study duration: 14 d Treatment effect: 0% vs. 0%; RR not estimable Insufficient COE	Studies: 1 Participants: 203 Study duration: 14 d Treatment effect: 66% vs. 58%; RR, 1.13 (95% CI, 0.91 to 1.40) Low COE for non–statistically different effect	No evidence	Studies: 1 Participants: 203 Study duration: 14 d Treatment effect: 3% vs. 6%; RR, 0.47 (95% CI, 0.12 to 1.82) Insufficient COE	Studies: 1 Participants: 209 Study duration: 14 d Treatment effect: 6% vs. 7%; RR, 1.36 (95% CI, 0.45 to 4.15) Low COE for non–statistically different effect	Studies: 1 Participants: 203 Study duration: 14 d Treatment effect: 22% vs. 15%; RR, 1.43 (95% CI, 0.79 to 2.58) Low COE for non–statistically different effect
Fluvoxamine vs. placebo (39, 40)	Studies: 2 Participants: 1649 Study duration: 15 to 28 d Treatment effect: 2% vs. 3%; RR, 0.71 (95% CrI, 0.24 to 2.10) Low COE for non–statistically different effect	Studies: 1 Participants: 152 Study duration: 15 d Treatment effect: 0% vs. 0%; RR not estimable Insufficient COE	No evidence	No evidence	Studies: 2 Participants: 1649 Study duration: 15 to 28 d Treatment effect: 9% vs. 12%; RR, 0.71 (95% CrI, 0.22 to 1.70) Low COE for non–statistically different effect	Studies: 1 Participants: 152 Study duration: 15 d Treatment effect: 1% vs. 7%; RR, 0.18 (95% CI, 0.02 to 1.50) Insufficient COE	Studies: 1 Participants: 152 Study duration: 15 d Treatment effect: 15% vs. 15%; RR, 0.98 (95% CI, 0.46 to 2.09) Low COE for non–statistically different effect

CI = confidence interval; COE = certainty of evidence; CrI = credible interval; HR = hazard ratio; OR = odds ratio; RR = risk ratio.
* The RR was self-calculated.

Regdanvimab. Two RCTs (n = 345; 1 with low risk of bias and 1 with some risk of bias) assessed regdanvimab, 20 to 80 mg/kg of body weight, compared with placebo (34, 42).

Although 1 study (n = 250) found that regdanvimab probably improved recovery (86.6% vs. 71.7%; RR, 1.21 [CI, 1.05 to 1.38]; moderate COE) (34), together the studies did not find a statistically significant effect on time to recovery (5.5 to 9.0 vs. 8.0 to 8.5 median days; low COE). The results for hospitalization due to COVID-19 (4.4% vs. 8.7%; RR, 0.51 [CI, 0.21 to 1.26]; 1 RCT; low COE) (34) and incidence of adverse events (29.4% vs. 30.7%; RR, 0.97 [CrI, 0.44 to 2.58]; 2 RCTs; low COE) (**Supplement Figure** 6) also did not differ statistically between groups. Evidence was insufficient to draw conclusions about any of the other outcomes.

Sotrovimab. One RCT (n = 1057; low risk of bias) assessed sotrovimab, 500 mg, compared with placebo (38).

Sotrovimab may reduce hospitalization due to COVID-19 (1.1% vs. 5.7%; RR, 0.20 [CI, 0.08 to 0.48]; low COE) and resulted in no statistical difference in incidence of adverse events (21.8% vs. 23.4%; RR, 0.93 [CI, 0.74 to 1.17]; moderate COE). Evidence was insufficient to draw conclusions about other outcomes.

Antibiotic or Antiparasitic Drugs

Azithromycin. One RCT (n = 263; some risk of bias) assessed azithromycin in a single 1.2-g dose compared with placebo (41).

Azithromycin may have no effect on recovery at day 14 (50.4% vs. 50.0%; RR, 1.02 [CI, 0.91 to 1.13]; low COE) and may increase the incidence of adverse events (56.6% vs. 26.4%; RR, 2.14 [CI, 1.42 to 3.23]; low COE). Evidence was insufficient to draw conclusions about other outcomes.

Chloroquine or Hydroxychloroquine. Three RCTs (n = 893; some risk of bias) assessed hydroxychloroquine, 800 mg on day 1 followed by 400 mg/d for 5 days then 600 mg/d for 9 days, compared with placebo (27, 28, 30).

Hydroxychloroquine may reduce the likelihood of recovery (60.9% vs. 78.4%; RR, 0.78 [CI, 0.62 to 0.97]; 1 RCT; low COE), but the median time to recovery (14 vs. 12 days; low COE) did not differ statistically between the treatment groups after 30 days (27). Hydroxychloroquine may not reduce risk for hospitalization due to COVID-19 (3.0% vs. 3.6%; RR, 0.90 [CrI, 0.37 to 2.21]; 3 RCTs; low COE) (**Supplement Figure 7**). Hydroxychloroquine may not result in any statistical difference in serious adverse events (2.2% vs. 2.9%; RR, 1.02 [CrI, 0.36 to 2.96]; 3 RCTs; low COE) (**Supplement Figure 8**) or any adverse events (22.2% vs. 20.9%; RR, 1.06 [CI, 0.74 to 1.53]; 1 RCT; low COE) (30). Evidence was insufficient to draw conclusions about other outcomes.

Ivermectin. Five RCTs (n = 2452; 4 with some risk of bias and 1 with high risk of bias) compared ivermectin,

200 to 1200 mcg/kg in a single dose or for 2 to 5 days, with placebo (26, 29, 47–49).

Ivermectin may not have any statistically significant benefit on all-cause mortality (2.0% vs. 2.3%; RR, 0.89 [CrI, 0.42 to 1.91]; low COE) (**Supplement Figure 9**), recovery (68.2% vs. 65.6%; RR, 1.04 [CrI, 0.61 to 1.72]; moderate COE) (**Supplement Figure 10**), or hospitalization due to COVID-19 (8.1% vs. 9.9%; RR, 0.81 [CI, 0.49 to 1.34]; low COE) (**Supplement Figure 11**). A sensitivity analysis without the study that had high risk of bias found similar results for reduced hospitalization (8.1% vs. 10.2%; RR, 0.78 [CrI, 0.46 to 1.28]). There was no statistical difference in incidence of adverse events (27.7% vs. 31.8%; RR, 0.89 [CrI, 0.67 to 1.16]; moderate COE) (**Supplement Figure 12**). Evidence was insufficient to draw conclusions about other outcomes.

Nitazoxanide. Two RCTs (n = 1567; some risk of bias) assessed nitazoxanide, 1200 or 500 mg/d, compared with placebo (32, 43).

Nitazoxanide resulted in no statistical difference in recovery (69.3% vs. 73.7%; RR, 0.94 [CI, 0.83 to 1.07]; moderate COE) (32), median number of days to sustained clinical recovery (13.3 [IQR, 6.3 to 21] vs. 12.4 [IQR, 7.2 to 21]; P = 0.88; moderate COE) (43), or hospitalization due to COVID-19 (0.7% vs. 1.1%; RR, 0.69 [CrI, 0.19 to 2.5]; low COE) (**Supplement Figure 13**). There were also no statistical differences in the incidence of serious adverse events (0.3% vs. 1.1%; RR, 0.33 [CrI, 0.07 to 1.56]; low COE) (**Supplement Figure 14**) or any adverse events (14.2% vs. 19.3%; RR, 0.79 [CrI, 0.38 to 1.62]; moderate COE) (**Supplement Figure 15**). Evidence was insufficient to draw conclusions about other outcomes.

Convalescent Plasma

Four RCTs (n = 2272; 2 with low risk of bias and 2 with some risk of bias) assessed convalescent plasma, 250 to 300 mL in a single dose, compared with placebo (24, 36, 37, 46).

Convalescent plasma may have no statistical effect on all-cause mortality (0.6% vs. 0.9%; RR, 0.68 [CrI, 0.20 to 2.34]; 4 RCTs; low COE) (**Supplement Figure 16**), incidence of serious adverse events (1.1% vs. 1.1%; RR, 1.09 [CrI, 0.38 to 3.78]; 4 RCTs; low COE) (**Supplement Figure 17**), or time to symptom resolution (12 vs. 12 median days; hazard ratio, 1.05 [CI, 0.85 to 1.30]; 1 RCT; low COE) (46). Evidence was insufficient to draw conclusions about other outcomes.

Other Drugs

Corticosteroids. One RCT (n = 215; low risk of bias) assessed ciclesonide, 1200 mcg inhaled twice daily or 200 mcg intranasally per day, compared with placebo (45).

Ciclesonide may result in no statistically significant difference for recovery (65.7% vs. 58.2%; RR, 1.13 [CI, 0.91 to 1.40]; low COE), incidence of serious adverse events (6.6% vs. 4.9%; RR, 1.36 [CI, 0.45 to 4.15]; low COE), or incidence of any adverse events (21.9% vs. 15.3%; RR, 1.43 [CI, 0.79 to 2.58]; low COE). Evidence was insufficient to draw conclusions about other outcomes.

Fluvoxamine. Two trials (n = 1649; 1 with low risk of bias and 1 with some risk of bias) assessed fluvoxamine, 100 mg/d, compared with placebo (39, 40).

Fluvoxamine may have no statistically significant effect on all-cause mortality (2.1% vs. 3.0%; RR, 0.71 [CrI, 0.24 to 2.10]; 2 RCTs; low COE) (**Supplement Figure 18**), hospitalization due to COVID-19 (9.1% vs. 12.2%; RR, 0.71 [CrI, 0.22 to 1.70]; 2 RCTs; low COE) (**Supplement Figure 19**), or any adverse events (15.0% vs. 15.3%; RR, 0.98 [CI, 0.46 to 2.09]; 1 RCT; low COE). Evidence was insufficient to draw conclusions about other outcomes.

Subgroup Analysis

One fluvoxamine trial (39) found no statistically significant interaction for the effect of age, sex, time from symptom onset, and comorbidities for hospitalization or extended emergency department visit due to COVID-19.

Several other trials reported comparisons of the study groups in population subsets but without testing for interaction. Most confirmed the overall result (30, 32, 35, 41, 43, 44, 46). Two studies reported an increased or decreased risk for hospitalization due to COVID-19 or recovery for certain subgroups despite the overall effect showing no difference between the groups (33, 34) (**Supplement Table 9**, available at Annals.org).

Surveillance

The first surveillance search yielded 6 eligible RCTs (50–55). The studies compared molnupiravir (51), ivermectin (50–52, 54), fluvoxamine (55), and the monoclonal neutralizing antibodies tixagevimab–cilgavimab (53) with placebo (**Supplement Table 10**, available at Annals.org). The study on tixagevimab–cilgavimab (53) reported a reduction in COVID-19–related deaths or progression to severe disease (4% vs. 10%; RR, 0.43 [CI, 0.25 to 0.75]) and an increase in any adverse events (29% vs. 36%; RR, 0.81 [CI, 0.67 to 0.98]). It was conducted before the emergence of the Omicron variant. The remaining 5 studies reported no beneficial or harmful effects for outcomes of interest (50–52, 54, 55).

DISCUSSION

This living, rapid review on 12 COVID-19 outpatient treatments, which included 26 RCTs conducted before dominance of the current Omicron variant, found that nirmatrelvir–ritonavir and the monoclonal antibodies casirivimab–imdevimab and regdanvimab had the strongest evidence for benefit in outpatients with COVID-19, with reduced hospitalizations, reduced all-cause mortality, or both. Molnupiravir may also reduce all-cause mortality and remdesivir may improve recovery, but evidence is less certain. However, these findings must be interpreted with caution because all studies were conducted before the dominance of the current Omicron variant. Specifically, a preprint article of the unblinded PANORAMIC (Platform Adaptive trial of NOvel antiviRals for eArly treatMent of covid-19 In the Community) trial (n = 25 783), which was conducted in the United Kingdom during dominance of the Omicron variant, reports no difference for hospitalization, mortality, or serious adverse events but improved

early sustained recovery and time to first reported recovery between molnupiravir plus usual care and usual care (56). However, as a preprint article that has not yet been subject to peer review, this study did not meet the inclusion criteria for our surveillance.

Several in vitro studies have found that the monoclonal antibodies that were found to be effective in our review (casirivimab–imdevimab, regdanvimab, and sotrovimab) are ineffective against the Omicron subvariant BA.5 (57–59). Because Omicron and its subvariants have become the dominant strains in the United States during 2022 (60), the U.S. Food and Drug Administration has revoked authorization for casirivimab–imdevimab (in January 2022) and sotrovimab (in May 2022) (61, 62). Regdanvimab was never approved in the United States. The antivirals remdesivir, molnupiravir, and nirmatrelvir–ritonavir have been shown to retain susceptibility to Omicron subvariants, including BA.5, similar to that for the ancestral strain (63). Despite retaining neutralizing activities, the absolute effect of antivirals to prevent hospitalization and death might be lower due to the reduced overall severity of the Omicron variant compared with previous variants (64). Current evidence does not support the efficacy of convalescent plasma and several drugs that were repurposed for use in outpatients with COVID-19, such as ivermectin, lopinavir–ritonavir, azithromycin, chloroquine or hydroxychloroquine, nitazoxanide, inhaled or intranasal corticosteroids, and fluvoxamine. Lopinavir–ritonavir and azithromycin may even have harmful effects, and hydroxychloroquine may lead to lower recovery rates.

We did not identify any results related to COVID-19 rebound, a phenomenon in which patients develop symptoms of COVID-19 after taking the drug (65). However, because rebound has also been observed in untreated persons with COVID-19 (66), clinical trials are needed to understand the effects of antivirals on rebound.

Our results are largely consistent with findings from other reviews, which were conducted in mixed populations of inpatients and outpatients and used standard of care as a comparison in addition to placebo. In line with our review, Cochrane reviews found beneficial effects for monoclonal antibodies (3) and nirmatrelvir–ritonavir (10) and no beneficial effects for chloroquine or hydroxychloroquine (5), convalescent plasma (9), ivermectin (6), or azithromycin (4). Other reviews showed that remdesivir increased recovery and reduced time to recovery and serious adverse events but also increased adverse events in hospitalized patients (67), and that fluvoxamine led to fewer hospitalizations in outpatients (68) when, unlike in this review, unpublished data were included.

This living, rapid review considered many aspects not evaluated in previous reviews. One of its strengths is its comprehensive assessment of the benefits and harms of 12 COVID-19 treatments of interest. Another strength of this study is its focus on placebo-controlled trials, which is the most rigorous study design for evaluating treatment efficacy because it ensures assay sensitivity (the ability to distinguish between effective and ineffective treatments) (69).

This review also has limitations. Although we restricted the literature search to only 1 database, evaluations of the Epistemonikos COVID-19 L·OVE Platform database have shown that it provides a comprehensive compilation of COVID-19 treatments, containing nearly all cited studies (70). To prevent missing relevant studies, we double-checked our list of included studies with that of the COVID-NMA database (15).

Another limitation of our review is the lack of sufficient data for some outcomes. Included studies provided very low rates of hospitalization and mortality and low power in a population with mild to moderate disease severity. Insufficient data also precluded the exploration of heterogeneity across studies (71). The reported subgroup analyses were predominantly limited to exploratory or post hoc analyses and relied on small sample sizes. Although these analyses are useful for generating new hypotheses, recommendations for clinical practice should rely on prespecified subgroup analyses (72).

Finally, the greatest limitation is that included studies were conducted before the Omicron variant became dominant and lacked information on vaccination or prior infection status, which reduces the generalizability of the findings.

In conclusion, some antivirals and some monoclonal antibodies may improve recovery and reduce the risk for hospitalization in outpatients with mild to moderate COVID-19 from previous variants of SARS-CoV-2. However, the benefits of these therapies, particularly monoclonal antibodies, may be limited against the currently dominant Omicron variants.

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Reproducible Research Statement: *Study protocol:* Available from Dr. Sommer (e-mail, isolde.sommer@donau-uni.ac.at). *Statistical code and data set:* Available from Mr. Emprechtinger (e-mail, robert.emprechtinger@donau-uni.ac.at).

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Supplemental Material*

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Contents

* This supplemental material was provided by the authors to give readers further details on their article. The material was not copyedited.

Supplement Table 1: Inclusion and Exclusion Criteria

	Criteria	
Category	**Inclusion**	**Exclusion**
Population	Adult (18 years or older) outpatients of all races and ethnicities with a symptomatic or asymptomatic, and confirmed diagnosis of COVID-19 (PCR or antigen detected)[1]	• Children under age 18 • Adults hospitalized due to COVID-19 • Adults with confirmed diagnosis of other severe corona viruses such as severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS), or other viral respiratory diseases, such as influenza. • Adults who were exposed to SARS-CoV-2 without a confirmed infection
	Subgroups of interest are based on: • patient characteristics (age, gender, comorbidities) • immunity status (prior SARS-CoV-2 infection, vaccination status, time since infection/vaccination) • type of SARS-CoV-2 variant • symptom duration • symptom severity	
Interventions	• chloroquine/hydroxychloroquine • convalescent plasma • lopinavir/ritonavir • ivermectin • molnupiravir • monoclonal antibodies approved by FDA or EMA at search date (bebtelovimab, tixagevimab+cilgavimab, sotrovimab, casirivimab+imdevimab, regdanvimab) • nirmatrelvir + ritonavir (Paxlovid) • nitazoxanide • remdesivir • fluvoxamine • antibiotics (azithromycin only) • corticosteroids (inhaled and systemic)	• Adjunct COVID-19 treatments (e.g. anticoagulants/ antiplatelet therapy, vitamins) • Combinations of interventions (except those approved as pair of agents e.g. casirivimab plus imdevimab [REGEN-COV]) • Antibiotics other than azithromycin
Control intervention	• Placebo • Usual care if no placebo-controlled study is available (as defined by study authors) • Different dose or duration of same treatment (if placebo group is present) • Dose: doses that are within the approved dosing range. For drugs that are not approved for COVID, apply doses approved for other indications. • Duration: use the duration defined for the primary outcome in the registration of the trial.	• Usual care • No treatment • Different treatments
Outcomes	• All-cause mortality • COVID-19 specific mortality • Recovery/Clinical improvement • Time to recovery/time to clinical improvement	• Studies that do not include at least one of the outcomes listed under the inclusion criteria

	• Admission to hospital due to COVID-19 • Incidence of adverse events (e.g., headache, fatigue, cough) • Incidence of serious adverse events (e.g. anaphylaxis) according to the FDA definition (73)	
Timing of intervention	No limitations	
Geography	No limitations	
Settings	• Outpatient settings (90%)	• Inpatient settings
Publication language	• English	• All other languages
Study design	1. RCTs	• Nonrandomized controlled trials • Cohort studies • Case-control studies • Case series • Case reports • Nonsystematic reviews • Studies without a control group • Systematic reviews and meta-analyses
Publication type	Any peer-reviewed publication reporting primary data	Abstracts, preprints, publications not reporting primary data (e.g., protocols)

EMA = European Medicines Agency; FDA = Food and Drug Administration; PCR = Polymerase Chain Reaction; RCT = randomized controlled trial.

Supplement Table 2: Search Strategy

COVID-19 L·OVE (https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d)
4th April 2022

Classification	Search within these results	Document type	Results
Hydroxychloroquine sulfate for (any Population)	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Randomised trials reporting data	76
Hydroxychloroquine sulfate for (any Population)	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Randomised trials not reporting data	90
Hydroxychloroquine sulfate for (any Population)	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Articles awaiting assessment	10
Chloroquine for (any Population)	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Randomised trials reporting data	8
Chloroquine for (any Population)	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Randomised trials not reporting data	28
Chloroquine for (any Population)	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Articles awaiting assessment	10
Convalescent plasma for (any Population)	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Randomised trials reporting data	29
Convalescent plasma for (any Population)	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Randomised trials not reporting data	36
Convalescent plasma for (any Population)	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Articles awaiting assessment	11
Lopinavir for (any Population)	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Randomised trials reporting data	22
Lopinavir for (any Population)	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Randomised trials not reporting data	31
Lopinavir for (any Population)	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Articles awaiting assessment	6
Ritonavir for (any Population)	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Randomised trials reporting data	27
Ritonavir for (any Population)	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Randomised trials not reporting data	40

Classification	Search within these results	Document type	Results
Ritonavir for (any Population)	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Articles awaiting assessment	9
Ivermectin for (any Population)	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Randomised trials reporting data	41
Ivermectin for (any Population)	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Randomised trials not reporting data	49
Ivermectin for (any Population)	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Articles awaiting assessment	7
Molnupiravir for (any Population)	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Randomised trials reporting data	9
Molnupiravir for (any Population)	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Randomised trials not reporting data	17
Molnupiravir for (any Population)	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Articles awaiting assessment	4
Bebtelovimab for (any Population)	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Randomised trials reporting data	1
Bebtelovimab for (any Population)	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Randomised trials not reporting data	0
Bebtelovimab for (any Population)	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Articles awaiting assessment	0
Tixagevimab/cilgavimab for (any Population)		Randomised trials reporting data	2
Tixagevimab/cilgavimab for (any Population)	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Randomised trials not reporting data	4
Tixagevimab/cilgavimab for (any Population)		Articles awaiting assessment	0
Sotrovimab for COVID-19		Randomised trials reporting data	8
Sotrovimab for COVID-19	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Randomised trials not reporting data	9
Sotrovimab for COVID-19		Articles awaiting assessment	4

Classification	Search within these results	Document type	Results
Casirivimab and/or imdevimab for COVID-19	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Randomised trials reporting data	16
Casirivimab and/or imdevimab for COVID-19	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Randomised trials not reporting data	6
Casirivimab and/or imdevimab for COVID-19		Articles awaiting assessment	7
Regdanvimab for COVID-19		Randomised trials reporting data	4
Regdanvimab for COVID-19		Randomised trials not reporting data	6
Regdanvimab for COVID-19		Articles awaiting assessment	0
Nirmatrelvir for COVID-19		Randomised trials reporting data	5
Nirmatrelvir for COVID-19		Randomised trials not reporting data	8
Nirmatrelvir for COVID-19		Articles awaiting assessment	4
Nitazoxanide for COVID-19		Randomised trials reporting data	10
Nitazoxanide for COVID-19	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Randomised trials not reporting data	15
Nitazoxanide for COVID-19		Articles awaiting assessment	2
Remdesivir for COVID-19	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Randomised trials reporting data	15
Remdesivir for COVID-19	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Randomised trials not reporting data	14
Remdesivir for COVID-19	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Articles awaiting assessment	10
Fluvoxamine for COVID-19		Randomised trials reporting data	6

Classification	Search within these results	Document type	Results
Fluvoxamine for COVID-19	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Randomised trials not reporting data	10
Fluvoxamine for COVID-19		Articles awaiting assessment	2
Azithromycin for COVID-19	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Randomised trials reporting data	16
Azithromycin for COVID-19	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Randomised trials not reporting data	30
Azithromycin for COVID-19	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Articles awaiting assessment	6
Corticosteroids for COVID-19	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Randomised trials reporting data	43
Corticosteroids for COVID-19	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Randomised trials not reporting data	70
Corticosteroids for COVID-19	mild OR moderate OR early OR outpatient* OR out-patient* OR non-hospital* OR nonhospital*	Articles awaiting assessment	30
		Total	923

Supplement Table 3: List of Eligible Preprints

Author, Year	Title Trial name	Registration number
Antiviral drugs		
Lopinavir/Ritonavir		
Lowe, 2022(74)	Favipiravir, lopinavir-ritonavir or combination therapy (FLARE): a randomised, double blind, 2x2 factorial placebo-controlled trial of early antiviral therapy in COVID-19 FLARE	NCT04499677
Monoclonal antibodies		
Bebtelovimab		
Dougan, 2022 (75)	Bebtelovimab, alone or together with bamlanivimab and etesevimab, as a broadly neutralizing monoclonal antibody treatment for mild to moderate, ambulatory COVID-19 NR	NCT04634409
Chloroquine/Hydroxychloroquine		
Amaravadi, 2021(76)	Hydroxychloroquine for SARS-CoV-2 positive patients quarantined at home: The first interim analysis of a remotely conducted randomized clinical trial NR	NCT04329923
Ivermectin		
Biber, 2021(77)	Favorable outcome on viral load and culture viability using Ivermectin in early treatment of non-hospitalized patients with mild COVID-19 – A double-blind, randomized placebo-controlled trial NR	NCT044297411
Mohan, 2021(78)	Ivermectin in mild and moderate COVID-19 (RIVET-COV): a randomized, placebo-controlled trial RIVET-COV	CTRI/2020/06/026001
Nitazoxanide		
Silva, 2021(79)	Efficacy of Nitazoxanide in reducing the viral load in COVID-19 patients. Randomized, placebo-controlled, single-blinded, parallel group, pilot study NR	NCT04463264
Other drugs		
Corticosteroids		
Clemency, 2021(80)	A randomized controlled trial of inhaled ciclesonide for outpatient treatment of symptomatic COVID-19 infections NR	NCT04377711

Author, Year	Title Trial name	Registration number
Antiviral drugs		
Lopinavir/Ritonavir		
Lowe, 2022(74)	Favipiravir, lopinavir-ritonavir or combination therapy (FLARE): a randomised, double blind, 2x2 factorial placebo-controlled trial of early antiviral therapy in COVID-19 FLARE	NCT04499677
Monoclonal antibodies		
Bebtelovimab		
Dougan, 2022(75)	Bebtelovimab, alone or together with bamlanivimab and etesevimab, as a broadly neutralizing monoclonal antibody treatment for mild to moderate, ambulatory COVID-19 NR	NCT04634409
Chloroquine/Hydroxychloroquine		
Amaravadi, 2021(76)	Hydroxychloroquine for SARS-CoV-2 positive patients quarantined at home: The first interim analysis of a remotely conducted randomized clinical trial NR	NCT04329923
Ivermectin		
Biber, 2021(77)	Favorable outcome on viral load and culture viability using Ivermectin in early treatment of non-hospitalized patients with mild COVID-19 – A double-blind, randomized placebo-controlled trial NR	NCT044297411
Mohan, 2021(78)	Ivermectin in mild and moderate COVID-19 (RIVET-COV): a randomized, placebo-controlled trial RIVET-COV	CTRI/2020/06/026001
Nitazoxanide		
Silva, 2021(79)	Efficacy of Nitazoxanide in reducing the viral load in COVID-19 patients. Randomized, placebo-controlled, single-blinded, parallel group, pilot study NR	NCT04463264
Other drugs		
Corticosteroids		
Clemency, 2021(80)	A randomized controlled trial of inhaled ciclesonide for outpatient treatment of symptomatic COVID-19 infections NR	NCT04377711

Supplement Table 4: List of Ongoing Studies

Title Registration Number Trial Name	Study Completion Date[a]
Antiviral drugs	
Lopinavir/Ritonavir	
Adaptive Randomized trial for therapy of COrona virus disease 2019 at home with oral antivirals EudraCT 2020-001528-32	NR
Trial of Early Therapies During Non-hospitalized Outpatient Window for COVID-19 NCT04372628	June 1, 2022
A randomized, open-label study to evaluate the efficacy and safety of Lopinavir-Ritonavir in patients with mild novel coronavirus pneumonia (COVID-19) ChiCTR2000029539	February 2, 2021
Molnupiravir	
Efficacy and Safety of Molnupiravir (MK-4482) in Non-Hospitalized Adult Participants With COVID-19 (MK-4482-002) NCT04575597	May 5, 2022
Nirmatrelvir/Ritonavir	
An interventional efficacy and safety, phase 2/3, double-blind, 2 arm study to investigate orally administered pf 07321332/ritonavir compared with placebo in nonhospitalized symptomatic adult participants with covid-19 who are at low risk of progressing to severe illness NCT05011513	November 30, 2022
Remdesivir	
A Phase 1b/2a Study in Participants With Early Stage COVID-19 to Evaluate the Safety, Efficacy, and Pharmacokinetics of Remdesivir Administered by Inhalation NCT04539262	March 22, 2021
WHO Public Health Emergency "Solidarity" Clinical Trial for COVID-19 Treatments NCT04647669	December 31, 2021
Monoclonal antibodies	
Casirivimab/Imdevimab	
Adaptive Platform Treatment Trial for Outpatients With COVID-19 (Adapt Out COVID) NCT04518410	June 22, 2023
A Phase 2 Study to Assess the Virologic Efficacy of REGN10933+REGN10987 Across Different Dose Regimens in Outpatients With SARS-CoV-2 Infection NCT04666441	September 21, 2021
Adaptive, randomized, placebo-controlled trial to evaluate the efficacy of monoclonal antibodies in outpatients with mild or moderate COVID-19 EudraCT 2021-002612-31	NR
Tixagevimab/cilgavimab	
A Phase III Randomized, Double-blind, Placebo-controlled, Multicenter Study to Determine the Safety and Efficacy of AZD7442 for the Treatment of COVID-19 in Non-hospitalized Adults NCT04723394	October 21, 2022

Title Registration Number Trial Name	Study Completion Date[a]
Antibiotic or antiparasitic drugs	
Azithromycin	
Chloroquine/hydroxychloroquine	
Preventing SARS-CoV-2 virus infection and severity of COVID-19 diseases during pregnancy with hydroxychloroquine EudraCT 2020-001587-29	NR
Pilot trial on early treatment with hydroxychloroquine in patients with COVID-19 who do not have hospital admission at diagnosis. EudraCT 2020-002449-41	NR
Effectiveness of Hydroxychloroquine in Covid-19 Patients: A Single Centred Single-blind RCT Study NCT04328272	June 28, 2020
Hydroxychloroquine for Outpatients With Confirmed COVID-19 NCT04342169	November 3, 2021
Pragmatic, Double-blind, Placebo-controlled Randomized Clinical Trial, Evaluating Hydroxychloroquine for Prevention of Hospitalization and Respiratory Complications in Non-hospitalized Patients With Confirmed or Probable COVID-19 NCT04466540	September 28, 2021
Double-blind, Randomized, Prospective, Parallel Study to Demonstrate the Efficacy and Safety of Outpatient Treatment of the Fixed Combination of Hydroxychloroquine With Azithromycin Versus Hydroxychloroquine Treatment and Placebo Treatment in Patients Diagnosed With Mild COVID-19 Infection NCT04964583	August 2021
Efficacy and Safety of the Use of Hydroxychloroquine, Favipiravir or Hydroxychloroquine + Favipiravir in Early SARS-CoV-2 (COVID-19) Treatment NCT04981379	February 16, 2021
Adaptive Randomized trial for therapy of Corona virus disease 2019 at home with oral antivirals EudraCT 2020-001528-32	NR
Ivermectin	
ACTIV-6: COVID-19 Outpatient Randomized Trial to Evaluate Efficacy of Repurposed Medications NCT04885530	March 2023
Prevention and Treatment for COVID -19 Associated Severe Pneumonia in The Gambia: a Single-Blinded Randomised Clinical Trial NCT04703608	July 2022
Ivermectin and Doxycycline in Combination or Ivermectin Alone for the Treatment of Adult Bangladeshi Patients Hospitalized for COVID-19: a Randomised, Double-blind, Placebo-controlled Trial. NCT04407130	November 20, 2020
Multicenter, Double-blind, Randomized, Placebo-controlled Study to Assess the Efficacy, Safety and Tolerability of Ivermectin in Mild Virus-positive Subjects (SARS-CoV)-2 With or Without Symptoms NCT04407507	January 29, 2021

Title Registration Number Trial Name	Study Completion Date[a]
A Randomized Double-blinded Placebo-controlled Outpatient Clinical Trial in High Risk Population Confirmed COVID-19 Patients Using Ivermectin and Doxycycline to Prevent COVID-19 Illness-related Hospitalization NCT04729140	March 28, 2022
Efficacy of Ivermectin in Outpatients With Non-severe COVID-19: A Randomized Controlled Trial NCT04834115	May 30, 2021
Randomized, Double-blind, Placebo-controlled Clinical Trial to Study the Efficacy and Therapeutic Safety of Ivermectin Versus Placebo Associated With Standard of Care Treatment in the Early Phase of Coronavirus Infection (COVID19) NCT04836299	December 5, 2021
Safety and Efficacy and of Ivermectin for the Prevention of Severe Disease in Patients With COVID-19: A Randomized, Controlled, Double-Blind Clinical Study. NCT04886362	December 2021
Randomized phase iia clinical trial to compare the efficacy of ivermectin versus placebo to obtain negative pcr results in patients with early phase COVID-19 EC INS No PER-034-20	NR
A Placebo-controlled, Randomized, Double-blind Study in COvid-19 Patients With iveRmectin; An inVEstigator iniTiaTEd Trial NCT04703205	May 31, 2022
A randomized double-blind placebo-controlled trial of oral ivermectin for outpatient treatment of those at high risk for hospitalization due to COVID-19 ACTRN12620000982910	NR
Ivermectin Treatment Efficacy in Covid-19 High Risk Patients (I-TECH Study): A Multicenter Open-label Randomized Controlled Trial NCT04920942	October 31, 2021
A randomized control trial to assess the efficacy and safety of ivermectin in the treatment of mild to moderate COVID 19 patients SLCTR/2021/020 and EC-21-EM02 and U1111-1266-8924	NR
Randomized Phase IIA Clinical Trial to Evaluate the Efficacy of Ivermectin to Obtain Negative PCR Results in Patients With Early Phase COVID-19 NCT04635943	April 30, 2021
Evaluation of the effect of Ivermectin in treatment of outpatients with COVID-19 IRCT20111224008507N4	NR
Effectiveness of Ivermectin on Outpatient Treatment of Covid-19 Patients IRCT20210213050344N1	NR
A randomized, double-blind, placebo-controlled study to assess the safety and efficacy of ivermectin in asymptomatic and mild severity COVID-19 patients EudraCT 2021-000166-15	NR

Title Registration Number Trial Name	Study Completion Date[a]
Ivermectin vs. Placebo for the Treatment of Patients With Mild to Moderate COVID-19 to Prevent Progression to Severe Infection and to Decrease Viral Shedding - A Double Blind , Randomized Controlled Trial NCT04429711	October 31, 2020
Evaluation of the Impact of the Administration of Single Dose of Ivermectin in the Early Phase of COVID-19 on the Time to Negativation of the SARS-COV-2 Viral Load Determinated by RT-PCR NCT05040724	June 2022
A Phase III Confirmatory Study of K-237-Multi-regional, Multi-center, Placebo Controlled, Randomized, Double Blind, Parallel Group Controlled Trial in Patients With Mild COVID-19 NCT05056883	September 30, 2022
A multicentre, phase III, double-blind, randomised, parallel, placebo-controlled trial to assess efficacy and safety of early administration of Ivermectin during 3 consecutive days to prevent SARS CoV-2 (COVID-19) hospitalisation in adults older than 50 years of age EudraCT 2020-005015-40	NR
A Phase 2 Double-blind Randomized Placebo-controlled Trial to Assess the Efficacy of Ivermectin in Combination With Favipiravir in Mild-to-moderate COVID-19 Adult Patients NCT05155527	June 2022
In vivo use of ivermectin (IVR) for treatment for corona virus infected patients: a randomized controlled trial ChiCTR2000033627	NR
Pragmatic study "CORIVER": Ivermectin as antiviral treatment for patients infected by SARS-COV2 (COVID-19) EudraCT 2020-001971-33	NR
Multicenter, randomized, double-blind, placebo-controlled study investigating efficacy, safety and tolerability of ivermectin HUVE-19 in patients with proven SARS-CoV-2 infection (COVID-19) and man. EudraCT 2020-002091-12	NR
Nitazoxanide	
The C3 Nitazoxanide for Mild to Moderate COVID-19 in HIV-infected and HIV-uninfected Adults With Enhanced Risk: a Double-blind, Randomised, Placebo-controlled Trial in a Resource-poor Setting NCT04523090	February 2022
Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate Efficacy and Safety of Nitazoxanide for Treatment of Mild or Moderate COVID-19 in Subjects at High Risk of Severe Illness NCT05157243	May 2022
Prospective, Randomized, Double-blind, Parallel, Placebo Controlled Study to Evaluate the Safety and Efficacy of Nitazoxanide 600 mg Three Times a Day to Treat Ambulatory Adult Subjects Diagnosed With COVID-19 With Mild Symptoms Assisted in the Public Health System of the City of Mesquita -RJ NCT04441398	September 2020
Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate Efficacy and Safety of Nitazoxanide in the Treatment of Mild COVID-19 in Subjects Not at High Risk of Severe Illness NCT05157269	April 2022
Convalescent plasma	

Title Registration Number Trial Name	Study Completion Date[a]
Reconvalescent Plasma / Camostat Mesylate Early in Sars-CoV-2 Q-PCR (COVID-19) Positive High-risk Individuals NCT04681430	October 29, 2021
Phase I/II Clinical Trial for Dose Escalation and Safety Assessment and Clinical Response of Anti-SARS-CoV-2 Serum Produced by Instituto Butantan NCT04834089	May 2022
Other drugs	
Corticosteroids	
ACTIV-6: COVID-19 Outpatient Randomized Trial to Evaluate Efficacy of Repurposed Medications NCT04885530	March 2023
Fluvoxamine	
Fluvoxamine for Early Treatment of Covid-19: a Fully-remote, Randomized Placebo Controlled Trial NCT04668950	September 28, 2021
ACTIV-6: COVID-19 Outpatient Randomized Trial to Evaluate Efficacy of Repurposed Medications NCT04885530	March 2023

[a] *As reported by the authors*

Abbreviations: COVID 19= Coronavirus Infection; NCT=; NR= not reported; RT- PCR= Reverse transcription polymerase chain reaction; RCT= randomized controlled trial; SARS CoV2= severe acute respiratory syndrome coronavirus type 2.

Supplement Table 5: Excluded Studies

Ineligible Study Design (n=1)

1. Pere M-M, Arvind G, Andrea A, et al. Convalescent plasma for outpatients with early COVID-19. medRxiv. 2021.

Ineligible Publication Type (n=112)

1. Abayomi A, Osibogun A, Ezechi O, Wright K, Ola B, Ojo O, et al. A multi-centre, randomized, double-blind, placebo-controlled clinical trial of the efficacy and safety of chloroquine phosphate, hydroxychloroquine sulphate and lopinavir/ritonavir for the treatment of COVID-19 in Lagos State: study protocol for a randomized controlled trial. Trials. 2021;22(1):869. doi: 10.1186/s13063-021-05675-x.
2. Asan Medical Center. Fluvoxamine for Adults With Mild to Moderate COVID-19: ClinicalTrials.gov; 2021 [03/30/2022]. Available from: https://clinicaltrials.gov/ct2/show/NCT04711863.
3. Ashraf S, Ashraf S, Farooq I, Ashraf S, Ashraf M, Imran MA, et al. Anti-COVID property of subcutaneous ivermectin in synergy with zinc among midlife moderately symptomatic patients: a structured summary of a study protocol for a randomised controlled trial. Trials. 2021;22(1):591. Epub 20210906. doi: 10.1186/s13063-021-05487-z. PubMed PMID: 34488858; PubMed Central PMCID: PMC8419386.
4. AstraZeneca. Phase III Study of AZD7442 for Treatment of COVID-19 in Outpatient Adults (TACKLE): ClinicalTrials.gov; 2021 [03/17/2022]. Available from: https://clinicaltrials.gov/ct2/show/NCT04723394.
5. Australia NT. A randomized double-blind placebo-controlled trial of oral ivermectin for outpatient treatment of those at high risk for hospitalization due to COVID-19: ANZCTR; 2020 [03/16/2022]. Available from: https://anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12620000982910.
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11. Bulgarian Drug Agency. Multicenter, randomized, double-blind, placebo-controlled study investigating efficacy, safety and tolerability of ivermectin HUVE-19 in patients with proven SARS-CoV-2 infection (COVID-19) and manifested clinical symptoms: EU Clinical Trials Register

(EU CTR); 2020 [03/15/2022]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-002091-12/BG.
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Supplement Table 6: Study Characteristics of Included Studies

Author, Year, Trial Name, Trial Registry No. Funding Risk of bias	Design, Country, Duration (days) Dominant variant at time of study (%)*	Eligibility criteria	N total (randomized), Interventions, N group	Population	Baseline characteristics	Recovery, symptom duration, all-cause mortality, COVID-19 specific mortality, Hospitalization due to COVID-19 (n/N (%))	Incidence of any adverse events, incidence of serious adverse events (n/N (%))
Antiviral drugs							
Lopinavir/Ritonavir							
Reis et al. 2021 (30) TOGETHER NCT04403100 Academic Foundation/non-profit professional organization Some concerns	RCT (double-blinded), Brazil 90 P.1 variant (gamma): NR	COVID-19 vaccine received: NR Previous SARS-CoV-2 infection: NR Presence and/or duration of symptoms: less than 8 days since onset of flulike symptoms Disease severity: mild Pregnant women: Not eligible	N=471 G1: 244 Lopinavir 1600 mg/Ritonavir 400 at day 1, Lopinavir 800 mg/Ritonavir 200 mg after G2: 227 Placebo	Age, years, mean (SD): median (range) G1: 54 (18-94) G2: 53 (18-80) female (%): G1: 55 G2: 53 Ethnicity (%): Non-white: G1: 97 G2: 96 Diagnostic tool: RT-PCR	Proportion of symptomatic participants (%): G1: 100 G2: 100 Duration of symptoms: NR Proportion of participants with previous infections: NR Time (days) since previous infection: NR Proportion of vaccinated participants: NR Disease severity (%): Mild: G1: 100 G2: 100 Currently pregnant (%): NA	Recovery[†] NR Symptom duration (time until symptom free): NR All-cause mortality: At 90 days: G1: 2/244 (1) G2: 1/227 (0.4) p=NR COVID-19 specific mortality: NR Hospitalization due to COVID: At 90 days G1: 14/244 (6) G2: 11/227 (5) HR (95%CI) 1.16 (0.53-2.56)	Any AE: At 90 days G1: 92/232 (40) G2: 46/220 (21) p=NR Serious AE: At 90 days G1: 20/232 (9) G2: 12/220 (6) p=NR
Molnupiravir							

Author, Year, Trial Name, Trial Registry No. Funding Risk of bias	Design, Country, Duration (days) Dominant variant at time of study (%)*	Eligibility criteria	N total (randomized), Interventions, N group	Population	Baseline characteristics	Recovery, symptom duration, all-cause mortality, COVID-19 specific mortality, Hospitalization due to COVID-19 (n/N (%))	Incidence of any adverse events, incidence of serious adverse events (n/N (%))
Jayk Bernal et al. 2022 (33) MOVe-OUT NCT04575597 Industry Low	RCT (double-blinded), US, Argentina, Brazil, Canada, Chile, Colombia, Egypt, France, Germany, Guatemala, Italy, Japan, Mexico, Philippines, Russia, South Africa, Spain, Taiwan, Ukraine, UK 29 B.1.617.2 variant (delta): 58 B.1.621 variant (mu): 21 P.1 variant (gamma): 11	COVID-19 vaccine received: Not eligible Previous SARS-CoV-2 infection: NR Presence and/or duration of symptoms: at least one sign or symptom of Covid-19 within 5 days before randomization Disease severity: mild or moderate Pregnant women: Not eligible	N=1,433 G1: 716 Molnupiravir 800mg G2: 717 Placebo	Age, years, median (range): G1: 42.0 (18–90) G2: 44.0 (18–88) female (%): G1: 54 G2: 49 Ethnicity (%): Non-white: G1: 44 G2: 43 Diagnostic tool: RT-PCR	Proportion of symptomatic participants (%): G1: 100 G2: 100 Duration of symptoms (Time from onset of Covid-19 signs or symptoms to randomization of ≤3 days – no. (%): G1: 48 G2: 48 Proportion of participants with previous infections (%): NR Time (days) since previous infection: NR Proportion of vaccinated participants: NA Disease severity (%): Mild Overall: 55 G1: 55 G2: 54 Moderate Overall: 45 G1: 44 G2: 45 Severe or unknown Overall: 1 G1: 1 G2: 1 Currently pregnant (%):	Recovery[†]: At 29 days: G1: 312/645 (48) G2: 314/650 (48) OR 1.04 (95% CI 0.84 to 1.29) Symptom duration (time until symptom free): NR All-cause mortality: At 29 days: G1: 1/709 (0.1) G2: 9/699 (1) p=NR COVID-19 specific mortality: At 29 days: G1: 1/709 (0.1) G2: 9/699 (1) p=NR Hospitalization due to COVID: At 29 days: G1: 44/709 (6) G2: 55/699 (8) p=NR	Any AE: At 29 days: G1: 216/710 (30) G2: 231/701 (33) difference (95% CI)−2.5% (−7.4 to 2.3) Serious AE: At 29 days: G1: 49/710 (7) G2: 67/701 (10) difference (95% CI) −2.7% (−5.6 to 0.2)

Author, Year, Trial Name, Trial Registry No. Funding Risk of bias	Design, Country, Duration (days) Dominant variant at time of study (%)*	Eligibility criteria	N total (randomized), Interventions, N group	Population	Baseline characteristics	Recovery, symptom duration, all-cause mortality, COVID-19 specific mortality, Hospitalization due to COVID-19 (n/N (%))	Incidence of any adverse events, incidence of serious adverse events (n/N (%))
					NA		
Fischer et al. 2022 (31) NA NCT04405570 Industry Low	RCT (double-blinded), U.S., 28 B.1.1.7 (alpha): NR B.1.617.2 (delta): NR	COVID-19 vaccine received: Not eligible Previous SARS-CoV-2 infection: NR Presence and/or duration of symptoms: at least one SARS-CoV-2 infection symptom within 7 days before study begin Disease severity: NR Pregnant women: Not eligible	N=204 G1: 23 Molnupiravir 200mg G2: 62 Molnupiravir 400mg G3: 55 Molnupiravir 800mg G4: 62 Placebo	Age, years median (range): G1: 32.0 (19-65) G2: 42.5 (19-82) G3: 42.0 (18-68) G4: 39.0 (19-71) female (%): G1: 48 G2: 52 G3: 49 G4: 55 Ethnicity (%): Non-white: G1: 26 G2: 10 G3: 11 G4: 13 Diagnostic tool: RT-PCR	Proportion of symptomatic participants (%): G1: 100 G2:100 G3: 100 G4: 100 Duration of symptoms: At baseline (median (range): G1: 4.00 (1.8–7.0) G2: 4.85 (2.5–7.1) G3: 4.60 (1.4–7.1) G4: 4.55 (1.8–7.5) Proportion of participants with previous infections (%): NR Time (days) since previous infection: NR Proportion of vaccinated participants: NA Disease severity (%): NR Currently pregnant (%): NA	Recovery[†]: NR Symptom duration (time until symptom free): Median (95% CI) G1: 9.0 days (6.0 to 13.0) G2: 5.5 days (4.0 to 8.0) G3: 8.0 days (6.0 to 12.0) G4: 8.5 days (7.0 to 11.0) p=NR All-cause mortality: NR COVID-19 specific mortality: NR Hospitalization due to COVID: NR	Any AE: At 28 days: G1: 11/23 (48) G2: 20/62 (32) G3: 11/55 (20) G4: 18/62 (29) p=NR Serious AE: At 28 days: G1: 0/23 (0) G2: 2/62 (3) G3: 1/55 (2) G4: 1/62 (2) p=NR
Nirmatrelvir/Ritonavir							

Author, Year, Trial Name, Trial Registry No. Funding Risk of bias	Design, Country, Duration (days) Dominant variant at time of study (%)*	Eligibility criteria	N total (randomized), Interventions, N group	Population	Baseline characteristics	Recovery, symptom duration, all-cause mortality, COVID-19 specific mortality, Hospitalization due to COVID-19 (n/N (%))	Incidence of any adverse events, incidence of serious adverse events (n/N (%))
Hammond et al. 2022 (35) NA NCT04960202 Industry Some concerns	RCT (double-blinded), US, Bulgaria, South Africa, Brazil, India, Mexico, Ukraine, Turkey, Japan , Spain, Russia, Argentina, Colombia, Poland, South Korea, Hungary, Taiwan, Malaysia, Czech Republic, Thailand, Puerto Rico 28 B.1.1.7 (alpha): NR B.1.617.2 (delta): NR	COVID-19 vaccine received: Not eligible Previous SARS-CoV-2 infection: not eligible Presence and/or duration of symptoms: at least one sign or symptom of Covid-19 on the day of randomization; symptom onset no more than 5 days before randomization Disease severity: NR Pregnant women: Not eligible	N=2,246 G1: 1,120 Nirmatrelvir 600mg/ritonavir 200mg G2: 1126 Placebo	Age, years, mean (SD): Median (range) G1: 45.0 (18.0–86.0) G2: 46.5 (18.0–88.0) female (%): G1: 50 G2: 48 Ethnicity (%): Non-white: G1: 29 G2: 28 Diagnostic tool: RT-PCR	Proportion of symptomatic participants (%): G1: 100 G2: 100 Duration of symptoms: G1: 3 (1) G2: 3 (1) Proportion of participants with previous infections: NA Time (days) since previous infection: NA Proportion of vaccinated participants: NA Disease severity (%): NR Currently pregnant (%): NA	Recovery[†]: NR Symptom duration (time until symptom free): NR All-cause mortality: At 28 days: G1: 0/1039 (0) G2: 12/1046 (1) p=NR COVID-19 specific mortality: NR Hospitalization due to COVID: At 28 days: G1: 8/1039 (1) G2: 65/1046 (6) Difference (SE) −5.62% (0.81) (95% CI −7.21 to −4.03)	Any AE: At 34 days: G1: 251/1109 (23) G2: 266/1115 (24) p=NR Serious AE: At 34 days: G1: 18/1109 (2) G2: 74/1115 (7) p=NR
Remdesivir							

Author, Year, Trial Name, Trial Registry No. Funding Risk of bias	Design, Country, Duration (days) Dominant variant at time of study (%)*	Eligibility criteria	N total (randomized), Interventions, N group	Population	Baseline characteristics	Recovery, symptom duration, all-cause mortality, COVID-19 specific mortality, Hospitalization due to COVID-19 (n/N (%))	Incidence of any adverse events, incidence of serious adverse events (n/N (%))
Gottlieb et al. 2021 (44) NCT04501952; EudraCT number, 2020-003510-12 Industry Some concerns	RCT (double-blinded), US, Denmark, Spain, UK 28 B B.1.1.7 (alpha): NR B.1.617.2 (delta): NR	COVID-19 vaccine received: Not eligible Previous SARS-CoV-2 infection: not eligible if required prior hospitalization for COVID-19 or treatment Presence and/or duration of symptoms: at least one ongoing symptom consistent with Covid-19, with onset of the first symptom within 7 days before randomization Disease severity: NR Pregnant women: Not eligible	N=584 G1: 292 Remdesivir 200 mg on day 1, 100 mg on days 2 and 3 G2: 292 Placebo	Age, years, mean (SD): G1: 50 (15) G2: 51 (15) female (%): G1: 47 G2: 49 Ethnicity (%): Non-white: G1: 21 G2: 18 Diagnostic tool: RT-PCR	Proportion of symptomatic participants (%): G1: 100 G2: 100 Duration of symptoms: Median time (IQR) - days G1: 5 (3–6) G2: 5 (4–6) Proportion of participants with previous infections: NR Time (days) since previous infection: NR Proportion of vaccinated participants: NA Disease severity (%): NR Currently pregnant (%): NA	Recovery[†]: G1: 61/169 (36) G2: 33/165 (20) Rate Ratio 1.92 (95% CI 1.26-2.94) Symptom duration (time until symptom free): NR All-cause mortality: At 28 days: G1: 0/279 (0) G2: 0/283 (0) COVID-19 specific mortality: NR Hospitalization due to any cause: At 28 days: G1: 5/279 (2) G2: 18/283 (6) HR 0.28 (95% CI 0.10-0.75)	Any AE: At 28 days: G1: 118 /279 (42) G2: 131/283 (46) p=NR Serious AE: At 28 days: G1: 5/279 (2) G2: 19/283 (7) p=NR
Monoclonal antibodies							
Casirivimab/Imdevimab							

Author, Year, Trial Name, Trial Registry No. Funding Risk of bias	Design, Country, Duration (days) Dominant variant at time of study (%)*	Eligibility criteria	N total (randomized), Interventions, N group	Population	Baseline characteristics	Recovery, symptom duration, all-cause mortality, COVID-19 specific mortality, Hospitalization due to COVID-19 (n/N (%))	Incidence of any adverse events, incidence of serious adverse events (n/N (%))
Weinreich et al. 2021 (25) Safety, Tolerability, and Efficacy of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies for the Treatment of Ambulatory Adult and Pediatric Patients With COVID-19 NCT04425629 Government Industry Some concerns	RCT (double-blinded), US, Mexico 29 B.1.1.7 (alpha): NR B.1.617.2 (delta): NR	COVID-19 vaccine received: Not eligible Previous SARS-CoV-2 infection: NR Presence and/or duration of symptoms: the onset of any Covid-19 symptom, occurring no more than 7 days before randomization, Disease severity: NR Pregnant women: Not eligible	N=5,607 (1040 excluded after randomization; safety population n=5,531) G1: 1,529 Casirivimab/imdevimab 2400 mg G2: 838 Casirivimab/imdevimab 1200 mg G3: 700 Casirivimab/imdevimab 8000 mg G4: 840 Placebo G5: 1,500 Placebo**	Age, years: At least 1 risk factor: Median (IQR) G1: 50.0 (39.0–60.0) G2: 48.5 (37.0–57.5) G3: 51.0 (40.0–59.0) G4: 48.0 (35.0–57.0) G5: 50.0 (37.0–58.0) female (%): G1: 52 G2: 53 G3: 48 G4: 50 G5: 53 Ethnicity (%): Non-white: G1: 14 G2: 19 G3: 15 G4: 18 G5: 15 Diagnostic tool: RT-PCR	Proportion of symptomatic participants (%): G1: 100 G2: 100 G3: 100 G4: 100 G5: 100 Duration of symptoms: Median (IQR) G1: 3.0 (2–5) G2: 3.0 (2–5) G3: 3.0 (2–5) G4: 3.0 (2–4) G5: 3.0 (2–5) Proportion of participants with previous infections (%): NR Time (days) since previous infection: NR Proportion of vaccinated participants (%): NA Disease severity (%): NR Currently pregnant (%): NA	Recovery†: NR Symptom duration (time until symptom free): At 29 days: Median days G1: 10 G2: 10 G3: NR G4: NR G5:14 p< 0.001 All-cause mortality: At 29 days: G1: 1/1355 (<0.1) G2: 1/736 (0.1) G3: 0/625 (0) G4: 1/748 (0.1) G5: 3/1341 (0.2) p=NR COVID-19 specific mortality: NR Hospitalization due to COVID: At 29 days: G1: 17/1355 (1) G2: 6/736 (1) G3: 13/625 (2) G4: 23/748 (3) G5: 59/1341 (4) p=NR	Any AE: At 45 days: G1: 142/1849 (8) G2: 59/827 (7) G3: 85/1012 (8) G4: NR G5: 189/1843 (10) Serious AE: At 45 days: G1: 24/1849 (1) G2: 9/827 (1) G3: 17/1012 (2) G4: NR G5: 74/1843 (4)

Author, Year, Trial Name, Trial Registry No. Funding Risk of bias	Design, Country, Duration (days) Dominant variant at time of study (%)*	Eligibility criteria	N total (randomized), Interventions, N group	Population	Baseline characteristics	Recovery, symptom duration, all-cause mortality, COVID-19 specific mortality, Hospitalization due to COVID-19 (n/N (%))	Incidence of any adverse events, incidence of serious adverse events (n/N (%))
Regdanvimab							
Kim et al. 2021 (42) NR NCT04593641 Government, Industry Some concerns	RCT (double-blinded), Multicountry, Republic of Korea and Romania 14 B.1.1.7 (alpha): NR	COVID-19 vaccine received: no vaccination within 4 weeks Previous SARS-CoV-2 infection: NR Presence and/or duration of symptoms: at least 1 or more symptoms and onset within 7 days before drug administration and oxygen saturation of 94% or more Disease severity: mild Pregnant women: Not eligible	N=18 G1: 5 Regdanvimab (CT-P59) 20mg/kg G2: 5 CT-P59 40mg/kg G3: 5 CT-P59 80mg/kg G4: 3 placebo	Age, years, median (IQR): G1: 59.0 (56–59) G2: 51.0 (48–52) G3: 52.0 (43–57) G4: 50.0 (49–57) female (%): G1: 60 G2: 60 G3: 0 G4: 33 Ethnicity (%): Non-white: G1: 100 G2: 0 G3: 0 G4: 33 Diagnostic tool: RT-PCR	Proportion of symptomatic participants (%): G1: 100 G2: 100 G3: 100 G4: 100 Duration of symptoms: median (IQR) days: G1: 4.0 (3–5) G2: 6.0 (5–6) G3: 4.0 (4–4) G4: 4.0 (4–6) Proportion of participants with previous infections: NR Time (days) since previous infection: NR Proportion of vaccinated participants: NR Disease severity (%): Mild: G1: 100 G2: 100 G3: 100 G4: 100 Currently pregnant (%): NA	Recovery[†]: NR Symptom duration (time until symptom free): G1: 4.4 days G2: 3.2 days G3: 2.5 days G4: 5.3 days p=NR All-cause mortality: NR COVID-19 specific mortality: NR Hospitalization due to COVID: NR	Any AE: At 14 days: G1: 3/5 (60) G2: 4/5 (80) G3: 3/5 (60) G4: 1/3 (33) p=NR Serious AE: At 14 days: G1: 0/5 (0) G2: 0/5 (0) G3: 0/5 (0) G4: 0/3 (0)

Author, Year, Trial Name, Trial Registry No. Funding Risk of bias	Design, Country, Duration (days) Dominant variant at time of study (%)*	Eligibility criteria	N total (randomized), Interventions, N group	Population	Baseline characteristics	Recovery, symptom duration, all-cause mortality, COVID-19 specific mortality, Hospitalization due to COVID-19 (n/N (%))	Incidence of any adverse events, incidence of serious adverse events (n/N (%))
Streinu-Cercel et al. 2021 (34) NCT04602000 and EudraCT 2020-003369-20 Government Industry Low	RCT (double-blinded), Republic of Korea, Romania, Spain, USA 28 B.1.1.7 (alpha): NR	COVID-19 vaccine received: Not eligible Previous SARS-CoV-2 infection: NR Presence and/or duration of symptoms: at least one infection-associated symptom within 7 and 2 days and an oxygen saturation of more than 94% Disease severity: mild to moderate Pregnant women: Not eligible	N=327 G1: 105 Regdanvimab 40 mg/kg G2: 111 Regdanvimab 80 mg/kg G3: 111 Placebo	Age, years, median (range): G1: 51.0 (42-60) G2: 51.0 (40-60) G3: 52.0 (41-60) female (%): G1: 44 G2: 47 G3: 57 Ethnicity (%): Non-White: G1: 10 G2: 13 G3: 13 Diagnostic tool: RT-PCR or antigen	Proportion of symptomatic participants (%): G1: 100 G2: 100 G3: 100 Duration of symptoms: Median (range) G1: 3.0 (2-4) G2: 3.0 (2-4) G3: 3.0 (2-4) Proportion of participants with previous infections (%): NR Time (days) since previous infection: NR Proportion of vaccinated participants: NA Disease severity (%): Moderate: G1: 61 G2: 59 G3: 54 Currently pregnant (%): NA	Recovery†: At 28 days: G1: 82/94 (87) G2: 79/92 (86) G3: 71/99 (72) RR 1.21 (95% CI 1.05 to 1.38) Symptom duration (time until symptom free): Median days (95%CI) G1: 6.9 (5.5–9.4) G2: 7.3 (5.7–9.3) G3: 8.8 (7.0–11.8) p=NR All-cause mortality: At 28 days: G1: 0/105 (0) G2: 0/110 (0) G3: 0/110 (0) COVID-19 specific mortality: NR Hospitalization due to COVID: At 28 Days: G1: 4/100 (4) G2: 5/103 (5) G3: 9/104 (9) p=NR	Any AE: At 28 Days: G1: 31/105 (30) G2: 27/110 (25) G3: 34/110 (31) p=NR Serious AE: At 28 days: G1: 0/105 (0) G2: 0/110 (0) G3: 0/110 (0)
Sotrovimab							

Author, Year, Trial Name, Trial Registry No. Funding Risk of bias	Design, Country, Duration (days) Dominant variant at time of study (%)*	Eligibility criteria	N total (randomized), Interventions, N group	Population	Baseline characteristics	Recovery, symptom duration, all-cause mortality, COVID-19 specific mortality, Hospitalization due to COVID-19 (n/N (%))	Incidence of any adverse events, incidence of serious adverse events (n/N (%))
Gupta et al. 2022 (38) COMET-ICE NCT04545060 Industry Low	RCT (double-blinded), USA, Canada, Brazil, Spain 29 B.1.1.7 (alpha): NR B.1.617.2 (delta): NR P.1 (gamma): NR	COVID-19 vaccine received: NR Previous SARS-CoV-2 infection: NR Presence and/or duration of symptoms: symptoms in the last five days before randomization Disease severity: mild to moderate Pregnant women: Not eligible	N=1057 G1=528 Sotrovimab 500 mg G2=529 Placebo	Age, years, median IQR: Overall: NR G1: 53 (41.5-62) G2: 53 (43-63) female (%): G1: 57 G2: 52 Ethnicity (%): Non-white: G1: 13 G2: 12 Diagnostic tool: RT-PCR or antigen	Proportion of symptomatic participants (%): G1: 100 G2: 100 Duration of symptoms (%): G1: ≤3 days- 59 4-5 days- 40 5 days- <1 G2: ≤3 days- 59 4-5 days- 41 5 days- 0 Proportion of participants with previous infections: NR Time (days) since previous infection: NR Proportion of vaccinated participants: NR Disease severity (%): NR Currently pregnant (%): NA	Recovery†: NR Symptom duration (time until symptom free): NR All-cause mortality: At 29 days: G1: 0/528 (0) G2: 2/529 (0.4) p=NR COVID-19 specific mortality: NR Hospitalization due to COVID: At 29 days: G1: 6/528 (1) G2: 30/529 (6) p=NR	Any AE: At day 29 G1: 114/523 (22) G2: 123/526 (23) p=NR Serious AE: At day 29 G1: 11/523 (2) G2: 32/526 (6) p=NR
Antibiotic or antiparasitic drugs							
Azithromycin							
Oldenburg et al. 2021 (41) ACTION: The Azithromycin for	RCT (double-blinded), U.S.	COVID-19 vaccine received: NR Previous SARS-	N=263 G1: 171 Azithromycin 1.2g oral	Age, years, mean (SD): median (IQR) G1: 42 (35-49) G2: 44 (35-51)	Proportion of symptomatic participants (%): G1: 93 G2: 93	Recovery† At 14 days: G1: 66/131 (50) G2: 35/70 (50) Prevalence ratio 1.01 (95%	Any AE: At 3 days: G1: 82/145 (57) G2: 19/72 (26) p=NR

Author, Year, Trial Name, Trial Registry No. Funding Risk of bias	Design, Country, Duration (days) Dominant variant at time of study (%)*	Eligibility criteria	N total (randomized), Interventions, N group	Population	Baseline characteristics	Recovery, symptom duration, all-cause mortality, COVID-19 specific mortality, Hospitalization due to COVID-19 (n/N (%))	Incidence of any adverse events, incidence of serious adverse events (n/N (%))
COVID-19 Trial, Investigating Outpatients Nationwide Study NCT04332107 Industry Foundation/non-profit professional organization Some concerns	21 B.1.1.7 (alpha): NR B.1.617.2 (delta): NR	CoV-2 infection: NR Presence and/or duration of symptoms: Participants were not required to be symptomatic Disease severity: NR Pregnant women: Not eligible	G2: 92 placebo	female (%): G1: 69 G2. 62 Ethnicity (%): Non-white: G1: 41 G2: 36 Diagnostic tool: RT-PCR or antigen	Duration of symptoms: median (IQR) G1: 3 (2-4.5) G2: 3 (2-4) Proportion of participants with previous infections: NR Time (days) since previous infection: NR Proportion of vaccinated participants: NR Disease severity (%): NR Currently pregnant (%): NA	CI 0.76 to 1.39) Symptom duration (time until symptom free): NR All-cause mortality: At 21 days: G1: 0/171 (0) G2: 0/92 (0) COVID-19 specific mortality: NR Hospitalization due to COVID: At 21 days: G1: 5/125 (4) G2: 0/72 (0) p=NR	Serious AE: At 21 days: G1: 0/171 (0) G2: 0/92 (0)
Chloroquine/Hydroxychloroquine							
Omrani et al. 2020 (28) Q-PROTECT NCT04349592 Government Some concerns	RCT (double-blinded), Qatar 21 B.1.1.7 (alpha): NR	COVID-19 vaccine received: vaccine not available at study time Previous SARS-CoV-2 infection: NA Presence and/or duration of symptoms: NR	N=456 G1: 152 Hydrochloroquine 600 mg oral /azithromycin 500 mg on day 1, 250 mg from day 2 G2: 152 Hydroxychloroquine 600 mg oral+placebo G3: 152 Placebo	Age, years, mean (SD): G1: median 42 G2: median 40 G3: median 41 female (%): G1: 1 G2: 2 G3: 1 Ethnicity (%): Non-white: NR	Proportion of symptomatic participants (%): NR Duration of symptoms: NR Proportion of participants with previous infections: NA Time (days) since previous infection: NR	Recovery†: NR Symptom duration (time until symptom free): NR All-cause mortality: At 21 days: G1: 0/152(0) G2: 0/152(0) G3: 0/152(0) COVID-19 specific	Any AE: NR Serious AE: At 21 days: G1: 0/152(0) G2: 0/152(0) G3: 0/152(0)

Author, Year, Trial Name, Trial Registry No. Funding Risk of bias	Design, Country, Duration (days) Dominant variant at time of study (%)*	Eligibility criteria	N total (randomized), Interventions, N group	Population	Baseline characteristics	Recovery, symptom duration, all-cause mortality, COVID-19 specific mortality, Hospitalization due to COVID-19 (n/N (%))	Incidence of any adverse events, incidence of serious adverse events (n/N (%))
		Disease severity: mild or no symptoms Pregnant women: Not eligible		Diagnostic tool: RT-PCR	Proportion of vaccinated participants: NA Disease severity (%): NR Currently pregnant (%): NA	mortality: At 21 days: G1: 0/152(0) G2: 0/152(0) G3: 0/152(0) Hospitalization due to COVID: At 21 days: G1: 4/152 (3) G2: 3/152 (2) G3: 4/152 (3) p=1.00	
Reis et al. 2021 (30) TOGETHER NCT04403100 Academic Foundation/non-profit professional organization Some concerns	RCT (double-blinded), Brazil 90 P.1 (gamma): NR B.1.617.2 (delta): NR	COVID-19 vaccine received: NR Previous SARS-CoV-2 infection: NR Presence and/or duration of symptoms: less than 8 days since onset of flulike symptoms Disease severity: mild Pregnant women: Not eligible	N=441 G1: 214 Hydroxychloroquine 800 mg at day 1,400 mg from day 2 G2: 227 Placebo	Age, years, mean (SD): median (range) G1: 53 (18-81) G2: 53 (18-80) female (%): G1: 57 G2: 53 Ethnicity (%): Non-white: G1: 98 G2: 96 Diagnostic tool: RT-PCR	Proportion of symptomatic participants (%): G1: 100 G2: 100 Duration of symptoms: NR Proportion of participants with previous infections: NR Time (days) since previous infection: NR Proportion of vaccinated participants: NR Disease severity (%): Mild G1: 100 G2: 100 Currently pregnant (%):	Recovery[†]: NR Symptom duration (time until symptom free): NR All-cause mortality: At 90 days: G1: 0/214 (0) G2: 1/227 (0.4) COVID-19 specific mortality: NR Hospitalization due to COVID: At 90 days G1: 8/214 (4) G2: 11/227 (5) HR (95%CI) 0.76 (0.30-1.88)	Any AE: At 90 days G1: 46/207 (22) G2: 46/220 (21) Serious AE: At 90 days G1: 11/207 (5) G2: 12/220 (6)

Author, Year, Trial Name, Trial Registry No. Funding Risk of bias	Design, Country, Duration (days) Dominant variant at time of study (%)*	Eligibility criteria	N total (randomized), Interventions, N group	Population	Baseline characteristics	Recovery, symptom duration, all-cause mortality, COVID-19 specific mortality, Hospitalization due to COVID-19 (n/N (%))	Incidence of any adverse events, incidence of serious adverse events (n/N (%))
					NA		
Schwartz et al. 2021 (27) ALBERTA HOPE COVID-19 NCT04329611 Government Industry Academic Some concerns	RCT (double-blinded), Canada 30 B.1.1.7 (alpha): NR B.1.617.2 (delta): NR	COVID-19 vaccine received Vaccination: NR Previous SARS-CoV-2 infection: NR Presence and/or duration of symptoms: symptom onset within previous 12 days Disease severity: NR Pregnant women: Not eligible	N=148 G1: 111 Hydroxychloroquine 800 mg oral on day 1, 400 mg after G2: 37 placebo	Age, years, mean (SD): G1: 46.7 G2: 46.9 female (%): G1: 41 G2: 54 Ethnicity: Non-white (%): G1: 68 G2: 58 Diagnostic tool: RT-PCR	Proportion of symptomatic participants (%): G1: 100 G2: 100 Duration of symptoms: mean (95% CI) G1: 14 (10-20) G2: 12 (7-18) Proportion of participants with previous infections: NR Time (days) since infection: NR Proportion of vaccinated participants: NR Disease severity (%): NR Currently pregnant (%): NA	Recovery[†]: At 30 days: G1: 67/110 (61) G2: 29/37 (78) Symptom duration (time until symptom free): median (95% CI) G1: 14 (10-20) G2: 12 (7-18) p=0.3 All-cause mortality: At 30 days: G1: 0/111 (0) G2: 0/37 (0) COVID-19 specific mortality: At 30 days: G1: 0/111 (0) G2: 0/37 (0) Hospitalization due to COVID: At 30 days: G1: 4/110 (4) G2: 0/37 (0)	Any AE: NR Serious AE: At 30 days: G1: 3/91 (3) G2: 0/33 (0) p=0.6
Ivermectin							

Author, Year, Trial Name, Trial Registry No. Funding Risk of bias	Design, Country, Duration (days) Dominant variant at time of study (%)*	Eligibility criteria	N total (randomized), Interventions, N group	Population	Baseline characteristics	Recovery, symptom duration, all-cause mortality, COVID-19 specific mortality, Hospitalization due to COVID-19 (n/N (%))	Incidence of any adverse events, incidence of serious adverse events (n/N (%))
Buonfrate et al. 2022 (48) COVER Study NCT04438850 Industry Academic Foundation/non-profit professional organization High	RCT (double-blinded), Italy 30 B.1.1.7 (alpha): NR B.1.617.2 (delta): NR B.1.1.529 (omicron): NR	COVID-19 vaccine received: NR Previous SARS-CoV-2 infection: NR Presence and/or duration of symptoms: NR Disease severity: mild to moderate Pregnant women: Not eligible	N=93 G1: 29 Ivermectin 600mg/kg plus placebo G2: 32 Ivermectin 1200 mg/kg G3: 32 placebo	Age, years, median (IQR) G1: 47.0 (31.0-62.0) G2:44.5 (31.0-55.5) G3: 50.0 (26.0-57.0) female (%): G1: 48 G2: 25 G3: 53 Ethnicity (%): Non-white: NR Diagnostic tool: RT-PCR	Proportion of symptomatic participants (%): G1: 83 G2: 91 G3: 84 Duration of symptoms: Median (IQR) G1: 4.0 (3.0-5.0) G2: 4.0 (3.0-6.0) G3: 4.0 (2.0-6.0) Proportion of participants with previous infections: NR Time (days) since previous infection: NR Proportion of vaccinated participants: G1: 3 G2: 0 G3: 3 Disease severity (%): COVID-19 severity score (%) no limitation of activities: G1: 83 G2: 84 G3: 84 limitation of activities: G1: 17 G2: 16 G3: 16 Currently pregnant (%): NA	Recovery†: At 30 days: G1: 19/24 (79) G2: 21/29 (72) G3: 21/27 (78) p=NR Symptom duration (time until symptom free) (median (IQR)): At 30 days: G1: 29.0 (13.5-32) G2: 14.0 (7-37) G3: 14.0 (13-30) All-cause mortality***: At 30 days: G1: 0/24 (0) G2: 0/29 (0) G3: 0/27(0) COVID-19 specific mortality***: At 30 days: G1: 0/24 (0) G2: 0/29 (0) G3: 0/27 (0) Hospitalization due to COVID: At 30 days*** G1: 1/29 (3) G2: 3/30 (10) G3: 0/30 (10) p=NR	Any AE: NR Serious AE: At 30 days***: G1: 1 (4) G2: 3 (10) G3: 0/30 (0) p=NR

Author, Year, Trial Name, Trial Registry No. Funding Risk of bias	Design, Country, Duration (days) Dominant variant at time of study (%)*	Eligibility criteria	N total (randomized), Interventions, N group	Population	Baseline characteristics	Recovery, symptom duration, all-cause mortality, COVID-19 specific mortality, Hospitalization due to COVID-19 (n/N (%))	Incidence of any adverse events, incidence of serious adverse events (n/N (%))
Chaccour et al. 2021 (29) none NCT04390022 Academic Some concerns	RCT (double-blinded), Spain 28 B.1.1.7 (alpha): NR B.1.617.2 (delta): NR	COVID-19 vaccine received: NR Previous SARS-CoV-2 infection: NR Presence and/or duration of symptoms: symptoms for no more than 72 hours before enrolment. Disease severity: mild to moderate Pregnant women: Not eligible	N=24 G1: 12 Ivermectin 400 mcg/kg body weight oral G2: 12 placebo	Age, years, mean (SD): Median (IQR) G1: 26 (19-36) G2: 26 (21-44) female (%): G1: 42 G2: 58 Ethnicity (%): Non-white: NR Diagnostic tool: RT-PCR	Proportion of symptomatic participants (%): G1: 100 G2: 100 Duration of symptoms: median (IQR) hours G1: 24 (24-48) G2: 48 (36-48) Proportion of participants with previous infections: G1: 0 G2: 0 Time (days) since previous infection: NR Proportion of vaccinated participants: NR Disease severity (%): NR Currently pregnant (%): NA	Recovery†: NR Symptom duration (time until symptom free): NR All-cause mortality: At 28 days: G1: 0/12 (0) G2: 0/12 (0) COVID-19 specific mortality: At 28 days G1: 0/12 (0) G2: 0/12 (0) Hospitalization due to COVID: G1: 0/12 (0) G2: 0/12 (0)	Any AE: At 28 days G1: 5/12 (42) G2: 5/12 (42) Serious AE: At 28 days G1: 0/12 (0) G2: 0/12 (0)
López-Medina et al. 2021 (26) (EPIC Trial) (EPIC) NCT04405843 Government Some concerns	RCT (double-blinded), Colombia 21 B.1.621 (mu): NR P.1 (gamma): NR	COVID-19 vaccine received: NR Previous SARS-CoV-2 infection: NR Presence and/or duration of symptoms:	N=476 G1: 238 Ivermectin 300 mcg/kg body weight G2: 238 placebo	Age, years, mean (SD): Median (IQR) G1: 37 (29.0-47.7) G2: 37 (28.7-49.2) female (%): G1: 61 G2: 55 Ethnicity (%): Non-white:	Proportion of symptomatic participants (%): G1: 100 G2: 100 Duration of symptoms: median (IQR) G1: 5 (4-6) G2: 5 (4-6) Proportion of participants with previous	Recovery†: At 21 days: G1: 164/200 (82) G2: 156/198 (79) p=NR Symptom duration (time until symptom free) (median(IQR)): At 21 days: G1: 10 (9-13)	Any AE: NR Serious AE: At 21 days: G1: 2/200 (1) G2: 2/198 (1) p=NR

Author, Year, Trial Name, Trial Registry No. Funding Risk of bias	Design, Country, Duration (days) Dominant variant at time of study (%)*	Eligibility criteria	N total (randomized), Interventions, N group	Population	Baseline characteristics	Recovery, symptom duration, all-cause mortality, COVID-19 specific mortality, Hospitalization due to COVID-19 (n/N (%))	Incidence of any adverse events, incidence of serious adverse events (n/N (%))
		within the last 7 days before randomisation Disease severity: mild Pregnant women: Not eligible		NR Diagnostic tool: RT-PCR or antigen	infections: NR Time (days) since previous infection: NR Proportion of vaccinated participants: NR Disease severity (%): Mild: G1: 100 G2: 100 Currently pregnant (%): NA	G2: 12 (9-13) All-cause mortality: At 21 days: G1: 0/200 (0) G2: 1/198 (1) COVID-19 specific mortality: NR Hospitalization due to COVID: NR	
Reis et al., 2022 (49) TOGETHER NCT04727424 Foundation/non-profit professional organization Some concerns	RCT (double-blinded), Brazil 28 P.1 (gamma): NR B.1.617.2 (delta): NR	COVID-19 vaccine received: Eligible Previous SARS-CoV-2 infection: NR Presence and/or duration of symptoms: less than 7 days Disease severity: NR Pregnant women: Not eligible	N=1,358 G1: 679 Ivermectin 400 mcg/kg body weight oral G2: 679 placebo	Age, years, mean (SD): Median (IQR) G1: 49 (39–57) G2: 49 (37–56) female (%): G1: 56 G2: 60 Ethnicity (%): Non-white: G1: 99 G2: 99 Diagnostic tool: RT-PCR or antigen	Proportion of symptomatic participants (%): G1: 100 G2: 100 Duration of symptoms: 0–3 days: n (%) G1: 302 (44.5) G2: 295 (43.4) 4-7 days: n (%) G1: 377 (55.5) G2: 384 (56.6) Proportion of participants with previous infections: NR Time (days) since previous infection: NR Proportion of vaccinated participants:	Recovery: NR Symptom duration (time until symptom free) (median(IQR)): At 28 days: G1: 14 (11 to 14) G2: 14 (11 to 14) All-cause mortality: At 28 days: G1: 21/679 (3) G2: 24/679 (4) COVID-19 specific mortality: NR Hospitalization due to COVID: At 28 days:	Any AE: At 28 days G1: 123/679 (18) G2:156/679 (23) Serious AE: At 28 days G1: 17/679 (3) G2: 18/679 (3)

Author, Year, Trial Name, Trial Registry No. Funding Risk of bias	Design, Country, Duration (days) Dominant variant at time of study (%)*	Eligibility criteria	N total (randomized), Interventions, N group	Population	Baseline characteristics	Recovery, symptom duration, all-cause mortality, COVID-19 specific mortality, Hospitalization due to COVID-19 (n/N (%))	Incidence of any adverse events, incidence of serious adverse events (n/N (%))
					NR Disease severity (%): NR Currently pregnant (%): NA	G1: 78/679 (12) G2: 93/679 (14)	
Vallejos et al. 2021 (47) IVER-COR COVID19 NCT04529525 Government Academic Low	RCT (double-blinded), Argentina 30 P.1 (gamma): NR C.37 (lambra): NR	COVID-19 vaccine received: NR Previous SARS-CoV-2 infection: NR Presence and/or duration of symptoms: NR Disease severity: mild to moderate Pregnant women: Not eligible	N=501 G1: 250 Ivermectin 24-48 mg G2: 251 Placebo	Age, years, mean (SD): G1: 42.58 (15.29) G2: 42.40 (15.75) female (%): G1: 44 G2: 50 Ethnicity (%): NR Diagnostic tool: RT-PCR	Proportion of symptomatic participants (%): G1: 96 G2: 96 Duration of symptoms: G1: 4 (3-5) G2: 4 (3-6) Proportion of participants with previous infections: NR Time (days) since previous infection: NR Proportion of vaccinated participants: NR Disease severity (%): NR Currently pregnant (%): NA	Recovery†: NR Symptom duration (time until symptom free): NR All-cause mortality: At 30 days: G1: 4/250 (2) G2: 3/251 (1) p=NR COVID-19 specific mortality: NR Hospitalization due to COVID: At 30 days: G1: 14/250 (6) G2: 21/251 (8) p=NR	Any AE: NR Serious AE: NR
Nitazoxanide							
Rocco et al. 2021 (32)	RCT (double-blinded),	COVID-19 vaccine received: NR	N=475 G1: 238 Nitazoxanide 500 mg oral	Age, years, (%): 18–39 years G1: 59 G2: 57	Proportion of symptomatic participants (%): G1: 100 G2: 100	Recovery†: At 5 days: G1: 135/194 (70) G2: 146/198 (74)	Any AE: At 5 days G1: 60/238 (25) G2: 60/237 (25)

Author, Year, Trial Name, Trial Registry No. Funding Risk of bias	Design, Country, Duration (days) Dominant variant at time of study (%)*	Eligibility criteria	N total (randomized), Interventions, N group	Population	Baseline characteristics	Recovery, symptom duration, all-cause mortality, COVID-19 specific mortality, Hospitalization due to COVID-19 (n/N (%))	Incidence of any adverse events, incidence of serious adverse events (n/N (%))
NCT04552483 Government Academic Some concerns	Brazil 14 P.1 (gamma): NR B.1.617.2 (delta): NR	Previous SARS-CoV-2 infection: NR Presence and/or duration of symptoms: clinical symptoms of COVID-19 no longer than 3 days Disease severity: mild Pregnant women: Not eligible	G2: 237 Placebo	40–59 years G1: 35 G2: 37 60–77 years G1: 6 G2: 6 female (%): G1: 48 G2: 58 Ethnicity (%): Non-White G1: 32 G2: 30 Diagnostic tool: RT-PCR	Duration of symptoms (median [IQR]): G1: 5 (4-5) G2: 5 (4-5) Proportion of participants with previous infections: NR Time (days) since previous infection: NR Proportion of vaccinated participants: NR Disease severity (%): Mild: G1: 100 G2: 100 Currently pregnant (%): NA	p=NR Symptom duration (time until symptom free): NR All-cause mortality: At 14 days: G1: 0/238 (0) G2: 0/237 (0) COVID-19 specific mortality: NR Hospitalization due to COVID: At 5 days: G1: 5/238 (2) G2: 5/237 (2) p=NR	p=NR Serious AE: At 5 days G1: 1/238 (0.4) G2: 1/237 (0.4)
Rossignol et al. 2022 (43) NCT04486313 Industry Some concerns	RCT (double-blinded), U.S. 28 B.1.617.2 (delta): NR B.1.1.529 (omicron): NR	COVID-19 vaccine received not eligible if received within 30 days prior to screening Previous SARS-CoV-2 infection: not eligible Presence and/or duration of symptoms: at least two	N=1,092 G1: 628 Nitazoxanide 1200 mg G2: 464 Placebo	Age, years, median (IQR): Overall: 40 (12−83) G1: 38 (12−83) G2: 42 (13−81) female (%): G1: 55 G2: 58 Ethnicity (%): Non-White G1: 36 G2: 41	Proportion of symptomatic participants (%): G1: 100 G2: 100 Duration of symptoms: Hours G1: 43.9 G2: 46.5 Proportion of participants with previous infections: NR Time (days) since previous infection:	Recovery†: NR Symptom duration (time until symptom free): Median (IQR) TSR (days) G1: 13.3 (6.3, >21) G2: 12.4 (7.2, >21) p=0.88 All-cause mortality: At 28 days: G1: 2/472 (0.4) G2: 0/463 (0) p=NR	Any AE: At 28 days: G1: 63/472 (13) G2: 75/463 (16) p=NR Serious AE: At 28 days: G1: 2/472 (0.4) G2: 7/463 (2) p=NR

Author, Year, Trial Name, Trial Registry No. Funding Risk of bias	Design, Country, Duration (days) Dominant variant at time of study (%)*	Eligibility criteria	N total (randomized), Interventions, N group	Population	Baseline characteristics	Recovery, symptom duration, all-cause mortality, COVID-19 specific mortality, Hospitalization due to COVID-19 (n/N (%))	Incidence of any adverse events, incidence of serious adverse events (n/N (%))
		respiratory symptom domains related to Covid-19 within 72 hours Disease severity: mild to moderate Pregnant women: Not eligible		Diagnostic tool: RT-PCR	NR Proportion of vaccinated participants: NR Disease severity (%): Moderate: G1: 37 G2: 33 Currently pregnant (%): NA	COVID-19 specific mortality: At 28 days: G1: 1/472 (0.2) G2: 0/463 (0) p=NR Hospitalization due to COVID: At 28 days: G1: 1/472 (0.2) G2: 3/463 (1) p=NR	
Convalescent plasma							
Alemany et al. 2022 (37) CONV-ERT NCT04621123 Industry Academic Foundation/non-profit professional organization Low	RCT (double-blinded) Spain 28 B.1.1.7 (alpha): NR B1.177: NR	COVID-19 vaccine received: Not eligible Previous SARS-CoV-2 infection: Not eligible Presence and/or duration of symptoms: symptom onset no more than 7 days before randomisation Disease severity: mild-to-moderate Pregnant	N=376 G1: 188 Convalescent plasma 250–300 mL IV G2: 188 Placebo	Age, years, median (IQR) G1: 56 (52–62) G2: 56 (53–63) female (%): G1: 44 G2: 48 Ethnicity (%): NR Diagnostic tool: RT-PCR or antigen	Proportion of symptomatic participants (%): G1: 100 G2: 100 Duration of symptoms: G1: 4.4 (1.4) G2: 4.4 (1.4) Proportion of participants with previous infections NA Time (days) since previous infection: NA Proportion of vaccinated participants: NA Disease severity (%): Mild:	Recovery[†]: NR Symptom duration (time until symptom free): Days (Median (IQR)) G1: 12·0 (6.0–21.3) G2: 12.0 (6.0–22.0) HR 1.05 (95% CI 0.85 to 1.30) All-cause mortality: At 28 days: G1: 0/188 (0) G2: 2/188 (1) RR 0.20 (95% CI, 0.01 to 4.14) COVID-19 specific mortality: NR	Any AE: At 28 days: G1: 24/188 (13) G2: 8/188 (4) p=NR Serious AE: At 28 days: G1: 1/188 (1) G2: 0/188 (0) p=NR

Author, Year, Trial Name, Trial Registry No. Funding Risk of bias	Design, Country, Duration (days) Dominant variant at time of study (%)*	Eligibility criteria	N total (randomized), Interventions, N group	Population	Baseline characteristics	Recovery, symptom duration, all-cause mortality, COVID-19 specific mortality, Hospitalization due to COVID-19 (n/N (%))	Incidence of any adverse events, incidence of serious adverse events (n/N (%))
		women: Not eligible			G1: 97 G2: 97 Moderate: G1: 3 G2: 3 Currently pregnant (%): NA	 Hospitalization due to COVID: At 28 days: G1: 22/188 (12) G2: 21/188 (11) p=0.76 RR 1.05 (95 CI, 0.78 to 1.41)	
Korley et al. 2021 (36) SIREN-C3PO NCT04355767 Government Academic Some concerns	RCT (single-blinded) U.S. 15 B.1.1.7 (alpha): NR B.1.617.2 (delta): NR	COVID-19 vaccine received: not eligible Previous SARS-CoV-2 infection: NR Presence and/or duration of symptoms: onset of symptoms within 7 days before enrollment Disease severity: NR Pregnant women: Eligible	N=511 G1: 257 Convalescent plasma 250 ml G2: 254 Placebo	Age, years,median (IQR) G1: 54 (42–62) G2: 54 (40–62) female (%): G1: 53 G2: 55 Ethnicity (%): Non-white: G1: 33 G2: 35 Diagnostic tool: RT-PCR	Proportion of symptomatic participants (%): NR Duration of symptoms: G1 (Median (IQR)): 4 (2–5) G2 (Median (IQR)): 3 (2–5) Proportion of participants with previous infections: NR Time (days) since previous infection: NR Proportion of vaccinated participants: NA Disease severity (%): NR Currently pregnant (%): G1: 1.2% G2: 1.2%	Recovery[†]: NR Symptom duration (time until symptom free): NR All-cause mortality: At 30 days: G1: 5/257 (2) G2: 1/254 (0.4) (risk difference (95% CI), −1.6 % point; −4.2 to 0.50); COVID-19 specific mortality: NR Hospitalization due to COVID: NR	Any AE: NR Serious AE: At 30 days: G1: 3/257 (1) G2: 0/254 (0) p=NR
Libster et al. 2021 (24) NR	RCT (double-blinded),	COVID-19 vaccine received: NR	N=160 G1: 80 Convalescent plasma 250 ml	Age, years, mean (SD): G1: 76.4 (8.7) G2: 77.9 (8.4)	Proportion of symptomatic participants (%): G1: 100 G2: 100	Recovery[†]: NR Symptom duration (time	Any AE: NR Serious AE:

Author, Year, Trial Name, Trial Registry No. Funding Risk of bias	Design, Country, Duration (days) Dominant variant at time of study (%)*	Eligibility criteria	N total (randomized), Interventions, N group	Population	Baseline characteristics	Recovery, symptom duration, all-cause mortality, COVID-19 specific mortality, Hospitalization due to COVID-19 (n/N (%))	Incidence of any adverse events, incidence of serious adverse events (n/N (%))
NCT04479163 Government Industry Foundation/non-profit professional organization Some concerns	Argentina 15 P.1 (gamma): NR C.37 (lambra): NR	Previous SARS-CoV-2 infection: NR Presence and/or duration of symptoms at least one Covid-19 related symptom for less than 48 hours Disease severity: mild Pregnant women: Not eligible	G2: 80 Placebo	female (%): G1: 68 G2: 58 Ethnicity (%): NR Diagnostic tool: RT-PCR	Duration of symptoms: NR Proportion of participants with previous infections: NR Time (days) since previous infection: NR Proportion of vaccinated participants: G1: 0 G2: 0 Disease severity (%): Mild: G1: 100 G2: 100 Currently pregnant (%): NA	until symptom free): NR All-cause mortality: At 15 days: G1: 2/80 (2) G2: 4/80 (5) COVID-19 specific mortality: At 15 days: G1: 2/80 (2) G2: 4/80 (5) Hospitalization due to COVID: NR	At 15 days: G1: 7/80 (9) G2: 12/80 (15) RR (95% CI): 0.58 (0.24–1.41)
Sullivan et al. 2022 (46) CSSC-004 NCT04373460 Government Industry Academic Foundation/non-profit professional organization	RCT (double-blinded), U.S., 28 B.1.1.7 (alpha): NR B.1.617.2 (delta): NR	COVID-19 vaccine received: Eligible Previous SARS-CoV-2 infection: NR Presence and/or duration of symptoms: symptom onset within 8 days before transfusion	N=1225 G1: 610 Convalescent plasma 250 ml G2: 615 Placebo	Age, years, Median (IQR) G1: 42 (32 - 54) G2: 44 (33 - 55) female (%): G1: 55 G2: 60 Ethnicity (%): Non-white: G1: 22 G2: 19	Proportion of symptomatic participants (%): G1: 100 G2: 100 Duration of symptoms: Median symptom duration before randomization (IQR) - days: G1: 5 (4-7) G2: 5 (4-7) Proportion of participants with previous infections: NR	Recovery[†]: NR Symptom duration (time until symptom free): NR All-cause mortality: At 28 days: G1: 0/592 (0) G2: 3/589 (1) p=NR COVID-19 specific mortality:	Any AE: At 28 days: Overall: 89/1181 (8) G1: 34/592 (6) G2: 55/589 (9) Rate difference (95% CI) 0.18 (0.03, 0.32) Serious AE: G1: 2/592 (0.3) G2: 0/589 (0) Rate difference (95% CI) -0.05 (-

Author, Year, Trial Name, Trial Registry No. Funding Risk of bias	Design, Country, Duration (days) Dominant variant at time of study (%)*	Eligibility criteria	N total (randomized), Interventions, N group	Population	Baseline characteristics	Recovery, symptom duration, all-cause mortality, COVID-19 specific mortality, Hospitalization due to COVID-19 (n/N (%))	Incidence of any adverse events, incidence of serious adverse events (n/N (%))
Low		Disease severity: NR Pregnant women: Eligible		Diagnostic tool: RT-PCR or antigen	Time (days) since previous infection: NR Proportion of vaccinated participants: Partially vaccinated (%): G1: 5 G2: 5 Fully vaccinated (%): G1: 12 G2: 13 Disease severity (%): NR Currently pregnant (%): G1: 0.3% G2: 0.2%	At 28 days: G1: 0/592 (0) G2: 3/589 (1) p=NR Hospitalization due to COVID: At 28 days: G1: 17/592(3) G2: 37/589 (6) absolute risk reduction (95% CI), 3.4% points (1.0 to 5.8)	0.11, 0.02)
Other drugs							
Corticosteroids							
Ezer et al. 2021 (45) CONTAIN NCT04435795 Industry Academic Foundation/non-profit professional organization	RCT (double-blinded), Canada 14 B.1.1.7 (alpha): NR B.1.617.2 (delta): NR	COVID-19 vaccine received: Not eligible Previous SARS-CoV-2 infection: NR Presence and/or duration of symptoms: at least one related symptom	N=215 G1: 108 Ciclesonide 1200 µg inhaled + 200 µg/day intranasal G2: 107 placebo	Age, years, median (IQR): G1: 35 (27-47) G2: 35 (27-45) female (%): G1: 51 G2: 56 Ethnicity (%): Non-white: G1: 38 G2: 41	Proportion of symptomatic participants (%): G1: 100 G2: 100 Duration of symptoms: Median (IQR) G1: 3 (2-4) G2: 3 (2-4) Proportion of participants with previous infections: NR	Recovery†: At 14 days: G1: 69/105 (66) G2: 57/98 (58) Adjusted risk difference 7.5% (95% CI, −5.9% to 20.8%) Symptom duration (time until symptom free): NR All-cause mortality: At 14 days:	Any AE: At 14 days: G1: 23/105 (22) G2: 15/98 (15) p=NR Serious AE: G1: 7/106 (7) G2: 5/103 (5) p=NR

Author, Year, Trial Name, Trial Registry No. Funding Risk of bias	Design, Country, Duration (days) Dominant variant at time of study (%)*	Eligibility criteria	N total (randomized), Interventions, N group	Population	Baseline characteristics	Recovery, symptom duration, all-cause mortality, COVID-19 specific mortality, Hospitalization due to COVID-19 (n/N (%))	Incidence of any adverse events, incidence of serious adverse events (n/N (%))
Low		Disease severity: NR Pregnant women: Not eligible		Diagnostic tool: RT-PCR	Time (days) since previous infection: NR Proportion of vaccinated participants: NA Disease severity (%): NR Currently pregnant (%): NA	G1: 0/108 (0) G2: 0/107 (0) COVID-19 specific mortality: At 14 days: G1: 0/108 (0) G2: 0/107 (0) Hospitalization due to COVID: At 14 days: G1: 3/105 (3) G2: 6/98 (6) Adjusted risk difference (stratification on sex), % (95% CI): 2.3 (−3.0 to 7.6)	
Fluvoxamine							
Lenze et al. 2020 (40) STOP COVID NCT04342663 Government Academic Some concerns	RCT (double-blinded), U.S., 15 B.1.427 and B.1.429 (epsilon)	COVID-19 vaccine received: NR Previous SARS-CoV-2 infection: NR Presence and/or duration of symptoms: symptomatic participants within 7 days of the first dose of study medication Disease severity:	N=181 (152 received) G1: 80 Fluvoxamine 100mg G2: 72 Placebo	Age, years, mean (SD): Median G1: 46 G2: 45 female (%): G1: 70 G2: 74 Ethnicity (%): Non-white: G1: 30 G2: 31 Diagnostic tool: RT-PCR	Proportion of symptomatic participants (%): G1: 100 G2: 100 Duration of symptoms: Median (IQR) G1: 4 (3-5) G2: 4 (3-5) Proportion of participants with previous infections: NR Time (days) since previous infection: NR Proportion of vaccinated participants:	Recovery[†]: NR Symptom duration (time until symptom free): NR All-cause mortality: At 15 days: G1: 0/80 (0) G2: 0/72 (0) COVID-19 specific mortality: At 15 days: G1: 0/80 (0) G2: 0/72 (0)	Any AE: At 15 days: G1: 12/80 (15) G2: 11/72 (15) p=NR Serious AE: At 15 days: G1: 1/80 (1) G2: 5/72 (7) p=NR

Author, Year, Trial Name, Trial Registry No. Funding Risk of bias	Design, Country, Duration (days) Dominant variant at time of study (%)*	Eligibility criteria	N total (randomized), Interventions, N group	Population	Baseline characteristics	Recovery, symptom duration, all-cause mortality, COVID-19 specific mortality, Hospitalization due to COVID-19 (n/N (%))	Incidence of any adverse events, incidence of serious adverse events (n/N (%))
		mild Pregnant women: Not eligible			NR Disease severity (%): Mild: G1: 100 G2: 100 Currently pregnant (%): NR	Hospitalization due to COVID: At 15 days: G1: 0/80 (0) G2: 4/72 (6) p=NR	
Reis et al. 2022 (39) TOGETHER NCT04727424 Foundation/non-profit professional organization Low	RCT (double-blinded), Brazil 28 P.1 (gamma): NR B.1.617.2 (delta): NR B.1.1.529 (omicron): NR	COVID-19 vaccine received: Not eligible Previous SARS-CoV-2 infection: NR Presence and/or duration of symptoms: less than 8 days Disease severity: mild Pregnant women: Not eligible	N=1497 G1: 741 Fluvoxamine 100mg G2: 756 Placebo	Age, years, median: G1: 50 G2: 49 female (%): G1: 55 G2: 60 Ethnicity (%): Non-white: G1: 99 G2: 99 Diagnostic tool: RT-PCR	Proportion of symptomatic participants (%): G1: 100 G2: 100 Duration of symptoms: 0-3 days (%): G1: 44 G2: 41 4-7 days (%): G1: 32 G2: 35 Unspecified (%): G1: 23 G2: 24 Proportion of participants with previous infections: NR Time (days) since previous infection: NR Proportion of vaccinated participants: NA Disease severity (%): Mild	Recovery[†]: NR Symptom duration (time until symptom free): NR All-cause mortality: At 28 days: G1: 17/741 (2) G2: 25/756 (3) p=NR COVID-19 specific mortality: NR Hospitalization due to COVID: At 28 days: G1: 75/741 (10) G2: 97/756 (13) p=0.10	Any AE: NR Serious AE: NR

Author, Year, Trial Name, Trial Registry No. Funding Risk of bias	Design, Country, Duration (days) Dominant variant at time of study (%)*	Eligibility criteria	N total (randomized), Interventions, N group	Population	Baseline characteristics	Recovery, symptom duration, all-cause mortality, COVID-19 specific mortality, Hospitalization due to COVID-19 (n/N (%))	Incidence of any adverse events, incidence of serious adverse events (n/N (%))
					G1: 100 G2: 100 Currently pregnant (%): NA		

*https://covariants.org/per-country, https://www.who.int/activities/tracking-SARS-CoV-2-variants, †as defined by the authors; **G5 included G4; ***data not included in the MA due to underdosage of ivermectin

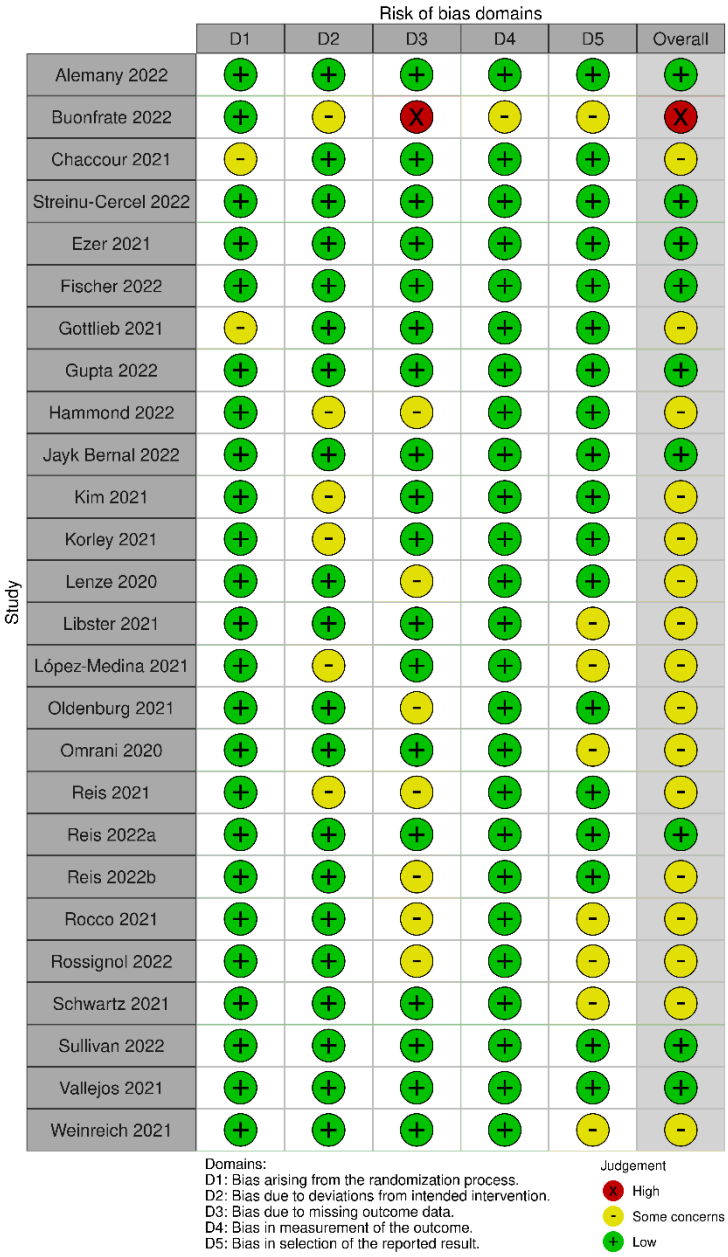
Abbreviations: AE= adverse events; CI= confidence interval; COVID-19= coronavirus disease; G (1,2,3,4,5)= group; IQR= interquartile range; kg= kilogram; mg= milligrams; HR= hazard ratio; N= number of participants; NCT= National Clinical Trial; NR= not reported; OR= odds ratio; PCR= polymerase chain reaction; RCT= randomized controlled trial; RR= risk ratio; SARSCoV-2= Severe acute respiratory syndrome coronavirus type 2; SD= standard deviation; SE= standard error; TSR= time from the first dose to sustained clinical recovery; UK= United Kingdom; US= United States; µg= microgram

Supplement Table 7: Definitions for Recovery

Author, Year	Definition of recovery
Oldenburg, 2021 (41)	Absence of symptoms
Schwartz, 2021 (27)	Symptom resolution
Ezer, 2021 (45)	Resolution of self-reported fever and all respiratory symptoms
Vallejos, 2021 (47)	RT-PCR negative
Buonfrate, 2022 (48)	Clinical resolution
Jayk Bernal, 2022 (33) **Reis, 2022 (49)**	Changes in WHO Clinical Progression Scale (which measures the clinical progression of Covid-19)
Rossignol, 2022 (43)	Participant symptom improvement
Streinu-Cercel, 2021 (34)	Absent or mild symptoms for at least 24 hours
Kim, 2021 (42)	Mild or absent reported symptoms for a minimum of 24 hours
Gottlieb, 2021 (44)	Mild or absent symptoms

Abbreviations: Covid-19= coronavirus disease; RT-PCR= reverse transcription polymerase chain reaction; WHO= World Health Organization.

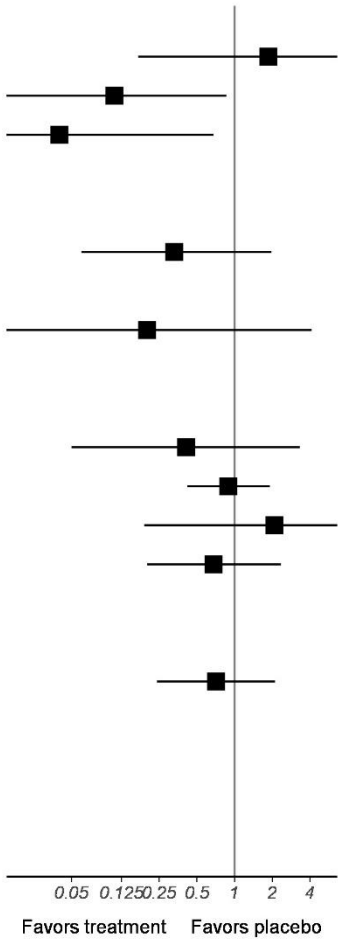
Supplement Figure 1: Risk of Bias



Supplement Figures Summary Plots

Supplement Figure 2: All-Cause Mortality – Summary Plot

Comparison	Trials	Participants	COE	RR [CrI]
Antiviral drugs				
Lopinavir/Ritonavir	*1*	*471*	*insufficient*	*1.86 [0.17; 20.38]**
Molnupiravir	*1*	*1,433*	*low*	*0.11 [0.01; 0.86]**
Nirmatrelvir/Ritonavir	*1*	*2,085*	*moderate*	*0.04 [0.00; 0.68]**
Remdesivir	*1*	*562*	*insufficient**	*
Monoclonal neutralizing antibodies				
Casirivimab/Imdevimab	*1*	*4,057*	*insufficient*	*0.33 [0.06; 1.97]**
Regdanvimab	*1*	*325*	*insufficient**	*
Sotrovimab	*1*	*1,057*	*insufficient*	*0.20 [0.01; 4.12]**
Antibiotic or antiparasitic drugs				
Azithromycin	*1*	*197*	*insufficient**	*
Chloroquine/Hydroxychloroquine	*3*	*1,045*	*insufficient*	*0.41 [0.05; 3.31]*
Ivermectin	*5*	*2,452*	*low*	*0.89 [0.42; 1.91]*
Nitazoxanide	*2*	*1,567*	*insufficient*	*2.08 [0.19; 22.35]*
Convalescent Plasma	*4*	*2,272*	*low*	*0.68 [0.20; 2.34]*
Other drugs				
Corticosteroids	*1*	*203*	*insufficient**	*
Fluvoxamine	*2*	*1,649*	*low*	*0.71 [0.24; 2.10]*

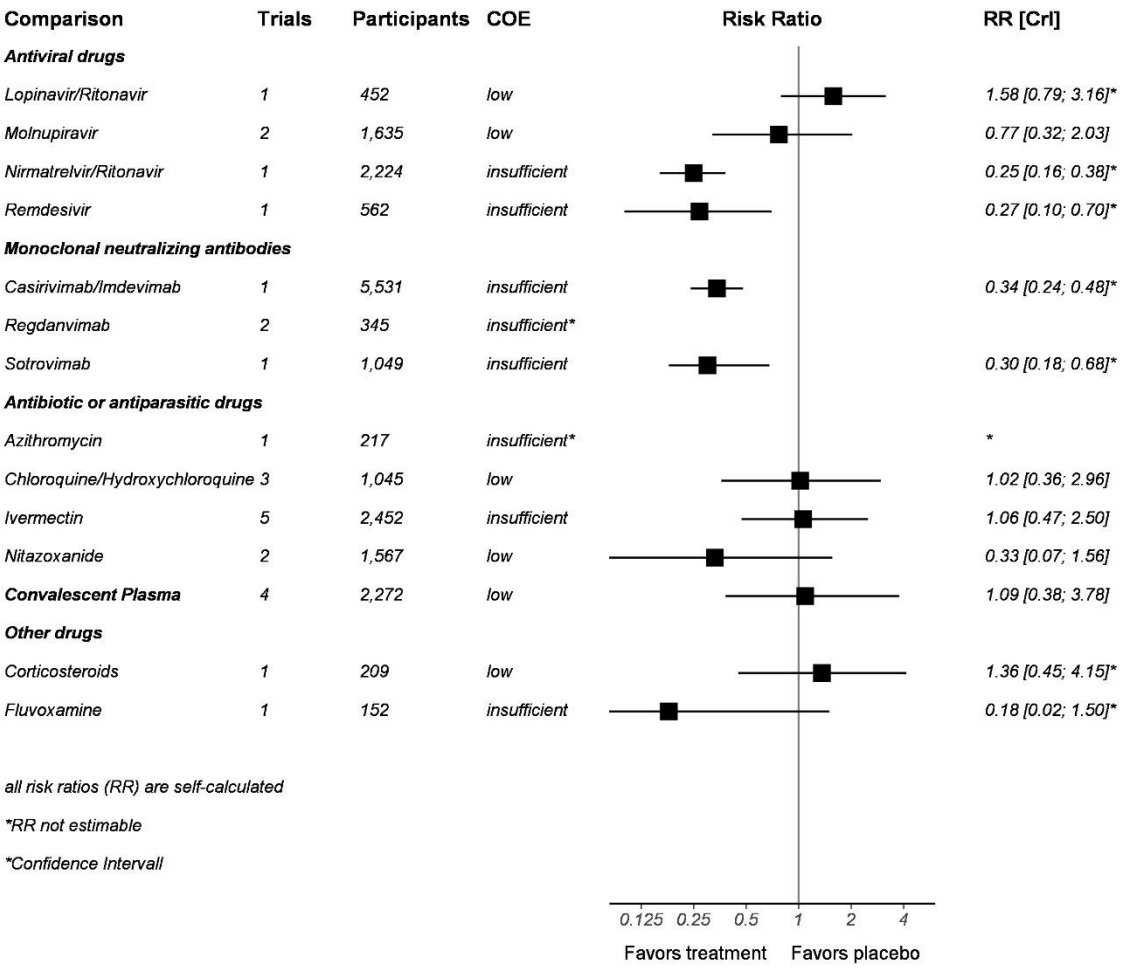


all risk ratios (RR) are self-calculated

**RR not estimable*

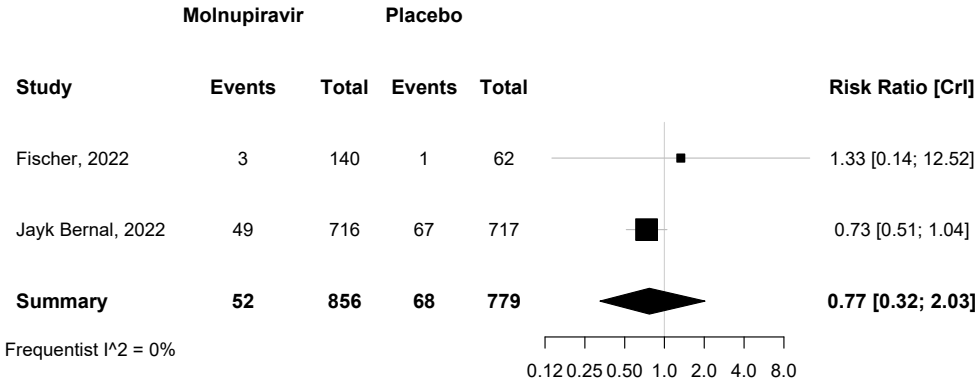
**Confidence Intervall*

Supplement Figure 3: Serious Adverse Events – Summary Plot

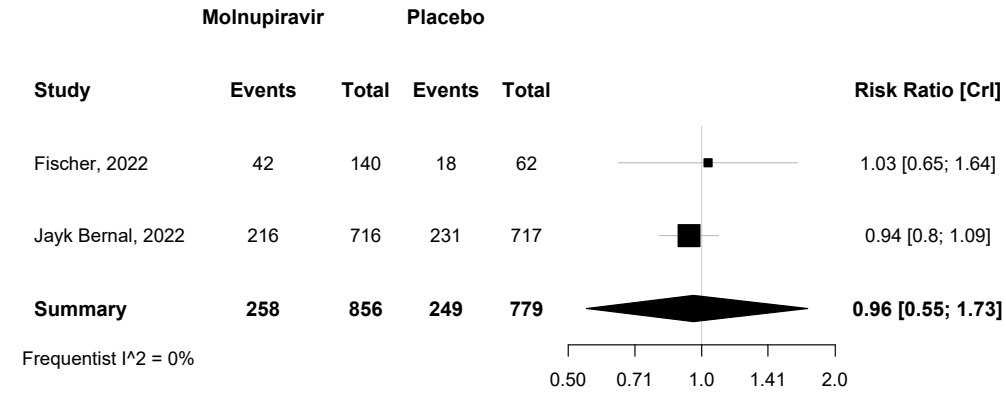


Supplement Figures Meta Analyses

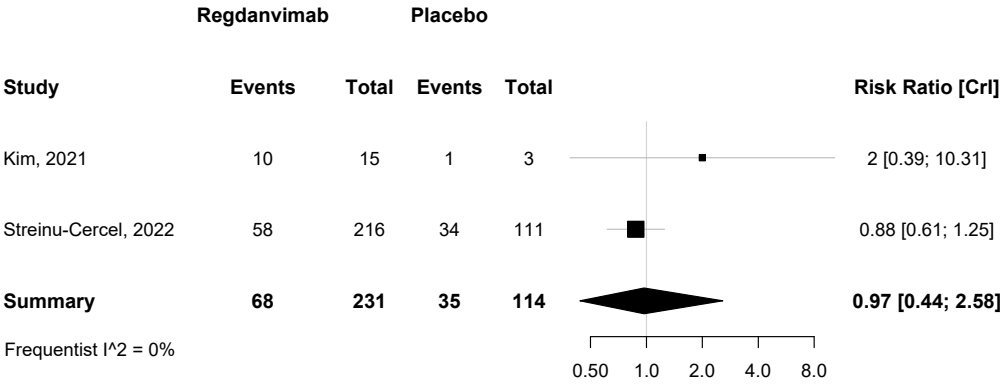
Supplement Figure 4: Serious Adverse Events: Molnupiravir Versus Placebo



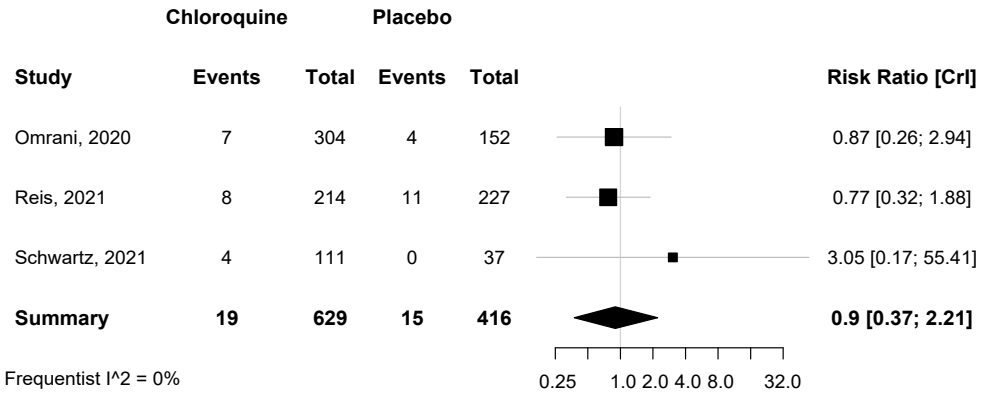
Supplement Figure 5: Any Adverse Events: Molnupiravir Versus Placebo



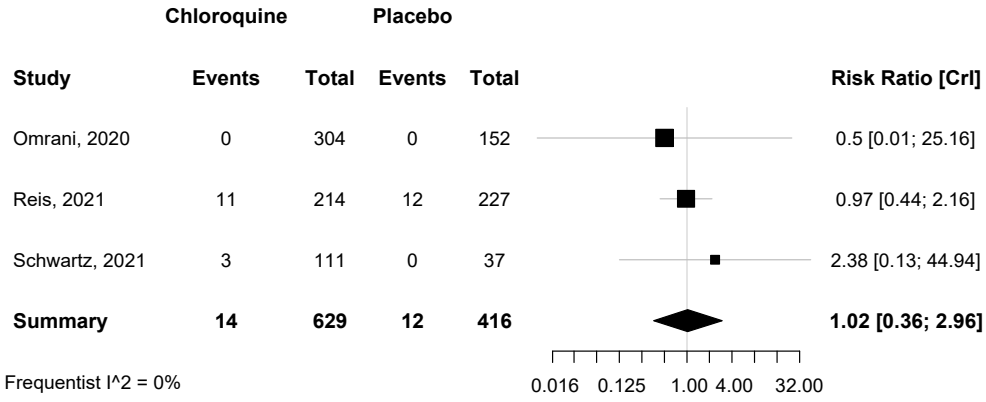
Supplement Figure 6: Any Adverse Events: Regdanvimab Versus Placebo



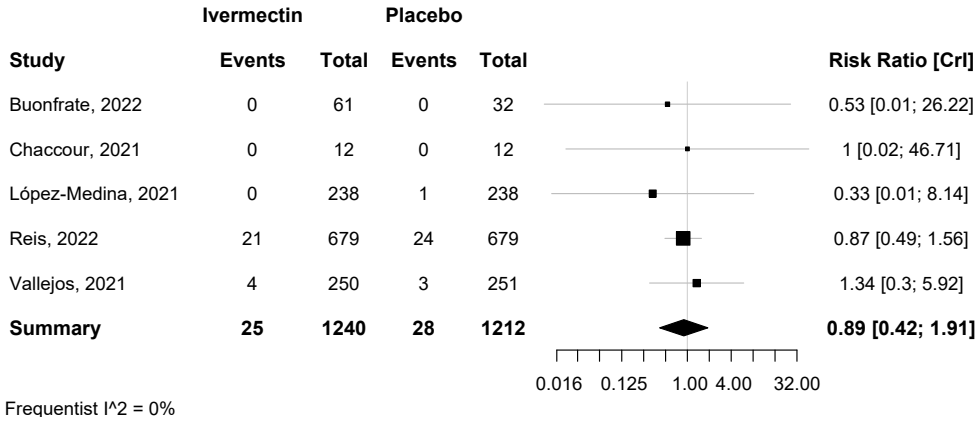
Supplement Figure 7: Admission to Hospital due to COVID-19: Chloroquine Versus Placebo



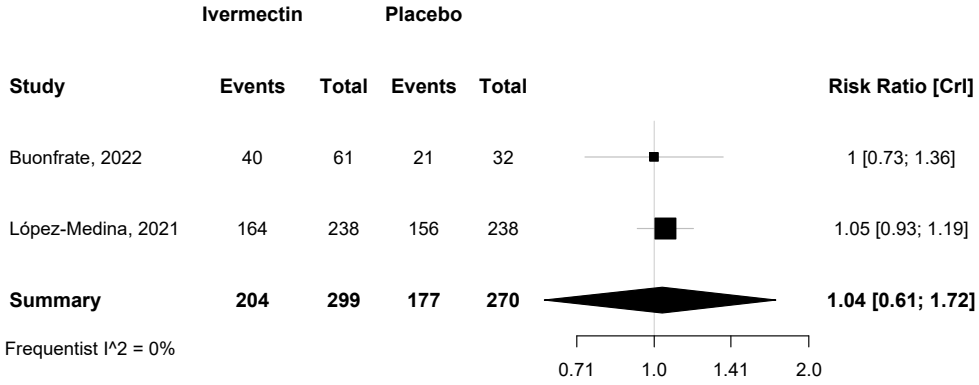
Supplement Figure 8: Serious Adverse Events: Chloroquine Versus Placebo



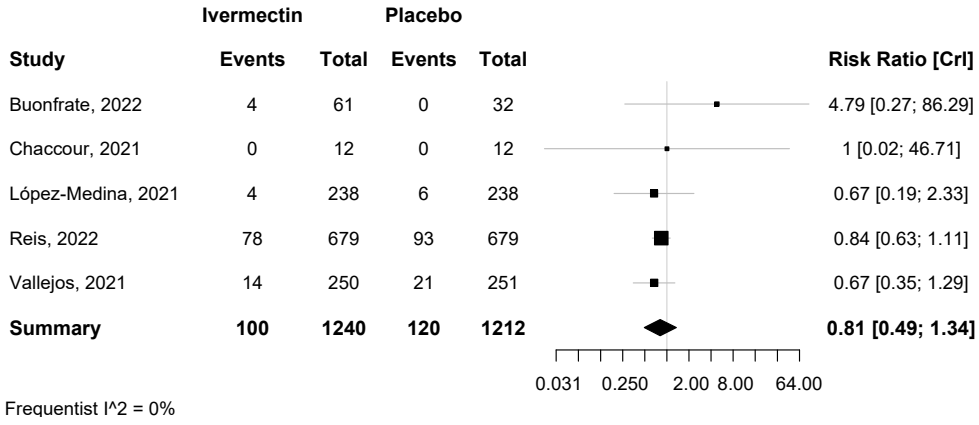
Supplement Figure 9: All-Cause Mortality: Ivermectin Versus Placebo



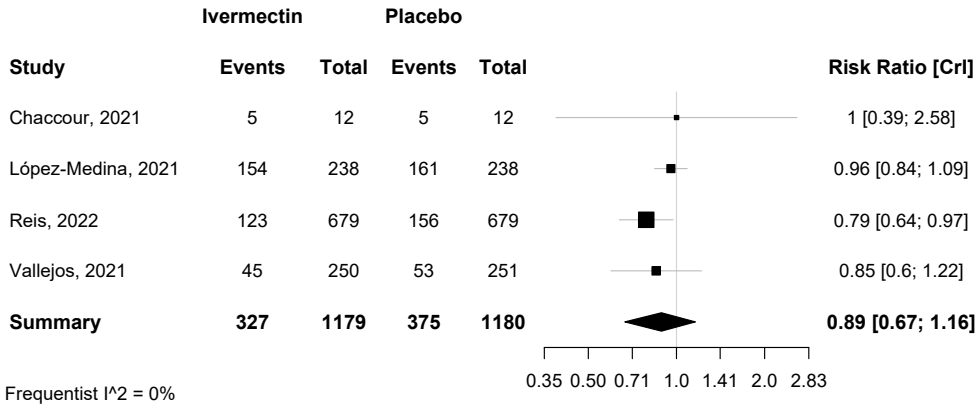
Supplement Figure 10: Recovery: Ivermectin Versus Placebo



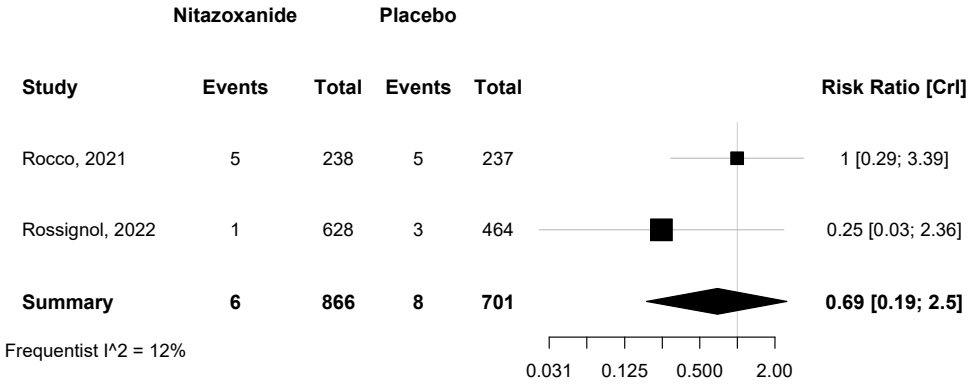
Supplement Figure 11: Admission to Hospital due to COVID-19: Ivermectin Versus Placebo



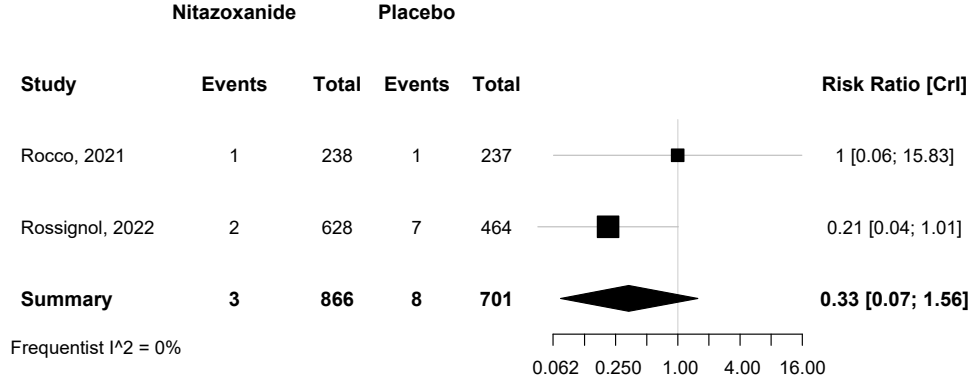
Supplement Figure 12: Any Adverse Events: Ivermectin Versus Placebo



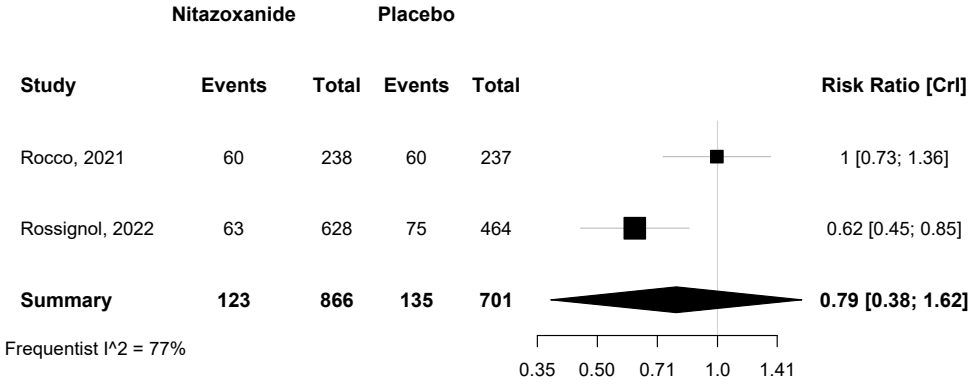
Supplement Figure 13: Admission to Hospital due to COVID-19: Nitazoxanide Versus Placebo



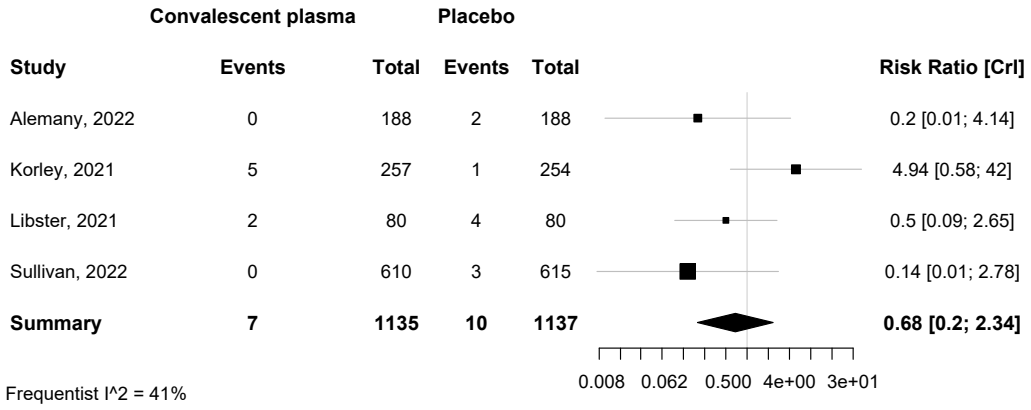
Supplement Figure 14: Serious Adverse Events: Nitazoxanide Versus Placebo



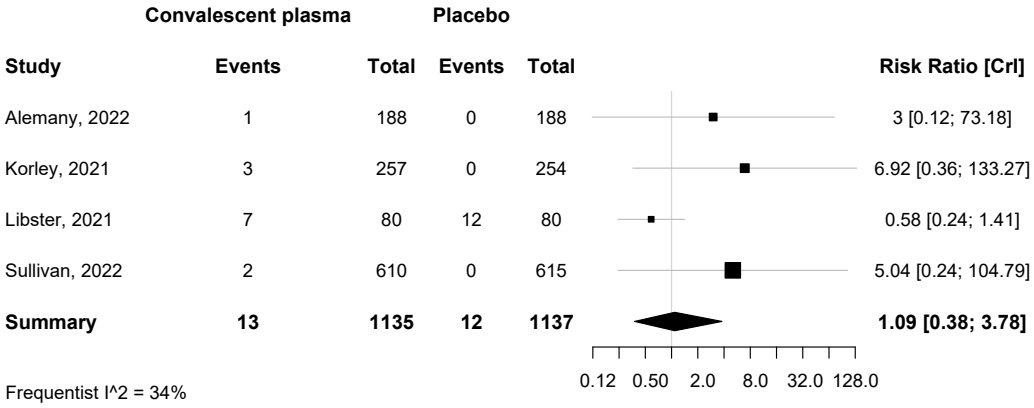
Supplement Figure 15: Any Adverse Events: Nitazoxanide Versus Placebo



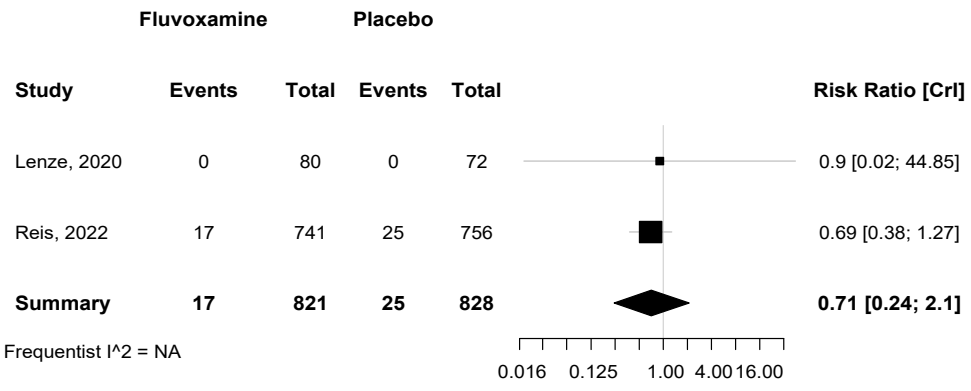
Supplement Figure 16: All-Cause Mortality: Convalescent Plasma Versus Placebo



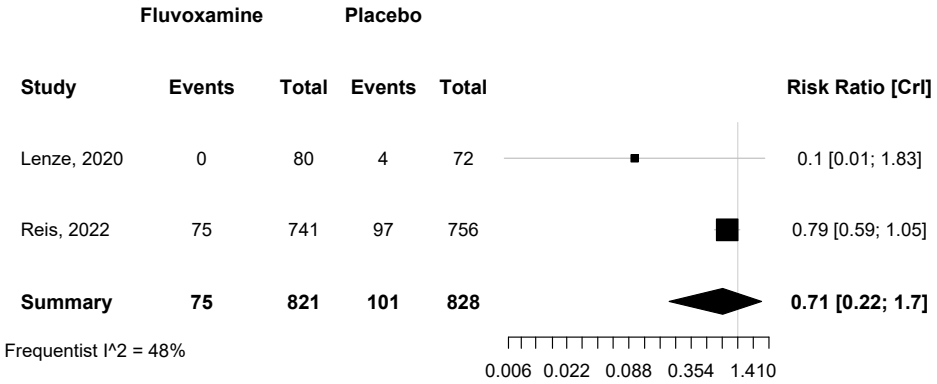
Supplement Figure 17: Serious Adverse Events: Convalescent Plasma Versus Placebo



Supplement Figure 18: All-Cause Mortality: Fluvoxamine Versus Placebo



Supplement Figure 19: Admission to Hospital due to COVID-19: Fluvoxamine Versus Placebo



Supplement Table 8: Summary of Findings Tables

Lopinavir/ritonavir compared to Placebo for Adults with Confirmed COVID-19 Infection?

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		Effect with placebo	Effect with lopinavir/ritonavir	Difference		
All-cause mortality follow-up: 90 days № of participants:471 (1 RCT)(30)	**RR 1.86** (0.17 to 20.38)	0.4%	**0.8%** (0.1 to 9)	**0.4% more** (0.4 fewer to 8.5 more)	◯◯◯ Insufficient[a]	The evidence is very uncertain about the effect of lopinavir/ritonavir on all-cause mortality compared to placebo.
COVID-19-specific mortality - not reported	-	-	-	-	-	
Recovery - not reported	-	-	-	-	-	
Time to recovery - not reported	-	-	-	-	-	
Admission to hospital due to COVID-19 follow-up: 90 days № of participants:471 (1 RCT)(30)	**HR 1.16** (0.53 to 2.56)	4.8%	**5.7%** (2.6 to 11.9)	**0.9% more** (2.2 fewer to 7.1 more)	⊕◯◯ Low[b]	Lopinavir/ritonavir may result in no difference in admission to hospital due to COVID-19 compared to placebo.
Serious adverse events follow-up: 90 days № of participants:452 (1 RCT)(30)	**RR 1.58** (0.79 to 3.16)	5.5%	**8.6%** (4.3 to 17.2)	**3.1% more** (1.1 fewer to 11.8 more)	⊕◯◯ Low[b]	Lopinavir/ritonavir may result in no difference in serious adverse events compared to placebo.
Adverse events follow-up: 90 days № of participants:452 (1 RCT)(30)	**RR 1.90** (1.40 to 2.57)	20.9%	**39.7%** (29.3 to 53.7)	**18.8% more** (8.4 more to 32.8 more)	⊕◯◯ Low[b]	Lopinavir/ritonavir may increase adverse events compared to placebo.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HR:** hazard Ratio; **no:** number; **RCT:** randomized controlled trial; **RR:** risk ratio

Explanations

a. Extremely few events; downgraded 3 steps for imprecision
b. Very few of events; downgraded 2 steps for imprecision

Molnupiravir compared to Placebo for Adults with Confirmed COVID-19 Infection

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		Effect with placebo	Effect with molnupiravir	Difference		
All-cause mortality follow-up: 29 days № of participants:1,433 (1 RCT)(33)	**RR 0.11** (0.01 to 0.86)	1.3%	**0.1%** (0 to 1.1)	**1.2% fewer** (1.2 fewer to 0.2 fewer)	⨁◯◯ Low[a]	Molnupiravir may result in a reduction in all-cause mortality compared to placebo.
COVID-19-specific mortality follow-up: 29 days № of participants:1,433 (1 RCT)(33)	**RR 0.11** (0.01 to 0.86)	1.3%	**0.1%** (0 to 1.1)	**1.2% fewer** (1.2 fewer to 0.2 fewer)	⨁◯◯ Low[a]	Molnupiravir may result in a reduction in COVID-specific mortality compared to placebo.
Recovery follow-up: 29 days № of participants:1,295 (1 RCT)(33)	**OR 1.04** (0.84 to 1.29)	48.3%	**48.4%** (44 to 54.7)	**0.1% more** (4.3 fewer to 6.4 more)	⨁⨁◯ Moderate[b]	Molnupiravir probably results in no difference in recovery compared to placebo.
Time to recovery follow-up: 28 days № of participants:202 (1 RCT)(31)	Median time: Molnupiravir 5.5 days (95% CI, 4.0 to 8.0) to 9.0 days (95% CI 6.0 vs. 12 days); Placebo 8.5 days (95% CI, 7.0 to 11.0), no statistically significant difference (effect size not reported)				⨁◯◯ Low[c]	Molnupiravir may result in no difference in time to recovery compared to placebo.
Admission to hospital due to COVID-19 follow-up: 29 days № of participants:1,408 (1 RCT)(33)	**RR 0.79** (0.54 to 1.16)	7.9%	**6.2%** (4.2 to 9.1)	**1.7% fewer** (3.6 fewer to 1.3 more)	⨁◯◯ Low[a]	Molnupiravir may result in no difference in admission to hospital due to COVID-19 compared to placebo.
Serious adverse events follow-up: range 28 days to 29 days № of participants:1,635 (2 RCTs)(31, 33)	**RR 0.77** (0.32 to 2.03)	8.7%	**6.1%** (2.8 to 17.7)	**2.6% fewer** (5.9 fewer to 9 more)	⨁◯◯ Low[d,e]	Molnupiravir may result in no difference in serious adverse events compared to placebo.
Adverse events follow-up: range 28 days to 29 days № of participants:1,635 (2 RCTs)(31, 33)	**RR 0.96** (0.55 to 1.73)	32.0%	**30.1%** (17.6 to 55.3)	**1.9% fewer** (14.4 fewer to 23.3 more)	⨁⨁◯ Moderate[f]	Molnupiravir probably results in no difference in adverse events compared to placebo.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval (1 study) or credible interval (≥2 studies); **no:** number; **OR:** odds ratio; **RCT**: randomized controlled trial; **RR:** risk ratio

Explanations

a. Very few events; downgraded 2 steps for imprecision , b. Confidence [0.84 to 1.29] intervals are wide and encompass appreciable benefits or harms; downgraded 1 step for imprecision
c. Sample size does not meet optimal information size; downgraded 2 steps for imprecision , d. I^2 very high; downgraded one step for inconsistency , e. Confidence [0.32 to 2.03] intervals are wide and encompass appreciable benefits or harms; downgraded 1 step for imprecision , f. Confidence intervals [0.55 to 1.73] are wide and encompass appreciable benefits or harms; downgraded 1 step for imprecision

Nirmatrelvir/Ritonavir compared to Placebo for Adults with Confirmed SARS-CoV-2 Infection

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		Effect with placebo	**Effect with nirmatrelvir/ritonavir**	**Difference**		
All-cause mortality follow-up: 28 days № of participants:2,085 (1 RCT)(35)	**RR 0.040** (0.002 to 0.680)	1.1%	**0.0%** (0 to 0.8)	**1.1% fewer** (1.1 fewer to 0.4 fewer)	⨁⨁◯ Moderate[a]	Nirmatrelvir/ritonavir probably results in a reduction in all-cause mortality compared to placebo.
COVID-19-specific mortality - not reported	-	-	-	-	-	
Recovery - not reported	-	-	-	-	-	
Time to recovery - not reported	-	-	-	-	-	
Admission to hospital due to COVID-19 follow-up: 28 days № of participants:2,085 (1 RCT)(35)	**RR 0.12** (0.06 to 0.26)	6.2%	**0.8%** (0.4 to 1.6)	**5.4% fewer** (5.8 fewer to 4.6 fewer)	⨁⨁◯ Moderate[a]	Nirmatrelvir/ritonavir probably results in a reduction in admission to hospital due to COVID-19 compared to placebo.
Serious adverse events follow-up: 34 days № of participants:2,224 (1 RCT)(35)	**RR 0.25** (0.16 to 0.38)	6.6%	**1.6%** (1.1 to 2.5)	**5.0% fewer** (5.6 fewer to 4.1 fewer)	◯◯◯ Insufficient[b]	The evidence is very uncertain about the effect of nirmatrelvir/ritonavir on serious adverse events compared to placebo.
Adverse events follow-up: 34 days № of participants:2,224 (1 RCT)(35)	**RR 0.95** (0.82 to 1.10)	23.9%	**22.6%** (19.6 to 26.2)	**1.3% fewer** (4.3 fewer to 2.4 more)	⨁⨁⨁ High	Nirmatrelvir/ritonavir results in no difference in adverse events compared to placebo.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **no:** number; **OR:** odds ratio; **RCT:** randomized controlled trial; **RR:** risk ratio

Explanations

a. Number of events does not meet optimal information size; downgraded 1 step for imprecision
b. Few events with chance effects; a significantly higher risk for serious adverse events for placebo than nirmatrelvir/ritonavir is not plausible; downgraded 3 steps for imprecision

Remdesivir compared to Placebo for Adults with Confirmed COVID-19 Infection

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		Effect with placebo	Effect with remdesivir	Difference		
All-cause mortality follow-up: 28 days № of participants:562 (1 RCT)(44)	not estimable	0.0%	**0.0%** (0 to 0)	**0.0% fewer** (0 fewer to 0 fewer)	◯◯◯ Insufficient[a]	The evidence is very uncertain about the effect of remdesivir on all-cause mortality compared to placebo.
COVID-19-specific mortality - not reported	-	-	-	-	-	
Recovery follow-up: 14 days № of participants:334 (1 RCT)(44)	**RR 1.80** (1.25 to 2.60)	20.0%	**36.1%** (25 to 52)	**16.1% more** (5 more to 32 more)	⊕◯◯ Low[b]	Remdesivir may increase recovery compared to placebo.
Time to recovery - not reported	-	-	-	-	-	
Admission to hospital due to COVID-19 follow-up: 28 days № of participants:562 (1 RCT)(44)	**HR 0.28** (0.10 to 0.75)	6.4%	**1.8%** (0.7 to 4.8)	**4.6% fewer** (5.7 fewer to 1.6 fewer)	◯◯◯ Insufficient[c,d]	The evidence is very uncertain about the effect of remdesivir on admission to hospital due to COVID-19 compared to placebo.
Serious adverse events follow-up: 28 days № of participants:562 (1 RCT)(44)	**RR 0.27** (0.10 to 0.70)	6.7%	**1.8%** (0.7 to 4.7)	**4.9% fewer** (6 fewer to 2 fewer)	◯◯◯ Insufficient[e]	The evidence is very uncertain about the effect of remdesivir on serious adverse events compared to placebo.
Adverse events follow-up: 28 days № of participants:562 (1 RCT)(44)	**RR 0.91** (0.76 to 1.10)	46.3%	**42.3%** (35.2 to 50.9)	**4.0% fewer** (11.1 fewer to 4.6 more)	⊕⊕◯ Moderate[f]	Remdesivir probably results in no difference in adverse events compared to placebo.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HR:** hazard Ratio; **no:** number; **RCT:** randomized controlled trial; **RR:** risk ratio

Explanations

a. Extremely few events; downgraded 3 steps for imprecision
b. Very few events; downgraded 2 steps for imprecision
c. hospitalization for any cause as outcome; downgraded 1 step for indirectness
d. Very few events; downgraded 2 steps for imprecision
e. Very few events with chance effects; a significantly higher risk for serious adverse events for placebo than remdesivir is not plausible; downgraded 3 steps for imprecision
f. Number of events does not meet optimal information size; downgraded 1 step for imprecision

Casirivimab/imdevimab compared to Placebo for Adults with Confirmed COVID-19 Infection

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		Effect with placebo	Effect with casirivimab/imdevimab	Difference		
All-cause mortality follow-up: 29 days № of participants:4,057 (1 RCT)(25)	**RR 0.33** (0.06 to 1.97)	0.2%	**0.1%** (0 to 0.4)	**0.1% fewer** (0.2 fewer to 0.2 more)	◯◯◯ Insufficient[a]	The evidence is very uncertain about the effect of casirivimab/imdevimab on all-cause mortality compared to placebo.
COVID-19-specific mortality - not reported	-	-	-	-	-	
Recovery - not reported	-	-	-	-	-	
Time to recovery follow-up: 29 days № of participants:3,432 (1 RCT)(25)	Median days: Casirivimab/imdevimab 10 (95% CI, NR) vs Placebo: 14 (95%CI, NR)[b]				⊕⊕⊕ High	Casirivimab/imdevimab reduces time to recovery compared to placebo.
Admission to hospital due to COVID-19 follow-up: 29 days № of participants:4,057 (1 RCT)(25)	**RR 0.30** (0.20 to 0.45)	4.4%	**1.3%** (0.9 to 2)	**3.1% fewer** (3.5 fewer to 2.4 fewer)	⊕⊕◯ Moderate[c]	Casirivimab/imdevimab probably results in a reduction in admission to hospital due to COVID-19 compared to placebo.
Serious adverse events follow-up: 29 days № of participants:5,531 (1 RCT)(25)	**RR 0.34** (0.24 to 0.48)	4.0%	**1.4%** (1 to 1.9)	**2.6% fewer** (3.1 fewer to 2.1 fewer)	◯◯◯ Insufficient[d]	The evidence is very uncertain about the effect of casirivimab/imdevimab on serious adverse events compared to placebo.
Adverse events follow-up: 29 days № of participants:5,531 (1 RCT)(25)	**RR 0.76** (0.63 to 0.90)	10.3%	**7.8%** (6.5 to 9.2)	**2.5% fewer** (3.8 fewer to 1 fewer)	◯◯◯ Insufficient[e]	The evidence is very uncertain about the effect of casirivimab/imdevimab on adverse events compared to placebo.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; NR; not reported; **no:** number; **OR:** odds ratio; **RR:** risk ratio; **vs:** versus

Explanations

a. Very few events; downgraded 3 steps for imprecision
b. Dosage of 8,000mg not considered in appraisal for time to recovery, as no data are reported for this study arm.
c. Few events; downgraded 1 step for imprecision
d. Few events with chance effects; a significantly higher risk for serious adverse events for placebo than Casirivimab/Imdevimab is not plausible; downgraded 3 steps for imprecision
e. A significantly higher risk for serious adverse events for placebo than Casirivimab/Imdevimab is not plausible; downgraded 3 steps for imprecision

Regdanvimab compared to Placebo for Adults with Confirmed COVID-19 Infection

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		Effect with placebo	Effect with regdanvimab	Difference		
All-cause mortality follow-up: 28 days № of participants:325 (1 RCT)(34)	not estimable	0.0%	**0.0%** (0 to 0)	**0.0% fewer** (0 fewer to 0 fewer)	◯◯◯ Insufficient[a]	The evidence is very uncertain about the effect of regdanvimab on all-cause mortality compared to placebo.
COVID-19-specific mortality - not reported	-	-	-	-	-	
Recovery follow-up: 28 days № of participants:285 (1 RCT)(34)	**RR 1.21** (1.05 to 1.38)	71.7%	**86.8%** (75.3 to 99)	**15.1% more** (3.6 more to 27.3 more)	⊕⊕◯ Moderate[b]	Regdanvimab probably increases recovery compared to placebo.
Time to recovery follow-up: range 14 days to 28 days № of participants:303 (2 RCTs)(34, 42)	Median days: Regdanvimab 5.5 (95% CI, 4.0 to 8.0) to 9.0 (95%CI, 6.0 to 13.0); Placebo: 8.0 (95% CI, 6.0 to 12.0) to 8.5 (95%CI. 7.0 to 11.0); no statistically significant difference (effect size NR)				⊕◯◯ Low[c]	Regdanvimab may result in no difference in time to recovery compared to placebo.
Admission to hospital due to COVID-19 follow-up: 28 days № of participants:307 (1 RCT)(34)	**RR 0.51** (0.21 to 1.26)	8.7%	**4.4%** (1.8 to 10.9)	**4.3% fewer** (6.8 fewer to 2.3 more)	⊕◯◯ Low[d]	Regdanvimab may result in no difference in admission to hospital due to COVID-19 compared to placebo.
Serious adverse events follow-up: range 14 days to 28 days № of participants:345 (2 RCTs)(34, 42)	not estimable	0.0%	**0.0%** (0 to 0)	**0.0% fewer** (0 fewer to 0 fewer)	◯◯◯ Insufficient[a]	The evidence is very uncertain about the effect of regdanvimab on serious adverse events compared to placebo.
Adverse events follow-up: range 14 days to 28 days № of participants:345 (2 RCTs)(34, 42)	**RR 0.97** (0.44 to 2.58)	30.7%	**29.4%** (13.5 to 79.2)	**0.3% fewer** (17.2 fewer to 48.5 more)	⊕◯◯ Low[b,e]	Regdanvimab may result in no difference in adverse events compared to placebo.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval (1 study) or credible interval (≥2 studies); NR; not reported; **no:** number; **RCT:** randomized controlled trial; **RR:** risk ratio

Explanations

a. No events; downgraded 3 steps for imprecision, b. Few events; downgraded 1 step for imprecision
c. Confidence intervals in both studies are too wide and encompass appreciable benefits or harms; downgraded 2 steps for imprecision
d. Very few events; downgraded 2 steps for imprecision, e. Confidence [0.44 to 2.58] intervals are wide and encompass appreciable benefits or harms; downgraded 1 step for imprecision

Sotrovimab compared to Placebo for Adults with Confirmed COVID-19 Infection

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		Effect with placebo	Effect with sotrovimab	Difference		
All-cause mortality follow-up: 29 days № of participants:1,057 (1 RCT)(38)	**RR 0.20** (0.01 to 4.12)	0.4%	**0.0%** (0 to 1.6)	**0.4% fewer** (0.4 fewer to 1.2 more)	◯◯◯ Insufficient[a]	The evidence is very uncertain about the effect of sotrovimab on all-cause mortality compared to placebo.
COVID-19-specific mortality - not reported	-	-	-	-	-	
Recovery - not reported	-	-	-	-	-	
Time to recovery - not reported	-	-	-	-	-	
Admission to hospital due to COVID-19 follow-up: 29 days № of participants:1,057 (1 RCT)(38)	**RR 0.20** (0.08 to 0.48)	5.7%	**1.1%** (0.5 to 2.7)	**4.6% fewer** (5.2 fewer to 2.9 fewer)	⊕◯◯ Low[b]	Sotrovimab may result in a reduction in admission to hospital due to COVID-19 compared to placebo.
Serious adverse events follow-up: 29 days № of participants:1,049 (1 RCT)(38)	**RR 0.35** (0.18 to 0.68)	6.1%	**2.1%** (1.1 to 4.1)	**4.0% fewer** (5 fewer to 1.9 fewer)	◯◯◯ Insufficient[c]	The evidence is very uncertain about the effect of sotrovimab on serious adverse events compared to placebo.
Adverse events follow-up: 29 days № of participants:1,049 (1 RCT)(38)	**RR 0.93** (0.74 to 1.17)	23.4%	**21.8%** (17.3 to 27.4)	**1.6% fewer** (6.1 fewer to 4 more)	⊕⊕◯ Moderate[d]	Sotrovimab probably results in no difference in adverse events compared to placebo.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **no:** number; **OR:** odds ratio; **RCT:** randomized controlled trial; **RR:** risk ratio

Explanations

a. Very few events; downgraded 3 steps for imprecision
b. Few events; downgraded 2 steps for imprecision
c. Very few events with chance effects; a significantly higher risk for serious adverse events for placebo than sotrovimab is not plausible; downgraded 3 steps for imprecision.
d. Confidence [0.74 to 1.17] intervals are wide and encompass appreciable benefits or harms; downgraded 1 step for imprecision

Antibiotics (Azithromycin) compared to Placebo for Adults with Confirmed COVID-19 Infection

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		Effect with placebo	Effect with azithromycin	Difference		
All-cause mortality follow-up: 21 days № of participants:197 (1 RCT)(41)	not estimable	0.0%	**0.0%** (0 to 0)	**0.0% fewer** (0 fewer to 0 fewer)	◯◯◯ Insufficient[a]	The evidence is very uncertain about the effect of antibiotics (azithromycin) on all-cause mortality compared to placebo.
COVID-19-specific mortality - not reported	-	-	-	-	-	
Recovery assessed with: Absence of symptoms follow-up: 14 days № of participants:201 (1 RCT)(41)	**RR 1.02** (0.91 to 1.13)	50.0%	50.4% (45.5 to 56.5)	0.6% more (4.5 fewer to 6.5 more)	⊕◯◯ Low[b]	Antibiotics (azithromycin) may result in no difference in recovery compared to placebo.
Time to recovery - not reported	-	-	-	-	-	
Admission to hospital due to COVID-19 follow-up: 21 days № of participants:197 (1 RCT)(41)	**RR 6.37** (0.36 to 113.59)	0.0%	**4.0%** (0 to 0)	**4.0% more** (0 fewer to 8 more)	◯◯◯ Insufficient[a]	The evidence is very uncertain about the effect of antibiotics (azithromycin) on admission to hospital due to COVID-19 compared to placebo.
Serious adverse events follow-up: 21 days № of participants:217 (1 RCT)(41)	not estimable	0.0%	**0.0%** (0 to 0)	**0.0% fewer** (0 fewer to 0 fewer)	◯◯◯ Insufficient[a]	The evidence is very uncertain about the effect of antibiotics (azithromycin) on serious adverse events compared to placebo.
Adverse events follow-up: 3 days № of participants:217 (1 RCT)(41)	**RR 2.14** (1.42 to 3.23)	26.4%	**56.6%** (37.5 to 85.2)	**30.2% more** (11.1 more to 58.8 more)	⊕◯◯ Low[b]	Antibiotics (azithromycin) may increase adverse events compared to placebo.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **no:** number; **RCT:** randomized controlled trial; **RR:** risk ratio

Explanations

a. Extremely few events; downgraded 3 steps for imprecision
b. Number of events does not meet optimal information size; downgraded 1 step for imprecision

Chloroquine/Hydroxychloroquine compared to Placebo for Adults with Confirmed COVID-19 Infection

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		Effect with placebo	Effect with chloroquine/hydroxychloroquine	Difference		
All-cause mortality follow-up: range 21 days to 90 days № of participants:1,045 (3 RCTs)(27, 28, 30)	**RR 0.41** (0.05 to 3.31)	0.2%	**0.0%** (0 to 0.8)	**0.2% fewer** (0.2 fewer to 0.6 more)	◯◯◯ Insufficient[a]	The evidence is very uncertain about the effect of chloroquine/hydroxychloroquine on all-cause mortality compared to placebo.
COVID-19-specific mortality follow-up: range 21 days to 30 days № of participants:604 (2 RCTs)(27, 28)	not estimable	0.0%	**0.0%** (0 to 0)	**0.0% fewer** (0 fewer to 0 fewer)	◯◯◯ Insufficient[b]	The evidence is very uncertain about the effect of chloroquine/hydroxychloroquine on COVID-specific mortality compared to placebo.
Recovery follow-up: 30 days № of participants:147 (1 RCT)(27)	**RR 0.78** (0.62 to 0.97)	78.4%	**60.9%** (48.6 to 76)	**17.5% fewer** (29.8 fewer to 2.4 fewer)	⊕◯◯ Low[c]	Chloroquine/Hydroxychloroquine may reduce recovery compared to placebo.
Time to recovery follow-up: 30 days № of participants:148 (1 RCT)(27)	Median time: Hydroxychloroquine 14.0 days (95% CI, 10.0 to 20.0) vs. Placebo 12.0 days (95% CI, 7.0 to 18.0); p=0.3 (effect size NR)				⊕◯◯ Low[c]	Chloroquine/Hydroxychloroquine may result in no difference in time to recovery compared to placebo.
Admission to hospital due to COVID-19 follow-up: range 21 days to 90 days № of participants:1,045 (3 RCTs)(27, 28, 30)	**RR 0.90** (0.37 to 2.21)	3.6%	**3.0%** (1.3 to 8)	**0.6% fewer** (2.3 fewer to 4.4 more)	⊕◯◯ Low[c]	Chloroquine/hydroxychloroquine may result in no difference in admission to hospital due to COVID-19 compared to placebo.
Serious adverse events follow-up: range 21 days to 90 days № of participants:1,045 (3 RCTs)(27, 28, 30)	**RR 1.02** (0.36 to 2.96)	2.9%	**2.2%** (1 to 8.5)	**0.7% fewer** (1.8 fewer to 5.7 more)	⊕◯◯ Low[c]	Chloroquine/hydroxychloroquine may result in no difference in serious adverse events compared to placebo.
Adverse events follow-up: 90 days № of participants:427 (1 RCT) (30)	**RR 1.06** (0.74 to 1.53)	20.9%	**22.2%** (15.5 to 32)	**1.3% more** (5.4 fewer to 11.1 more)	⊕◯◯ Low[c]	Chloroquine/hydroxychloroquine may result in no difference in adverse events compared to placebo.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval (1 study) or credible interval (≥2 studies); **no:** number; **RCT:** randomized controlled trial; **RR:** risk ratio; vs: versus

Explanations

a. Extremely few events; downgraded 3 steps for imprecision; b. No events; downgraded 3 steps for imprecision, c. Very few of events; downgraded 2 steps for imprecision

Ivermectin compared to Placebo for Adults with Confirmed COVID-19 Infection

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		Effect with placebo	Effect with ivermectin	Difference		
All-cause mortality follow-up: range 21 to 30 days № of participants:2,452 (5 RCTs)(26, 29, 47-49)	**RR 0.89** (0.42 to 1.91)	2.3%	**2.0%** (1.0 to 4.4)	**0.3% fewer** (1.3 fewer to 2.1 more)	⨁◯◯ Low[a]	Ivermectin may result in no difference in all-cause mortality compared to placebo..
COVID-19-specific mortality follow-up: range 21 to 30 days № of participants:593 (3 RCTs)(26, 29, 48)	**RR 0.55** (0.07 to 4.37)	0.4%	**0.0%** (0 to 1.5)	**0.4% fewer** (0.3 fewer to 1.2 more)	◯◯◯ Insufficient[b,c]	The evidence is very uncertain about the effect of ivermectin on COVID-specific mortality compared to placebo.
Recovery follow-up: range 21 to 30 days № of participants:569 (2 RCTs)(26, 48)	**RR 1.04** (0.61 to 1.72)	65.6%	**68.2%** (40 to 100)	**2.6% more** (25.6 fewer to 47.2 more)	⨁⨁◯ Moderate[d]	Ivermectin probably results in no difference in recovery compared to placebo.
Time to recovery follow-up: range 21 to 30 days № of participants:1,836 (3 RCTs)(26, 48, 49)	Time to recovery in three trials: ivermectin 10 to 29 days (IQR varied from 9 to 37 days) compared with placebo 12 to 14 days (IQR varied from 9 to 30 days)[d]				◯◯◯ Insufficient[b,e]	The evidence is very uncertain about the effect of ivermectin on time to recovery compared to placebo.
Admission to hospital due to COVID-19 follow-up: range 21 to 30 days № of participants:2,452 (5 RCTs)(26, 29, 47-49)	**RR 0.81** (0.49 to 1.345)	9.9%	**8.1%** (4 to 18.3)	**1.8% fewer** (5.0 fewer to 3.4 more)	⨁◯◯ Low[f]	Ivermectin may result in no difference in admission to hospital due to COVID-19 compared to placebo.
Serious adverse events follow-up: range 21 to 30 days № of participants:2,452 (5 RCTs)(26, 29, 47-49)	**RR 1.06** (0.47 to 2.5)	1.7%	**1.9%** (0.6 to 6.6)	**0.2% more** (0.9 fewer to 2.5 more)	◯◯◯ Insufficient[b,a]	The evidence is very uncertain about the effect of ivermectin on serious adverse events compared to placebo.
Adverse events follow-up: range 21 to 30 days № of participants:2,359 (4 RCTs)(26, 29, 47, 49)	**RR 0.89** (0.67 to 1.16)	31.8%	**27.7%** (19.4 to 40.0)	**4.1% fewer** (10.5 fewer to 5.1 more)	⨁⨁◯ Moderate[g]	Ivermectin probably results in no difference in adverse events compared to placebo.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval (1 study) or credible interval (≥2 studies); **IQR:** interquartile range; **no:** number; **RCT**: randomized controlled trial; **RR:** risk ratio

Explanations

a. Very few events; downgraded 2 steps for imprecision, b. One of three trials was high risk of bias; downgraded 1 step for risk of bias, c. Extremely few events; downgraded 3 steps for imprecision, d. One of two trials was high risk of bias; downgraded 1 step for risk of bias, e. Interquartile range vary; downgraded 2 steps for imprecision, f. Credible intervals are wide and encompass appreciable benefits or harms; downgraded 2 step for imprecision, g. Credible intervals are wide and encompass appreciable benefits or harms; downgraded 1 step for imprecision

Nitazoxanide compared to Placebo for Adults with Confirmed SARS-CoV-2 Infection

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		Effect with placebo	Effect with nitazoxanide	Difference		
All-cause mortality follow-up: range 14 days to 28 days № of participants:1,567 (2 RCTs)(32, 43)	**RR 1.61** (0.07 to 39.42)	0.0%	**0.2%** (0 to 0)	**0.2% more** (0.1 fewer to 2.7 more)	◯◯◯ Insufficient[a]	The evidence is very uncertain about the effect of nitazoxanide on all-cause mortality compared to placebo.
COVID-19-specific mortality follow-up: mean 28 days № of participants:1,092 (1 RCT)(43)	**RR 2.68** (0.13 to 55.74)	0.0%	**0.2%** (0 to 0)	**0.2% more** (0.1 fewer to 5.9 more)	◯◯◯ Insufficient[a]	The evidence is very uncertain about the effect of nitazoxanide on COVID-specific mortality compared to placebo.
Recovery follow-up: mean 5 days № of participants:392 (1 RCT)(32)	**RR 0.94** (0.83 to 1.07)	73.7%	**69.6%** (61.2 to 78.9)	**4.1% fewer** (12.5 fewer to 5.2 more)	⊕⊕◯ Moderate[b]	Nitazoxanide probably results in no difference in recovery compared to placebo.
Time to recovery № of participants:379 (1 RCT)(43)	Median days 13.3 (IQR 6.3 to 21) vs. 12.4 (IQR 7.2 to 21); p=0.88				⊕⊕◯ Moderate[b]	Nitazoxanide probably results in no difference in time to recovery compared to placebo.
Admission to hospital due to COVID-19 follow-up: range 5 days to 28 days № of participants:1,567 (2 RCTs)(32, 43)	**RR 0.69** (0.19 to 2.50)	1.1%	**0.7%** (0.2 to 2.9)	**0.4% fewer** (0.9 fewer to 1.7 more)	⊕◯◯ Low[c]	Nitazoxanide may result in no difference in admission to hospital due to COVID-19 compared to placebo.
Serious adverse events follow-up: range 5 days to 28 days № of participants:1,567 (2 RCTs)(32, 43)	**RR 0.33** (0.07 to 1.56)	1.1%	**0.3%** (0.1 to 1.8)	**0.8% fewer** (1.1 fewer to 0.6 more)	⊕◯◯ Low[c]	Nitazoxanide may result in no difference in serious adverse events compared to placebo.
Adverse events follow-up: range 5 days to 28 days № of participants:1,567 (2 RCTs)(32, 43)	**RR 0.79** (0.38 to 1.62)	19.3%	**14.2%** (7.3 to 31.2)	**5.1% fewer** (11.9 fewer to 11.9 more)	⊕⊕◯ Moderate[d]	Nitazoxanide probably results in no difference in adverse events compared to placebo.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval (1 study) or credible interval (≥2 studies); **IQR:** interquartile range; **no:** number; **RCT:** randomized controlled trial; **RR:** risk ratio

Explanations

a. Extremely few events; downgraded 3 steps for imprecision, b. Sample size does not meet optimal information size; downgraded 1 step for imprecision
c. Very few events; downgraded 2 steps for imprecision, d. Number of events does not meet optimal information size; downgraded 1 step for imprecision

Convalescent Plasma compared to Placebo for Adults with Confirmed COVID-19 Infection

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		Effect with placebo	Effect with convalescent plasma	Difference		
All-cause mortality follow-up: range 15 days to 28 days № of participants:2,272 (4 RCTs)(24, 36, 37, 46)	**RR 0.68** (0.20 to 2.34)	0.9%	**0.6%** (0.2 to 2.1)	**0.3% fewer** (0.7 fewer to 1.2 more)	⨁◯◯ Low[a]	Convalescent plasma may result in no difference in all-cause mortality compared to placebo.
COVID-19-specific mortality follow-up: range 15 days to 28 days № of participants:1,385 (2 RCTs) (24, 46)	**RR 0.37** (0.08 to 1.84)	1.0%	**0.3%** (0.1 to 1.9)	**0.7% fewer** (0.9 fewer to 0.8 more)	◯◯◯ Insufficient[b]	The evidence is very uncertain about the effect of convalescent plasma on COVID-specific mortality compared to placebo.
Recovery - not reported	-	-	-	-	-	
Time to recovery follow-up: 30 days № of participants:376 (1 RCT)(37)	Convalescent plasma 12·0 median days (IQR 6.0–21.3) vs. placebo 12.0 (6.0–22.0); HR 1.05 (95% CI 0.85 to 1.30)				⨁◯◯ Low[a]	Convalescent plasma may result in no difference in time to recovery compared to placebo.
Admission to hospital due to COVID-19 follow-up: 28 days № of participants:1601 (2 RCTs)(37, 46)	**RR 0.70** (0.30 to 1.65)	7.2%	**4.9%** (2.2 to 11.9)	**2.3% fewer** (5.1 fewer to 4.7 more)	◯◯◯ Insufficient[a,c]	The evidence is very uncertain about the effect of convalescent plasma on admission to hospital due to COVID-19 compared to placebo.
Serious adverse events follow-up: range 15 days to 28 days № of participants: 2,272 (4 RCTs)(24, 36, 37, 46)	**RR 1.09** (0.38 to 3.78)	1.1%	**1.1%** (0.4 to 4)	**0.1% more** (0.7 fewer to 2.9 more)	⨁◯◯ Low[a]	Convalescent plasma may result in no difference in serious adverse events compared to placebo.
Adverse events follow-up: 28 days № of participants:1,601 (2 RCTs)(37, 46)	**RR 1.20** (0.41 to 3.89)	7.8%	**7.3%** (3.2 to 30.5)	**0.5% fewer** (4.6 fewer to 22.7 more)	◯◯◯ Insufficient[a,c]	The evidence is very uncertain about the effect of convalescent plasma on adverse events compared to placebo.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval (1 study) or credible interval (≥2 studies); **IQR**: interquartile range; **HR:** hazard ratio; **no:** number; **RCT:** randomized controlled trial; **RR:** risk ratio

Explanations

a. Very few events; downgraded 2 steps for imprecision
b. Extremely few events; downgraded 3 steps for imprecision
c. Conflicting results between 2 RCTs; downgraded 1 step for inconsistency

Corticosteroids compared to Placebo for Adults with Confirmed COVID-19 Infection

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		Effect with placebo	**Effect with corticosteroids**	**Difference**		
All-cause mortality follow-up: 14 days № of participants:203 (1 RCT)(45)	not estimable	0.0%	**0.0%** (0 to 0)	**0.0% fewer** (0 fewer to 0 fewer)	◯◯◯ Insufficient[a]	The evidence is very uncertain about the effect of corticosteroids on all-cause mortality compared to placebo.
COVID-19-specific mortality follow-up: 14 days № of participants:215 (1 RCT)(45)	not estimable	0.0%	**0.0%** (0 to 0)	**0.0% fewer** (0 fewer to 0 fewer)	◯◯◯ Insufficient[a]	The evidence is very uncertain about the effect of corticosteroids on COVID-specific mortality compared to placebo..
Recovery follow-up: 14 days № of participants:203 (1 RCT)(45)	**RR 1.13** (0.91 to 1.40)	58.2%	**65.7%** (52.9 to 81.4)	**7.5% more** (5.2 fewer to 23.3 more)	⊕◯◯ Low[b]	Corticosteroids may result in no difference in recovery compared to placebo.
Time to recovery - not reported	-	-	-	-	-	
Admission to hospital due to COVID-19 follow-up: 14 days № of participants:203 (1 RCT)(45)	**RR 0.47** (0.12 to 1.82)	6.1%	**2.9%** (0.7 to 11.1)	**3.2% fewer** (5.4 fewer to 5 more)	◯◯◯ Insufficient[a]	The evidence is very uncertain about the effect of corticosteroids on admission to hospital due to COVID-19 compared to placebo.
Serious adverse events follow-up: 14 days № of participants:209 (1 RCT)(45)	**RR 1.36** (0.45 to 4.15)	4.9%	**6.6%** (2.2 to 20.1)	**1.7% more** (2.7 fewer to 15.3 more)	⊕◯◯ Low[b]	Corticosteroids may result in no difference in serious adverse events compared to placebo.
Adverse events № of participants:203 (1 RCT)(45)	**RR 1.43** (0.79 to 2.58)	15.3%	**21.9%** (12.1 to 39.5)	**6.6% more** (3.2 fewer to 24.2 more)	⊕◯◯ Low[b]	Corticosteroids may result in no difference in adverse events compared to placebo.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **no:** number; **RCT:** randomised controlled trial; **RR:** risk ratio

Explanations

a. Extremely few events; downgraded 3 steps for imprecision
b. Very few events; downgraded 2 steps for imprecision

Fluvoxamine compared to Placebo for Adults with Confirmed COVID-19 Infection

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		Effect with placebo	Effect with fluvoxamine	Difference		
All-cause mortality follow-up: range 15 days to 28 days № of participants:1,649 (2 RCTs)(39, 40)	**RR 0.71** (0.24 to 2.10)	3.0%	**2.1%** (0.7 to 6.3)	**0.9% fewer** (2.3 fewer to 3.3 more)	⨁◯◯ Low[a]	Fluvoxamine may result in no difference in all-cause mortality compared to placebo.
COVID-19-specific mortality follow-up: 15 days № of participants:152 (1 RCT)(40)	not estimable	0.0%	**0.0%** (0 to 0)	**0.0% fewer** (0 fewer to 0 fewer)	◯◯◯ Insufficient[b]	The evidence is very uncertain about the effect of fluvoxamine on COVID-specific mortality compared to placebo.
Recovery - not reported	-	-	-	-	-	
Time to recovery - not reported	-	-	-	-	-	
Admission to hospital due to COVID-19 follow-up: range 15 days to 28 days № of participants:1,649 (2 RCTs)(39, 40)	**RR 0.71** (0.22 to 1.70)	12.2%	**9.1%** (2.7 to 20.7)	**3.1% fewer** (9.5 fewer to 8.5 more)	⨁◯◯ Low[c,d]	Fluvoxamine may result in no difference in admission to hospital due to COVID-19 compared to placebo.
Serious adverse events follow-up: 15 days № of participants:152 (1 RCT)(40)	**RR 0.18** (0.02 to 1.50)	6.9%	**1.3%** (0.1 to 10.4)	**5.6% fewer** (6.8 fewer to 3.5 more)	◯◯◯ Insufficient[e]	The evidence is very uncertain about the effect of fluvoxamine on serious adverse events compared to placebo.
Adverse events follow-up: 15 days № of participants:152 (1 RCT)(40)	**RR 0.98** (0.46 to 2.09)	15.3%	**15.0%** (7 to 31.9)	**0.3% fewer** (8.3 fewer to 16.7 more)	⨁◯◯ Low[a]	Fluvoxamine may result in no difference in adverse events compared to placebo.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval (1 study) or credible interval (≥2 studies); **no:** number; **OR:** odds ratio; **RCT:** randomized controlled trial; **RR:** risk ratio

Explanations

a. Few events; downgraded 2 steps for imprecision
b. No events; downgraded 3 steps for imprecision
c. Confidence intervals [0.22 to 1.70] are wide and encompass appreciable benefits or harms; downgraded 1 step for imprecision
d. Few events; downgraded 1 step for imprecision, e. Very few events; downgraded 3 steps for imprecision

Supplement Table 9: Subgroup Results

Author, Year	Age	Gender	Comorbidity	Other
Admission to hospitalization due to COVID-19				
Ivermectin				
Reis et al. 2022(49)	Age ≤50 yr: G1: 38/335 G2: 39/347 RR 1.01 (95% CI 0.66 to 1.53) Age >50 yr: G1: 53/295 G2: 66/283 RR 0.77 (95% CI 0.56 to 1.06)	Female: G1:47/383 G2:59/408 RR (95% CI): 0.85 (0.59–1.21) Male: G1:53/296 G2:52/271 RR 0.93 (95% CI 0.66 to 1.32)	Body-mass index <30: G1: 38/345 G2: 48/333 RR 0.77 (95% CI 0.51 to 1.14) Body-mass index ≥30: G1:60/330 G2:63/339 RR 0.98 (95% CI 0.71 to 1.34) Cardiovascular disease = Yes: G1:47/282 G2:53/272 RR (95% CI): 0.86 (0.60–1.22) Cardiovascular disease = No: G1:53/397 G2:58/407 RR 0.94 (95% CI 0.66 to 1.32) Lung disease = Yes: G1:4/14 G2:5/14 RR 0.83 (95% CI 0.28 to 2.26) Lung disease = No: G1:96/665 G2:106/664 RR 0.90 (95% CI 0.70 to 1.17)	Smoking status = Current: G1: 5/50 G2:5/59 RR 1.18 (0.38 to 3.63) Smoking status = Former: G1:15/94 G2:13/73 RR 0.89 (95% CI 0.46 to 1.75) Smoking status = Never: G1:80/535 G2:93/545 RR 0.88 (95% CI 0.67 to 1.15) Time since onset of symptoms: 0–3 days: G1: 41/282 G2:35/276 RR 1.14 (95% CI 0.76 to 1.74) 4–7 days: G1:43/242 G2:43/241 95% CI 1.00 (0.68 to 1.46)
Lopinavir/Ritonavir, Chloroquine				
Reis et al. 2021 (30)	Age <50 G1: 0/77 RR 0.13 (95% CI 0.01 to 2.54) G2: 3/89 RR 0.81 (95% CI 0.17 to 3.89) G3: 3/72 Age >=50 G1: 8/133 RR 1.13 (95% CI 0.44 to 2.92) G2: 11/149 RR 1.38 (95% CI 0.57 to 3.34) G3: 8/150	Female G1: 5/122 RR 1.24 (95% CI 0.24 to 4.51) G2: 3/134 RR 1.83 (95% CI 0.45 to 7.50) G3: 4/121 Male G1: 3/92 RR 0.49 (95% CI 0.13 to 1.85) G2: 11/110 RR 0.33 (95% CI 0.09 to 1.13) G3: 7/106	Diabetes = no G1: 5/173 RR 0.58 (95% CI 0.20 to 1.69) G2: 9/200 RR 0.90 (95% CI 0.37 to 2.22) G3: 9/180 Diabetes = yes G1: 3/40 RR 1.76 (95% CI 0.31 to 10.03) G2: 5/43 RR 2.73 (95% CI 0.56 to 13.36) G3: 2/47 Cardiac Disease = no G1: 4/111 RR 1.06 (95% CI 0.27 to 4.15) G2: 6/111 RR 1.59 (95% CI 0.46 to 5.50) G3: 4/118 Cardiac Disease = yes G1: 4/103 RR 0.60 (95% CI 0.18 to 2.00) G2: 8/133 RR 0.94 (95% CI 0.35 to 2.50) G3: 7/109	Symptom Onset <120 hours G1: 1/37 RR 3.24 (95% CI 0.14 to 77.01) G2: 2/34 RR 5.86 (95% CI 0.29 to 117.86) G3: 0/40 Symptom Onset >=120 hours G1: 7/177 RR 0.67 (95% CI 0.27 to 1.70) G2: 12/210 RR 0.97 (95% CI 0.44 to 2.25) G3: 11/187

Author, Year	Age	Gender	Comorbidity	Other
			Lung Disease = no G1: 8/190 RR 0.87 (95% CI 0.35 to 2.16) G2: 13/229 RR 1.18 (95% CI 0.53 to 2.62) G3: 10/207 Lung Disease = yes G1: 0/24 RR 0.28 (95% CI 0.01 to 6.50) G2: 1/15 RR 1.33 (95% CI 0.09 to 19.64) G3: 1/20	
Molnupiravir				
Jayk Bernal et al. 2022 (33)	Incidence of hospitalization or death: At day 29: >60 years: G1: 12/118; G2: 16/127; ARR −2.4 (95% CI −10.6 to 5.8) ≤60 years: G1: 36/591; G2: 52/572; ARR(95% CI) -3.0 (-6.1, 0-0)	Incidence of hospitalization or death: At day 29: Female G1: 16/379; G2: 27/344; ARR(95% CI) -3.6 (95% CI -7.4 to -0.2) Male G1: 32/330;G2: 41/355; ARR(95% CI) -1.9 (95% CI -6.5 to 2.8)	Incidence of hospitalization or death: At day 29: Obesity = yes G1: 29/535; G2: 46/507; ARR -3.7 (95% CI -6.9 to -0.5) Obesity = no G1: 19/174; G2: 22/192; ARR -0.5 (95% CI -7.1 to 6.2) Diabetes Mellitus = yes G1: 17/107; G2: 17/117; ARR 1.4 (95% CI -8.2 to 11-1) Diabetes Mellitus = no G1: 31/602; G2: 51/582; ARR -3.6 (95% CI -6.6 to -0.7) Serious Heart condition = yes G1: 8/86; G2: 9/78; ARR -2.2 (95% CI -12.4 to 7-5) Serious Heart condition = no G1: 40/623; G2: 59/621; ARR -3.1 (95% CI -6.2 to -0.1)	Incidence of hospitalization or death: At day 29: Days since onset of symptoms = ≤3 G1:25/339; G2: 28/335; ARR -1.0 (95% CI -5.2 to 3.2) Days since onset of symptoms = >3 G1: 23/370; G2: 40/364; ARR -4.8 (95% CI -9.0 to -0.7) Baseline Covid-19 severity = mild G1: 19/395; G2: 27/376; ARR -2.4 (95% CI −5.9 to 1.0) Baseline Covid-19 severity = moderate G1: 29/311; G2: 40/321; ARR -3.1 (95% CI -8.1 to 1.8) Variant = Gamma G1: 0/37; G2: 9/47; ARR -19.1 (95% CI -32.6 to -8.9) Variant = Delta G1: 18/237; G2: 22/221; ARR -2.4 (95% CI -7.8 to 2.9) Variant = Mu G1: 6/75; G2: 13/82; ARR -7.9 (95% CI -18.5 to 2.6) Other G1: 5/47; G2: 7/38; ARR (95% CI -24.4 to 7.4)
Nirmatrelvir/Ritonavir				
Hammond et al. 2022 (35)	At 28 days: <65 yr: G1: 7/908; G2: 46/909 -4.35% difference (95% CI -5.91 to -2.79) ≥65 yr: G1: 1/131; G2: 20/137 -13.93% difference (95% CI -20.07 to -7.80)	At 28 days: Female G1: 4/519; G2: 25/506; -4.23% difference (95% CI -6.29 to -2.17) Male G1: 4/520; G2: 41/540; -6.93% difference (95% CI -9.32 to -4.53)	BMI = <25 G1: 1/209; G2: 9/207; -3.88% difference (95% CI -6.83 to -0.94) BMI = 25 to <30 G1: 3/458; G2: 28/466; -5.44% difference (95% CI -0.75 to -3.13) BMI = ≥30 G1: 4/371; G2: 29/373; -6.85% difference (95% CI -9.82 to -3.87) Diabetes mellitus = yes G1: 2/125; G2: 9/127; -5.51% difference (95% CI -10.51 to -0.52) Diabetes mellitus = no G1: 6/913; G2: 57/919; -5.63% difference (95% CI -7.30 to -3.96) Number of comorbidities = 0-1	At 28 days: Time since symptom onset = ≤3 days G1: 5/697; G2: 44/682; -5.81% difference (95% CI -7.78 to −3.84) Time since symptom onset = >3 days G1: 3/342; G2: 22/364; -5.23% difference (95% CI -7.91 to -2.55)

Author, Year	Age	Gender	Comorbidity	Other
			G1: 4/829; G2: 43/832; -4.76% difference (95% CI -6.37 to -3.16) Number of comorbidities = 2-3: G1: 4/206; G2: 23/211; -8.96% difference (95% CI -13.59 to -4.32) Number of comorbidities = at least 4: G1: 0/4; G2: 0/3; 0.00 (0.00 to 0.00)	
Remdesivir				
Gottlieb et al. 2021 (44)	age ≥60 years G1: 1/83 (1.2); G2: 9/87 (10.3); HR 0.11 (95% CI 0.01 to 0.86)	Male G1: 1/148 (0.7); G2: 9/145 (6.2); HR 0.11 (95% CI 0.01 to 0.84)	Diabetes mellitus G1: 2/173 (1.2); G2: 14/173 (8.1); HR 0.14 (95% CI 0.03 to 0.63) Obesity G1: 1/154 (0.6); G2: 9/156 (5.8); HR 0.11 (95% CI 0.01 to 0.88) Hypertension G1: 2/138 (1.4); G2: 10/130 (7.7); HR 0.17 (95% CI 0.04 to 0.76) Chronic lung disease: G1: 0/67; G2: 4/68 (5.9) Cardiovascular or cerebrovascular disease G1: 0/20; G2: 2/24 (8.3) Current cancer G1: 0/12; G2: 2/18 (11.1)	Incidence of hospitalization or death at day 28: residence in the United States G1: 2/264; G2: 12/267; HR 0.17 (95% CI 0.04 to 0.76) Ethnic group = not Hispanic or Latinx G1: 2/146 (1.4); G2: 8/158 (5.1); HR 0.26 (95% CI 0.06 to 1.22) Ethnic group: Hispanic or Latinx: G1: 0/123; G2: 6/112 (5.4)
Regdanvimab				
Streinu-Cercel et al. 2021 (34)	NR	NR	NR	mild versus moderate disease severity at 28 days: G1: 0/38 vs 4/62 (6.5%) *RR 0.18 (95% CI 0.01 to 3.24)* G2: 0/40 vs 5/63 (7.9%) *RR 0.14 (95% CI 0.01 to 2.50)* G3: 0/46 vs 9/57 (15.8%) *RR 0.06 (95% CI 0.004 to 1.09)* subgroup moderate severity: all treatments versus placebo at 28 days: G1+G2: 9/125 (7.2%) G3: 9/57 (15.8%) *RR 0.46 (95% CI 0.19 to 1.09)*
Convalescent Plasma				
Sullivan et al. 2022 (46)	NR	Female G1: 9/323 (3%) G2: 21/352 (6%) Male G1: 8/269 (3%)	NR	NR

Author, Year	Age	Gender	Comorbidity	Other
		G2: 16/237 (7%)		
Fluvoxamine				
Reis et al. 2022 (39)	Age: <=50 G1: 23/368 (6.3%) G2: 41/379 (10.8%) HR 0.57 (95% CI 0.34 to 0.95) Age >50 G1: 50/327 (15.3%) G2: 72/328 (22.0%) HR 0.67 (95% CI 0.47 to 0.96) p (interaction)=0.60	Female G1: 28/409 (6.8%) G2: 61/453 (13.5%) HR 0.49 (95% CI 0.31 to 0.77) Male G1: 51/376 (13.6%) G2: 58/303 (19.1%) HR 0.80 (95% CI 0.55 to 1.16) p (interaction)=0.10	BMI = <30 G1: 34/355 (9.6%) G2: 52/373 (13.9%) HR 0.67 (95% CI 0.44 to 1.03) BMI = >30 G1: 44/376 (11.7%) G2: 67/375 (17.9%) HR 0.64 (95% CI 0.44 to 0.94) p (interaction)=0.87 Cardiovascular disease = no G1: 79/733 G2: 117/747 HR 0.67 (95% CI 0.45 to 1.00) Cardiovascular disease = yes G1: 0/4 (0%) G2: 2/8 (25%) HR 0.65 (95% CI 0.44 to 0.97) p (interaction)=0.94 Chronic kidney disease = no G1: 78/704 (11.1%) G2: 115/702 (16.4%) HR 0.66 (95% CI 0.50 to 0.88) Chronic kidney disease = yes G1: 1/35 (2.9%) G2: 4/54 (7.4%) HR 0.37 (95% CI 0.04 to 3.35) p (interaction)=0.60	Time from onset of symptoms = 0-3 days G1: 30/328 (9.1%) G2: 39/310 (12.6%) HR 0.72 (95% CI 0.45 to 1.15) Time from onset of symptoms = 4-7 days G1: 31/239 (13.0%) G2: 44/267 (16.5%) HR 0.77 (95% CI 0.49 to 1.23) p (interaction)=0.82
Recovery				
Azithromycin				
Oldenburg et al. 2021 (41)	absence of symptoms at 14 days: Age <=60 G1: 61/121 (50%) G2: 31/62 (50%) *RR 1.01 (95% 0.74 to 1.37)* Age >60 G1: 5/10 (50%) G2: 4/8 (50%) *RR 1.00 (95% CI 0.39 to 2.53)*	NR	NR	NR
Time to recovery				
Regdanvimab				

Author, Year	Age	Gender	Comorbidity	Other
Streinu-Cercel et al. 2021 (34)				mild versus moderate disease severity at day 14: median (95% CI) G1: 4.4 (2.2–7.7) vs 5.7 (4.1–7.3) G2: 5.5 (3.2–7.6) vs 7.3 (5.6–10.7) G3: 6.9 (4.8–8.8) vs 10.8 (6.8–n.c.)

BMI: Body Mass Index; RR: risk ratio; HR: hazard ratio; ARR: absolute risk reduction; CI: confidence interval; NR: not reported; G1: group 1; G2: group 2; G3: group 3

Supplement Table 10: Studies Identified in First Surveillance Search (August 17, 2022)

Author, Year ***Risk of bias***	***Population***	***N total (randomized),*** ***Interventions,*** ***N group***	***Outcomes*** ***(Follow-up Duration)***	***Summary of Results***
Biber, 2022 (50) Some concerns	Adults with molecular confirmation of COVID-19 by RT-PCR, who received results within the first 7 days from symptom onset. Asymptomatic cases were also included within 5 days from molecular diagnosis.	N=116 Ivermectin 12 or 15 mg: 57 Placebo: 59	• Admission to hospital due to COVID-19 • Incidence of adverse events (14 days)	No statistically significant difference was observed for the outcomes of interest between the two groups.
Caraco, 2022 (51) Low	Adults with mild or moderate, laboratory confirmed Covid-19 with onset of Covid-19 signs and/or symptoms up to (and including) 7 days before randomization.	N=302 Molnupiravir 200mg: 75 Molnupiravir 400mg: 77 Molnupiravir 800mg: 76 Placebo: 74	• All-cause mortality • COVID-19-related mortality • Admission to hospital due to COVID-19 • Incidence of adverse events • Incidence of serious adverse events (29 days)	No statistically significantly difference was observed for the outcomes of interest between the two groups.
Mirahmadizadeh, 2022 (52) Some concerns	Adults with mild symptomatic COVID-19 confirmed by RT-PCR test and symptom onset-to-visit interval of less than 48 h.	N=393 Ivermectin 12 mg: 131 Ivermectin 24 mg: 131 Placebo: 131	• All-cause mortality • COVID-19-related mortality • Recovery • Symptom duration time until symptom free) • Admission to hospital due to COVID-19 • Incidence of adverse events • Incidence of serious adverse events	No statistically significantly difference was observed for the outcomes of interest between the two groups.

			(28 and 29 days)	
Montgomery, 2022 (53) Low	Adults with a documented laboratory-confirmed SARS-CoV-2 infection, as determined by RT-PCR or an antigen test from any respiratory tract specimen collected 3 days or less before enrolment (day 1), a WHO Clinical Progression Scale score of more than 1 to less than 4, and who had not received a COVID-19 vaccination.	N=910 Tixagevimab–cilgavimab 600 mg: 456 Placebo: 454	• All-cause mortality • COVID-19-related mortality • Admission to hospital due to COVID-19 • Incidence of adverse events • Incidence of serious adverse events (29 days)	The incidence of COVID-19 deaths or progression to severe disease (RR 0.43; 95% CI 0.025 to 0.75). and incidence of adverse events (29% vs 36%; 0.81; 95% CI 0.67 to 0.98) were statistically significantly lower in the tixagevimab–cilgavimab group compared to placebo. There were three COVID-19-reported deaths in the tixagevimab–cilgavimab group and six in the placebo group.
Rezai, 2022 (54) Low	Patients, aged 5 years or more, weight more than 15 kg, with positive diagnostic by RT-PCR assay for SARS-CoV-2 using a nasopharyngeal swab ≤ 4 days prior to screening or positive rapid COVID-19 test, without evidence of viral pneumonia or hypoxia*.	N=582 Ivermectin 6, 12, 18, 24 or 30 mg: 282 Placebo:300	• All-cause mortality • Recovery • Admission to hospital due to COVID-19 • Incidence of adverse events • Incidence of serious adverse events (5 and 7 days)	No statistically significantly difference was observed for the outcomes of interest between the two groups.
Seo, 2022 (55) Low	Adult patients with SARS-CoV-2 infection laboratory-confirmed by RT-PCR; patients with symptom onset less than 7 days after randomization and had positive RT-PCR results within 3 days of randomization were enrolled.	N=52 Fluvoxamine 100 mg: 26 Placebo: 26	• Admission to hospital due to COVID-19 • Incidence of serious adverse events (10 days)	No statistically significantly difference was observed for the outcomes of interest between the two groups.

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