Supplemental Material*

Sommer I, Dobrescu A, Ledinger D, et al. Outpatient treatment of confirmed COVID-19. A living, rapid review for the American College of Physicians. Ann Intern Med. 2022. [Epub ahead of print]. doi:10.7326/M22-2202

Contents

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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.
6. Ayudas Diagnosticas Sura S.A.S. Ivermectina Colombia (IVERCOL) (IVERCOL): ClinicalTrials.gov; 2021 [03/17/2022]. Available from: https://clinicaltrials.gov/ct2/show/NCT04886362.
7. Azidus Brasil. Efficacy and Safety of Nitazoxanide 600 mg to Treat Mild Ambulatory COVID-19 Patients: ClinicalTrials.gov; 2020 [03/16/2022]. Available from: https://clinicaltrials.gov/ct2/show/NCT04441398.
8. Barcelona Institute for Global Health. Hydroxychloroquine efficacy in preventing SARS-CoV-2 infection and CoVid-19 disease severity during pregnancy: EU Clinical Trials Register (EU CTR); 2020 [03/15/2022]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-001587-29.
9. Biber A, Mandelboim M, Harmelin G, Lev D, Ram L, Shaham A, et al. 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 2021 [September, 5 2022]. 2021.05.31.21258081]. Available from: http://medrxiv.org/content/early/2021/05/31/2021.05.31.21258081.abstract.
10. Brown LK, Freemantle N, Breuer J, Dehbi HM, Chowdhury K, Jones G, et al. Early antiviral treatment in outpatients with COVID-19 (FLARE): a structured summary of a study protocol for a randomised controlled trial. Trials. 2021;22(1):193. Epub 20210308. doi: 10.1186/s13063-021-05139-2. PubMed PMID: 33685502; PubMed Central PMCID: PMC7938371.
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-19: 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-19: At 29 days: G1: 45/709 (6) G2: 64/699 (9) 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-19: 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-19: 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 COVID-19: At 28 days: G1: 2/279 (1) G2: 15/283 (5) HR 0.13 (95% CI 0.0.03-0.59)	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-19: 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-19: 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-19: 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-19[§]: At 29 days: G1: 3/528 (1) G2: 28/529 (5) 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-19: 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 Disease severity:	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 Diagnostic tool:	Proportion of symptomatic participants (%): NR Duration of symptoms: NR Proportion of participants with previous infections: NA Time (days) since previous infection: NR Proportion of vaccinated participants:	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 mortality:	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 (%))
		mild or no symptoms Pregnant women: Not eligible		RT-PCR	NA Disease severity (%): NR Currently pregnant (%): NA	At 21 days: G1: 0/152(0) G2: 0/152(0) G3: 0/152(0) Hospitalization due to COVID-19: NR	
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 (%): NA	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-19: 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)
Schwartz et al. 2021 (27) ALBERTA HOPE	RCT (double-blinded), Canada	COVID-19 vaccine received Vaccination: NR	N=148 G1: 111 Hydroxychloroquine 800 mg oral on	Age, years, mean (SD): G1: 46.7 G2: 46.9	Proportion of symptomatic participants (%): G1: 100 G2: 100	Recovery[†]: At 30 days: G1: 67/110 (61) G2: 29/37 (78)	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 (%))
COVID-19 NCT04329611 Government Industry Academic Some concerns	30 B.1.1.7 (alpha): NR B.1.617.2 (delta): 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	day 1, 400 mg after G2: 37 placebo	female (%): G1: 41 G2: 54 Ethnicity: Non-white (%): G1: 68 G2: 58 Diagnostic tool: RT-PCR	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	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-19: At 30 days: G1: 4/110 (4) G2: 0/37 (0)	At 30 days: G1: 3/91 (3) G2: 0/33 (0) p=0.6
Ivermectin							
Buonfrate et al. 2022 (48) COVER Study NCT04438850 Industry Academic Foundation/non-profit	RCT (double-blinded), Italy 30 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: NR	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	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)	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:	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 (%))
professional organization High	B.1.1.529 (omicron): NR	Disease severity: mild to moderate Pregnant women: Not eligible		Ethnicity (%): Non-white: NR Diagnostic tool: RT-PCR	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	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-19: At 30 days*** G1: 1/29 (3) G2: 3/30 (10) G3: 0/30 (10) p=NR	
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	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	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:	Recovery†: NR Symptom duration (time until symptom free): NR All-cause mortality: At 28 days: 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)

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 (%))
		more than 72 hours before enrolment. Disease severity: mild to moderate Pregnant women: Not eligible		Diagnostic tool: RT-PCR	G1: 0 G2: 0 Time (days) since previous infection: NR Proportion of vaccinated participants: NR Disease severity (%): NR Currently pregnant (%): NA	COVID-19 specific mortality: At 28 days G1: 0/12 (0) G2: 0/12 (0) Hospitalization due to COVID-19: 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: within the last 7 days before randomisation Disease severity: mild Pregnant women: Not eligible	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: NR Diagnostic tool: RT-PCR or antigen	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 infections: NR Time (days) since previous infection: NR Proportion of vaccinated participants: NR Disease severity (%): Mild: G1: 100	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) 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	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 (%))
					G2: 100 Currently pregnant (%): NA	COVID-19: 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: NR Disease severity (%): NR Currently pregnant (%): NA	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-19: At 28 days: G1: 78/679 (12) G2: 93/679 (14)	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)
Vallejos et al. 2021 (47) IVER-COR COVID19	RCT (double-blinded), Argentina	COVID-19 vaccine received: NR Previous SARS-	N=501 G1: 250 Ivermectin 24-48 mg	Age, years, mean (SD): G1: 42.58 (15.29) G2: 42.40 (15.75) female (%):	Proportion of symptomatic participants (%): G1: 96 G2: 96	Recovery†: NR Symptom duration (time until symptom free):	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 (%))
NCT04529525 Government Academic Low	30 P.1 (gamma): NR C.37 (lambra): NR	CoV-2 infection: NR Presence and/or duration of symptoms: NR Disease severity: mild to moderate Pregnant women: Not eligible	G2: 251 Placebo	G1: 44 G2: 50 Ethnicity (%): NR Diagnostic tool: RT-PCR	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	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-19: At 30 days: G1: 14/250 (6) G2: 21/251 (8) p=NR	
Nitazoxanide							
Rocco et al. 2021 (32) NCT04552483 Government Academic Some concerns	RCT (double-blinded), Brazil 14 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: clinical symptoms of COVID-19 no longer than 3 days	N=475 G1: 238 Nitazoxanide 500 mg oral G2: 237 Placebo	Age, years, (%): 18–39 years G1: 59 G2: 57 40–59 years G1: 35 G2: 37 60–77 years G1: 6 G2: 6 female (%): G1: 48 G2: 58 Ethnicity (%):	Proportion of symptomatic participants (%): G1: 100 G2: 100 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	Recovery[†]: At 5 days: G1: 135/194 (70) G2: 146/198 (74) 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	Any AE: At 5 days G1: 60/238 (25) G2: 60/237 (25) p=NR Serious AE: At 5 days G1: 1/238 (0.4) G2: 1/237 (0.4)

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 (%))
		Disease severity: mild Pregnant women: Not eligible		Non-White G1: 32 G2: 30 Diagnostic tool: RT-PCR	Proportion of vaccinated participants: NR Disease severity (%): Mild: G1: 100 G2: 100 Currently pregnant (%): NA	mortality: NR Hospitalization due to COVID-19[§]: At 5 days: G1: 5/238 (2) G2: 5/237 (2) p=NR	
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 respiratory symptom domains related to Covid-19 within 72 hours Disease severity: mild to moderate Pregnant women: Not eligible	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 Diagnostic tool: RT-PCR	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: NR Proportion of vaccinated participants: NR Disease severity (%): Moderate: G1: 37 G2: 33 Currently pregnant (%): NA	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 COVID-19 specific mortality: At 28 days: G1: 1/472 (0.2) G2: 0/463 (0) p=NR Hospitalization due to COVID-19[§]: At 28 days: G1: 1/472 (0.2)	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 (%))
						G2: 4/463 (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 women: Not eligible	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: G1: 97 G2: 97 Moderate: G1: 3 G2: 3 Currently pregnant (%): NA	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 Hospitalization due to COVID-19: At 28 days: G1: 22/188 (12) G2: 21/188 (11) p=0.76 RR 1.05 (95 CI, 0.78 to 1.41)	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
Korley et al. 2021 (36)	RCT (single-blinded)	COVID-19 vaccine received: not eligible	N=511 G1: 257	Age, years,median (IQR) G1: 54 (42–62)	Proportion of symptomatic participants (%): NR	Recovery†: NR	Any 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 (%))
SIREN-C3PO NCT04355767 Government Academic Some concerns	U.S. 15 B.1.1.7 (alpha): NR B.1.617.2 (delta): NR	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	Convalescent plasma 250 ml G2: 254 Placebo	G2: 54 (40–62) female (%): G1: 53 G2: 55 Ethnicity (%): Non-white: G1: 33 G2: 35 Diagnostic tool: RT-PCR	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%	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-19: G1: 46/257 (18) G2: 56/254 (22) P=NR	Serious AE: At 30 days: G1: 3/257 (1) G2: 0/254 (0) p=NR
Libster et al. 2021 (24) NR NCT04479163 Government Industry Foundation/non-profit professional organization Some concerns	RCT (double-blinded), Argentina 15 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 at least one Covid-19 related symptom for less than 48 hours	N=160 G1: 80 Convalescent plasma 250 ml G2: 80 Placebo	Age, years, mean (SD): G1: 76.4 (8.7) G2: 77.9 (8.4) female (%): G1: 68 G2: 58 Ethnicity (%): NR 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:	Recovery[†]: NR Symptom duration (time 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)	Any AE: NR Serious AE: At 15 days: G1: 7/80 (9) G2: 12/80 (15) RR (95% CI): 0.58 (0.24–1.41)

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 Pregnant women: Not eligible			G1: 0 G2: 0 Disease severity (%): Mild: G1: 100 G2: 100 Currently pregnant (%): NA	G2: 4/80 (5) Hospitalization due to COVID-19: NR	
Sullivan et al. 2022 (46) CSSC-004 NCT04373460 Government Industry Academic Foundation/non-profit professional organization Low	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 Disease severity: NR Pregnant women: Eligible	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 Diagnostic tool: RT-PCR or antigen	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 Time (days) since previous infection: NR Proportion of vaccinated participants: Partially vaccinated (%): G1: 5 G2: 5 Fully vaccinated (%): G1: 12 G2: 13	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: At 28 days: G1: 0/592 (0) G2: 3/589 (1) p=NR Hospitalization due to COVID-19: At 28 days: G1: 17/592(3) G2: 37/589 (6) absolute risk reduction (95% CI), 3.4% points (1.0	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 (-0.11, 0.02)

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 (%): NR Currently pregnant (%): G1: 0.3% G2: 0.2%	to 5.8)	
Other drugs							
Corticosteroids							
Ezer et al. 2021 (45) CONTAIN NCT04435795 Industry Academic Foundation/non-profit professional organization Low	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 Disease severity: NR Pregnant women: Not eligible	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 Diagnostic tool: RT-PCR	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 Time (days) since previous infection: NR Proportion of vaccinated participants: NA Disease severity (%): NR Currently pregnant (%): NA	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: 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-19: 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 (%))
						G1: 6/105 (6) G2: 3/98 (3) 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: mild Pregnant women: Not eligible	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: NR Disease severity (%): Mild: G1: 100 G2: 100 Currently pregnant (%): NR	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) Hospitalization due to COVID-19: At 15 days: G1: 0/80 (0) G2: 4/72 (6) p=NR	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
Reis et al. 2022 (39)	RCT (double-blinded), Brazil	COVID-19 vaccine received: Not eligible	N=1497 G1: 741	Age, years, median: G1: 50	Proportion of symptomatic participants (%): G1: 100	Recovery†: NR	Any 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 (%))
TOGETHER NCT04727424 Foundation/non-profit professional organization Low	28 P.1 (gamma): NR B.1.617.2 (delta): NR B.1.1.529 (omicron): NR	Previous SARS-CoV-2 infection: NR Presence and/or duration of symptoms: less than 8 days Disease severity: mild Pregnant women: Not eligible	Fluvoxamine 100mg G2: 756 Placebo	G2: 49 female (%): G1: 55 G2: 60 Ethnicity (%): Non-white: G1: 99 G2: 99 Diagnostic tool: RT-PCR	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 G1: 100 G2: 100 Currently pregnant (%): NA	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-19: At 28 days: G1: 75/741 (10) G2: 97/756 (13) p=0.10	Serious AE: NR

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

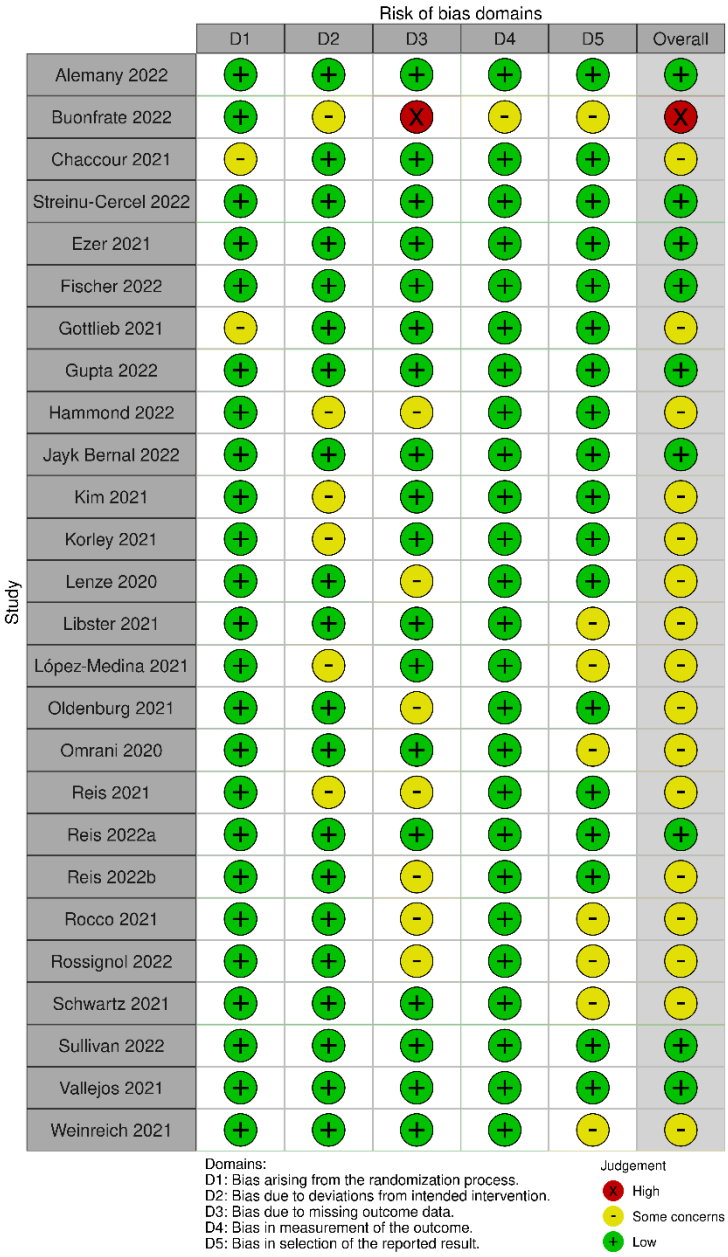
Abbreviations: AE= adverse events; CI= confidence interval; COVID-19= coronavirus disease; G (1,2,3,4,5)= group; IQR= interquartile range; kg= kilogram; mg= milligrams; HR= hazard ratio; N= number of participants; NCT= National Clinical Trial; NR= not reported; OR= odds ratio; PCR= polymerase chain reaction; 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

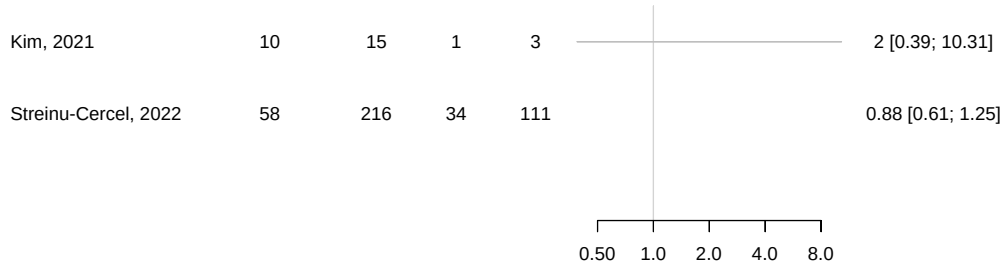
Supplement Figure 3: Serious Adverse Events – Summary Plot

Supplement Figures Meta Analyses

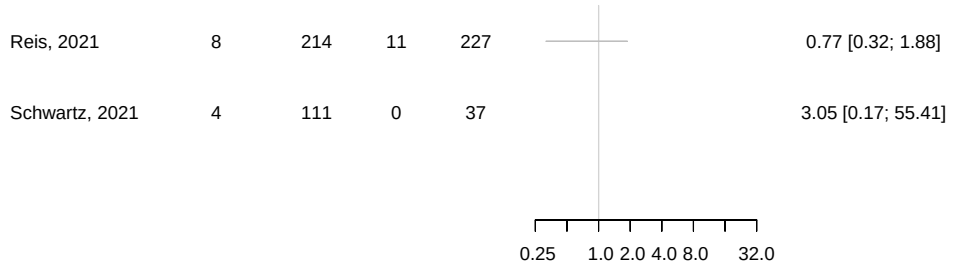
Supplement Figure 4: Serious Adverse Events: Molnupiravir Versus Placebo

Supplement Figure 5: Any Adverse Events: Molnupiravir Versus Placebo

Supplement Figure 6: Any Adverse Events: Regdanvimab Versus Placebo



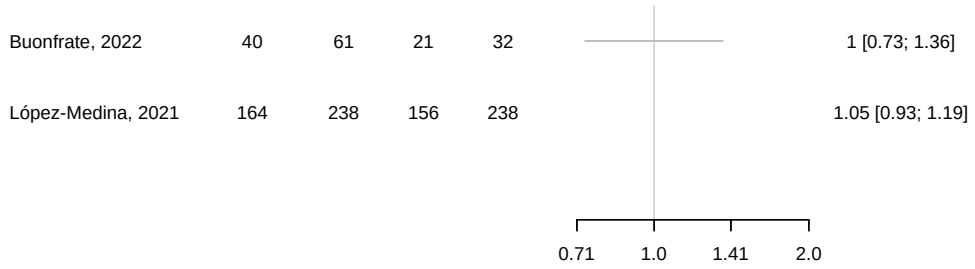
Supplement Figure 7: Admission to Hospital due to COVID-19: Chloroquine Versus Placebo



Supplement Figure 8: Serious Adverse Events: Chloroquine Versus Placebo

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

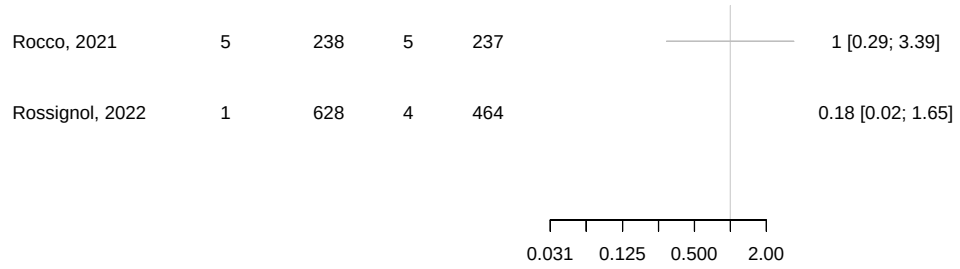
Supplement Figure 10: Recovery: Ivermectin Versus Placebo



Supplement Figure 71: Admission to Hospital due to COVID-19: Ivermectin Versus Placebo

Supplement Figure 8: Any Adverse Events: Ivermectin Versus Placebo

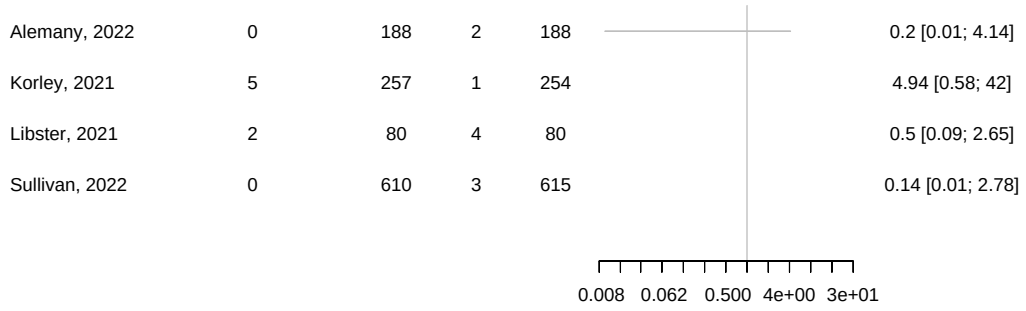
Supplement Figure 9: Admission to Hospital due to COVID-19: Nitazoxanide Versus Placebo



Supplement Figure 104: Serious Adverse Events: Nitazoxanide Versus Placebo

Supplement Figure 11: Any Adverse Events: Nitazoxanide Versus Placebo

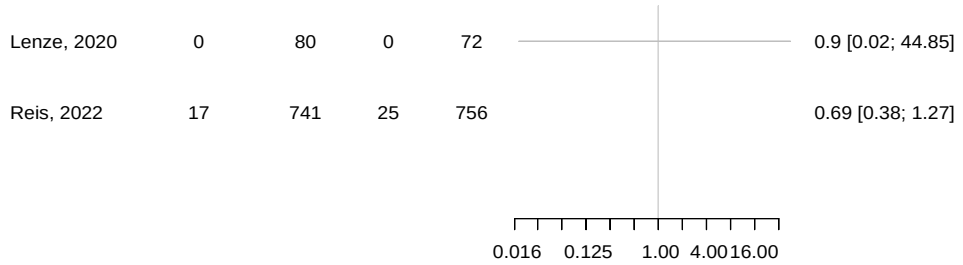
Supplement Figure 12: All-Cause Mortality: Convalescent Plasma Versus Placebo



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

Supplement Figure 14: Serious Adverse Events: Convalescent Plasma Versus Placebo

Supplement Figure 19: All-Cause Mortality: Fluvoxamine Versus Placebo



Supplement Figure 20: Admission to Hospital due to COVID-19: Fluvoxamine Versus Placebo

Supplement Table 8: Summary of Findings Tables

			;			

		ffect with placebo	ffect with chloroquine/hydroxychloroquine			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
[redacted]						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		

;

;

		ffect with placebo	Effect with convalescent plasma			
	-	-	-	-	-	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
				.		

	-	-	-	-	-	

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)	
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%) G2: 16/237 (7%)	NR	NR
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	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

Author, Year	Age	Gender	Comorbidity	Other
			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	
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				
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 (28 and 29 days)	No statistically significantly difference was observed for the outcomes of interest between the two groups.

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.