EUnetHTA Joint Action 3 WP4

"Rolling Collaborative Review" of Covid-19 treatments

DARUNAVIR FOR THE TREATMENT OF COVID-19

Project ID: RCR10
Monitoring Report

Version 8.0, March 2021

Template version February 2021

This Rolling Collaborative Review Living Document is part of the project / joint action '724130 / EUnetHTA JA3' which has received funding from the European Union's Health Programme (2014-2020)

DOCUMENT HISTORY AND CONTRIBUTORS

Version	Date	Description of changes
V 1.0	**17/08/2020**	First version
V 2.0	**22/09/2020**	Second version
V 3.0	**14/10/2020**	Third version
V 4.0	**17/11/2020**	Fourth version
V 5.0	**14/12/2020**	Fifth version
V 6.0	**25/01/2021**	Sixth version
V 7.0	**15/02/2021**	Seventh version
V 8.0	**15/03/2021**	Eighth version

Major changes from previous version

Chapter, page no.	Major changes from version 7.0
Table 4-6, 23	The evidence base did not change One completed and published trial was omitted from Table 4-6.
Table 4-5, 21 to Table 4-6, 23	The recruitment status of ongoing trials was verified and updated when indicated
Appendix, 26	The Appendix tables are updated. Table 6-2 Search strategy to identify observational studies now only displays the search strategy performed for the current version of the report. Details on search strategies for version 1 to 7 can be found in previous versions of this report. The Flow diagrams are changed to reflect the latest update

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)	Swiss Network for Health Technology Assessment (SNHTA), Switzerland
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
Austrian Institute for Health Technology Assessment (AIHTA), Austria	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).

Copyright

How to cite this assessment

Please cite this assessment as follows:

EUnetHTA Rolling Collaborative Review (RCR10) Authoring Team. Darunavir for the treatment of COVID-19. Diemen (The Netherlands): EUnetHTA; 2021. [date of citation]. 34 pages. Report No.: RCR10, V8.0. Available from: https //www.eunethta.eu.

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

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

AE	Adverse Event
ARDS	Acute respiratory distress syndrome
ARR	Absolute Risk Reduction
ATC	Anatomical Therapeutic Chemical [Classification System]
ATMP	Advanced therapy medicinal product
BID	Two times a day
CI	Confidence Interval
CT	Computed Tomography
DOI	Declaration of interest
DRV/c	Cobistat-boosted darunavir
EUnetHTA	European Network of Health Technology Assessment
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HCQ	Hydroxychloroquine
HR	Hazard Ratio
HRQOL	Health-related Quality of Life
HY/RD	Ritonavir/darunavir & hydroxychloroquine
HY/AZ	Hydroxychloroquine & azithromycin
ICD	International Classification of Diseases
ITT	Intention-to-treat
LPV/r	Lopinavir/ritonavir
MD	Mean Difference
MeSH	Medical Subject Headings
mg	milligram
NA	Not applicable
NR	Not reported
OR	Odds Ratio
PP	Per Protocol
QOD	Every other day
QID	Four times a day
RCT	Randomized Controlled Trial
RCR	Rolling Collaborative Review
REA	Relative Effectiveness Assessment
RR	Relative Risk
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious Adverse Event
SD	Standard Deviation
SE	Standard Error
SMD	Standardized Mean Difference
SmPC	Summary of product characteristics
SoC	Standard of Care
SOP	Standard Operating Procedure
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	Darunavir (Prezista®) in combination with ritonavir or cobicistat and other (antiretroviral) treatment or standard of care. Darunavir is an HIV protease inhibitor acting on the reproductive cycle of HIV, inhibiting the replication of HIV-1 in infected cells. Darunavir is the active substance in Prezista® and acts by selectively inhibiting the cleavage of HIV-1 encoded Gag-Pol polyproteins in infected cells and preventing the formation of mature virus particles. **MESH Terms** • Darunavir
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) Safety: observational studies (comparative or single-arm prospective studies and registries)

2.2 Sources of information

According to the project plan, this Rolling Collaborative Review is based on three main sources 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. DEPLazio provides updates for the SoF table on a monthly basis to the EUnetHTA partners authoring the respective Rolling CR documents who are integrating this information accordingly.

The literature search is conducted 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. Appendix Table 6-1 describes in detail the sources searched, the search terms used and the dates at which the searches are executed.

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. The process of study selection is depicted as a flow diagram in Appendix Figure 6-1.

Risk of bias is assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [1].

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 [2]. Network meta-analysis (NMA) is performed for the primary outcome. For rating the certainty of the evidence, the GRADE approach is being used [3].

- Sources: http://deplazio.net/farmacicovid/index.html for SoF (or https://covid-nma.com/)

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

The literature search is conducted on a monthly basis.

The sources and search methods are described in more detail in Appendix Table 6-2.

Population	See project Scope
Intervention	Darunavir (Prezista®) as a mono-therapy, Darunavir (Prezista®) in combination with ritonavir or cobicistat and other (antiretroviral) treatment or standard of care. Darunavir is an HIV protease inhibitor acting on the reproductive cycle of HIV, inhibiting the replication of HIV-1 in infected cells. Darunavir is the active substance in Prezista® and acts by selectively inhibiting the cleavage of HIV-1 encoded Gag-Pol polyproteins in infected cells and preventing the formation of mature virus particles. (1) **MeSH terms** • Darunavir; COVID-19; Coronavirus Disease 2019
Comparison	Any active treatment, placebo, or standard of care.
Outcomes	See project Scope
Study design	Inclusion criteria: Prospective non-randomised controlled trials, prospective case series (i.e. comparative or single-arm prospective studies), registries Exclusion criteria: retrospective studies, case studies / case reports, observational studies that do not report safety data

Two researchers from NIPHNO carry out title and abstract screening and assess the full texts of all potentially eligible studies. The study selection process is depicted in a flow diagram (Appendix Figure 6-2).
One researcher of SNHTA extracts the data and assesses the risk of bias using Robins-I (https://training.cochrane.org/handbook/current/chapter-25). For prospective single arm studies, the checklist for prevalence studies of the Johanna Briggs Institute is used to assess the methodological rigor and applicability [4].

Results are presented in tabular form for all included studies.

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/
  - International Clinical Trials Registry Platform (ICTRP): https://clinicaltrials.gov/ct2/who_table

Inclusion criteria: Randomised controlled trials, Controlled trials

One researcher of SNHTA 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 and scholar.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 6-3.

Data are presented in tabular form.

3 ABOUT THE TREATMENT

3.1 Mode of Action

Darunavir, also known as Prezista®, TMC-114 or Darunavir-Mylan, is a nonpeptidic protease inhibitor (PI) that inhibits the replication of HIV-1 in infected cells. Darunavir is the active substance in Prezista® and acts by selectively inhibiting the cleavage of HIV-1 encoded Gag-Pol polyproteins in infected cells and preventing the formation of mature virus particles [5].

3.2 Regulatory Status

Prezista® (ATC-code J05AE10) co-administered with low dose ritonavir is authorised in the European Union in combination with other antiviral medicinal products to treat adults and children aged three years or over who are infected with human immunodeficiency virus (HIV-1), a virus that causes acquired immune deficiency syndrome (AIDS). Prezista® co-administered with cobicistat is indicated with other antiretroviral medicines for treatment of HIV-1 in adults [5]. Prezista® is given orally in tablet form or as oral suspension. Darunavir is approved for medical use in the European Union as of 2007 and is on the WHO's list of essential medicines.

3.3 Level of Evidence

The efficacy and safety of Prezista® co-administered with low dose ritonavir has been analysed in six main phase II-III studies in over 1500 HIV patients: two phase 2 open label single-arm studies in paediatric patients and four randomised controlled trials in adult HIV patients [5].

The flow diagrams depict the screening process to identify eligible studies evaluating darunavir as treatment modality for COVID-19 (section 6.4 Flow diagrams). In total, nine unique studies (11 reports) were included, concerning two completed RCTs, two observational studies and five ongoing RCTs (Table 4-1 to Table 4-6).

One RCT evaluated the use of a single-tablet regimen containing 800 mg of darunavir and 150 mg of cobicistat per day (DRV/c) for 5 days [6]. All participants also received interferon alpha 2b and standard of care (SoC) as per guideline recommendation in China. The pilot trial included 30 patients with laboratory-confirmed SARS-CoV-2 infection excluding severe and critical COVID-19 at study entry (Table 4-3). Three reports describing the RCT "PEP COV-2" were identified [7-9]. The Spanish trial consisted of a RCT focusing on prevention of COVID-19 in contacts of confirmed cases and a RCT focusing on treatment of confirmed COVID-19 patients with mild to moderate disease. Outcome data from the prevention part of the trial were published in February 2021 and fall outside the scope of this report [9]. In the trial on treatment, the aim was to evaluate hydroxychloroquine (HCQ) plus cobicistat-boosted darunavir (DRV/c) versus no antiviral treatment. A protocol modification occurred on 4 April 2020, to use HCQ alone after findings of no benefit of the protease inhibitor lopinavir / ritonavir. Of the 169 outpatients randomised to the experimental group, 90 received HCQ plus DRV/c, the remainder received HCQ only. One hundred eighty four outpatients received usual care as control intervention. Additional trial descriptions are found in the Table 4-3.

The search in bibliographic databases did not identify additional observational studies for this update of the report. Four citations to published reports were found, 3 the Cochrane COVID-19 study register and

one in Google Scholar. All of these were excluded because of retrospective design or because no safety outcomes were reported [10-13]. The current evidence is based on two previously identified observational uncontrolled studies, which are described in Table 4-4. The studies were conducted in Italy and aimed at the evaluation of a combination therapy including darunavir. A protocol modification occurred in both studies, to provide the combination therapy without darunavir, so that the authors described two consecutive series of patients rather than one. The smaller study evaluated darunavir co-administered with low dose ritonavir in combination with hydroxychloroquine (HY) to assess safety endpoints in 61 hospitalised COVID-19 patients with pneumonia [12]. The second series of patients received the HY plus azithromycin (n=52) and is not further considered in this report. The other study was published as a letter to the editor, describing a multivariable analyses in 328 patients who received standard of care consisting of hydroxychloroquine (HCQ; 400 mg twice daily for 5–20 days), short-term initial antibiotic coverage, and anti-inflammatory treatment with tocilizumab and/or methylprednisolone. Of these, 151 received ritonavir boosted darunavir (DRV/r) and 177 did not, either because of contraindications to DRV/r or because of a protocol change that removed DRV/r from the standard of care protocol.

4 SUMMARY

Darunavir with low dose ritonavir (DRV/r) or cobicistat (DRV/c) in combination with other (antiviral) treatment has been suggested as a possible treatment in the context of the COVID-19 pandemic.

4.1 Effectiveness and Safety evidence from RCTs

Cobicistat boosted darunavir plus standard of care versus standard of care

The outcome data related to the Chinese trial in hospitalised patients with moderate COVID-19 are depicted in the summary of findings table Table 4-1. The trial estimates favoured control over DRV/c on virologic, clinical and safety outcomes, but estimates were very uncertain due to the wide confidence intervals and risk of bias [6].

Hydroxychloroquine plus cobicistat boosted darunavir on top of standard of care versus standard of care

With regard to the Spanish trial BCN PEP-CoV-2 in outpatients with mild to moderate Covid-19, we only address outcome data for the two arms as described in the original protocol [7, 8]. The outcome data are depicted in Table 4-2 and were abstracted from the published appendix. No between group differences could be calculated for the outcomes viral load as the authors omitted the description of the number of persons contributing by trial arm. Nevertheless, the reported data allows the conclusion that difference were not statistically significant at any of the reported time points. For all other outcomes, 74 patients in de DRV/c plus HCQ group and 155 in the usual care group contributed to the analyses The dataset relates to participants randomised to HCQ plus DRV/c up to April 4 2020 and controls randomised to usual care up to April 28, 2020. The evidence was of very low certainty for the outcomes mortality, viral load, clinical progression and severe adverse events, so that effects of the darunavir-based treatment remain unclear. Any adverse events was measured but not reported for the comparison of interest to this report.

4.2 Safety evidence from observational studies

With respect to the smaller uncontrolled study in 61 hospitalised COVID-19 patients with pneumonia [14], the combination therapy increased the corrected QT interval, while 1 out of 61 (1.6%) patients experienced malignant ventricular arrhythmia during the 7 day follow-up. Seven (11%) of the patients died in hospital. The other study described several safety outcomes of interest. Nobody was withdrawn because of adverse events. Fifty-seven persons experienced adverse event in the standard of care with DRV/r, 13.9% experiences grade 4/5 adverse events. The most frequent adverse event was liver enzyme elevations in 40.4% of patients. Additional outcome data is found in Table 4-4.

The evidence base for the safety of darunavir in persons with COVID-19 is limited, although there is extensive experience with the use of darunavir in persons with HIV, and generally, the drug has a good safety profile [15].

4.3 Ongoing studies

Four ongoing randomised trials of interest were identified in the register of clinicaltrials.gov, the EU Clinical Trial register and through citation checking (Table 4-5 and Table 4-6). A fifth trial identified previously is completed and published so that it is no longer listed in the tables describing ongoing studies [7, 8]. All trials evaluated combination therapies. One moderate sized multi-arm trial (n=320) in Thailand is evaluating various combinations of agent, including the combination of

- DRV/r plus Oseltamivir plus Hydroxychloroquine in persons with mild to critically illness in COVID-19 and

- Favipiravir plus DRV/r plus Hydroxychloroquine 400 in moderate to critically illness in COVID-19.

Another RCT is enrolling 80 adults in Thailand to evaluate the combined use of ivermectin versus hydroxychloroquine plus DRV/r in asymptomatic carrier of SARS-CoV2. A three-arm Chinese trial is planning to enrol 100 hospitalized non-severe COVID-19 patients to evaluate DRV/c with standard of care containing thymosin in comparison with LPV/r with standard of care versus standard of care only. The fourth trial concerns an Italian multicenter, 5-arm randomized open label controlled trial with adaptive design, aiming to enrol minimally 175 and maximally 435 outpatients to compare a treatment scheme with DRV/c with other antiviral treatment modalities or no antiviral treatment.

4.4 Scientific conclusion about status of evidence generation

The conclusion is that based on the latest clinical data there is no evidence base to support the use of darunavir with either ritonavir or cobicistat.

EUNETHTA received a statement from Johnson & Johnson who indicated that it had no clinical nor pharmacological evidence to support the inclusion of DRV/cobicistat in treatment guidelines for COVID-19, nor are there published data on the safety and efficacy profile of DRV/cobicistat in treatment of COVID-19.[16]

EUNETHTA will continue to monitor the compound until high quality RCTs prove it’s (in)efficacy in Covid-19.

Table 4-1. Summary of findings (SoF) table for published RCTs related to effectiveness and safety of Darunavir

Patient or population: moderate COVID-19 infection
Setting: Hospital
Intervention: darunavir / cobicistat & interferon alpha 2b inhaling on top of standard care
Comparison: interferon alpha 2b inhaling & standard care

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute Effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with standard care[a]	Risk with Darunavir / Cobicistat					
All-cause mortality at 14 days			Not estimable	Not estimable	30 (1)	very low[b,c,d]	No death
SARS-CoV-2 clearance at 7 days	600 per 1000	468 per 1000 (234 to 924)	RR 0.78 (0.39 to 1.54)	132 fewer per 1.000 (from 366 fewer to 324 more)	30 (1)	very low[b,d,e]	
Time to SARS-CoV-2 clearance (follow up duration of maximally 25 days)	-	-	HR 0.82 (0.36 to 1.88) p=0.64	-	30 (1)	very low[b,d,e]	Trial authors reported that time of SARS-CoV-2 clearance did not differ between the two groups (median, 8 days in the experimental versus 7 days in the control group)
Clinical progression Worsening as measured on CT, day 7	467 per 1000	700 per 1000 (243 to 1000)	RR 1.5 (0.52 to 4.38)	233 more per 1000 (from 224 fewer to 1000 more)	30 (1)	very low[b,d,e]	Own calculation of RR based on reported frequencies
Progression to critical COVID-19 disease, up to day 14	0 per 1000	0 per 1000 (0 to 0)	RR 3.00 (0.13 to 68.26)	0 fewer per 1000 (from 0 fewer to 0 fewer)	30 (1)	very low[b,d,e]	One patient in the experimental group developed ARDS
Number of patients with serious adverse events	-	-	Not estimable		30 (1)	very low[c,f,g]	All adverse events were mild
Withdrawals due to AEs	-	-	Not estimable		30 (1)	very low[c,f,g]	No withdrawals due to AEs
Number of patients with any adverse event	467 per 1000	532 per 1000 (261 to 1000)	RR 1.14 (0.56 to 2.35)	65 more per 1.000 (from 205 fewer to 630 more)	30 (1)	very low[b,e,g]	

Source: based on publication by Chen et al, 2020 [6] & ClinicalTrials.gov NCT04252274. Outcome data from the department of Epidemiology Lazio Regional Health Service (DEPLazio) in Italy [17]; descriptions and layout modified by Swiss Network for health Technology Assessment (SNHTA); GRADE assessments adapted from covid-nma.com, except for the outcome any adverse events which was assessed by SNHTA; outcomes data and GRADE-assessment added by SNHTA for the outcomes: worsening as measured on CT, day 7; number of patients with serious adverse event; withdrawals due to AEs.
Abbreviations: RR=relative risk; ARDS=acute respiratory distress syndrome; CT=computed tomography; HR=hazard ratio; AEs=adverse events.
GRADE Working Group grades of evidence

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute Effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with standard care[a]	Risk with Darunavir / Cobicistat					
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect **Explanations** a. Background risk as observed in the trial. The risk with Darunavir / Cobicistat is calculated from the reported relative risk and the background risk. b. Downgraded one level for risk of bias: some concerns or high risk of bias due to concerns regarding randomization process, deviation from intended intervention, and selection of the reported results c. Downgraded by two levels for imprecision: no events in both groups and very low number of participants d. Downgraded by one level for indirectness: single study from a single institution, therefore results in this population might not be generalizable to other settings e. Downgraded by two levels for Imprecision: due to wide confidence interval consistent with the possibility for benefit and the possibility for harm and very low number of participants f. Downgraded by two levels for risk of bias: some concerns or high risk due to concerns during the randomization process, deviation from intended intervention, missing data and selection of reported results g. Not downgraded for indirectness: assuming that adverse event rates, and the corresponding relative risks, are similar across diverse settings						

Table 4-2. Summary of findings (SoF) table for published RCTs related to effectiveness and safety of combination therapy with Darunavir

Patient or population: mild to moderate COVID-19 infection
Setting: outpatients
Intervention: Hydroxychloroquine plus cobicistat boosted darunavir on top of standard care
Comparison: standard care

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute Effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with standard care[a]	Risk with HCQ + DRV/c					
All-cause mortality at 28 days			Not estimable	Not estimable	229 (1)[7, 8]	very low[b,c,d]	No death
Reduction in viral load at 7 days Viral load at day 7 Reduction in viral load at 3 days Viral load at day 3	-2.94 (SE 0.21) 4.31 (SD 1.30) -1.27 (SE 0.14) 6.39 (SD 1.83)	-3.78 (SE 0.61) 3.55 (SD 0.88) -1.76 (SE 0.20) 6.74 (SD 1.52)	Mean difference of -0.84 (unclear to unclear) Mean difference of -0.76 (unclear to unclear) Mean difference of -0.49 (unclear to unclear) Mean difference of 0.35 (unclear to unclear)		unclear (1) [7, 8]	very low[b,d,e]	The number of participants contributing to these outcome is not reported by trial arm. The confidence interval of the difference in means cannot be calculated validly, but it is evident that all confidence

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute Effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with standard care[a]	Risk with HCQ + DRV/c					
							intervals included the value of no difference.
Clinical progression Not hospitalized with resolution of symptoms at home, up to 28 days	923	932 per 1000 (867 to1000)	RR 1.01 (0.94 to 1.09)	9 more per 1000 (from 55 fewer to 83 more)	229 (1) [7, 8]	very low[b,d,e]	Own calculation of RR based on reported frequencies
Clinical progression Hospitalized without mechanical ventilation, up to 28 days	71 per 1000	67 per 1000 (24 to 187)	RR 0.95 (0.34 to 2.64)	4 fewer per 1000 (from 47 fewer to 116 more)	229 (1) [7, 8]	very low[b,d,e,f]	Own calculation of RR based on reported frequencies
Clinical progression Hospitalized with mechanical ventilation, up to 28 days	0 per 1000	0 per 1000	Not estimable		229 (1) [7, 8]	very low[b,c,e]	No events
Number of patients with severe adverse events	77 per 1000	67 per 1000 (25 to 185)	RR 0.87 (0.32 to 2.39)	10 fewer per 1000 (from 53 fewer to 108 more)	229 (1) [7, 8]	Very low[b,d,e,f]	Own calculation of RR based on reported frequencies
Withdrawals due to AEs	-	-	-	-			Not measured
Number of patients with any adverse event							Only reported for the comparison HCQ ± DRV/c + SoC versus SoC

Source: based on publication by Mitjà et al, 2020 [7, 8] & ClinicalTrials.gov NCT04304053).. Outcome data from and GRADE assessment by Swiss Network for health Technology Assessment (SNHTA)
Abbreviations: RR=relative risk; 95% CI= 95% Confidence Interval; HCQ=Hydrochloroquine; DRV/c=cobicistat boosted darunavir; SE=standard error; SD= standard deviation; AEs=adverse events.
GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Explanations

a. Background risk as observed in the trial. For binary outcomes, the risk with Darunavir based therapy is calculated from the reported relative risk and background risk.
b. Downgraded one level for risk of bias: some concerns or high risk of bias due to concerns regarding deviation from intended intervention and missing outcome data.
c. Downgraded by two levels for imprecision: no events in both groups
d. Downgraded by one level for imprecision: due to wide confidence interval consistent with the possibility for benefit and the possibility for harm

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute Effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with standard care[a]	Risk with HCQ + DRV/c					
e. Downgraded by one level for indirectness: outcome data from a single multicentre study, results in this population might not be generalizable to other settings. In addition, due to the protocol deviation, the DRV/c intervention was stopped early around 4th of April 2020, whereas the enrolment to the control group continued up to about 28 April 2020. f. All of these concerned hospitalisation because of pneumonia, which were resolved at the end of the trial.							

Table 4-3 Study characteristics of included RCTs

Author, year, reference number/Study name/Study ID	Chen 2020 [6] ClinicalTrials.gov Identifier: NCT04252274	Mitja 2020 [7-9] ClinicalTrials.gov Identifier: NCT04304053; EudraCT ID: 2020-001031-27 BCN PEP CoV-2 Study
Study design, study phase	Phase 3 Two-arm open label randomised controlled trial with parallel group assignment Blinding: none	Phase 3 Study 1: cluster randomised trial evaluating effects in contacts of infected individuals, focusing on prevention, not of interest to this report [9]; Study 2: randomised two-arm open label controlled trial with parallel group assignment on confirmed cases, focusing on treatment. Independent randomisation using a computer generated random-number list [7, 8]. Blinding: Laboratory technicians were blinded throughout the trial [8]
Centres (single centre or multicentre), country, setting	Single center / China / Hospital	Multicenter / Spain / Outpatients
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	N=30 Mean age : 47.2 18 males (60%) Severity: Mild: n=0 / Moderate: n=30/ Severe: n=0 Critical: n=0	Study 2, description for the overall population. Data not available for the comparison DRV/c + HCQ versus control. N= 353 Mean age: 41.6 years 86 males (29%) Severity: Mild to Moderate: n=353 / Severe: n=0 Critical: n=0
Inclusion criteria	All the participants had laboratory-confirmed SARS-CoV-2 infection and were willing to participate the study, as evidenced by signing an informed consent.	Study 2: • Aged ≥18 years with mild symptoms of COVID-19 (ie, fever, acute cough, shortness of breath, sudden olfactory or gustatory loss, or influenza-like illness) for fewer than 5 days before enrollment

		• Nonhospitalized • positive PCR test for SARSCoV-2 in the baseline nasopharyngeal swab
Exclusion criteria	• hypersensitivity to darunavir, cobicistat, or any excipients; • patients with severe liver injury (Child-Pugh Class C); • patients receiving concomitant medications that are highly dependent on cytochrome P450 3A clearance, and for which the elevated plasma concentrations are associated with serious or life-threatening events; • subjects considered to be unable to complete the study (eg, severely and critically ill patients) or not suitable for the study by researchers. Patients who met any of the following criteria were classified as severe cases: respiratory rate 30 times/min, pulse oxygen saturation 93% at resting, or ratio between partial pressure of oxygen in arterial blood and fraction of inspired oxygen (PaO2/ FiO2) 300 mmHg. Critical illness was defined as respiratory failure that needed mechanical ventilation or shock or exacerbation of any comorbidity that required transfer to the intensive care unit.	Study 2 • moderate to severe COVID-19 disease (eg, required hospitalization) • any condition that might preclude following the study procedures safely (eg, mental disability), • known allergy or hypersensitivity to study drugs • known retinal and severe liver or renal diseases, history of cardiac arrhythmia, known electrocardiographic QT interval prolongation or other diseases that could be exacerbated by study drugs (eg, psoriasis), • active treatment with medications that are contraindicated with study drugs, or were living with human immunodeficiency virus (HIV) • Females who were pregnant (verbally declared or positive pregnancy test) or breastfeeding
Intervention (generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	N=15 Darunavir/cobicistat (800mg/150mg) Co-Intervention: Standard care Duration : 5 days	Study 2 N=169 overall; . n=90 received HCQ & DRV/c; n= 79 received HCQ only**. • therapeutic regimen of hydroxychloroquine (HCQ, Dolquine) once daily (200 mg tablets) 800 mg on day 1, and 400 mg once daily on days 2-7 & cobistat boosted darunavir (DRV/c, Rezolsta), once daily, consisting of 800 mg Darunavir & 150 mg cobicistat for 7 days As of 4 April 2020, a protocol modification occured to use HCQ alone after findings of no benefit of the protease inhibitor lopinavir/ritonavir in in vitro studies and negative results in trials evaluating closely related HIV protease inhibitors. Severity: Mild to Moderate: n=169 / Severe: n=0 Critical: n=0
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)	N=15 Standard care: all participants received interferon alpha 2b and standard of care as per guideline recommendation in China	Study 2 N=184 no intervention: standard of care Severity: Mild to Moderate: n=184 / Severe: n=0 Critical: n=0

Primary Outcome(s)	• SARS-CoV-2 clearance rate at day 7 after randomization (as indicated in the publication)	Study 2 • reduction of viral RNA load in nasopharyngeal swabs at days 3 and 7 after treatment start. At clinicaltrials.gov an additional primary outcome was described: Clinical outcome in index cases [Time Frame: Up to 28 days after start of treatment]: time from randomization to complete resolution of symptoms at an extended 28-days follow At EudraCT, primary outcome was originally described as: Symptom type, duration and severity among SARS-CoV-2 positive cases
Patient-relevant secondary outcome(s)	• All-cause mortality at 14 days • Time to SARS-CoV-2 clearance (follow up duration of maximally 25 days) • Worsening as measured on CT, day 7 • Progression to critical COVID-19 disease, up to day 14 • Number of patients with any adverse event • Number of patients with severe adverse events • Withdrawals due to AEs	• clinical progression measured using a simplified version of the WHO progression scale [17] (1, not hospitalized with or without resumption of normal activities; 2, hospitalized, requiring supplemental oxygen; 3, hospitalized, requiring invasive mechanical ventilation; and 4, death) • time from randomization to complete resolution of symptoms within the 28-day follow-up period. Resolution of symptoms was assessed sequentially using a symptoms questionnaire designed to gather information on the type of symptom and last day experienced; complete resolution was considered when no COVID-19–related symptoms were reported at all Safety outcomes: • AEs that occurred during treatment • SAEs • AEs of special interest (ie, cardiac) • premature discontinuation of therapy.
Follow-up (days, months)	Up to 14 days	Up to 28 days
Sponsor/ lead institution	Shanghai Public Health Clinical Center	Fundacio Lluita Contra la SIDA, Spain

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19; ** Only outcome data for the comparison HCQ + DRV/c cobicistat-boosted darunavir versus usual care was used in this report. We excluded outcome data in participants who, after the protocol modification, received HCQ only. Outcome data were abstracted from the published appendix [7].

Table 4-4. Summary of safety from observational studies (AE and SAE) of Darunavir

Author, year	Moschini, 2020 [14]	Nicolini, 2020 [18]
Country	Italy	Italy
Sponsor / lead institution	Non commercial	University of Genoa, Genoa, Italy
Intervention/Product (drug name)	Cohort 1: Ritonavir/darunavir (DRV/r) & hydroxychloroquine (HY) Cohort 2: Hydroxychloroquine & azithromycin (HY/AZ).	Cohort 1: standard of care (SoC) with Ritonavir/darunavir (DRV/r) Cohort 2: SoC without DRV/r SoC consisted of - hydroxychloroquine (HY): 400 mg, bid for 5–20 days - short-term initial antibiotic coverage, dosage not reported - anti-inflammatory treatment with tocilizumab and/or methylprednisolone, dosage not reported
Dosage	DRV/r: 800/100 mg qid; HY: 200 mg bid; AZ: 500 mg qid	- DRV/r : 800/100 mg once daily for 5–10 days - HY: 400 mg, bid for 5–20 days - short-term initial antibiotic coverage: dosage not reported - anti-inflammatory treatment with tocilizumab and/or methylprednisolone: dosage not reported
Comparator	None	None
Study design	Designed as a single arm observational cohort study with prospective and consecutive enrollment of patients. An unplanned protocol amendment required DRV/r to be stopped. DRV/r was replaced by azithromycin, which resulted in a second cohort Uncontrolled design	Designed as a single arm observational studies with consecutive enrollment of patients. An unplanned protocol amendment required DRV/r to be stopped. The study continued without DRV/r, which resulted in a second cohort Uncontrolled design‡
Setting	Hospital	Hospital
Number of pts	HY & DRV/r: n=61 (enrollment 2-8 March 2020) HY & AZ: n=52 (enrollment 9-15 March 2020)	DRV/r: n=151 (enrollment 28 february to 23 March 2020) no DRV/r: n=177 (enrollment 24 March to 29 March 2020, but also including those enrolled from 28 February to 23 March who had contraindication to DRV/r)
Inclusion criteria	- patients with confirmed clinical and radiological diagnosis of SARS-CoV-2 pneumoni admitted to hospital - postive RT-PCR assay for SARS-Cov-2 in respiratory tract sample - ECG recording at baseline, , 3 and 7 days after start of treatment - Full treatment for 7 days of HY/ DRV/r (March 2 to 8, 2020) - Full treatment for 7 days of HY/AZ (March 9 to 15, 2020 when hospital treatment protocol had changed)	- HIV negative adult patients consecutively hospitalized for COVID-19 between February 28 and March 29, 2020 who received standard of care

Author, year	Moschini, 2020 [14]	Nicolini, 2020 [18]
Exclusion criteria	- QTc>500 ms on baseline ECG - History of severe systolic dysfunction - History of arrhythmias, bradycardia <50bpm - Concomitant medication that could cause QTc prolongation or early interruption of the medical therapy due to side effects	- None reported
Age of patients (yrs)	HY & DRV/r: 67 HY & AZ: 68	Overall: mean 68 (± 13.79)
Disease severity	not reported	Overall: 223 (68%) had severe disease; "328 adults with COVID-19, most of whom had severe pneumonia"
Follow-up (months)	HY & DRV/r: 7 days HY & AZ: 7 days	Overall: median 21 (IQR 11–29) days
Loss to follow-up, n (%)	Overall 11 of 124 (8.9%) eligible patients excluded due to appearance of drug-related side effects	Not reported
RoB*	Relating to the HY & DRV/r arm: methodological limitations detected† related to • small sample size • unclear sampling • suboptimal statistical analyses • inadequate response rate.	Relating to the HY & DRV/r arm: methodological limitations detected† related to • small sample size • insufficient coverage of the identified sample.
Safety – Outcomes*		
Overall AEs, n (%)	-	86‡ (57%) in the SoC + DRV/r cohort §
Serious AE (SAE), n (%)	-	Grade 4/5 AE: n=21‡ (13.9%) in the SoC + DRV/r cohort #
Most frequent AEs n (%)	-	In the SoC + DRV/r cohort #: - Liver enzyme elevations: 61‡ (40.4%) - Creatinine increase: 14‡ (9.3%) - Microbiologically documented bloodstream, pulmonary, or urinary infections: 30‡ (19.9%) - Cardiovascular disorders: 20‡ (13.2%) - Mild diarrhea: 11 (7.3%)
Most frequent SAEs, n (%)	-	-
AEs of special interest, n (%)	Malignant ventricular arrhythmias HY & DRV/r: N=1 (1.6%) #	-
Death as SAE, n (%)	HY & DRV/r: 7 (11%) #	-
Withdrawals due AEs, n (%)	-	SoC with DRV/r: 0 (%)

* by arms, if available, (Robins-I): https://training.cochrane.org/handbook/current/chapter-25. † risk of bias not assessed, Robins-I is not applicable to uncontrolled study designs, the checklist for prevalence studies of the Johanna Briggs Institute is used to assess the methodological rigor and applicability [4]; ǂ from own calculations; § the authors reported the muliple adjusted HR for DRV/r vs no DRV/r for time to first AE, but as we consider this an uncontrolled study, we omitted these estimates; # outcome data was reported also for the cohort without DRV/r, which we omitted as we consider the design as uncontrolled.

Source: [14, 18]

Abbreviations: HY=hydroxychloroquine; AZ=azithromycin; SoC = standard of care; DRV/r = ritonavir boosted darunavir; IQR=interquartal range; AE=adverse event; SAE=serious adverse event; HR = Hazard Ratio.

Table 4-5. Ongoing trials of combination therapies including Darunavir/ Ritonavir

Trial Identifier/registry ID(s)/contact	ClinicalTrials.gov identifier: NCT04435587 Trial acronym: IDRA-COVID19 Contact: Yupin Suputtamongkol, ysuputtamongkol@gmail.com; Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand; Tel +66817545573	ClinicalTrials.gov Identifier: NCT04303299 Acronym: previously THDMS-COVID-19; currently fight COVID-19 Contact: Subsai Kongsaengdao skhongsa@gmail.com; Rajavithi Hospital, Bangkok, Thailand; Tel. +66818180890
Study design, study phase	Open label two-arm randomised controlled study with parallel group design. Outcome assessors are masked for allocation status. Phase 2-3*, treatment	Open label eight-arm randomised controlled study with parallel group design. PROBE design - prospective randomised open blinded evaluation). Outcome assessors are masked for allocation status. Phase 3, treatment
Recruitment status	Recruiting (last update posted at trial registry at 11 January 2021)	Recruiting (last update posted at trial registry 10 March 2021)
Number of Patients, Disease severity*	80 Asymptomatic or Afebrile COVID-19 Infection	320 Mild to critical COVID-19
Setting (hospital, ambulatory,..)	Hospital	In- and outpatients
Intervention (generic drug name and dosage)	Darunavir/ritonavir & hydroxychloroquine. Details: combined hydroxychloroquine (Vermectin), 400 mg bid on day 1, then 200 mg bid on Day 2-5 plus darunavir/ ritonavir 400/100 mg every 12 hours for 5 days. In addition oral zinc sulfate combination treatment, 200mg twice daily. This is the control trial arm as described by the principal investigator.	Darunavir / ritonavir & favipiravir & chloroquine or Darunavir / ritonavir & oseltamivir ± chloroquine Details: • Favipiravir lopinavir /Ritonavir for mod. to severe: Lopinavir 800 mg (or 10 mg/kg) per day and Ritonavir 200 mg (or 2.5 mg/kg) per day plus Favipiravir 2400 mg, 2400 mg, and 1200 mg every 8 h on day 1, and a maintenance dose of 1200 mg twice a day in Mild COVID19 In moderate to critically ill COVID19 • Darunavir /ritonavir favipiravir chloroquine mod-severe: Darunavir 400 mg every 8 hours Ritonavir 200 mg (or 2.5 mg/kg) per day plus Favipiravir 2400 mg, 2400 mg, and 1200 mg every 8 h on day 1, and a maintenance dose of 1200 mg twice a day plus Hydroxychloroquine 400 mg per day In moderate to critically ill COVID19

Comparator (standard care or generic drug name and dosage)	Ivermectin Details: oral ivermectin, 600 mcg/kg/day once daily for 3 days. In addition oral zinc sulfate combination treatment, 200mg twice daily. This is the experimental trial arm as described by the principal investigator.	• Oseltamivir plus Chloroquine in Mild COVID19: Oseltamivir 300mg (or 4-6 mg/kg) per day plus Hydroxychloroquine 800 mg per day In mild COVID19 • Darunavir and Ritonavir plus oseltamivir: Darunavir 400 mg every 8 hours Ritonavir 200 mg (or 2.5 mg/kg) per day plus plus Oseltamivir 300mg (or 4-6 mg/kg) per day plus Hydroxychloroquine 400mg per day in Mild COVID19 • Lopinavir and Ritonavir plus Oseltamivir in mild COVID19: Lopinavir 800 mg (or 10 mg/kg) per day and Ritonavir 200 mg (or 2.5 mg/kg) per day plus Oseltamivir 300 mg (or 4-6 mg /kg) per day In mild COVID19 • Lopinavir and Ritonavir Oseltamivir moderate to severe COVID19: Lopinavir 800 mg (or 10 mg/kg) per day and Ritonavir 200 mg (or 2.5 mg/kg) per day plus Oseltamivir 300 mg (or 4-6 mg /kg) per day In moderate to critically ill COVID19 • Darunavir /ritonavir oseltamivir chloroquine mod-severe: Darunavir 400 mg every 8 hours Ritonavir 200 mg (or 2.5 mg/kg) per day plus Oseltamivir 300 mg (or 4-6 mg /kg) per day plus Hydroxychloroquine 400 mg per day In moderate to critically ill COVID19 Conventional Quarantine: “Patient who unwilling to treatment and willing to quarantine in mild COVID19”
Primary Outcome(s)	Adverse event rates [Time Frame: after first dose until day 28 of follow up]	SARS-CoV-2 eradication time [Time Frame: Up to 24 weeks]
Sponsor/ lead institution, country (also country of recruitment if different)	Mahidol University, Thailand	Rajavithi Hospital, Thailand, Bangkok

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

Abbreviations: bid=twice per day; mg = milligram. * authors wrongly labeled the trial as phase 4

Table 4-6. Ongoing trials of combination therapies including Darunavir/ Cobicistat

Trial Identifier/registry ID(s)/contact	Chinese Clinical Trial registry ID: ChiCTR2000029541 Trial acronym: not reported Contact: wangxinghuan@whu.edu.cn; 169 Donghu Road, Wuchang District, Wuhan, Hubei, China; Tel. +86 18971387168 / +86 15729577635	EudraCT ID: 2020-001528-32 Other ID: ARCO-Home study Contact: simone.lanini@inmi.it; Istituto Nazionale per le Malattie Infettive Lazzaro Spallanzani; Dipartimento di Epidemiologia Digno, Via Portuense, Roma, 00149, Italy
Study design, study phase	Single center randomised three-arm controlled trial with parallel group assignment. Blinding not described. Block randomisation method using software. Phase not reported	Multicenter, 5-arm randomized open label controlled trial with adaptive design Phase 3
Recruitment status	Not yet recruiting (last update posted at trial registry at 12 Feb. 2020)	Ongoing (last update at registry on 24 June 2020, at AIFA 23 November 2020)
Number of Patients, Disease severity*	100 Non-severe, non-critical, with 2019-nCoV pneumonia	Minimal 175 to maximal 435 (adaptive design) Symptomatic, not meeting criteria for immediate hospitalization (national early warning score-NEWS = 2 criteria)
Setting (hospital, ambulatory,..)	Hospitalised	Outpatients
Intervention (generic drug name and dosage)	Darunavir & cobicistat & thymosin Details: • DRV/c group (n=40): DRV/c (800mg/150mg QD) + Conventional treatment containing thymosin (1.6 mg SC QOD) • LPV/r group (n=40): LPV/r (400mg/100mg bid) + Conventional treatment containing thymosin (1.6 mg SC QOD) Both intervention groups also receive standard of care as described below.	Darunavir & cobicistat Details: • Trial arm darunavir/cobicistat (Rezolsta, Janssen-Cilag) 800/150 mg SID for 14 days • Trial arm idrossiclorochina (plaquenil, Sanofi-Aventis) 400 mg BID on day 1, 200 mg BID on day 2 to 10 • Trial arm lopinavir/ritonavir (Kaletra, AbbVie) 400/100 mg BID for 14 days Trial arm favipiravir (avigan, Fujifilm) 1.800 mg BID on day 1, 800 mg BID on day 2 to 10
Comparator (standard care or generic drug name and dosage)	Standard of care (n=20): Conventional treatment containing thymosin (1.6 mg SC QOD)	Trial arm: no antiviral treatment
Primary Outcome(s)	Time to conversion of 2019-nCoV RNA result from RI sample	• Proportion of participants with undetectable SARS-CoV-2 gene E and gene M at day 7 after randomization. Proportion of participants who need not hospitalization (NEWS = 2) by day 14 after randomization.
Sponsor/ lead institution, country (also country of recruitment if different)	Zhongnan Hospital of Wuhan University, Hubei, China	Istituto Nazionale Per Le Malattie Infettive "Lazzaro Spallanzani"; Italy

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

Abbreviations: SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; HCQ= hydroxychloroquine; mg=milligram; QOD= every other day; DRV/c = cobistat-boosted darunavir; LPV/r = lopinavir/ritonavir; BID = twice daily

5 REFERENCES

[1.] Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019): Cochrane; 2019. Available from: http://www.training.cochrane.org/handbook.

[2.] DerSimonian R LN. Meta-analysis in clinical trials. Controlled Clinical Trials 1986;7:177-88.

[3.] Balshem H HM, Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH. GRADE guidelines: 3. Rating the quality of evidence. Journal of Clinical Epidemiology 2011;64:401-6.

[4.] Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and incidence data. Int J Evid Based Healthc. 2015;13(3):147–53.

[5.] Gilzad-Kohan H, Jamali F. Anti-Inflammatory Properties of Drugs Used to Control COVID-19 and their Effects on the Renin-Angiotensin System and Angiotensin-Converting Enzyme-2. J Pharm Pharm Sci. 2020;23:259-77. 10.18433/jpps31346.

[6.] Chen J, Xia L, Liu L, Xu Q, Ling Y, Huang D, et al. Antiviral Activity and Safety of Darunavir/Cobicistat for the Treatment of COVID-19. Open Forum Infect Dis. 2020;7(7):ofaa241. 10.1093/ofid/ofaa241.

[7.] Mitjà O, Corbacho-Monné M, Ubals M, Tebe C, Peñafiel J, Tobias A, et al. Hydroxychloroquine for Early Treatment of Adults with Mild Covid-19: A Randomized-Controlled Trial. Clin Infect Dis. 2020:ciaa1009. 10.1093/cid/ciaa1009.

[8.] Mitjà O, Corbacho M, G-Beiras C, Tebé C, Tobias A, Ballana E, et al. Hydroxychloroquine Alone or in Combination with Cobicistat-Boosted Darunavir for Treatment of Mild COVID-19: A Cluster-Randomized Clinical Trial (5/27/2020). Available from: https://ssrn.com/abstract=3615997 or http://dx.doi.org/10.2139/ssrn.3615997.

[9.] Mitjà O, Corbacho-Monné M, Ubals M, Alemany A, Suñer C, Tebé C, et al. A Cluster-Randomized Trial of Hydroxychloroquine for Prevention of Covid-19. The New England journal of medicine. 2021;384(5):417-27. 10.1056/NEJMoa2021801.

[10.] Desai A, Caltagirone G, Sari S, Pocaterra D, Kogan M, Azzolini E, et al. The Use of Antiviral Agents against SARS-CoV-2: ineffective or Time and Age Dependent Result? A Retrospective, Observational Study among COVID-19 Older Adults. Journal of clinical medicine. 2021;10(4):686. 10.3390/jcm10040686.

[11.] Kim EJ, Lee YH, Park JS, Lee J, Lee SY, Kim Y, et al. Clinical features and prognostic factors of critically ill patients with COVID-19 in Daegu, South Korea: a multi-center retrospective study. Medicine. 2021;100(7):e24437. 10.1097/MD.0000000000024437.

[12.] Milic J, Novella A, Meschiari M, Menozzi M, Santoro A, Bedini A, et al. Darunavir/cobicistat is associated with negative outcomes in HIV-negative patients with severe COVID-19 pneumonia. AIDS research and human retroviruses. 2021;Epub ahead of print. 10.1089/AID.2020.0305.

[13.] Atipornwanich K., Akksilp S., Sawanpanyalert N., Srisubat A., et al. Various Combination of Antiviral Treatment of COVID-19 Pneumonia; A Preliminary Observational Study. The Lancet. 2020. https://dx.doi.org/10.2139/ssrn.3633173.

[14.] Moschini L, Loffi M, Regazzoni V, Di Tano G, Gherbesi E, Danzi GB. Effects on QT interval of hydroxychloroquine associated with ritonavir/darunavir or azithromycin in patients with SARS-CoV-2 infection. Heart Vessels. 2021;36(1):115-20. 10.1007/s00380-020-01671-4.

[15.] Ghosh R, Chakraborty A, Biswas A, Chowdhuri S. Identification of polyphenols from Broussonetia papyrifera as SARS CoV-2 main protease inhibitors using in silico docking and molecular dynamics simulation approaches. J Biomol Struct Dyn. 2020(Aug 7):1-14. 10.1080/07391102.2020.1802347.

[16.] Ibrahim MAA, Abdelrahman AHM, Hegazy M-EF. In-silico drug repurposing and molecular dynamics puzzled out potential SARS-CoV-2 main protease inhibitors. J Biomol Struct Dyn. 2020(Jul 20):1-12. 10.1080/07391102.2020.1791958.

[17.] Cruciani F, De Crescenzo F, Vecchi S, Saulle R, Mitrova Z, Amato L, et al. Should Darunavir/Cobicistat vs standard treatment be used for COVID-19? Italy: Department of Epidemiology Lazio Regional Health Service (DEPLazio); 2020 [Available from: http://deplazio.net/farmacicovid/index.html.

[18.] Nicolini LA, Mikulska M, Signori A, Di Biagio A, Portunato F, Vena A, et al. Reply to: "Antiviral Activity and Safety of Darunavir/Cobicistat for Treatment of COVID-19". Open Forum Infect Dis. 2020;7(8):ofaa321. 10.1093/ofid/ofaa321.

[19.] COVID-19: a living systematic map of the evidence [web page] London: EPPI Centre, University College London [updated 04. February 2021; cited 09. February 2021]. Available from: http://eppi.ioe.ac.uk/cms/Projects/DepartmentofHealthandSocialCare/Publishedreviews/COVID-19Livingsystematicmapoftheevidence/tabid/3765/Default.aspx.

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 is responsible 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 (Appendix Table 6-1). DEPLazio searched 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.

The methods described above are part of a living review of pharmacological agents for the treatment of Covid-19 conducted by the Department of Epidemiology of the Regional Health Service Lazio, Italy, to inform national regulatory agencies and clinicians, available at https://www.deplazio.net/farmacicovid. The review is registered on Prospero (CRD42020176914).

Table 6-1 Search strategy to identify randomised controlled studies

Database	URL	Search line / Search terms	Date of search
Pubmed	pubmed.ncbi.nlm.nih.gov	1. (((((("Coronavirus"[Mesh]) OR (coronavirus*[Title/Abstract] OR coronovirus*[Title/Abstract] OR coronavirinae*[Title/Abstract] OR Coronavirus*[Title/Abstract] OR Coronovirus*[Title/Abstract] OR Wuhan*[Title/Abstract] OR Hubei*[Title/Abstract] OR Huanan[Title/Abstract] OR "2019-nCoV"[Title/Abstract] OR 2019nCoV[Title/Abstract] OR nCoV2019[Title/Abstract] OR "nCoV-2019"[Title/Abstract] OR "COVID-19"[Title/Abstract] OR COVID19[Title/Abstract] OR "CORVID-19"[Title/Abstract] OR CORVID19[Title/Abstract] OR "WN-CoV"[Title/Abstract] OR WNCoV[Title/Abstract] OR "HCoV-19"[Title/Abstract] OR HCoV19[Title/Abstract] OR CoV[Title/Abstract] OR "2019 novel*"[Title/Abstract] OR Ncov[Title/Abstract] OR "n-cov"[Title/Abstract] OR "SARS-CoV-2"[Title/Abstract] OR "SARSCoV-2"[Title/Abstract] OR "SARSCoV2"[Title/Abstract] OR "SARS-CoV2"[Title/Abstract] OR SARSCov19[Title/Abstract] OR "SARS-Cov19"[Title/Abstract] OR "SARSCov-19"[Title/Abstract] OR "SARS-Cov-19"[Title/Abstract] OR Ncovor[Title/Abstract] OR Ncorona*[Title/Abstract] OR Ncorono*[Title/Abstract] OR NcovWuhan*[Title/Abstract] OR NcovHubei*[Title/Abstract] OR NcovChina*[Title/Abstract] OR NcovChinese*[Title/Abstract])) OR ((((respiratory*[Title/Abstract] AND (symptom*[Title/Abstract] OR disease*[Title/Abstract] OR illness*[Title/Abstract] OR condition*))[Title/Abstract] OR "seafood market*"[Title/Abstract] OR "food market*")[Title/Abstract] AND (Wuhan*[Title/Abstract] OR Hubei*[Title/Abstract] OR China*[Title/Abstract] OR Chinese*[Title/Abstract] OR Huanan*))[Title/Abstract])) OR ("severe acute respiratory syndrome*")) OR ((corona*[Title/Abstract] OR corono*)[Title/Abstract] AND (virus*[Title/Abstract] OR viral*[Title/Abstract] OR virinae*)[Title/Abstract])) AND (((((((randomized controlled trial [1]) OR (controlled clinical trial [1])) OR (randomized [tiab])) OR (placebo [tiab])) OR (clinical trials as topic [mesh: noexp])) OR (randomly [tiab])) OR (trial [ti]))) NOT (animals [mh] NOT humans [mh]) AND (2019/10/01:2020[dp])	28/02/2021

Database	URL	Search line / Search terms	Date of search
Ovid MEDLINE(R) ALL)	ovidsp.dc2.ovid.com	1. exp coronavirus/ 2. ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw. 3. (coronavirus* or coronovirus* or coronavirinae* or Coronavirus* or Coronovirus* or Wuhan* or Hubei* or Huanan or "2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCoV or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese*).ti,ab,kw. 4. (((respiratory* adj2 (symptom* or disease* or illness* or condition*)) or "seafood market*" or "food market*") adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw. 5. ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (China* or Chinese* or Huanan*)).ti,ab,kw. 6. "severe acute respiratory syndrome*".ti,ab,kw. 7. or/1-6 8. randomized controlled trial.pt. 9. controlled clinical trial.pt. 10. random*.ab. 11. placebo.ab. 12. clinical trials as topic.sh. 13. random allocation.sh. 14. trial.ti. 15. or/8-14 16. exp animals/ not humans.sh. 17. 15 not 16 18. 7 and 17 19. limit 18 to yr="2019 -Current"	28/02/2021
OVID EMBASE	ovidsp.dc2.ovid.com	1. exp Coronavirinae/ or exp Coronavirus/ 2. exp Coronavirus infection/ 3. ((("Corona virinae" or "corona virus" or Coronavirinae or coronavirus or COVID or nCoV) adj4 ("19" or "2019" or novel or new)) or (("Corona virinae" or "corona virus" or Coronavirinae or coronavirus or COVID or nCoV) and (wuhan or china or chinese)) or "Corona virinae19" or "Corona virinae2019" or "corona virus19" or "corona virus2019" or Coronavirinae19 or Coronavirinae2019 or coronavirus19 or coronavirus2019 or COVID19 or COVID2019 or nCOV19 or nCOV2019 or "SARS Corona virus 2" or "SARS Coronavirus 2" or "SARS-COV-2" or "Severe Acute Respiratory Syndrome Corona virus 2" or "Severe Acute Respiratory Syndrome Coronavirus 2").ti,ab,kw. 4. or/1-3 5. Clinical-Trial/ or Randomized-Controlled-Trial/ or Randomization/ or Single-Blind-Procedure/ or Double-Blind-Procedure/ or Crossover-Procedure/ or Prospective-Study/ or Placebo/ 6. (((clinical or control or controlled) adj (study or trial)) or ((single or double or triple) adj (blind$3 or mask$3)) or (random$ adj (assign$ or allocat$ or group or grouped or patients or study or trial or distribut$)) or (crossover adj (design or study or trial)) or placebo or placebos).ti,ab. 7. 5 or 6 8. 4 and 7 9. limit 8 to yr="2019 -Current"	28/02/2021
Additional search strategy as executed by SNHTA			
Google	scholar.google.com & google.com	Performed on all identified ongoing studies: google and google scholar search using trial registry ID or trial acronym as search term (0 new RCT with outcome data)	12/03/'21
PubMed	pubmed.ncbi.nlm.nih.gov	Performed on all identified ongoing studies: PubMed search using trial registry ID or trial acronym as search terms (0 new RCTs with outcome data)	12/03/'21

6.2 Search strategy to identify observational studies

As of October 2020, NIPHNO is responsible for setting up the search strategy to identify observational studies. Before that date, SNHTA was responsible.

From September to December 2020, we received records that EPPI Centre has screened after searching weekly in Medline and Embase (until beginning of November 2020), from November onwards Microsoft Academics Graph (MAG). We supplemented these studies with a weekly search in Scopus (Elsevier). Detailed descriptions of the EPPI and NIPHNO searches are given at their websites [13, 19]. The retrieved hits were imported to a reference management tool, Endnote (Clarivate Analytics), for deduplication. We then searched the EndNote database using the generic names and synonyms for the included COVID-19 drugs.

From January onwards, an information specialist at NIPHNO has conducted searches in Medline (Ovid), Embase (Ovid) and Scopus (Elsevier) using the search strategy described in table 6.2. To screen the references, two reviewers use a binary machine learning (ML) classifier. References that scored above the identified threshold of 30% certainty to be relevant were retained for screening; while those scoring below this threshold score were set aside.

Prior to using the binary ML classifier score to discard low scoring records, we screened 1028 references manually to train the classifier. The classifier is continuously being updated a long with new references being screened. References that have been set aside, can potentially be picked up in a later stage by a new classifier version. For drugs that have less than 5 publications included in the training batch, we combine the classifier with manual text word searches.

Table 6-2 depicts both the search strategy executed by NIPHNO and the search strategy by SNHTA.

Table 6-2 Search strategy to identify observational studies

Database	URL	Search terms / Search modality	Date of search	Hits
Search strategy as executed by NIPHNO for version 8 of the report				902
Embase 1974 to 2021 **Ovid MEDLINE(R) ALL 1946 to 2021**		Lines 1 and 2 are copies of Ovid's Expert searches for covid-19 in MEDLINE and Embase 1 ((((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.) or (2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus* or corona virus or pandemi*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp. or COVID-19.rx,px,ox,sh. or severe acute respiratory syndrome coronavirus 2.os.) use medall [COVID-19 in MEDLINE]	From 4/2/2021 until 26/2/2021	

		2 ((((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.) or (coronavirus disease 2019 or 2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or severe acute respiratory syndrome coronavirus 2 or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus* or corona virus or pandemi*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp. or (coronavirus disease 2019 or severe acute respiratory syndrome coronavirus 2).sh,dj.) use oemezd [COVID-19 in Embase] 3 (COVID-19 serotherapy/ or Immunization, Passive/ or tocilizumab/ or camostat/ or nafamostat/ or AP301 peptide/ or Interleukin 1 Receptor Antagonist Protein/ or alunacedase alfa/ or darunavir/ or favipiravir/ or sarilumab/ or exp Interferons/ or gimsilumab/ or canakinumab/ or REGN-COV-2/ or bamlanivimab/ or baricitinib/ or molnupiravir/ or Aspirin/ or mavrilimumab/ or exp Vitamin D/dt or Vitamin D Deficiency/dt or Ivermectin/) use medall [MeSH-terms for drugs in MEDLINE] 4 (Hyperimmune globulin/dt or tocilizumab/ or camostat/ or camostat mesilate/ or nafamstat/ or solnatide/ or anakinra/ or darunavir/ or favipiravir/ or sarilumab/ or exp Interferon/ or gimsilumab/ or canakinumab/ or baricitinib/ or acetylsalicylic acid/ or mavrilimumab/ or exp Vitamin D/dt or Vitamin D Deficiency/dt or ivermectin/) use oemezd [Emtree-terms for drugs in Embase] 5 ((convalescent adj (plasma or sera or serum)) or serotherap* or ((atoxin or hyperimmunoglobulin or hyperimmune globulin or hyperimmune gammaglobulin) adj therap*) or passive immuni?ation or (tocilizumab or atlizumab or (MRA adj monoclonal antibod*) or MSB-11456 or MSB11456 or R-1569 or R1569 or RO-4788533 or RO4788533 or Actemra or Roactemra) or (camostat* or FOY-305 or FOY305 or FOY S 980) or (nafamostat or nafamstat or FUT-175 or FUT175) or (solnatide or AP301 or AP-301 or (TIP adj peptide)) or (anakinra or ((interleukin 1 or IL1 or IL-1) adj2 (antagonist or block* or inhibitor*)) or IL-1Ra or Kineret) or (alunacedase or APN01 or APN-01 or rhACE2 or recombinant human angiotensin converting enzyme 2 or GSK-2586881 or GSK2586881) or (darunavir or prezista or TMC-114 or TMC114 or UIC-94017 or UIC94017) or (favipi?avir or T-705 or T705 or Avigan or Olumiant) or (sarilumab or REGN-88 or REGN88 or SAR-153191 or SAR153191 or Kevzara) or (interferon* or (IFN adj1 (alpha* or beta* or gamma*)) or novaferon or CL-884 or CL884) or (gimsilumab or KIN-1901 or KIN1901 or morab-022 or morab022) or (canakinumab or ACZ-885 or ACZ885 or immunoglobulin G1 or Ilaris) or (REGN-CoV-2 or REGN-CoV2 or antibody cocktail or ((casirivimab or REGN-10933 or REGN10933) and (imdevimab or REGN-10987 or REGN10987))) or (bamlanivimab or LY-CoV555 or LYCoV555 or LY-3819253 or LY3819253) or (baricitinib or LY-3009104 or		

Database	URL	Search terms / Search modality	Date of search	Hits
		LY3009104 or INCB-028050 or INCB028050 or INCB-28050 or INCB28050 or Olumiant) or (molnupiravir or MK-4482 or MK4482 or EIDD-2801 or EIDD2801) or (aspirin or acetylsalicylic acid) or (mavrilimumab or immunoglobulin G4 or CAM-3001 or CAM3001) or ((vitamin? D? or D?-vitamin?) adj4 (high-dose* or highdose* or supplement*)) or (ivermect* or MK-933 OR MK933)).mp,bt,ot,du,dy,tn,nm. [other terms (title, abstract, author keywords and more) in MEDLINE and Embase] 6 (202009* or 202010* or 202011 or 202012* or 202101* or 202102*).dt. use medall [time limits in MEDLINE] 7 (202009* or 202010* or 202011 or 202012* or 202101* or 202102*).dc. use oemezd [time limits in Embase] 8 (1 and (3 or 5) and 6) use medall 9 (2 and (4 or 5) and 7) use oemezd		
Search by SNHTA performed for version 8 of the report				
Google / PubMed	scholar.google.com/ & google.com & pubmed.gov	Performed on all identified ongoing studies: google and google scholar search using trial registry ID or trial acronym as search term	12/03/'21	1 new
Cochrane COVID-19 Register	https://covid-19.cochrane.org	Filtered by "darunavir"	10/03/'21	47 3 new

6.3 Search strategy to identify ongoing studies

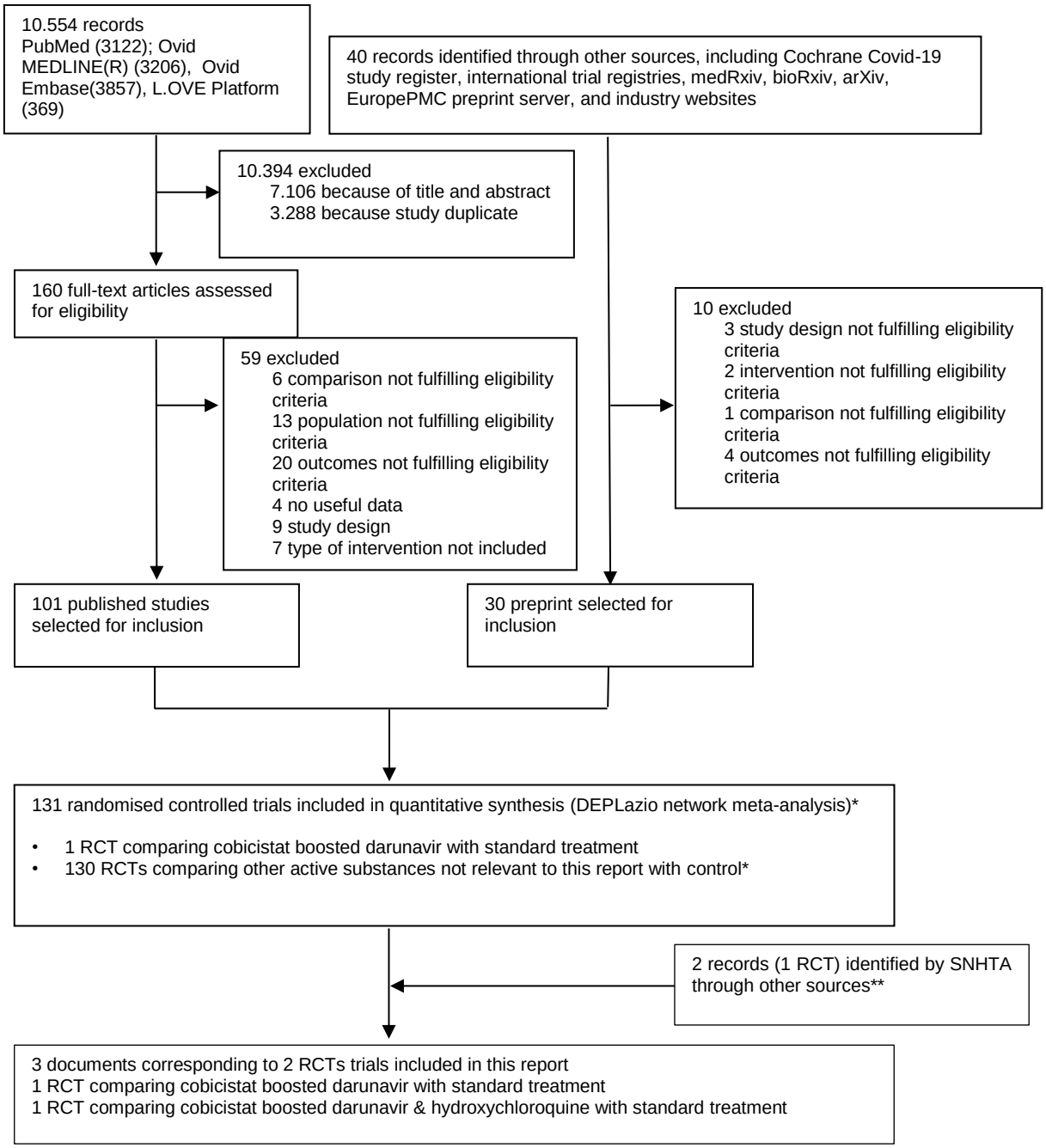
SNHTA is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and darunavir are described in Table 6-3.

Table 6-3 Search strategy to identify ongoing studies

Database	URL	Search terms / Search modality	Date of search	Hits retrieved
ClinicalTrials.gov	https://clinicaltrials.gov/	Basic search mode* Terms used at "condition or disease": • covid-19 • SARS Terms used at "other terms": • Darunavir • Rezolsta Synonyms for COVID-19 and darunavir are automatically searched	12/03/'21	10 0 new
ICTRP COVID-19 collection accessed through search platform of clincaltrials.gov	https://clinicaltrials.gov/ct2/who_table	Basic search mode Terms used: • darunavir • Rezolsta • Prezista • TMC 114	10/03/'21	7 0 new
ISRCTN	https://www.isrctn.com/	Basic search mode Search terms: • covid-19 and darunavir • covid-19 and Prezista • covid-19 and tmc-114 • covid-19 and tmc114 • covid-19 and drv • covid-19 and Rezolsta The same intervention terms were combined with the term «SARS», giving identical hits	10/03/'21	0 0 new
European Clinical Trials Registry	https://www.clinicaltrialsregister.eu/	Basic search mode Search terms: • covid-19 and darunavir • covid-19 and prezista • covid-19 and «TMC-114» • covid-19 and TMC114 • covid-19 and Rezolsta • SARS and darunavir • SARS and prezista • SARS and «TMC-114» • SARS and TMC114 • SARS and Rezolsta	10/03/'21	4 0 new
Cochrane COVID-19 Register	https://covid-19.cochrane.org	Filtered by "darunavir"	10/03/'21	47 3 new
Citation screening	-	Citation screening of all systematic reviews evaluating darunavir, identified in NIH LitCovid and NIPH (n = 2 systematic reviews)	13/10/'20	1 0 new

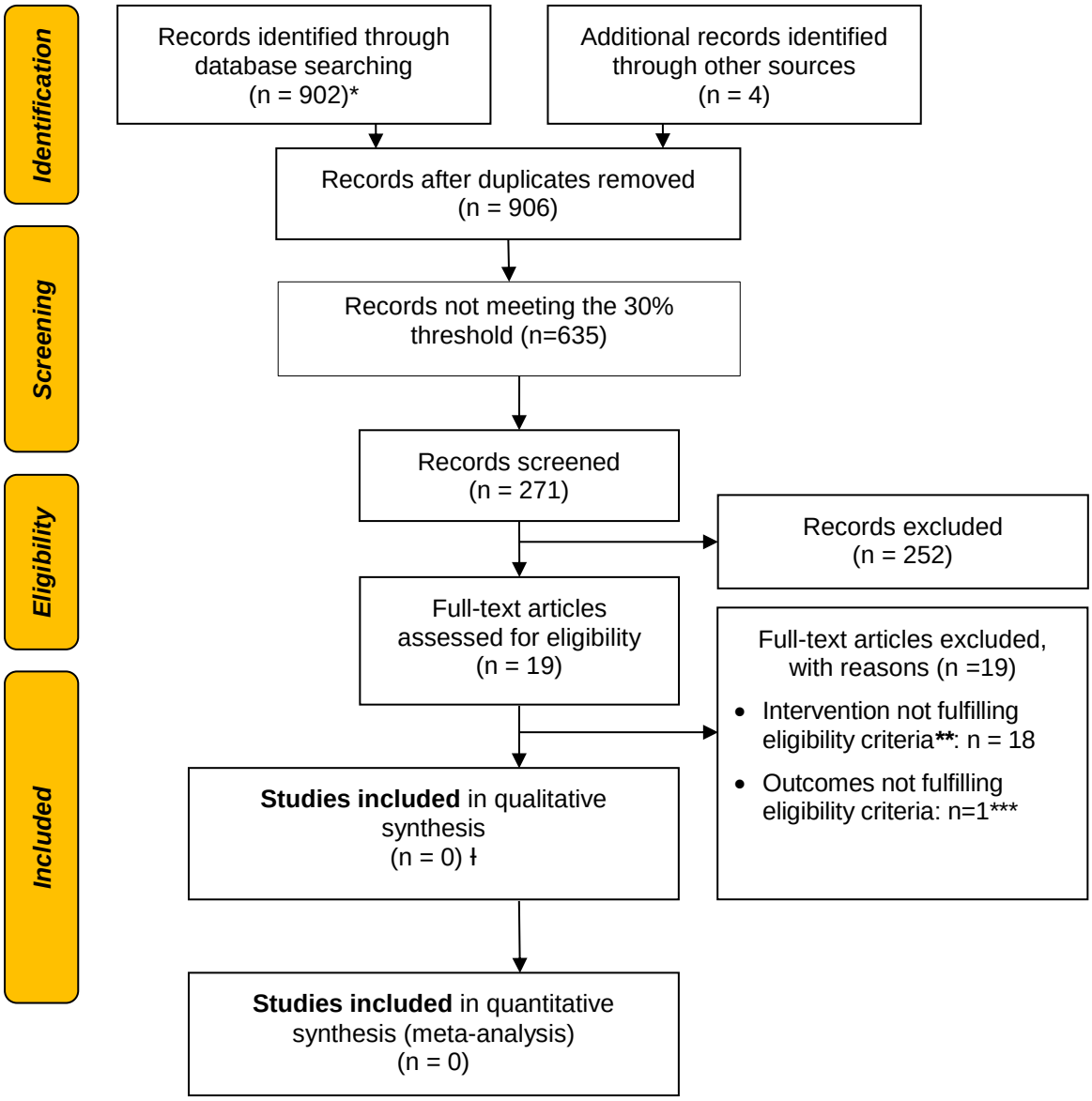
***** In Basic Search mode, one term was added to the field "condition or disease" and one term in the field "other terms".

6.4 Flow diagrams



Appendix Figure 6-1. Flow diagram depicting the selection process of RCTs

RCT = randomised controlled trial; * The selection process was part of an external project, see https://www.deplazio.net/farmacicovid and Prospero ID CRD42020176914



Appendix Figure 6-2. Flow diagram depicting the selection process of observational studies

* Hits from searches executed by NIPHNO in the period 4 February to 26 February 2021
** studies evaluating active substances relevant to other EUnetHTA rolling collaborative reviews
*** [13]
ł the two studies identified by searches executed by SNHTA in version 1 and 2 of this report are not listed here (Table 6-2)