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EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

"Rolling Collaborative Review" of Covid-19 treatments

IVERMECTIN FOR THE TREATMENT OF COVID-19

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Monitoring Report

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V 2.0	**15/03/2021**	Second version
V 3.0	**20/04/2021**	Third version
V 4.0	**17/05/2021**	Fourth version
V 5.0	**11/06/2021**	Fifth version
V 6.0	**13/07/2021**	Sixth version
V 7.0	**13/08/2021**	Seventh version
V 8.0	**13/09/2021**	Eighth version
V 9.0	**13/12/2021**	Ninth version

Major changes from previous version

Chapter, page no.	Major changes from version 8.0
-	No major changes; ongoing studies updated

Disclaimer

The content of this “Rolling Collaborative Review” (RCR) represents a consolidated view based on the consensus within the Authoring Team; it cannot be considered to reflect the views of the European Network for Health Technology Assessment (EUnetHTA), EUnetHTA’s participating institutions, the European Commission and/or the Consumers, Health, Agriculture and Food Executive Agency or any other body of the European Union. The European Commission and the Agency do not accept any responsibility for use that may be made of the information it contains.

Rolling Collaborative Review team

Author(s)	Agency for Health Technology Assessment and Tariff System (AOTMiT), Poland
Co-Author(s)	Department of Epidemiology Lazio Regional Health Service (DEPLazio), Italy

Further contributors

Project Management	
Zorginstituut Nederland (ZIN), Netherlands	Coordination between involved parties throughout the assessment Coordination of RCR

Conflict of interest

All authors and co-authors involved in the production of this living document have declared they have no conflicts of interest in relation to the technology and comparator(s) assessed according to the EUnetHTA declaration of interest (DOI) form. Conflict of Interest was evaluated following the EUnetHTA Procedure Guidance for handling DOI form (https://eunethta.eu/doi).

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Contact the EUnetHTA Secretariat EUnetHTA@zinl.nl with inquiries about this assessment.

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LIST OF ABBREVIATIONS

AE	Adverse Event
AOTMiT	Agency for Health Technology Assessment and Tariff System
ASA	Acetylsalicylic acid
AZM	Azithromycin
BID	Bis in die
CI	Confidence Interval
DOI	Declaration of interest
DOX	Doxycycline
EUnetHTA	European Network of Health Technology Assessment
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HCQ	Hydroxychloroquine
HR	Hazard Ratio
ICD	International Classification of Diseases
IQR	Interquartile range
IVM	Ivermectin
MD	Mean Difference
MeSH	Medical Subject Headings
MNT	Montelukast
NA	Not applicable
NR	Not reported
PLB	Placebo
PO	Per os
RCT	Randomized Controlled Trial
RCR	Rolling Collaborative Review
REA	Relative Effectiveness Assessment
RR	Relative Risk
SAE	Serious Adverse Event
SD	Standard Deviation
SMD	Standardized Mean Difference
SoC	Standard of Care
SoF	Summary of findings
TNR4	Ivermectin + Azithromycin + Montelukast + Acetylsalicylic acid
WP4	Work Package 4

1 OBJECTIVE

The aim of this EUnetHTA Rolling Collaborative Review is

- to inform health policy at the national/regional and at the European level at an early stage in the life-cycle of therapies which interventions are currently undergoing clinical trials,
- to monitor (ongoing studies and their results) permanently - in the format of a Living Document - potential therapies against covid-19,
- to present comparative data on effectiveness and safety of potential therapies and
- to support preparations for an evidence-based purchasing of regional/ national health politicians, if necessary.

To avoid redundancies and duplication, the EUnetHTA Rolling Collaborative Review will reuse sources from international initiatives to collect information and data on Covid-19 treatments.

The scope of the Rolling Collaborative Review is of descriptive nature. These **EUnetHTA Rolling Collaborative Reviews are not meant to substitute a joint Relative Effectiveness Assessment (REA)** adhering to the agreed procedures and aiming at critical appraisal of the clinical evidence based on the Submission Dossier submitted by the (prospective) Marketing Authorization Holder (MAH).

2 METHODS

This Rolling Collaborative Review is prepared according to the project plan ("Rolling Collaborative Review (RCR) on Covid-19 treatments: Project description and planning", published on the EUnetHTA website) and will be updated monthly. Monthly updates are published on the EUnetHTA Covid-19 Website (https://eunethta.eu/covid-19-treatment/) and on the EUnetHTA Rolling Collaborative Review Sharepoint page each 15th of the month.

2.1 Scope

Table 2-1 Scope of the RCR

Description	Project Scope
Population	**Disease** • SARS-CoV-2 is a novel coronavirus causing a respiratory illness termed Covid-19. The full spectrum of Covid-19 ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multi-organ failure, and death. **ICD-Codes** (https://www.who.int/classifications/icd/covid19/en) • An emergency ICD-10 code of 'U07.1 COVID-19, virus identified' is assigned to a disease diagnosis of COVID-19 confirmed by laboratory testing. • An emergency ICD-10 code of 'U07.2 COVID-19, virus not identified' is assigned to a clinical or epidemiological diagnosis of COVID-19 where laboratory confirmation is inconclusive or not available. • Both U07.1 and U07.2 may be used for mortality coding as cause of death. See the International guidelines for certification and classification (coding) of COVID-19 as cause of death following the link below. • In ICD-11, the code for the confirmed diagnosis of COVID-19 is RA01.0 and the code for the clinical diagnosis (suspected or probable) of COVID-19 is RA01.1. **MeSH-terms** • COVID-19, Coronavirus Disease 2019 **Target population** (https://www.covid19treatmentguidelines.nih.gov/overview/management-of-covid-19/)

	• Asymptomatic or pre-symptomatic Infection: Individuals who test positive for SARS-CoV-2 by virologic testing using a molecular diagnostic (e.g., polymerase chain reaction) or antigen test, but have no symptoms. • Mild Illness: Individuals who have any of the various signs and symptoms of COVID 19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnoea, or abnormal chest imaging. • Moderate Illness: Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO2) ≥94% on room air at sea level. • Severe Illness: Individuals who have respiratory frequency >30 breaths per minute, SpO2 <94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mmHg, or lung infiltrates >50%. • Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.
Intervention	Ivermectin
Comparison	Any active treatment, placebo, or standard of care. **Rationale**: Since there is no gold standard treatment any comparator is acceptable as well as the above listed interventions.
Outcomes	<u>Main outcome:</u> • All-cause Mortality (Survival) <u>Additional Outcomes:</u> Efficacy: • Length of hospital stay, • Viral burden (2019-nCoV RT-PCR negativity), • Clinical progression (WHO Clinical Progression Scale measured daily over the course of the study), • Rates of hospitalization and of patients entering ICU, • Duration of mechanical ventilation, • Quality of life. Safety: • Adverse events (AE), • Severe adverse events (SAE), • Withdrawals due to AEs, • Most frequent AEs, • Most frequent SAEs. **Rationale:** We will give priority according to the Core Outcome Set for Clinical Trials on Coronavirus Disease 2019 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102592/pdf/main.pdfc) and a minimal common outcome measure set for COVID-19 clinical research from the WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection.
Study design	Efficacy: randomised controlled trials (RCT)

2.2 Sources of information

According to the project plan, this Rolling Collaborative Review is based on two main sources and one optional source of information, as described below:

1. Summary of findings(SoF) table for published RCTs related to effectiveness and safety:

This table is based on the living systematic review and Network Meta-Analysis (NMA) created by the partnering institute of DEPLazio: find the PROSPERO protocol here. provided until the 31st of May 2021 updates for the SoF table on a monthly basis to the EUnetHTA partners authoring the respective Rolling CR documents and who have integrated this information accordingly.

From June 2021 on AOTMiT has updated the SoF table monthly with the use of covid-nma.com. (COVID-NMA initiative: find the living review protocol here).

From June 2021, the literature search is used from COVID-NMA initiative according living review protocol [1], [2], [3], or is conducted by authors of this RCR in the following databases:

- PubMed
- MEDLINE, accessed via OVID
- Embase, accessed via OVID

Population	People affected by COVID-19, as defined by the authors of the studies. No limits in terms of gender or ethnicity. SARS-CoV-2 is a novel coronavirus causing a respiratory illness termed Covid-19. It started spreading in December 2019, and was declared a pandemic by the World Health Organisation on 11th March 2020. The full spectrum of Covid-19 ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multi-organ failure, and death.
Intervention	Interventions for the treatment of people affected by COVID-19, including pharmacological interventions (e.g. antibiotics, antibodies, antimalarial, antiviral, antiretroviral, immune-suppressors/modulators, kinase inhibitors) and their combinations.
Comparison	Any active treatment, placebo, or standard of care.
Outcomes	All-cause mortality Additional outcomes: Length of hospital stay, 2019-nCoV RT-PCR negativity, PaO2/FiO2, Duration of mechanical ventilation, radiological imaging, Adverse events, Severe adverse events.
Study design	Randomised controlled trials (RCT); no restriction on language of publication

To identify preprints of preliminary reports of work that have not been peer-reviewed, the following sources are searched:

- medRxiv Health Sciences
- bioRxiv Biology

In addition to the sources and strategies described above, registers of ongoing studies are screened. Key conferences and conference proceedings are considered.

Data extraction, Risk of bias assessment, data synthesis:

Two reviewers from DEPLazio are screening search results, assessing full texts of studies and extract study characteristics and outcome data according to pre-defined criteria. T

Risk of bias is assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [4]. or reused from one living SR/MA source [2]. Each study was presented with the Cochrane Risk of bias 2 (RoB 2) tool for RCTs [5].

Dichotomous outcomes are analysed by calculating the relative risk (RR) for each trial with the uncertainty in each result being expressed by its 95% confidence interval (CI).Continuous outcomes are analysed by calculating the mean difference (MD) with the relative 95% CI when the study used the same instruments for assessing the outcome.

The standardised mean difference (SMD) is applied when studies used different instruments. Pairwise meta-analyses is performed for primary and secondary outcomes using a random-effects model in RevMan for every treatment comparison [6]. Network meta-analysis (NMA) is performed for the primary outcome. For rating the certainty of the evidence, the GRADE approach is being used [7].

From June 2021, if new RCTs are published, certainty of evidence have been reused from already published living systematic reviews/meta-analysis (SRs/MA) source from the international COVID-NMA initiative.

- Sources: https://covid-nma.com/ for SoF (access: 13/09/2021)

2. Table(s) on published (peer reviewed) observational studies for safety results:

From June 2021, only RCTs are used for assessment of safety.

3. Table(s) on ongoing trials:

The following clinical trial registries are searched on a monthly basis:

- ClinicalTrials.gov: https://clinicaltrials.gov/
- ISRCTN: https://www.isrctn.com/
- European Clinical Trials Registry: https://www.clinicaltrialsregister.eu/

Inclusion criteria: Randomised controlled trials, Controlled trials

One researcher of AOTMiT is searching and extracting the data for the eligible studies. At the drafting stage of each update, the author team verifies whether the status of previously identified studies has changed. This is done by verifying the date of the last update posted in the trial registers. In addition, trial register IDs of all previously identified studies are entered in both PubMed and Google (google.com) to verify if previously identified studies have been published since the last update. In Google, the first 10 hits are screened for this purpose.

Search methods are described in more detail in Table 6-1.

Data are presented in tabular form.

3 ABOUT THE TREATMENT

3.1 Mode of Action

Ivermectin is a broad-spectrum antiparasitic medicine which in recent years has been intensively studied with respect to its potential antiviral action in vitro [8-11]. Ivermectin is a macrocyclic lactone and avermectin derivative. It is composed of two homological components 22,23–dihydroavermectin B1a and 22,23–dihydroavermectin B1b [12].

The mechanism of action of ivermectin is based on its capability to increase cell membrane permeability to chloride ions which leads to neural or muscle cell hyperpolarization, neuromuscular motor paralysis and death. [13] The increase of cell membrane permeability results from ivermectin's interaction with glutamate-gated and gamma-aminobutyric acid (GABA)-gated chloride channels leading to increased conductance of chloride ions. Ivermectin is safe for mammals as they do not have glutamate-gated chloride channels, and ivermectin does not readily cross the blood/brain barrier (SPC) [14].

Moreover, ivermectin has an anti-inflammatory potential resulting from its ability to inhibit lipopolysaccharide-induced pro-inflammatory cytokine production. It has been observed on animal models of dermatitis [15].

The proposed anti-SARS-CoV-2 action of ivermectin comes from its *in vitro* ability to prevent viral proteins from entering the nucleus. It is mediated by the binding of ivermectin to the host nuclear transport importin α/β1 heterodimer (IMPα/β1), which leads to its destabilization and prevention of IMPα/β1 binding to the viral proteins. This allows for more efficient antiviral response [14, 16].

3.2 Regulatory Status

Ivermectin is not approved by the European Medicines Agency (EMA) or the American Food and Drug Administration (FDA) for COVID-19 patients. It is approved by the Food and Drug Administration (FDA) for the treatment of [17, 18]:

- onchocerciasis,
- strongyloidiasis;

and for topical use in the treatment of:

- inflammatory lesions of rosacea,
- head lice infestation.

Ivermectin is not approved by the European Medicines Agency (EMA) for the use in humans, however, it was granted a product-specific waiver for the treatment of rosacea (topical use) [19].

Ivermectin is not FDA or EMA-approved for the treatment of any viral infections, nor it is authorised in Covid-19 patients [17, 20].

3.3 Level of Evidence

25 RCTs have documented the effectiveness and safety of ivermectin. Except for one study, all included RCTs were conducted in non-European countries. Among these, 9 were designed as multicenter and 14 were double-blinded. Study population size ranged from 24 to 501 patients. The population included in the studies was heterogeneous in terms of disease severity. Mild patients were included in ten studies, mild to moderate patients in nine studies, mild to severe patients in two studies, severe in one study, mild to critical patients in one study and severe to critical in one study. Furthermore, there was a wide variation in standards of care across trials. Ivermectin dosing and duration of treatment was also heterogeneous. A detailed description of methodology of included RCTs is presented in Table 4-7, Table 4-8, Table 4-9, Table 4-10 and Table-11.

Moreover, 48 ongoing studies are reported in international clinical trial registries.

4 SUMMARY

4.1 Effectiveness and Safety evidence from RCTs

There are six different comparisons for ivermectin. The data are presented in Table 4-1, Table 4-2, Table 4-3, Table 4-4, Table 4-5 and Table 4-6.

Ivermectin versus standard care / placebo

18 RCTs contributed to the estimates presented in the Summary of Findings Table 4-1. Certainty of the evidence was very low to high for particular outcomes listed in the table.

Currently available evidence shows that ivermectin compared with standard treatment doesn't reduce the risk of 28-days all-cause mortality in mild outpatients and hospitalized patients (4 RCTs, 1255 patients, low certainty of evidence and 8 RCTs, 850 patients, very low certainty of evidence, respectively). Only one study [21] reported statistically significant results in terms of deaths in favour of ivermectin (RR 0.18; 95% CI: 0.06; 0.55) in mild-severe patients. Data on clinical improvement, WHO

progression score level 7 or above, viral negative conversion at day 7, frequency of any adverse events and severe adverse events is not conclusive, as there is no statistically significant difference between study arms regardless severity of disease.

It should be noted that the results of the currently largest clinical trials Lopez-Medina 2021 (238 vs 238 patients) and Vallejos 2021 (250 vs 251 patients) do not confirm the efficacy of ivermectin in COVID-19 (non-hospitalized patients).

The results should be analysed taking into account the heterogeneity od included RCTs, especially in terms of ivermectin dosing regimens, standard care therapies, eligibility criteria (including patients with varying baseline characteristics), methodology od studies – blinding / non-blinding, sample size, follow-up period and method of analysis of results (ITT, mITT or per protocol analysis).

Ivermectin + doxycycline vs standard care / placebo

The certainty of the evidence from three RCTs [22-24] contributing to this comparison was very low for particular outcomes listed in Table 4-2.

No significant difference was observed in 28-days all-cause mortality (2 RCTs, 448 patients) and in 60-days all-cause mortality in severe patients (1 RCT, 140 patients). In one study [22], in mild-moderate population, proportion of patients with clinical improvement over 7 days was in favour of the group of patients receiving ivermectin in combination with doxycycline compared with standard care/placebo (RR 1.41; 95% CI: 1.15 to 1.72). In the same study proportion of patients required more than 12 days for clinical improvement was higher in standard care/placebo compared with ivermectin in combination with doxycycline in mild/moderate population (RR 0.63; 95% CI: 0.45 to 0.87). In 2 RCTs [22, 24], progression of COVID-19 disease in the subpopulation of severely ill patients was statistically significantly lower in ivermectin + doxycycline group (RR 0.50; 95% CI: 0.28 to 0.82).

Data from one RCT indicate that ivermectin in combination with doxycycline could reduce the time to SARS-CoV-2 clearance compared to standard of care/placebo, but may increase the duration of hospitalization (the certainty of evidence is very low). Data on frequency of viral negative conversion at day 7, frequency of any adverse events and severe adverse events are not conclusive, as there is no statistically significant difference between study arms.

The results should be analysed taking into account very low certainty of evidence and the heterogeneity od included RCTs in terms of control arms, eligibility criteria (including patients with varying severity of disease symptoms) and follow-up period.

Ivermectin + doxycycline versus hydroxychloroquine + azithromycin

The certainty of the evidence from one study (125 patients) [25] contributing to this comparison was moderate for particular outcomes listed in Table 4-3. Ivermectin in combination with doxycycline compared to hydroxychloroquine with azithromycin has no influence on SARS-CoV-2 clearance or frequency of any adverse events.

Ivermectin vs lopinavir/ritonavir

The certainty of the evidence from one study (62 patients) [26] contributing to this comparison was very low for particular outcomes listed in Table 4-4. No deaths were reported within the study population. Ivermectin significantly reduced time to SARS-CoV-2 clearance in the whole ivermectin group as well as in the ivermectin 6 mg group and the ivermectin 12 mg group compared to lopinavir/ritonavir.

Ivermectin vs hydroxychloroquine

The certainty of the evidence from one RCT [27] contributing to this comparison was very low to low for particular outcomes listed in Table 4-5. Data (69 patients) on all-cause mortality, clinical improvement frequency of any adverse events and severe adverse events are not conclusive, as there is no statistically significant difference between study arms.

It should be noted that the pre-print for one study [28] has been retracted on July 14th, therefore its presentation in version 7.0 of the RCR was abandoned.

Ivermectin vs chloroquine

The certainty of the evidence from one study (114 patients) [29] contributing to this comparison was moderate for particular outcomes listed in Table 4-6. Data on all-cause mortality, clinical improvement, progression of COVID-19 disease and number of patients with respiratory distress syndrome is not conclusive, as there is no statistically significant difference between study arms.

4.1 Safety evidence from observational studies

From June 2021, only RCTs are used for assessment of safety. Previous evidence from prospective observational studies can be found in version 4.0, May 2021.

4.2 Ongoing studies

According to the databases of clinicaltrials.gov, ISRCTN and EudraCT, there are currently 41, 2 and 6 ongoing studies for ivermectin with indications related to COVID-19, respectively. Making up to 48 ongoing studies[1] on ivermectin with indications related to COVID-19 (Table 4-12 –Table 4-21).

4.3 Scientific conclusion about status of evidence generation

The current evidence is not sufficient to support the use of ivermectin for COVID-19 and requires validation in larger, high quality RCTs evaluating fixed dosing schedules. At the moment, conclusions on the efficacy of ivermectin are of high uncertainty.

[1] One study is duplicated in two bases.

Table 4-1 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of ivermectin versus standard of care / placebo

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence^
	Risk with SoC / PLB	Risk with IVM			
Mild outpatients					
All-cause mortality D28 [30-33]	6 per 1000	7 per 1000 (2 to 25)	RR 1.05 (0.27 to 4.02)	1255 (4 RCTs)	low
All-cause mortality D60 [30]	4 per 1000	8 per 1000 (1 to 92)	RR 2.00 (0.18 to 21.91)	476 (1 RCT)	very low
Clinical improvement D28 [30] [34]	650 per 1000	683 per 1000 (605 to 774)	RR 1.05 (0.93 to 1.19)	526 (2 RCTs)	low
WHO progression score (level 7 or above) D28 [30, 31, 33]	4 per 1000	8 per 1000 (1 to 88)	RR 1.43 (0.55 to 3.72)	1001 (3 RCTs)	low
WHO progression score (level 7 or above) D60 [30]	14 per 1000	20 per 1000 (3 to 91)	RR 2.00 (0.37 to 10.82)	476 (1 RCT)	very low
Adverse events [30, 31, 33-35]	359 per 1000	345 per 1000 (305 to 388)	RR 0.96 (0.85 to 1.08)	1167 (5 RCTs)	moderate
Serious adverse events [30, 31, 33-35]	3 per 1000	3 per 1000 (0 to 24)	RR 1.00 (0.14 to 7.04)	1167 (5 RCTs)	low
Viral negative conversion D7 [31, 33-36]	517 per 1000	626 per 1000 (466 to 843)	RR 1.21 (0.90 to 1.63)	805 (5 RCTs)	very low
Hospitalized patients					
All-cause mortality D28 [21, 23, 30, 37-41]	60 per 1000	32 per 1000 (13 to 79)	RR 0.53 (0.21 to 1.31)	850 (8 RCTs)	very low
All-cause mortality D60 [42, 43]	300 per 1000	168 per 1000 (66 to 414)	RR 0.56 (0.22 to 1.38)	98 (2 RCT)	very low
Viral negative conversion D7 [23, 39, 41-46]	318 per 1000*	321 per 1000 (258 to 401)*	RR 1.01 (0.81 to 1.26)	607 (8 RCTs)	very low
Clinical improvement D28 [27, 39, 41, 46]	756 per 1000*	756 per 1000 (681 to 839)*	RR 1.00 (0.91 to 1.11)	372 (4 RCTs)	low
WHO progression score level 7 or above D28 [23, 39, 40]	0 per 1000	0 per 1000 (1 to 36)	RR 1.55 (0.07 to 35.89)	245 (3 RCTs)	low
Adverse events [23, 27, 39, 40, 42, 43]	222 per 1000*	191 per 1000 (131 to 276)*	RR 0.86 (0.59 to 1.24)	416 (6 RCTs)	low
Serious adverse events [23, 27, 39, 40, 42, 43]	12 per 1000*	14 per 1000 (2 to 80)*	RR 1.11 (0.19 to 6.44)	416 (6 RCTs)	very low

^ detailed GRADE assessment on covid-nma.com; * calculated by AOTMiT
Sources:covid-nma.com
Abbreviations: CI=Confidence interval; IVM=Ivermectin; PLB=Placebo, RR=Risk ratio, SoC=Standard of care.

Table 4-2 Summary of findings (SoF) table for RCTs related to effectiveness and safety of ivermectin + doxycycline versus standard of care / placebo

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence
	Risk with SoC / PLB	Risk with IVM + DOX			
All-cause mortality D28 [22, 23]^	13 per 1000	2 per 1000 (0 to 37)	RR 0.14 (0.01 to 2.75)	448 (2 RCTs)	very low
All-cause mortality D60 or more, severe patients [24]^	86 per 1000	28 per 1000 (6 to 137)	RR 0.33 (0.07 to 1.60)	140 (1 RCT)	very low
Progression of COVID-19 disease mild / moderate ill patients [22, 24]^^^	65 per 1000	32 per 1000 (18 to 53)	**RR 0.50 (0.28 to 0.82)**	496 (2 RCT)	very low
Progression of COVID-19 disease severe ill patients [24]^^	318 per 1000	92 per 1000 (13 to 649)	RR 0.29 (0.04 to 2.04)	33 (1 RCT)	very low
Early Clinical Improvement D7 [22]^^^	555 per 1000	783 per 1000 (638 to 955)	**RR 1.41 (1.15 to 1.72)**	400 (1 RCT)	very low
Clinical improvement (Late Clinical Recovery) D12<**[22]^	335 per 1000	211 per 1000 (151 to 291)	**RR 0.63 (0.45 to 0.87)**	400 (1 RCT)	very low
Length of stay in hospital [23]^^	-	SMD 0.11 higher (0.46 lower to 0.68 higher)	-	48 (1 RCT)	very low
Time to SARS-CoV 2 clearance [23]^^	-	SMD 0.31 lower (0.88 lower to 0.26 higher)	-	48 (1 RCT)	very low
Viral negative conversion D7 [22, 23]^	647 per 1000	1068 per 1000 (317 to 1,000)	RR 1.65 (0.49 to 5.50)	448 (2 RCTs)	very low
Adverse events [22, 23]^	85 per 1000	274 per 1000 (20 to 1000)	RR 3.23 (0.23 to 45.46)	448 (2 RCTs)	very low
Serious adverse events [22, 23]^	Ivermectin+Doxyxycline : 2/224; Placebo: 0/224; Absolute effects were not calculated due to zero events in the control group		RR 5.00 (0.24 to 103.49)	446 (2 RCTs)	very low

^ outcome data and GRADE assessment adapted from covid-nma.com;
^^ outcome data and GRADE assessment provided by DEPLazio;
^^^ added by AOTMiT;
Sources: DEPLazio: Cruciani F, De Crescenzo F, Vecchi S, Saulle R, Mitrova Z, Amato L, Davoli M; covid-nma.com
*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
** Number of the patients required more than 12 days for clinical improvement – Corrected by AOTMiT – originally “clinical improvement D28”;
Abbreviations: CI=Confidence interval; DOX=Doxycycline; RR=Risk ratio; IVM=Ivermectin; SMD= Standardized mean difference

Table 4-3 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of ivermectin + doxycycline versus HCQ + AZM

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence
	Risk with HCQ + AZM	Risk with IVM			
SARS-CoV-2 clearance [25]	871 per 1000	949 per 1000 (854 to 1000)	RR 1.09 (0.98 to 1.22)	125 (1 RCT)	moderate
Number of patients with any adverse event [25]	419 per 1000	302 per 1000 (188 to 486)	RR 0.72 (0.45 to 1.16)	125 (1 RCT)	moderate

Source: Cruciani F, De Crescenzo F, Vecchi S, Saulle R, Mitrova Z, Amato L, Davoli M
Abbreviations: AZM=azhitromicine CI=Confidence interval; HCQ=hydroxychloroquine; IVM=Ivermectin; RR=Risk ratio.

Table 4-4 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of ivermectin versus lopinavir/ritonavir

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence
	Risk with lopinavir/ritonavir	Risk with IVM			
All-cause mortality [26]	No deaths reported			62 (1 RCT)	very low
Time to SARS-CoV-2 clearance [26]	-	SMD 0.77 lower (1.32 lower to 0.22 lower)	-	62 (1 RCT)	very low
All-cause mortality (Ivermectin 6mg) [26]	No deaths reported			41 (1 RCT)	very low
Time to SARS-CoV-2 clearance (Ivermectin 6mg) [26]	-	SMD 0.55 lower (1.18 lower to 0.07 higher)	-	41 (1 RCT)	very low
All-cause mortality (Ivermectin 12mg) [26]	No deaths reported			41 (1 RCT)	very low
Time to SARS-CoV-2 clearance (Ivermectin 12mg) [26]	-	SMD 0.78 lower (1.42 lower to 0.14 lower)	-	41 (1 RCT)	very low

Source: Cruciani F, De Crescenzo F, Vecchi S, Saulle R, Mitrova Z, Amato L, Davoli M
Abbreviations: CI=Confidence interval; IVM=Ivermectin; RR=Risk ratio, SMD=Standardized mean difference.

Table 4-5 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of ivermectin versus hydroxychloroquine

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence
	Risk with HCQ	Risk with IVM			
All-cause mortality D28^[27]	61 per 1000	78 per 1000 (32 to 607)	RR 2.29 (0.48 to 11.02)	69 (1 RCT)	very low
Clinical improvement D28^[27]	909 per 1000	891 per 1000 (755 to 1000)	RR 0.98 (0.83 to 1.15)	69 (1 RCT)	very low
Adverse events^[27]	30 per 1000	28 per 1000 (2 to 426)	RR 0.92 (0.06 to 14.07)	69 (1 RCT)	low
Serious adverse events^[27]	30 per 1000	28 per 1000 (2 to 426)	RR 0.92 (0.06 to 14.07)	69 (1 RCT)	low

^ outcome data and GRADE assessment adapted from covid-nma.com
Source: covid-nma.com
Abbreviations: CI=Confidence interval; HCQ=hydroxychloroquine; IVM=Ivermectin; RR=Risk ratio, SMD=Standardized mean difference.

Table 4-6 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of ivermectin versus chloroquine

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence
	Risk with CQ	Risk with IVM			
All-cause mortality [29]	213 per 1000	245 per 1000 (126 to 482)	RR 1.15 (0.59 to 2.26)	114 (1 RCT)	moderate
Progression of COVID-19 disease [29]	197 per 1000	264 per 1000 (134 to 519)	RR 1.34 (0.68 to 2.64)	114 (1 RCT)	moderate
Number of patients with respiratory distress syndrome [29]	213 per 1000	264 per 1000 (136 to 511	RR 1.24 (0.64 to 2.40)	114 (1 RCT)	moderate

Source: Cruciani F, De Crescenzo F, Vecchi S, Saulle R, Mitrova Z, Amato L, Davoli M
Abbreviations: CI=Confidence interval; CQ=chloroquine IVM=Ivermectin; RR=Risk ratio, SMD=Standardized mean difference.

Table 4-7 Study characteristics of included RCTs

Author, year, reference number/Study name/Study ID	Niae et al. 2020 [21] IRCT20200408046987N1	Ravikirti et al. 2021 [41] CTRI/2020/08/027225	Krolewiecki et al. 2020 [40] NCT004381884	Chaccour et al. 2021 [31] NCT04390022	Ahmed et al. 2020 [23] NCT04407130
Study design, study phase	randomized, double-blind, placebo-controlled, phase 2	randomized, double-blind, placebo-controlled	a pilot, randomized, controlled, open-label, outcome-assessor blinded	randomized, double-blind, phase 2	randomized, double-blind, placebo-controlled, phase 2
Centres (single centre or multicentre), country, setting	multicenter Iran	single-centre India	multicenter Argentina	single-centre Spain	Bangladesh
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	180 patients mean age: 56 (45-67) female: 50% mild to severe	115 patients mean age: 52.5 (SD: 14.7) female: 27.7% mild to moderate	45 patients mean age: 40,89 (SD: 12.48) male: 56% mild to moderate (3 to 5 from the WHO 8-category ordinal scale	24 patients ivermectin: median age 26 (IQR: 19-36), male: 58% placebo: median age 26 (IQR: 21-44) mild	72 patients mean age: 42 female: 54% mild
Inclusion criteria	age >18 years; signed the informed consent; clinical symptoms of suggestive of COVID-19 pneumonia: cough (with or without sputum), fever, pleuritic chest pain or dyspnea; mild to severe COVID-19 disease confirmed by chest computed tomography scan findings compatible with COVID-19 or positive rRT-PCR	all patients above the age of 18 admitted with a diagnosis of COVID -19 (on the basis of a positive RT-PCR or Rapid Antigen Test report) at AIIMS, Patna, India with mild or moderate disease as defined by the ministry of health and family welfare guidelines and not meeting any of the exclusion criteria	age 18 to 69 years; COVID-19 confirmed with RT-PCR; hospitalized with disease stages 3 to 5 from the WHO 8-Category ordinal scale of clinical status and no requiring intensive care unit admission; symptoms onset ≤ 5 days at recruitment, absence of use of drugs with potential activity against SARS-CoV-2	18-59 years; Consecutive outpatients attending the Emergency Room of the Clínica Universidad de Navarra with symptoms compatible with COVID-19, no more than 72 h of fever or cough and a positive PCR for SARS-CoV-2; Negative pregnancy test for women of child bearing age*; Consent to participate in the study; The patient should, in the investigator's opinion, be able to comply with all the requirements of the clinical trial (including home follow up during isolation)	age 18–65 years; admitted to hospital within the last 7 days; presence of a fever (>37.5ºC), cough, and/or sore throat; diagnosed positive for SARS-CoV-2 by rRT-PCR
Exclusion criteria	presence of severe immunosuppression (e.g., use of immune-suppressants and HIV positive), pregnant women, chronic kidney disease, malignancy, and indications that the patients were unable and/or unlikely to comprehend and/or follow the protocol	known allergy to or adverse drug reaction with ivermectin; unwillingness or inability to provide consent to participate in the study; prior use of ivermectin during the course of this illness; pregnancy and lactation	the use of immunomodulators within 30 days of recruitment, pregnancy, breast feeding, poorly controlled comorbidities and known allergies to IVM	ivermectin allergy; hypersensitivity to any component of Stromectol®; COVID-19 Pneumonia (diagnosed by the attending physician; identified in a chest X-ray); fever or cough present for > 48 hours; positive IgG against SARS-CoV-2 by rapid test; indicated co-morbidities (or any other disease that might interfere with the study	allergic to ivermectin or doxycycline, or if there was the potential for a drug–drug interaction with ivermectin or doxycycline; had chronic illnesses (e.g., ischemic heart disease, heart failure, documented cardiomyopathy, chronic kidney disease, chronic liver

Author, year, reference number/Study name/Study ID	Niae et al. 2020 [21] IRCT20200408046987N1	Ravikirti et al. 2021 [41] CTRI/2020/08/027225	Krolewiecki et al. 2020 [40] NCT004381884	Chaccour et al. 2021 [31] NCT04390022	Ahmed et al. 2020 [23] NCT04407130
				in the eyes of the investigator): e.g. immunosuppression, COPD,diabetes; recent travel history to countries that are endemic for Loa loa; current use of CYP 3A4 or P-gp inhibitor drugs such as quinidine, amiodarone, diltiazem, spironolactone, verapamil, clarithromycin, erythromycin, itraconazole, ketoconazole, cyclosporine, tacrolimus, indinavir, ritonavir or cobicistat; use of critical CYP3A4 substrate drugs such as warfarin.	disease); had received ivermectin and/or doxycycline in the last 7 days; were pregnant or lactating; or had participated in any other clinical trial within the last month
Intervention (generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	1. ivermectin: single dose (200 mcg/kg, 1 pill per day), 30 patients: 26.7% mild, 70% moderate, 3.3% severe; 2. ivermectin: three low interval doses of ivermectin (200, 200, 200 mcg/kg , 3 pills in 1, 3 and 5 interval days), 30 patients: 6.7% mild, 66.7% moderate, 20% severe; 3. ivermectin: single dose (400 mcg/Kg, 2 pills per day), 30 patients: 13.3% mild, 70% moderate, 16.7% severe; 4. ivermectin: three high interval doses of ivermectin (400, 200, 200 mcg/kg, 4 pills in 1, 3 and 5 interval days), 30 patients: 6.7% mild, 76.7% moderate, 16.7% severe	ivermectin (12 mg on day 1 and day 2 of admission) 57 patients: 76.4% mild, 23.6% moderate	ivermectin 0.6 mg/kg/day for 5 days + SoC 34 patients	ivermectin (Stromectol®, single dose of 400 mcg/kg) 12 patients	**ivermectin:** oral IVM alone (12 mg once daily for 5 days); 24 patients **ivermectin + doxycycline**: (12 mg IVM single dose and 200 mg doxycycline on day 1, followed by 100 mg every 12 h for the next 4 days); 24 patients
Comparator(s) (standard care or generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate,	1. common regimen: hydroxychloroquine 200mg/kg twice per day), 30 patients: 13.3% mild, 76.7% moderate, 10% severe; 2. placebo plus common regimen, 30 patients: 16.7% mild, 76.7% moderate, 6.7% severe	placebo 58 patients: 80.7% mild, 19.3% moderate	SoC, 15 patients	placebo 12 patients	placebo, 24 patients

Author, year, reference number/Study name/Study ID	Niae et al. 2020 [21] IRCT20200408046987N1	Ravikirti et al. 2021 [41] CTRI/2020/08/027225	Krolewiecki et al. 2020 [40] NCT004381884	Chaccour et al. 2021 [31] NCT04390022	Ahmed et al. 2020 [23] NCT04407130
Severe, Critical COVID-19)					
Primary Outcome(s)	clinical recovery	negative RT-PCR on day 6	reduction in SARS-CoV-2 viral load between baseline and day-5	positive SARS-CoV-2 PCR	time required for virological clearance (a negative rRT-PCR result on nasopharyngeal swab); remission of fever (≥37.5^{o}C) and cough within 7 days.
Patient-relevant secondary outcome(s)	duration of hospitalization, duration of low O_2 saturation, tachypnea off, fever off, mortality	symptom free on day 6, discharged by day 10, admission to ICU, discharde, in-hospital mortality	clinical evolution at day-7, relationship between IVM plasma concentrations and the primary outcome, and frequency and severity of adverse events	progression of symptoms (fever, cough), adverse events, all-cause mortality	failure to maintain an SpO2 >93% despite oxygenation and days on oxygen support, duration of hospitalization, all-cause mortality, serious adverse drug events
Follow-up (days, months)	45 days	10 days	21-30 days	28 days	14 days
Sponsor/ lead institution	Qazvin University of Medical Sciences and Science and Technology Park	All India Institute of Medical Sciences. Sun Pharma Pvt. Ltd. (placebo provision)	supported by grant IP-COVID-19-625 from Agencia Nacional de Promoción de la Investigación, el Desarrollo Tecnológico y la Innovación, Argentina and Laboratorio ELEA/Phoenix, Argentina	Idipharma SL, ISGlobal, the University of Navarra, the Spanish Ministry of Science and Innovation through the “Centro de Excelencia Severo Ochoa 2019–2023”; Program (CEX2018–000,806-S), and support from the Generalitat de Catalunya through the CERCA Program	Beximco Pharmaceutical Limited, Bangladesh

Table 4-8 Study characteristics of included RCTs, continued

Author, year, reference number/Study name/Study ID	Lopez-Medina et al. 2021 [30] NCT04405843	Mohan et al. 2021 [39] CTRI/2020/06/026001	Shah Bukhari et al. 2021 [44] NCT04392713	Podder et al. 2020 [45]	Beltran-Gonzalez et al. 2021 [27] NCT04391127	Kishoria et al. 2020 [46]
Study design, study phase	randomized, double-blind, placebo controlled, phase 2/3	randomized, double-blind, placebo controlled	randomized, open-label	randomized, open-label	randomized, double-blind, placebo controlled	randomized, open-label
Centres (single centre or multicentre), country, setting	single-centre Colombia	single-centre India	single-centre Pakistan	single-centre Bangladesh	single-centre Mexico	single-centre India
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	476 patients median age: 37 (IQR: 29-48) female: 58% mild	125 patients mean age: 35.3 male: 89% mild to moderate	100 patients mean age: 40.6 male: 73% mild	62 patients mean age: NR males: 71% mild to moderate	106 patients mean age: 53 males: 62% moderate to severe	32 patients mean age: 38.5 male: 72% mild
Inclusion criteria	adult men and non–pregnant or breast-feeding women over 18 years of age; SARS CoV2 / COVID 19 disease confirmed by RT-PCR in any of the laboratories that report to the Departmental Health Secretary, approved for the diagnosis of COVID-19 by the National Institute of Health; onset of symptoms began within the previous 7 days and they had mild disease, defined as being at home or hospitalized but not receiving high-flow nasal oxygen or mechanical ventilation (invasive or noninvasive).	age >18 years; diagnosed (based on a positive result on either SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) or the rapid antigen test); non-severe COVID-19 (i.e. room air saturation (SpO2) >90%, no hypote	15-65 years; any gender; COVID-19 positive, proven by RT-PCR; Mild (fever <38oC quelled without treatment with or without cough, no dyspnea, no gasping, no chronic disease, no imaging findings of pneumonia) to moderate (fever, respiratory symptoms, imaging findings of pneumonia) severity of the disease; consent for trial, stated their willingness to comply with all study procedures, agreed for admission for the trial period (14 days); able to take oral medication	consecutive RT-PCR positive eligible mild to moderate COVID-19 cases of more than 18 years of age, of both sexes	age 16 to 90 years; hospitalized; positive RT-PCR for SARS-CoV-2 by nasal and oropharyngeal swabbing; pneumonia, diagnosed by X-ray or high-resolution chest CT scan, with a pattern suggesting involvement due to coronavirus; recently established hypoxemic respiratory failure or acute clinical deterioration of pre-existing lung or heart disease	patients aged 18 years and above; positive test after completion of standard care treatment for SARS-CoV-2 confirmed by reverse transcriptase–polymerase-chain-reaction (RT-PCR) assay; mild/ asymptomatic; no comorbidities rendering high-risk patients; informed consent obtained
Exclusion criteria	medical history of liver disease; history of allergy to ivermectin or any of its	pregnancy or lactation; known hypersensitivity to ivermectin; chronic	Positive pregnancy test (all females were tested); severe symptoms likely	Known pre-existing hypersensitivity to Ivermectin, pregnant and	Required high oxygen volumes (face mask > 10 L/ min) ; had predictors	Allergy or hypersensitivity to ivermectin and/or its inactive ingredients; respiratory

Author, year, reference number/Study name/Study ID	Lopez-Medina et al. 2021 [30] NCT04405843	Mohan et al. 2021 [39] CTRI/2020/06/026001	Shah Bukhari et al. 2021 [44] NCT04392713	Podder et al. 2020 [45]	Beltran-Gonzalez et al. 2021 [27] NCT04391127	Kishoria et al. 2020 [46]
	components; belonging to another clinical trial that evaluates the efficacy of an investigational drug against COVID-19. The use of other treatments outside of clinical trials is allowed; patients who were asymptomatic; severe pneumonia; received ivermectin within the previous 5 days; subjects receiving Warfarin, erdafitinib, or quinidine; hepatic dysfunction or liver function test results more than 1.5 times the normal level.	kidney disease with creatinine clearance <30 mL/min; elevated transaminase levels (>5 x upper limit of normal); myocardial infarction or heart failure within 90 days prior to enrolment, prolonged corrected QT interval (>450 ms) on electrocardiogram; any other severe comorbidity as per investigator's assessment, no informed consent	due to cytokine release syndrome; uncontrolled co-morbidities; malignant diseases; diabetes mellitus; chronic kidney disease; cirrhosis liver with CPT class B or C; immunocompromised; history of ivermectin allergy; patients taking CYP 3A4 inhibitors or inducers; oxygen requirements equivalent to FiO2 ≥50% in moderate severity patients	lactating mothers, and patients taking other antimicrobials or hydroxychloroquine	of a poor response to high-flow oxygen nasal prong therapy ; required mechanical ventilation	distress or requiring intensive care; used immunosuppressants (including systemic corticosteroids) in the last 30 days; known HIV infection with CD4 count <300 cell/ L; pregnancy or lactating patients; medical conditions such as malabsorption syndromes affecting proper ivermectin absorption; autoimmune disease and/or decompensated chronic diseases; Uncontrolled, intercurrent diseases including renal impairment, hepatic impairment, symptomatic congestive heart failure, unstable chest angina or heart arrhythmia; treated in any other study in the previous 30 days; concomitant administration of enzyme inducers (such as carbamazepine) that could affect the effectiveness of the drug and those receiving CYP3A4 substrates (such as statins) due to the risk of increased toxicity
Intervention (generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe,	ivermectin: 300 mcg/kg/d for 5 days 238 patients	1. ivermectin: 12 mg 40 patients mild 67.5%, moderate 32.5% 2. ivermectin: 24 mg 40 patients mild 60%, moderate 40%	ivermectin: 12 mg 50 patients	ivermectin: 200 mcg/kg + standard care 32 patients mild 81.3%, moderate 18.8%	ivermectin: 12 mg in patients weighing < 80 kg and 18 mg in those >80 kg 36 patients	ivermectin: 12 mg 19 patients

Author, year, reference number/Study name/Study ID	Lopez-Medina et al. 2021 [30] NCT04405843	Mohan et al. 2021 [39] CTRI/2020/06/026001	Shah Bukhari et al. 2021 [44] NCT04392713	Podder et al. 2020 [45]	Beltran-Gonzalez et al. 2021 [27] NCT04391127	Kishoria et al. 2020 [46]
Critical COVID-19)						
Comparator(s) (standard care or generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	placebo 238 patients	placebo + standard care 45 patients mild 64.4%, moderate 35.6%	standard care (oral vitamin C 500mg once daily, oral vitamin D3 200,000 IU once weekly, and oral paracetamol 500 mg SOS) 50 patients	standard care (antipyretics, cough suppressants, and capsule doxycycline (100 mg every 12 hours for seven days) to treat possible community-acquired pneumonia as part of the local working protocol) 30 patients mild 80% moderate 20%	1. placebo 37 patients 2. hydroxychloroquine 400 mg every 12 hours on the first day, followed by 200 mg every 12 hours for another 4 days. 33 patients	standard care (hydroxychloroquine 400 mg twice a day paracetamol 500mg as required. vitamin c 1 tab twice a day)
Primary Outcome(s)	time to resolution of symptoms, time to recovery	RT-PCR negativity at day 5; viral load reduction at day 5	negative PCR	time needed for resolution of fever, cough, shortness of breath and finally, full recovery from all symptoms and the negative result of repeat RT-PCR on day 10	mean days of hospital stay; rate of respiratory deterioration, requirement of invasive mechanical ventilation or dead; mean of oxygenation index delta	negative throat swab report for SARS-CoV-2 conducted by RT-PCR after 48 hours of day one of research therapy
Patient-relevant secondary outcome(s)	clinical deterioration, clinical conditions (based on the 8-category ordinal WHO scale), development of fever and duration of fever, mortality, escalation of care (new-onset hospitalization in the general ward or intensive care unit or new onset supplementary oxygen requirement for more than 24 hours), adverse events	qualitative and quantitative results of RT-PCR on day 3 and 7 after intervention; time to clinical resolution; frequency of clinical worsening; clinical status of the subject on day 14 (8-point WHO ordinal scale); and hospital-free days at day 28, adverse events	adverse events			hospital discharge, adverse effects
Follow-up (days, months)	21 days	28 days	28 days	10 days	no data	6 days

Author, year, reference number/Study name/Study ID	Lopez-Medina et al. 2021 [30] NCT04405843	Mohan et al. 2021 [39] CTRI/2020/06/026001	Shah Bukhari et al. 2021 [44] NCT04392713	Podder et al. 2020 [45]	Beltran-Gonzalez et al. 2021 [27] NCT04391127	Kishoria et al. 2020 [46]
Sponsor/ lead institution	Centro de Estudios en Infectologia Pediatrica in Cali; Tecnoquimicas	Department of Science and Technology, Government of India; WindLas BioTech Ltd. Haryana	Department of Medicine Combined Military Hospital Lahore	(self-financed)	Aguascalienes State Health Institute	Department of Pharmacology,Dr.S.N.Medical College,Jodhpur
*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19 **Abbreviations:** IVM=Ivermectin; IQR=Interquartile range; SoC=Standard of Care.						

Table 4-9 Study characteristics of included RCTs, continued

Author, year, reference number/Study name/Study ID	Chachar et al. 2020 [34] NCT04739410	Okumus et al. 2021 [42] NCT04646109	Pott-Junior et al. 2021 [43] NCT04431466	Hashim et al. 2020 [24] NCT04591600	Mahmud [22] NCT04523831
Study design, study phase	randomized, open-label,	randomized, single blinded, phase 3	randomized, double-blind phase 2a	randomized, open-label, outcome-assessor blinded, phase 1, 2	randomized, double-blind, placebo controlled, phase 3
Centres (single centre or multicentre), country, setting	single-center Pakistan	multicenter Turkey	single-center Brazil	multicenter Iraq	single-center Bangladesh
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	50 patients mean age: 41.8 male: 62% mild	66 patients mean age: 61.8 male: 61% severe to critical	32 patients mean age: 49.2 male: 44% mild	140 patients mean age 50.1 (SD: 9.3) vs 47.2 (SD: 7.8) male: 52% mild-moderate, severe, critical	400 patients mean age: 39.6 male: 59% mild to moderate
Inclusion criteria	All patients diagnosed with COVID-19 infection with positive reverse transcriptase RT-PCR test, who were willing to participate in this study; Patients having age of 18-75 years; Patients of both genders male and female; Patients who had mild symptoms of Corona virus disease and RT- PCR positive for SARSCov-2; Ability to take oral medication and were willing to adhere to the drug intake regimen	Patients who were hospitalized with a pre-diagnosis of "severe COVID-19 pneumonia" and thereafter diagnosis of COVID-19; Confirmed microbiologically with PCR positivity in respiratory tract samples; Patients with at least one of the criteria below were accepted as patients with severe COVID-19 pneumonia: a. Presence of tachypnea ≥ 30/minute; SpO2 level < 90% in room air; PaO2/FiO2 <300 in oxygen receiving patient; b. Presence of specific radiological finding for COVID-19 in lung tomography (bilateral lobular, peripherally located, diffuse patchy ground glass opacities); c. Mechanical ventilation requirement; d. Acute organ dysfunction findings; patients with SOFA (sepsis-related organ failure assessment) score >2	18 years and older; an Eastern Cooperative Oncology Group (ECOG) score of 0-1; a National Early Warning Score (NEWS) of 0-4; and had SARS-CoV-2 infection confirmed by real-time reverse transcription polymerase chain reaction (RT-PCR) testing performed on nasopharyngeal swab specimens.	COVID-19 patients diagnosed by clinical, radiological and laboratory PCR testing, at different stages of the disease (mild-moderate, severe, and critical according to WHO guidelines), who were symptomatic for no more than three days for mild-moderate cases, no more than two days after being severe cases, and no more than one day after being critical cases, outpatients or inpatients	18 years and older; COVID-19 infection, confirmed by polymerase chain reaction (PCR) test within 3 days from enrollment; Only mild and moderate COVID-19 infected cases; Able to provide informed consent
Exclusion criteria	Known severe allergic reactions to Ivermectin; Pregnancy or breastfeeding;	children < 18 years old; pregnancy; active breast feeding; concurrent	Not able to ingest / absorb the drug orally through spontaneous ingestion or by	no data	Unable to take oral medication; Pregnant or breast feeding lady; Patients with severe

Author, year, reference number/Study name/Study ID	Chachar et al. 2020 [34] NCT04739410	Okumus et al. 2021 [42] NCT04646109	Pott-Junior et al. 2021 [43] NCT04431466	Hashim et al. 2020 [24] NCT04591600	Mahmud [22] NCT04523831
	Severe symptoms likely attributed to Cytokine Release Storm; Malignant diseases; Chronic kidney disease; Cirrhosis liver with Child class B or C	autoimmune disease; chronic liver or kidney disease; Immunosuppression; SNP mutation in MDR-1/ABCB1 gene and/or haplotypes and mutations of the CYP3A4 gene; patients with known ivermectin allergy	gastro / enteral tubes; any clinical observation (clinical / physical evaluation) or laboratory findings which, in the investigators opinion, would have put the patient at risk to participate in the study; any abnormal ECG findings that require additional evaluation; known hypersensitivity to the drug components used during the study; pregnancy or breastfeeding; body weight less than 15 kg; an estimated glomerular filtration rate (CKD-Epidemiology Collaboration, CKD-EPI) below 30 mL/min; and values of aspartate aminotransaminase (AST) or alanine aminotransaminase (ALT) 5-fold above the upper limit of normality.		COVID symptoms or admission in ICU/HDU; Alanine Aminotransferase (ALT) or aspartate aminotransferase (AST) more than 5 upper limit of normal (ULN); On non-invasive positive pressure ventilation or mechanical ventilation at time of study entry; Known hypersensitivity to Doxycycline or ivermectin or its components
Intervention (generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	ivermectin: 12 mg (2 days) + standard care 25 patients mild 100%	ivermectin: 200 mcg/kg enterally once daily for 5 days. (9 mg between 36–50 kg, 12mg between 51–65 kg, 15mg between 66–79 kg and 200 mcg/kg in > 80 kg) 36 patients	1. ivermectin + SoC: 100 mcg/kg 7 patients, mild 100% 2. ivermectin + SoC: 200 mcg/kg 14 patients, mild 100% 3. ivermectin + SoC: 400 mcg/kg 7 patients, mild 100%	ivermectin + doxycycline + SoC: IVM 200 mcg/kg PO per day for 2 days, in some patients third dose 200 mcg/kg PO per day was given 7 days after the first dose; doxycycline 100 mg capsule PO every 12h per day, for 5-10 days, based on the clinical improvement of patients; 70 patients: 48% mild-moderate, 11% severe; 11% critical	ivermectin + doxycycline + SoC (IVM 12 mg, doxycycline 100 mg), 5 days 200 patients
Comparator(s) (standard care or generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	standard care (symptomatic treatment) 25 patients mild 100%	SoC (hydroxychloroquine (2x400mg loading dose followed by 2x200mg, po, 5 days), favipiravir (2x1600mg loading dose followed by 2x600mg maintenance dose, po, total 5 days) and azithromycin (500mg rst day loading dose, followed by 250mg/day, po, total 5 days) (HFA), was applied to all	SoC 4 patients	SoC 70 patients: 48% mild-moderate, 22% severe; 0% critical	placebo 200 patients

Author, year, reference number/Study name/Study ID	Chachar et al. 2020 [34] NCT04739410	Okumus et al. 2021 [42] NCT04646109	Pott-Junior et al. 2021 [43] NCT04431466	Hashim et al. 2020 [24] NCT04591600	Mahmud [22] NCT04523831
		patients in the control and study group) 30 patients			
Primary Outcome(s)	improvement of symptoms like fever, cough, sore throat, headache, shortness of breath, lethargy, and fatigue at day 7	clinical responses and drug side effects obtained in patients on the 5th day	Time to undetectable SARS-CoV-2 viral load in the nasopharyngeal swab (day 7)	mortality rate	early clinical improvement, late clinical recovery
Patient-relevant secondary outcome(s)	-	mortality	adverse events	time to recovery, progression of the disease	clinical deterioration, persistently positive for RT-PCR of Covid-19, all-cause mortality, serious adverse events
Follow-up (days, months)	7 days	90 days	28 days	patients were monitored till recovery or death	
Sponsor/ lead institution		Afyonkarahisar Health Science University	Federal University of S˜ao Carlos, Brazi	Alkarkh Health Directorate-Baghdad	Dhaka Medical College, Popular pharmaceutical provided drugs and the placebo

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: IVM=Ivermectin; IQR=Interquartile range; SoC=Standard of Care

Table 4-10 Study characteristics of included RCTs, continued

Author, year, reference number/Study name/Study ID	Chowdhury et al. 2020 [25] NCT04434144	Galan et al. 2021 [29] RBR-8h7q82	Babalola et al. 2021 [26]	Shahbaznejad et al. 2021 [37] IRCT20111224008507N3
Study design, study phase	randomized, open-label	randomized, double-blind, placebo controlled, phase 2	randomized, double blind, controlled trial, of a parallel group, dose-response design	randomized, double blind, controlled trial, phase 3
Centres (single centre or multicentre), country, setting	single-centre Bangladesh	single-centre Brazil	Nigeria	multicenter Iran
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	116 patients mean age: 33.94 years (±14.12) male: 72% mild to moderate	168 patients mean age: 53.4 (±15.6) male: 58.2% severe	63 patients mean age: 44.1 (SD14.7) male: 68% asymptomatic or mild/moderate symptoms	73 patients mean age: 46.4 male: 52.2 moderate to severe
Inclusion criteria	SARS-CoV-2 infection by RT PCR at Chakoria Upazilla Health Complex, Cox's Bazar; Bangladesh from May 2nd to June 5th, 2020; with and without symptoms	laboratory test confirming infection by SARS-CoV-2 (positive serologic test IgM or rt-PCR); hospitalized with a clinical, epidemiological, and radiological picture compatible with COVID-19; over 18 years old; present a severe form of the disease characterized by one of the following clinical signs: dyspnea, tachypnea (>30 bpm), peripheral oxygen saturation <93% (pulse oximeter evaluation), PaO2/FiO2 ratio <300, or infiltrate pulmonary>50% of the parenchyma seen on chest tomography or chest radiography.	COVID 19 PCR proven positive patients, who gave informed, written consent to participate in the study, and were either asymptomatic or had mild/moderate symptoms	Hospitalized patients (age >5 years, weight >15 kg) with any of the following: a positive result of COVID-19 RT-PCR; or clinical complaints of COVID-19 with a history of contact with a COVID-19 patient; or abnormalities in chest computed tomography scan compatible with COVID-19 (ground-glass opacity, halo sign, reversed halo sign, and patchy infiltration).
Exclusion criteria	unstable comorbid conditions like bronchial asthma, COPD, ischemic heart disease, uncontrolled diabetes mellitus, advanced renal and hepatic disease, carcinoma, hospitalized, and immuno-compromised patients	under 18 years old; indigenous people; patients not fluent in Portuguese; unable to understand the objectives and methods of the study; critically ill patients who are not accompanied by legal representatives; those who reject participation in the study; patients with cardiac arrhythmia that include prolongation of the QT interval; previous use of any of the medications surveyed for more than 24 h.	COVID 19 negative patients, patients who had COVID pneumonia or requiring ventilator therapy, renal failure, thromboembolic complications, or unconscious by reduced Glasgow Coma Scale	History of chronic liver and/or renal disease; receiving treatment with warfarin, angiotensin-converting enzyme inhibitors, or angiotensin II receptor antagonists; acquired immunodeficiency; pregnant women and lactating mothers.
Intervention (generic drug name and dosage, time frame; number of	ivermectin (200µgm/kg single dose) + doxycycline (100 mg BID for 10 days); additionally symptomatic treatment for fever, headache, cough, myalgia, etc.;	ivermectin: (14 mg once at day 0 + 1 placebo tablet at day 0, and once daily from day 1 to day 2, + 1 placebo tablet daily from day 3 to 4, total dose 42 mg)	**ivermectin 6mg** (given every 84 hours) twice a week, 21 patients; **ivermectin 12mg** (given every 84 hours) for 2 weeks, 21 patients	**Ivermectin + SoC** 0.2 mg/kg orally once-off (weight-based doses, i.e. 15-24 kg: 3 mg; 25-30 kg: 6 mg; 36-50 kg: 9 mg; 51-80 kg: 12 mg; >80 kg: 0.2 mg/kg).

Author, year, reference number/Study name/Study ID	Chowdhury et al. 2020 [25] NCT04434144	Galan et al. 2021 [29] RBR-8h7q82	Babalola et al. 2021 [26]	Shahbaznejad et al. 2021 [37] IRCT20111224008507N3
randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	60 patients	53 patients		35 patients severe: 37.1%
Comparator(s) (standard care or generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	hydroxychloroquine (400 mg 1st day, then 200 mg BID for 9 days) + azithromycin (500 mg daily for 5 days); additionally symptomatic treatment for fever, headache, cough, myalgia, etc.; 56 patients	1. hydroxychloroquine: (400 mg twice on day 0, and once daily from day 1 to day 4, total dose 2.4 g) 54 patients 2. chloroquine: (450 mg, twice on day 0, and once daily from day 1 to day 4, total dose 2.7 g) 61 patients	lopinavir / ritonavir daily for 2 weeks, 20 patients	standard care (hydroxychloroquine and/or lopinavir/ritonavir) 38 patients severe: 52.9%
Primary Outcome(s)	negative PCR, resolution of symptoms	need for supplemental oxygen, need for invasive ventilation, need for admission to the intensive care unit (ICU)	time to SARS-CoV-2 negativity	clinical improvement
Patient-relevant secondary outcome(s)	adverse effects	mortality, adverse events	adverse effects, symptomatic improvement, mortality	durations of hospital stay, fever, dyspnea, and cough, duration of supplemental oxygen with noninvasive ventilation, mortality, adverse events
Follow-up (days, months)	patients were followed until PCR negativity or symptom resolution	90 days	day seven was used as a midway point in the trial	7 days
Sponsor/ lead institution	Upazila Health & Family Planning Officer's (UHFPO) Office, Chakoria, Cox's Bazar	Universidade Federal de Roraima		Mazandaran University of Medical Sciences

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: IVM=Ivermectin; IQR=Interquartile range; SoC=Standard of Care

Table 4-11 Study characteristics of included RCTs, continued

Author, year, reference number/Study name/Study ID	Abd-Elsalam et al. 2021 [38] NCT04403555	Aref et al. 2021 [36] NCT04716569	Biber et al. 2021 [35] NCT04429711	Chachla et al. 2021 [32] NCT04784481	Vallejos et al. 2021 [33] NCT04529525
Study design, study phase	randomized, open-label phase 2/3	randomized, open-label	randomized, double-blind, placebo controlled	randomized, open-label, phase 1/2	randomized, double-blind, placebo controlled, phase 2/3
Centres (single centre or multicentre), country, setting	multi-centre Egypt	single-centre Egypt	multi-centre Israel	multi-centre Argentina	multi-centre Argentina
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	164 patients median age: 40.9 male: 50% mild to moderate	114 patients mean age: 45.2 male: 72% mild	116 patients median age: 35 male: 59% mild	254 patients median age: 40.0 male: 48% mild	501 patients mean age: 42.49 male: 52.7% mild to moderate
Inclusion criteria	adult patients from ages 20 to 65; mildly to moderately affected COVID-19 infection confirmed by pharyngeal swab polymerase chain reaction	diagnosed as mild COVID-19 - defined as symptomatic case with lymphopenia or leucopenia with no radiological signs for pneumonia; confirmed by real-time PCR test positive for SARS-CoV-2 using upper respiratory tract swabs; written informed consent.	18 years of age or older; not pregnant; with molecular confirmation of COVID-19 by RT-PCR up to seven days from symptoms onset (symptomatic cases were also included within 5 days from molecular diagnosis)	over 18 years of age of any sex; Outpatients infected by SARS-CoV-2 confirmed by positive RT-PCR test; Women of childbearing age with a negative pregnancy test; Mild disease-patients with two or more of the following symptoms: fever less than 38·5°C and higher than 37.5°C according to Ministry of Health, Argentina, isolated diarrheal episodes, hyposmia or hypogeusia, mild desaturation (between 96 and 93%), dyspnea, polyarthralgia, persistent headache, abdominal pain, erythema of the kidney, nonspecic rash	over 18 years of age, residing in the province of Corrientes at the time of diagnosis with confirmed COVID-19 diagnosis by RT-PCR (CFX96 qPCR, Bio-Rad) for SARS-CoV2 detection in the last 48 h; weight ≥48 kg
Exclusion criteria	allergy or contraindication to the drugs used in the study; pregnant and lactating mothers; patients with cardiac problems	patients with severe COVID-19*; Patients indicated to receive systemic ivermectin according to the Egyptian management protocol for COVID-19 patients; chronic ENT disorders such as chronic sinusitis, nasal allergy, patients using nasal spray preparation; systemic or local use of steroids due to any	weight below 40kg; known allergy to the drugs; unable to take oral medication; participating in another RCT for treatment of COVID-19; patients who had RT-PCR results with Ct (cycle threshold) value >35 in first two consecutive; patients with comorbidities of cardiovascular disease,	hypersensitivity or allergy to ivermectin; pregnant or lactating; children or adolescents under 18 years of age; patients with neurological pathology, renal insuciency, hepatic insuciency; weight less than 40kg; patients with concomitant use of drugs that act on GABA, barbiturate and benzodiazepine receptors;	required current home oxygen use or required hospitalization for COVID-19 at the time of diagnosis or had a history of hospitalization for COVID-19; pregnant or breastfeeding women; known allergy to ivermectin or the components of ivermectin or placebo tablets; presence of mal-absorptive syndrome, presence of any other concomitant acute

Author, year, reference number/Study name/Study ID	Abd-Elsalam et al. 2021 [38] NCT04403555	Aref et al. 2021 [36] NCT04716569	Biber et al. 2021 [35] NCT04429711	Chachla et al. 2021 [32] NCT04784481	Vallejos et al. 2021 [33] NCT04529525
		cause; allergic to ivermectin; children and pregnant women.	diabetes, chronic respiratory disease (excluding mild intermittent asthma), hypertension, and or cancer were defined as high-risk patients; severe infection (defined as need for invasive or non-invasive ventilator support, ECMO, or shock requiring vasopressor support)	patients who have not completed / signed the informed consent	infectious disease; known history of severe liver disease, and recent or expected need for dialysis. Concomitant use of hydroxychloroquine or chloroquine or antiviral drugs due to a viral pathology other than COVID-19 at the time of admission was prohibited as was the use of ivermectin up to 7 days before randomization.
Intervention (generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	ivermectin: 12 mg per day (orally for 3 days) + standard care 82 patients	ivermectin: 70 mcg/mL by intranasal spray twice a day 57 patients	ivermectin: Weight 40-69 kg = 12mg orally once a day for 3 days; weight ≥70kg =15mg orally once a day for 3 days 57 patients	ivermectin: orally 4 tablets of 6 mg = 24 mg every 7 days for 4 weeks + standard care (symptomatic treatment) 110 patients	ivermectin: <80 kg, 80–110 kg, or above 110 kg received 24 mg, 36 mg, or 48 mg at inclusion and 24 h the after first dose + standard of care 250 patients
Comparator(s) (standard care or generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	standard care 82 patients	standard care 57 patients	placebo 59 patients	standard care (symptomatic treatment: 500 mg paracetamol every 6 or 8h, no more than 4 tablets daily; 100mg aspirin, 1 tablet per day with breakfast; 150mg Ranitidine, 1 tablet in the morning, and 1 tablet at night) 144 patients	placebo + standard care 251 patients
Primary Outcome(s)	all-cause mortality	clinical improvements of the presenting manifestations with recording the recovery duration for every manifestation	viral clearance at day 6	proportion of patients with symptoms (fever, diarrhea, taste and/or smell disturbance, SpO2, polyarthralgia, headache, body pain, abdominal pain, ALRI symptoms and signs)	hospitalization for any reason of patients with COVID-19

Author, year, reference number/Study name/Study ID	Abd-Elsalam et al. 2021 [38] NCT04403555	Aref et al. 2021 [36] NCT04716569	Biber et al. 2021 [35] NCT04429711	Chachla et al. 2021 [32] NCT04784481	Vallejos et al. 2021 [33] NCT04529525
Patient-relevant secondary outcome(s)	length of hospital stay, the need for mechanical ventilation, safety		adverse events	discharge from outpatient care, adverse events	time to hospitalization in those who required it, use of invasive mechanical ventilatory support (MVS), time to invasive MVS in those who required it, adverse events, all-cause mortality
Follow-up (days, months)	30 days	until complete recovery from COVID-19 and the recovery durations of all symptoms	14 days	28 days	30 days after the final visit
Sponsor/ lead institution	Tanta and Assiut University Hospitals, Egypt	South Valley University, Faculty of Medicine	no data	Ministry of Public Health, Tucumán, Argentina	The Ministry of Public Health of the Province of Corrientes in coordination with the Corrientes Institute of Cardiology “Juana F. Cabral”
*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19 **Abbreviations:** IVM=Ivermectin; IQR=Interquartile range; SoC=Standard of Care.					

Table 4-12 Ongoing trials of single agent ivermectin

Trial Identifier/registry ID(s)/contact	NCT04510233	NCT04729140 COVIVER-OUT PLUS	NCT04834115	NCT04429711	NCT04703205 CORVETTE-01
Study design, study phase	Phase 2 Randomized, parallel, open-label. Ivermectin Inhalation Forms in the Management of COVID-19 Egyptian Patients.	Phase 4 Randomized, parallel-group, double-blinded, prospective, Placebo-controlled. Outpatient Clinical Trial in High Risk Population Confirmed COVID-19 Patients Using Ivermectin and Doxycycline to Prevent COVID-19 Illness-related Hospitalization	Phase III A Randomised, Double-Blind, Placebo-Controlled trial with two parallel groups that evaluates the efficacy of ivermectin in reducing hospitalization in outpatients with COVID-19.	Randomized, parallel-group, double-blinded. 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	Phase 2 Randomized, parallel-group, double-blinded. Study in COvid-19 Patients With iveRmectin; An inVEstigator iniTiaTEd Trial.
Recruitment status	Not yet recruiting	Recruiting	Recruiting	Recruiting	Recruiting
Number of Patients, Disease severity*	60, mild to moderate	150, n.a.	400, n.a.	100, n.a.	240, mild to moderate
Setting (hospital, ambulatory,..)	n.a.	Ambulatory	n.a.	n.a.	n.a.
Intervention (generic drug name and dosage)	(1) Ivermectin (nasal spray): 1 ml in each nostril two times daily. (2) Ivermectin: 6 mg orally three times daily.	(1) Ivermectin (days 1–2: 200 mcg/kg) + Doxycycline (100 mg twice a day for seven days). (2) Ivermectin (days 1–2: 200 mcg/kg) + placebo (twice a day for seven days)	Ivermectin (200 mcg/kg single dose, orally, maximum dose 18 mg)	Ivermectin: 12–15mg/day for 3 days, orally.	Ivermectin: day 1: 200 µg/kg, single oral dose (fasting state)
Comparator (standard care or generic drug name and dosage)	SoC: oxygen via masks or ventilators	Placebo	Placebo (inactive medication tablets indistinguishable from ivermectin tablets)	Placebo	Placebo
Primary Outcome(s)	Negative PCR result of SARS-Cov2 RNA	Decreased admission rate to the hospital secondary to respiratory illness related to COVID-19	Proportion of patients with hospitalization criteria at day 30.	Viral clearance at day 6.	Period until the COVID-19 PCR test (SARS-CoV-2 nucleic acid detection) becomes negative.
Sponsor/ lead institution, country (also country of recruitment if different)	Tanta University, Egypt	Max Health, Subsero Health United States, Florida	Facultad de Ciencias Médicas - Universidad Nacional de Asunción, Paraguay	Sheba Medical Center, Israel	Kitasato University, Japan

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: HCQ= Hydroxychloroquine, SoC=Standard of Care.

Table 4-13 Ongoing trials of single agent ivermectin, continued

Trial Identifier/registry ID(s)/contact	NCT04425707	NCT04510194 COVIDOUT	NCT05060666 2021-002445-15 PREVENT-COVID	NCT04373824	NCT04951362
Study design, study phase	Randomized, parallel-group, open label. The Use of Ivermectin In the Treatment of COVID 19 Patients.	Phase 2/3 Randomized, parallel Outpatient Treatment of COVID-19 With Metformin	Phase 3 Prophylaxis of COVID-19 Disease With Ivermectin in COVID-19 Contact Persons	Non-randomized, crossover-groups, open label	Phase 2/3 Randomized, Parallel Assignment, Open Label clinical trial: Studying the Expected Effect of Ivermectin Nanosuspension as Nasal Spray Upon Post covid19 Persistant Anosmia
Recruitment status	Recruiting	Recruiting	Not yet recruiting	Recruiting	Recruiting
Number of Patients, Disease severity*	100, mild to moderate	1160, n.a.	412, asymptomatic	50, n.a.	117, n.a.
Setting (hospital, ambulatory,..)	Hospital	ambulatory	ambulatory	hospital	n.a.
Intervention (generic drug name and dosage)	(1) Ivermectin (2) Ivermectin + SoC: hydroxychloroquine	Ivermectin, 28 mg if weight < 104 kg, 42 mg if weight > 104 kg. Metformin, 1,500 mg daily + Ivermectin, 28 mg if weight < 104 kg, 42 mg if weight > 104 kg	Ivermectin, orally, 2 doses of administered with 48 hours time interval. The dosage based on body weight: 15 mg for 40-60 kg 18 mg for 60-80 kg 24 mg for > 80 kg	Ivermectin, days 1–2: 200 to 400 mcg/kg + SoC	ivermectin nanosuspension nasal spray
Comparator (standard care or generic drug name and dosage)	SoC: hydroxychloroquine	(1) Metformin, 1,500 mg daily, (2) Fluvoxamine, 50 mg twice a day for 14 days, (3) Metformin, 1,500 mg daily + Fluvoxamine, 50 mg twice a day for 14 days, (4) Placebo	placebo	SoC	corticosteroid nasal spray / saline nasal spray
Primary Outcome(s)	The role of Ivermectin in the cure of COVID 19 patients	Decreased oxygenation, Emergency department utilization for Covid-19 symptoms	Occurrence of a COVID-19 disease up to the final visit (day 14)	Test for virus at 1, 3 & 5 days from beginning of trial drug started for the patient in the hospital	regaining of smell
Sponsor/ lead institution, country (also country of recruitment if different)	Ministry of Health and Population, Egypt	University of Minnesota, USA	Infectopharm Arzneimittel GmbH, Germany	Max Healthcare Insititute Limited, India	South Valley University, Egypt

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: SoC=Standard of Care.

Table 4-14 Ongoing trials of single agent ivermectin, continued

Trial Identifier/registry ID(s)/contact	NCT04716569	NCT04937569	NCT04703608 PaTS-COVID	NCT04445311	NCT05076253
Study design, study phase	Phase 2/Phase 3 Randomized, parallel-group, open-label. Evaluation of Ivermectin Mucoadhesive Nanosuspension as Nasal Spray in Management of Early Covid-19.	Phase 3 Randomized, Sequential Assignment, open-label clinical trial: Ivermectin Versus Standard Treatment in Mild COVID-19	Single blind non-identical placebo-controlled study of prevention and treatment for COVID -19 associated severe pneumonia	Phase 2/Phase 3 Randomized, parallel-group, open-label. Use of Ivermectin as a Therapeutic Option for Patients With COVID-19.	Phase 1, 2 Efficacy and Safety of Ivermectin in Treatment of Mild to Moderate COVID-19 Infection: a Randomized, Double Blind Placebo Controlled Trial
Recruitment status	Recruiting	Not yet recruiting	Recruiting	Recruiting	Recruiting
Number of Patients, Disease severity*	150, n.a.	1644; mild	1200, mild, moderate	100, n.a.	72, mild to moderate
Setting (hospital, ambulatory,..)	n.a.	n.a.	household	n.a.	n.a.
Intervention (generic drug name and dosage)	Ivermectin: intranasal spray	4-days course of Ivermectin 400 microgram/kg body weight maximum 4 tablets (6mg / tablet) once daily	(1) IC: Ivermectin 0.3-0.4 mg/kg daily for 3 days; HH: Ivermectin 0.3-0.4mg/kg daily for 3 days / Placebo; (2) Aspirin 150 mg daily for 28 days or until hospital discharge (whichever is sooner)	Ivermectin (3 days) +SoC	Ivermectin, orally, 12 mg per day for 5 days
Comparator (standard care or generic drug name and dosage)	Regular protocol drugs	Standard treatment only	placebo	SoC	placebo
Primary Outcome(s)	Progress of Symptoms (Fever, Cough, Sore Throat, Myalgia, Diarrhoea, Shortness of Breath) with radiological assessment and blood tests.	Rate of ICU admission in mild COVID-19 cases	(1) Percentage of patients with mild disease/moderate pneumonia progressing to severe pneumonia; Percentage of HH members that get infected with SARS-CoV-2; (2) Percentage of COVID-19 associated severe pneumonia patients worsening their condition	Time to be symptoms free	Viral clearance of SARS-CoV-2 intervention (viral load from RT-PCR test)
Sponsor/ lead institution, country (also country of recruitment if different)	South Valley University, Egypt	Assiut University, Egypt	London School of Hygiene and Tropical Medicine, Great Britain Gambia	Zagazig University, Egypt	Bangkok Metropolitan Administration Medical College and Vajira Hospital, Thailand

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: SoC=Standard of Care.

Table 4-15 Ongoing trials of single agent ivermectin, continued

Trial Identifier/registry ID(s)/contact	NCT05056883	NCT04374019	NCT04727424	NCT04472585 SIZI-COVID-PK
Study design, study phase	Phase 3 A Phase III Confirmatory Study of K-237-A Multicenter, Placebo Controlled, Randomized, Double Blind, Parallel Group Controlled Trial in Patients With Mild COVID-19	Phase 2 Randomised, open label, multi-arm trial for rapid efficacy and toxicity assessment of multiple therapies immediately after COVID19 positive testing in high-risk individuals.	Phase 3 Multicenter, prospective, adaptive, double-blinded, randomized, placebo-controlled, parallel-group study to evaluate the effect of fluvoxamine, ivermectin and metformin in reducing hospitalization of patients with mild COVID-19 and a high risk of complications	Phase 1/Phase 2 Randomized, controlled, multi-armed, open-label, interventional, parallel-group study of efficacy of subcutaneous Ivermectin with or without Zinc in COVID-19 patients
Recruitment status	Recruiting	Recruiting	Recruiting	Recruiting
Number of Patients, Disease severity*	1000, mild	240, n.a.	2724, mild	60, mild to moderate
Setting (hospital, ambulatory,..)	n.a.	n.a.	ambulatory	n.a.
Intervention (generic drug name and dosage)	Ivermectin, orally, 3mg	Ivermectin; orally, on days 1–2: weight < 75 kg: 12 mg total daily dose, weight > 75 kg: 15 mg total daily dose	Ivermectin: 6 mg, orally: 3 tabs if weight 40–60 kg, single dose; 4 tabs if weight > 60 kg, single dose	Ivermectin, sub-cutaneous injection, 200 ug/kg every 48 hours + SoC + placebo (empty capsule)
Comparator (standard care or generic drug name and dosage)	placebo	Camostat Mesilate; days 1–14: 600 mg total daily dose, orally (arm D) Artemesia annua, tea or coffee, days 1–14: 1350 mg total daily dose (arm E) Artesunate, days 1-14: n.a. (arm F)	(1) Fluvoxamine Maleate 100 mg orally, twice a day for 9 days; (2) Metformin HCL 750 mg twice a day for 9 days; (3) placebo	(1) Ivermectin, sub-cutaneous injection, 200 ug/kg every 48 hours + Zinc Sulphate 20mg 8 hourly + SoC; (2) placebo (injectable and empty capsule) + SoC
Primary Outcome(s)	Time from the start of study drug administration to 168 hours until the clinical symptoms reach an improving trend	Proportion of patients experiencing clinical deterioration.	Evaluation of emergency visits and observation unit stay > 12 hours, Hospitalization due to COVID-19 progression	Time needed to turn positive COVID-19 PCR to negative, Time taken for alleviation of symptoms, Severity of symptoms
Sponsor/ lead institution, country (also country of recruitment if different)	Kowa Company, Ltd., Japan	University of Kentucky Markey Cancer Center, United States	Cardresearch, Brazil	Sheikh Zayed Federal Postgraduate Medical Institute, Pakistan

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: SoC=Standard of Care.

Table 4-16 Ongoing trials of single agent ivermectin, continued

Trial Identifier/registry ID(s)/contact	NCT04602507	NCT04836299 SAINTBO	NCT04681053 CCOVID-1	NCT04885530 ACTIV-6	NCT04886362 IVERCOL01
Study design, study phase	Phase 2 Randomized, double-blinded, parallel assignment, placebo-controlled study	Phase II Randomized, double-blind, Placebo-controlled parallel clinical trial to "Study the efficacy and therapeutic safety of Ivermectin associated with standard of care treatment versus placebo with standard of care treatment in the early phase of coronavirus infection (COVID19).	Phase 3 Non-randomized, parallel-group, open-label. Efficacy and Safety of Inhaled Ivermectin in the Treatment of SARS-COV-2 (COVID-19).	Phase 3 Double-Blind, Randomized Trial, Parallel Assignment, Placebo-Controlled platform protocol, where participants will be randomized to study drugs or placebo based on the arms that are actively enrolling at the time of randomization.	Phase 2/3 A parallel, prospective, double-blind, placebo-controlled clinical trial of safety and efficacy and of Ivermectin for the prevention of severe disease in patients with COVID-19
Recruitment status	Recruiting	Not yet recruiting	Recruiting	Recruiting	Not yet recruiting
Number of Patients, Disease severity*	100, severe	90, mild to moderate	80, mild to moderate	15 000, mild to moderate	966, mild to moderate
Setting (hospital, ambulatory,..)	hospital	n.a.	n.a.	ambulatory	ambulatory
Intervention (generic drug name and dosage)	Ivermectin; orally, 400 µg/kg (2 drops per kg), single dose.	Ivermectin (600 µg/kg single dose) + SoC	Ivermectin Powder: 6 mg for 3 days (1) oral and inhaled (2) oral (3) inhaled	Ivermectin, orally, approx. 300-400 µg/kg daily for 3 days	Ivermectin, orally, 600 mcg/kg every 12 hours for 5 days.
Comparator (standard care or generic drug name and dosage)	Placebo	Placebo + SoC	SoC	Placebo	Placebo
Primary Outcome(s)	Admission to the intensive care unit.	Evolution of viral load; Clinical remission	Rate of virological cure by Rt-PCR. All PCR for COVID-19 must be negative	Number of hospitalizations as measured by patient reports; Number of deaths as measured by patient reports; Number of symptoms as measured by patient reports	Proportion of patients progressing to severe COVID-19 (at least one of the following: Hypoxemia and need for supplemental oxygen in home care program; or Need for hospitalization; or Death from any cause.
Sponsor/ lead institution, country (also country of recruitment if different)	CES University, Colombia	Universidad Mayor de San Simón, Cochabamba Bolivia	Mansoura University, Egypt	National Center for Advancing Translational Science, Vanderbilt University Medical Center, United States	Ayudas Diagnosticas Sura S.A.S, Columbia

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: SoC=Standard of Care.

Table 4-17 Ongoing trials of single agent ivermectin, continued

Trial Identifier/registry ID(s)/contact	NCT04891250 ZIT	2020-001971-33 CORIVER	2020-001474-29 SAINT	2021-000166-15 IVM-2021-01	ISRCTN86534580 PRINCIPLE
Study design, study phase	Phase 4 Patients with moderate to severe COVID-19 disease will be randomized to either Ivermectin (Intervention) or Standard of Care (Control arm) in a 1:1 ratio.	Phase 3 A Randomised, Double-Blind, Parallel-Group, Placebo-Controlled Pragmatic study: Ivermectin as antiviral treatment for patients infected by SARS-COV2 (COVID-19)	Phase 2 Randomised, Double-Blind, Placebo-Controlled study to evaluate the potential of ivermectin to reduce COVID-19 transmission	A randomized, double-blind, placebo-controlled study to assess the safety and efficacy of ivermectin in asymptomatic and mild severity COVID-19 patients	Phase 3 Platform Randomised trial of Treatments in the Community for Epidemic and Pandemic Illnesses
Recruitment status	Not yet recruiting	Ongoing, n.a.	Ongoing, n.a.	Ongoing, n.a.	Ongoing, n.a.
Number of Patients, Disease severity*	800, moderate to severe	45, n.a.	24, n.a.	70, asymptomatic and mild	6,000; n.a.
Setting (hospital, ambulatory,..)	n.a.	n.a.	n.a.	n.a.	ambulatory
Intervention (generic drug name and dosage)	(1) Ivermectin (treatment), n.a. (2) Ivermectin (prophylaxis), n.a.	Ivermectin, orally, 200 to 400 µg/kg	Ivermectin, orally, 3 mg	Ivermectin, orally	Ivermectin, orally, 3 mg (300µg/kg body weight), once daily for 3 days
Comparator (standard care or generic drug name and dosage)	(1) SoC, n.a. (2) SoC, n.a.	(1) hydroxychloroquine, oral, 400 mg; (2) azithromycin, oral, 400 mg; (3) placebo	placebo	placebo	(1) Favipiravir, orally, day 1: 9 x 200 mg (1800mg) twice a day, day 2–4: 4 x 200 mg (800mg) twice daily. (2) Colchicine , orally, 500 mg, once daily for 14 days (3) SoC
Primary Outcome(s)	All-cause COVID-19 related mortality The proportion of patients on Ivermectin prophylaxis who test positive for COVID 19 using PCR after initially testing negative at enrolment	Comparison of clinical cure, microbiology, need for hospital admission due to clinical or analytical, blood gas and/or radiological deterioration	Proportion of patients with a positive SARS-CoV-2 PCR from a nasopharyngeal swab	Percentage of SARS-CoV-2 virus copy number at Day 7 compared to baseline (i.e. 100 * (the number of virus copies at Day 7 / number of virus copies at Screening))	Time taken to self-reported recovery, defined as the first instance that a participant reports feeling recovered from possible COVID-19; Hospitalisation and/or death
Sponsor/ lead institution, country (also country of recruitment if different)	University of Zambia, Centre for Infectious Disease Research in Zambia, Ministry of Health, Zambia	Hospital Universitario Virgen de las Nieves Spain	Clínica Universidad de Navarra/Universidad de Navarra Spain	Cortex Pharma Services Hungary	Department of Health / University of Oxford, United Kingdom

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: SoC=Standard of Care.

Table 4-18 Ongoing trials of single agent ivermectin, continued

Trial Identifier/registry ID(s)/contact	ISRCTN90437126	2020-002283-32 COVER	2021-002024-21 IVER-FNUSA-21	NCT05041907 PLATCOV	NCT05040724 IVERCoV
Study design, study phase	Phase 3 Randomized, Double-Blinded, Placebo-Controlled trial. Study on the effects of using ivermectin to prevent COVID-19 in an adult population in Brazil.	Phase 2 Randomized, double-blind, multi centre phase II, proof of concept, dose finding clinical trial on Ivermectin for the early Treatment of COVID-19	Phase 3 Randomized placebo controlled clinical trial evaluating the safety and efficacy of ivermectin in hospitalized patients with Covid-19 disease	Phase 2 Finding Treatments for COVID-19: A Trial of Antiviral Pharmacodynamics in Early Symptomatic COVID-19	Evaluation of the Impact of the Administration of Single Dose of Ivermectin in the Early Phase of COVID-19
Recruitment status	Ongoing, n.a.	Ongoing, n.a.	Ongoing, n.a.	Recruiting	Active, not recruiting
Number of Patients, Disease severity*	800, asymptomatic	122, n.a.	136, n.a.	750, symptomatic	200, symptomatic
Setting (hospital, ambulatory,..)	n.a.	n.a.	hospital	n.a.	ambulatory
Intervention (generic drug name and dosage)	Ivermectin, orally, 400 µg/kg	(1) Ivermectin, orally, 600 µg/kg for 5 days (2) Ivermectin, orally, 1200 µg/kg for 5 days	Ivermectin, orally, 3 mg	Ivermectin, 600 mcg/kg/day for 7/7	Ivermectin, orally, 3mg
Comparator (standard care or generic drug name and dosage)	placebo	placebo	placebo	1) Favipiravir 2) Monoclonal antibodies 3) No treatment 4) Remdesivir	placebo
Primary Outcome(s)	Covid-19 case diagnosis (conversion from being asymptomatic pre-treatment to symptomatic post-treatment for COVID-19) by using a questionnaire for screening clinical symptoms of COVID-19, at baseline, and at 7, 14, 30 and 90 days.	1. Number of serious adverse drug reaction (SADR). 2. Quantitative viral load at Day 7 as measured by quantitative, digital droplet PCR.	1. Severity, expectations, intensity AE and association with IP and placebo 2. Nature of AE, duration 3. Improvement by at least one grade at the 8-level Ordinal Scale S1 assessment level, assessed on day 10 after the first IP / placebo administration	1) Rate of viral clearance for repurposed drugs; 2) Rate of viral clearance of positive control; 3) Rate of viral clearance for small novel molecule drugs	Negativation of the RT-PCR test on nasopharyngeal samples of SARS-CoV-2 (Day 3)
Sponsor/ lead institution, country (also country of recruitment if different)	Clinical Research Institute Scinet, Brazil	Ospedale Classificato Equiparato Sacro Cuore Don Calabria - Presidio Ospedaliero Accreditato, Italy	Fakultní nemocnice u sv. Anny v Brně, Czech Republic	University of Oxford, Thailand	Raincy Montfermeil Hospital Group, France

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: SoC=Standard of Care.

Table 4-19 Ongoing trials of combination therapies ivermectin

Trial Identifier/registry ID(s)/contact	NCT04712279 IVACOV	NCT04360356	NCT04351347	NCT04435587 IDRA-COVID	NCT04392427
Study design, study phase	Phase 2/Phase 3 Randomized, parallel-group. High-Dose Ivermectin for Mild-to-Moderate COVID-19	Phase 2/Phase 3 Randomized, parallel-group, double-blinded. Clinical Trial Evaluating Safety and Efficacy of Ivermectin and Nitazoxanide Combination as Adjuvant Therapy in COVID-19 Newly Diagnosed Egyptian Patients	Phase 2/Phase 3 Open label, randomized study evaluating the efficacy of ivermectin and nitazoxanide in Covid-19 treatment	Open label, randomised controlled study of oral ivermectin versus combined of hydroxychloroquine plus darunavir/ ritonavir treatment among asymptomatic carriers of SARS-CoV2.	Phase III, Randomised, Sequential Assignment
Recruitment status	Not yet recruiting	Not yet recruiting	Recruiting	Recruiting	Not yet recruiting
Number of Patients, Disease severity*	294, mild to moderate	100, n.a.	300, n.a.	80, mild	100, n.a.
Setting (hospital, ambulatory,..)	n.a.	n.a.	n.a.	n.a.	n.a.
Intervention (generic drug name and dosage)	(1) Ivermectin (0,6 mg/kg/day q.d.) + HCQ (200 mg/day q.d) (2) Ivermectin (1,0 mg/kg/day q.d.) + HCQ (200 mg/day q.d.)	Ivermectin (200 mcg/kg once orally on empty stomach) +Nitazoxanide (500 mg twice daily orally with meal for 6 days)	(1) Invermectin, n.a., (2) Nitazoxanide with Ivermectin, n.a.	Ivermectin, 600 mcg/kg/day, once daily for 3 days + Zinc sulfate 100mg/tab, 2 tabs every 12 hours for 3 days	Nitazoxanide + Ribavirin + Ivermectin
Comparator (standard care or generic drug name and dosage)	Placebo + HCQ (200 mg/day q.d.)	SoC: Oxygen via Ventilators	SoC	HCQ: day 1: 400 mg bid, days 2–5: 200mg bid + Darunavir/ritonavir, 400/100mg every 12 hours for 5 days + Zinc sulfate, 100/tab, 2 tab severy 12 hours for 5 days	no treatment
Primary Outcome(s)	Treatment efficacy as assessed by World Health Organization (WHO) Clinical Progression Scale.	COVID-19 PCR analysis (within 10 days)	Number of patients with improvement or died	Adverse event rates, Efficacy for shortening duration of SAR-CoV2 detection by PCR	Negative test result for COVID-19
Sponsor/ lead institution, country (also country of recruitment if different)	Corpometria Institute, Brazil	Tanta University, Egypt	Tanta University, Egypt	Mahidol University, Thailand	Mansoura University, Egypt

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: HCQ= Hydroxychloroquine, SoC=Standard of Care.

Table 4-20 Ongoing trials of combination therapies ivermectin, continued

Trial Identifier/registry ID(s)/contact	NCT04768179 IVCOM	NCT04482686	NCT04399746 IvAzCol	NCT04392713	NCT04447235 TITAN
Study design, study phase	Phase 2/Phase 3 Randomized, parallel-group, open label. The Safety & Efficacy of Low-dose Aspirin/ Ivermectin Combination Therapy in Management of COVID-19 Patients.	A Phase II Double-Blind Randomized Placebo-Controlled Trial of Combination Therapy to Treat COVID-19 Infection	Non-Randomized, Parallel Assignment A Pilot Study for COVID-19 Outpatient Treatment With the Combination of Ivermectin-azithromycin-cholecalciferol	A Randomized Controlled Parallel Trial on Efficacy of Ivermectin in COVID-19	Phase II A randomized, doubled-blind and placebo-controlled trial evaluating the use of ivermectin plus losartan for prophylaxis of severe events in cancer patients with recent diagnosis of covid-19
Recruitment status	Not yet recruiting	Active, not recruiting	Recruiting	Recruiting	Recruiting
Number of Patients, Disease severity*	490, moderate to severe	30, n.a.	30, mild	100, mild to moderate	176, n.a.
Setting (hospital, ambulatory,..)	n.a.	ambulatory	ambulatory	n.a.	n.a.
Intervention (generic drug name and dosage)	(1) Ivermectin (3-day 200 mcg/kg/day) + Aspirin (14-day 75mg/day) + SoC; (2) Ivermectin (3-day 600 mcg/kg/day) + Aspirin (14-day 75mg/day) + SoC	Ivermectin (on days 1 and 4) + Doxycycline Hcl + Zinc + Vitamin D3 + Vitamin C (on days 1–10)	Ivermectin (6 mg once daily in day 0,1,7 and 8) + Azithromycin (500 mg once daily for 4 days) + Cholecalciferol (400 IU twice daily for 30 days).	Ivermectin, 12 mg single dose + chloroquine as per hospital protocol	Ivermectin, on day 1: 12 mg, losartan 50 mg orally once daily for 15 consecutive days
Comparator (standard care or generic drug name and dosage)	SoC	Placebo and Vitamin D3, Vitamin C, and Zinc (on days 1–10)	no treatment	chloroquine as per hospital protocol	placebo
Primary Outcome(s)	SARS COV 2 Viral load; World Health Organization COVID-19 ordinal improvement score.	Time to Non-Infectivity by RT-PCR, Time to Symptom progression in days as measured by NEWS scoring system, Time to Symptom improvement as measured by NEWS scoring system, Efficacy of Treatment as measured by Titer, Efficacy of Treatment as measured by RT-PCR	Viral clearance	Negative PCR	Incidence of severe complications due COVID-19 infection
Sponsor/ lead institution, country (also country of recruitment if different)	Makerere University Ministry of Health, Uganda	ProgenaBiome, United States	Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado, Mexico	Combined Military Hospital, Pakistan	Instituto do Cancer do Estado de São Paulo, Brasil

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: HCQ= Hydroxychloroquine, SoC=Standard of Care.

Table 4-21 Ongoing trials of combination therapies ivermectin, continued

Trial Identifier/registry ID(s)/contact	NCT04551755	NCT04779047	NCT04944082	NCT04959786 MANS-NRIZ
Study design, study phase	Phase 2 Randomized, parallel-group, double-blinded, triple masking. The Safety and Efficacy Outcome of Ivermectin Plus Doxycycline in Treatment of RT-PCR Positive Adult Mild Covid-19 Cases.	Phase 4 Randomized, parallel-group, open label. Comparative therapeutic efficacy and safety of Remdesivir plus Lopinavir/ Ritonavir and Tocilizumab vs Hydroxychloroquine plus Ivermectin and Tocilizumab in COVID-19 patients.	Phase 4 Randomized, parallel assignment, open-label. Remdesivir Versus Remdesivir- Ivermectin Combination Therapy in Severe and Critically Ill Covid-19	Phase 2/3 Randomized, Parallel Assignment Effect of a Combination of Nitazoxanide, Ribavirin and Ivermectin Plus Zinc Supplement on the Clearance of COVID-19: Extension Study
Recruitment status	Not yet recruiting	Recruiting	Not yet recruiting	Recruiting
Number of Patients, Disease severity*	188, mild	150, severe	60, severe	100, moderate to severe
Setting (hospital, ambulatory,..)	n.a.	hospital	hospital	hospital
Intervention (generic drug name and dosage)	Ivermectin (12mg and 12 mg after 12 hours) + Doxycycline (days 1–10: 100 mg t.i.d.) + SoC SoC: paracetamol, antihistamine, montelukast, vitamin C, vitamin D.	(1) Remdesivir (day 1: 200 mg, days 2–6: 100 mg, i.v., once daily) + TCZ (800 mg once) + LPV/r (400/100 mg once daily for 5 days)	Remdesivir only (dose 200 mg day one, 100 mg daily days 2–5), duration may extend to 10 days of remdesivir (200 mg day one, 100 mg daily days 2–10) + ivermectin 4 tablet (6mg) once daily before meal for four days	Ivermectin + Ribavirin + Nitazoxanide + Zinc (orally
Comparator (standard care or generic drug name and dosage)	Placebo	(2) HCQ (day 1: 400 mg twice daily, days 2–6: 200 mg twice daily) + TCZ (800 mg once + Ivermectin (36 mg at day 1,3 and 6)	Remdesivir only (dose 200 mg day one, 100 mg daily days 2–5), duration may extend to 10 days of remdesivir (200 mg day one, 100 mg daily days 2–10)	SoC
Primary Outcome(s)	Outcome measure of symptoms associated with covid, fever and cough; Negative RT-PCR test on day 5 of treatment	Proportion of cured patients in the interventional group versus the proportion of cured patients in the control group before and after starting drugs.	Improvement in level of oxygenation; Need for ventilator support; Length of hospital stay; Development of complication; Mortality	(1) Stabilization of oxygen – at room air more than 90% (2) In-hospital and 28-day mortality
Sponsor/ lead institution, country (also country of recruitment if different)	Bangladesh Medical Research Council (BMRC), Bangladesh	Beni-Suef University, Egypt	Assiut University, Egypt	Mansoura University, Egypt

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: AZM=Azithromycin, HCQ= Hydroxychloroquine, LPV/r=Lopinavir/Ritonavir, RXB=Rivaroxaban, SoC=Standard of Care, TCZ=Tocilizumab.

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6 APPENDIX

6.1 Search strategy to identify randomised controlled trials

DEPLazio, the Department of Epidemiology of the Regional Health Service Lazio in Rome, Italy has been responsible till May 2021 for setting up the search strategy to identify randomised controlled trials (RCTs). DEPLazio performed a search in Medline, PubMed, and Embase, which has been updated weekly from March 2020. The search has been done in medRxiv.org (https://www.medrxiv.org/), bioRxiv.org (https://www.bioRxiv.org/), and arXiv.org (https://www.arXiv.org/) for preprints of preliminary reports of randomised trials. The Cochrane Covid-19 Study Register (https://covid-19.cochrane.org/), ClinicalTrials.gov (www.clinicaltrials.gov) and World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en/) were search in addition. Other sources included journal alerts, contact with researchers, websites such as Imperial College, London School of Hygiene and Tropical Medicine, and Eurosurveillance. We applied no restriction on language of publication.

We included randomised controlled trials (RCTs) comparing any pharmacological intervention against another pharmacological intervention or placebo or standard care (SC), for the treatment of individuals with COVID-19. We excluded studies comparing two dosages of the same pharmacological agent. We did not exclude studies on individuals with a comorbid disorder.

Four authors independently screened the references retrieved by the search, selected the studies, and extracted the data, using a predefined data-extraction sheet. The same reviewers discussed any uncertainty regarding study eligibility and data extraction until consensus was reached; conflicts of opinion were resolved with other members of the review team. Two authors independently assessed the risk of bias of the included studies with the Cochrane tool. Three authors used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, to evaluate the strength of evidence.

From June 2021, literature search strategy and results from COVID-NMA initiative were used, according living review protocol [1] [3]. Randomised controlled trials (RCTs) comparing any pharmacological intervention against another pharmacological intervention or placebo or standard care (SC), for the treatment of individuals with COVID-19 were included. Early-phase clinical trials, single-arm trials, non-randomized studies or modelling studies of interventions for COVID-19 were excluded, as well as studies about prognosis, systematic reviews and meta-analyses and diagnostic test accuracy studies. Details can be found in COVID-NMA Protocol [2].

6.2 Search strategy to identify ongoing studies

AOTMiT is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and Ivermectin are described in Appendix Table 6-1.

Table 6-1 Search strategy to identify ongoing studies

Database	URL	Search line / search terms	Date of search	Hits retrieved
ClinicalTrials.gov	https://clinicaltrials.gov/	Basic search mode* Terms used at Condition or disease: • covid-19 Terms used at "other terms": • Ivermectin • D11AX22	10/12/2021	41 (5 new)**
ISRCTN	https://www.isrctn.com/	Basic search mode Search terms: 1. covid-19 and ivermectin 2. covid-19 and Stromectol 3. covid-19 and Soolantra 4. covid-19 and Sklice 5. covid-19 and Mectizan 6. covid-19 and Invermectina 7. covid-19 and Invomec 8. covid-19 and Stromectal 9. covid-19 and D11AX22 10. SARS-CoV-2 and ivermectin 11. SARS-CoV-2 and Stromectol 12. SARS-CoV-2 and Soolantra 13. SARS-CoV-2 and Sklice 14. SARS-CoV-2 and Mectizan 15. SARS-CoV-2 and Invermectina 16. SARS-CoV-2 and Invomec 17. SARS-CoV-2 and Sktromectal 18. SARS-CoV-2 and D11AX22	10/12/2021	2 (0 new)
European Clinical Trials Registry	https://www.clinicaltrialsregister.eu/	Basic search mode* Search terms: 1. covid-19 and ivermectin 2. covid-19 and Stromectol 3. covid-19 and Soolantra 4. covid-19 and Sklice 5. covid-19 and Mectizan 6. covid-19 and Invermectina 7. covid-19 and Invomec 8. covid-19 and Stromectal 9. covid-19 and D11AX22 10. SARS-CoV-2 and ivermectin 11. SARS-CoV-2 and Stromectol 12. SARS-CoV-2 and Soolantra 13. SARS-CoV-2 and Sklice 14. SARS-CoV-2 and Mectizan 15. SARS-CoV-2 and Invermectina 16. SARS-CoV-2 and Invomec 17. SARS-CoV-2 and Sktromectal 18. SARS-CoV-2 and D11AX22	10/12/2021	6 (1 new)**

***** In Basic Search mode, one term was added to the field "condition or disease" and one term in the field "other terms".
** One study is duplicated in two bases.