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EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

EUnetHTA Joint Action 3 WP4

**“Rolling Collaborative Review” of Covid-19 treatments**

**DARUNAVIR FOR THE TREATMENT OF COVID-19**

**Project ID: RCR10**  
Monitoring Report

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V 1.1	10/09/2020	Literature searches, Literature screening, Data extraction
V 1.2	15/09/2020	Data extraction and analysis complete
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V 3.0	14/10/2020	Third version
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### Major changes from previous version

Chapter, page no.	Major changes from version 4.0
<b>Table 4-3, 15</b>	Exclusion criteria were added in the Table describing observational studies
<b>Summary, 11-12</b>	The pool of included studies did not change
<b>Table 4-2, 14</b>	A table describing included RCTs was added
<b>Table 4-4, 18 to Table 4-6, 22</b>	Structure of the Tables describing ongoing trials has changed. Contact details to Principle Investigators are added. Actual status of all ongoing trials listed in Tables 4 are verified, no changes of relevance to Darunavir occurred since the last version of this report.
<b>Appendix</b>	The Flow diagram depicting the selection process of ongoing studies is omitted, the selection process is described in the Appendix tables

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## 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 \(https://eunethta.eu/doi\)](https://eunethta.eu/doi).

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## 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
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/services/covid-19/>) and on the EUnetHTA Rolling Collaborative Review Sharepoint page each 15<sup>th</sup> of the month.

### 2.1 Scope

**Table 2-1. Scope of the RCR**

Description	Project Scope
<b>Population</b>	<p><b>Disease</b></p> <ul style="list-style-type: none"> <li>• 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.</li> </ul> <p><b>ICD-Codes</b> (<a href="https://www.who.int/classifications/icd/covid19/en">https://www.who.int/classifications/icd/covid19/en</a>)</p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• 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.</li> <li>• 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.</li> <li>• 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.</li> </ul> <p><b>MeSH-terms</b></p> <ul style="list-style-type: none"> <li>• COVID-19, Coronavirus Disease 2019</li> </ul> <p><b>Target population</b> (<a href="https://www.covid19treatmentguidelines.nih.gov/overview/management-of-covid-19/">https://www.covid19treatmentguidelines.nih.gov/overview/management-of-covid-19/</a>)</p>

	<ul style="list-style-type: none"> <li>• 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.</li> <li>• 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.</li> <li>• Moderate Illness: Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO<sub>2</sub>) ≥94% on room air at sea level.</li> <li>• Severe Illness: Individuals who have respiratory frequency &gt;30 breaths per minute, SpO<sub>2</sub> &lt;94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO<sub>2</sub>/FiO<sub>2</sub>) &lt;300 mmHg, or lung infiltrates &gt;50%.</li> <li>• Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.</li> </ul>
<p><b>Intervention</b></p>	<p>Darunavir (Prezista®) in combination with ritonavir or cobicistat and other (antiretroviral) treatment or standard of care.</p> <p>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)</p> <p><b>MESH Terms</b></p> <ul style="list-style-type: none"> <li>• Darunavir</li> </ul>
<p><b>Comparison</b></p>	<p>Any active treatment, placebo, or standard of care.</p> <p><b>Rationale:</b> Since there is no gold standard treatment any comparator is acceptable as well as the above listed interventions.</p>
<p><b>Outcomes</b></p>	<p><u>Main outcome:</u></p> <ul style="list-style-type: none"> <li>• All-cause Mortality (Survival)</li> </ul> <p><u>Additional Outcomes:</u></p> <p>Efficacy:</p> <ul style="list-style-type: none"> <li>• Length of hospital stay,</li> <li>• Viral burden (2019-nCoV RT-PCR negativity),</li> <li>• Clinical progression (WHO Clinical Progression Scale measured daily over the course of the study),</li> <li>• Rates of hospitalization and of patients entering ICU,</li> <li>• Duration of mechanical ventilation,</li> <li>• Quality of life.</li> </ul> <p>Safety:</p> <ul style="list-style-type: none"> <li>• Adverse events (AE),</li> <li>• Severe adverse events (SAE),</li> <li>• Withdrawals due to AEs,</li> <li>• Most frequent AEs,</li> <li>• Most frequent SAEs.</li> </ul> <p><b>Rationale:</b> We will give priority according to the Core Outcome Set for Clinical Trials on Coronavirus Disease 2019 (<a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102592/pdf/main.pdf">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102592/pdf/main.pdf</a>) 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.</p>
<p><b>Study design</b></p>	<p>Efficacy: randomised controlled trials (RCT)        Safety: observational studies (comparative or single-arm prospective studies and registries)</p>

## 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:

- Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library
- MEDLINE, accessed via OVID
- Embase, accessed via OVID

<b>Population</b>	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.
<b>Intervention</b>	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.
<b>Comparison</b>	Any active treatment, placebo, or standard of care.
<b>Outcomes</b>	All-cause mortality  Additional outcomes: Length of hospital stay, 2019-nCoV RT-PCR negativity, PaO <sub>2</sub> /FiO <sub>2</sub> , Duration of mechanical ventilation, radiological imaging, Adverse events, Severe adverse events.
<b>Study design</b>	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 Search strategy to identify randomised controlled studies 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 using the following sources:

- <https://www.fhi.no/en/qk/systematic-reviews-hta/map/>

Search methods are described in more detail in Appendix Table 6-2.

<b>Population</b>	See project Scope
<b>Intervention</b>	<p>Darunavir (Prezista®) as a mono-therapy, Darunavir (Prezista®) in combination with ritonavir or cobicistat and other (antiretroviral) treatment or standard of care.</p> <p>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)</p> <p><b>MeSH terms</b></p> <ul style="list-style-type: none"> <li>• Darunavir</li> </ul>
<b>Comparison</b>	Any active treatment, placebo, or standard of care.
<b>Outcomes</b>	See project Scope
<b>Study design</b>	<p>Inclusion criteria: Prospective non-randomised controlled trials, prospective case series (i.e. comparative or single-arm prospective studies), registries</p> <p>Exclusion criteria: retrospective studies, case studies / case reports, observational studies that do not report safety data</p>

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/>

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<sup>®</sup>, 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<sup>®</sup> 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<sup>®</sup> (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<sup>®</sup> co-administered with cobicistat is indicated with other antiretroviral medicines for treatment of HIV-1 in adults [5]. Prezista<sup>®</sup> 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<sup>®</sup> 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). The evidence base remained the same when compared to the previous version of this rolling collaborative review. In total, nine unique studies (11 reports) were included, concerning two completed RCTs, two observational studies and five ongoing RCTs.

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 4-2). Two reports describing the RCT "PEP COV-2" were identified [7, 8]. The Spanish trial aimed 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 168 outpatients randomised to the experimental group, 90 received HCQ plus DRV/c, the remainder received HCQ only. One hundred eighty four outpatients received usual COVID-19 surveillance as control intervention. Additional trial descriptions

are found in the Table of ongoing studies, EudraCT ID: 2020-001031-27; clinicaltrials.gov ID: NCT04304053).

Two observational uncontrolled studies were identified, which are described in Table 4-3. 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 [13]. 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

The outcome data related to the Chinese trial 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].

With regard to the Spanish trial, we only address outcome data for the two arms as described in the original protocol [7, 8]. We narratively describe the outcome data, which will be considered for inclusion in the summary of findings table in the next update of this report. Five patients (6.8%) in the HCQ plus DRV/c group and 11 (7.1%) in the control group required hospitalisation without the need of mechanical ventilation. Sixty-nine (93.2%) patients in the HCQ plus DRV/c group and 143 (92.3%) in the control group achieved resolution of symptoms at home without the need of hospitalisation. No death or hospitalisation requiring mechanical ventilation occurred in either trial arm during 28 days of follow-up. At day seven, the viral load in throat swabs expressed in Log<sub>10</sub> copies per ML were 3.55 (standard error SE 0.88) in the HCQ plus DRV/c group and 4.31 (SE 1.3) in the control group. This related to a reduction of 3.78 (SE 0.61 in the experimental and 2.94 (SE 0.21) in the control group.

### 4.2 Safety evidence from observational studies

With respect to the smaller uncontrolled study in 61 hospitalised COVID-19 patients with pneumonia [9], 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 4-3.

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 [10].

### 4.3 Ongoing studies

Five ongoing randomised trials of interest were identified in the register of clinicaltrials.gov, the EU Clinical Trial register and through citation checking (Table 4-4; Table 4-5; Table 4-6). 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. The largest randomised open label controlled trial with parallel group assignment evaluated DRV/c (Rezolsta) & Hydroxychloroquine (Dolquine). This Spanish trial enrolled outpatients persons with mild to moderate COVID-19 for the treatment part of the trial, and enrolled contacts of cases for the prevention part of the trial. The treatment results are now published and described in the paragraph “Effectiveness and Safety evidence from RCTs” [7, 8]. 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 fifth 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.[11]

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:** 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 Darunavir / Cobicistat	Risk with standard care <sup>a</sup>					
All-cause mortality at 14 days			Not estimable	Not estimable	30 (1)	very low <sup>b</sup>	No death
SARS-CoV-2 clearance at 7 days	468 per 1000	600 per 1000	RR 0.78 (0.39 to 1.54)	132 fewer per 1.000 (from 366 fewer to 324 more)	30 (1)	very low <sup>b</sup>	
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 <sup>b</sup>	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)
Worsening as measured on CT, day 7	700 per 1000	467 per 1000	RR 1.5 (0.52 to 4.38)		30 (1)	very low <sup>b</sup>	Own calculation of RR based on reported frequencies
Progression to critical COVID-19 disease, up to day 14	0 per 1000	0 per 1000	RR 3.00 (0.13 to 68.26)	0 fewer per 1.000 (from 0 fewer to 0 fewer)	30 (1)	very low <sup>b</sup>	One patient in the experimental group developed ARDS
Number of patients with any adverse event	532 per 1000	467 per 1000	RR 1.14 (0.56 to 2.35)	65 more per 1.000 (from 205 fewer to 630 more)	30 (1)	very low <sup>b</sup>	
Number of patients with severe adverse events	-	-	Not estimable		30 (1)	very low <sup>b</sup>	All adverse events were mild
Withdrawals due to AEs	-	-	Not estimable		30 (1)	very low <sup>b</sup>	No withdrawals due to AEs

**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 because high risk of performance bias and unclear risk of selection bias; downgraded two levels for very small sample size (<200)

**Source:** based on publication by Chen et al, 2020 [6] & ClinicalTrials.gov NCT04252274. Outcome data and GRADE assessment from the department of Epidemiology Lazio Regional Health Service (DEPLazio), Italy [12]; descriptions and layout modified by Swiss Network for health Technology Assessment (SNHTA); outcomes data and GRADE-assessment added by SNHTA for the outcomes: worsening as measured on CT, day 7; number of patients with severe adverse event; withdrawals due to AEs.

**Abbreviations:** RR=relative risk; ARDS=acute respiratory distress syndrome; CT=computed tomography; HR=hazard ratio; AEs=adverse events.

**Evaluation of the quality of the tests according to the GRADE Working Group**

High Quality: We are very confident that the real effect is close to that of the estimated effect

Moderate Quality: We are moderately confident in the effect estimation: the real effect may be close to the estimated effect, but there is a possibility that it is substantially different

Low Quality: Our confidence in the effect estimation is limited: the real effect may be substantially different from the estimated effect

Very Low Quality : We have very little confidence in estimating the effect: the actual effect is likely to be substantially different from the estimated one.

**Table 4-2 Study characteristics of included RCTs**

<b>Author, year, reference number/Study name/Study ID</b>	<b>Chen 2020 [6]</b> <b>ClinicalTrials.gov Identifier: NCT04252274</b>
<b>Study design, study phase</b>	Two-arm open label randomised controlled trial with parallel group assignment, phase 3 Blinding: none
<b>Centres (single centre or multicentre), country, setting</b>	Single center / China
<b>Patient population (number of included patients/ Mean age and sex/ Disease severity*)</b>	N=30 Mean age : 47.2 18 males (60%) Severity: Mild: n=0 / Moderate: n=30/ Severe: n=0 Critical: n=0
<b>Inclusion criteria</b>	All the participants had laboratory-confirmed SARS-CoV-2 infection and were willing to participate the study, as evidenced by signing an informed consent.
<b>Exclusion criteria</b>	<ul style="list-style-type: none"> <li>hypersensitivity to darunavir, cobicistat, or any excipients;</li> <li>patients with severe liver injury (Child-Pugh Class C);</li> <li>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;</li> <li>subjects considered to be unable to complete the study (eg, severely and critically ill patients) or not suitable for the study by researchers.</li> </ul> <p>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 (PaO<sub>2</sub>/ FiO<sub>2</sub>) 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.</p>
<b>Intervention (generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)</b>	N=15 Darunavir/cobicistat (800mg/150mg) Co-Intervention: Standard care Duration : 5 days
<b>Comparator(s) (standard care or generic drug name and dosage, time frame; number of</b>	N=15 Standard care: all participants received interferon alpha 2b and standard of care as per guideline recommendation in China

<b>randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)</b>	
<b>Primary Outcome(s)</b>	<ul style="list-style-type: none"> <li>SARS-CoV-2 clearance rate at day 7 after randomization (as indicated in the publication)</li> </ul>
<b>Patient-relevant secondary outcome(s)</b>	<ul style="list-style-type: none"> <li>All-cause mortality at 14 days</li> <li>Time to SARS-CoV-2 clearance (follow up duration of maximally 25 days)</li> <li>Worsening as measured on CT, day 7</li> <li>Progression to critical COVID-19 disease, up to day 14</li> <li>Number of patients with any adverse event</li> <li>Number of patients with severe adverse events</li> <li>Withdrawals due to AEs</li> </ul>
<b>Follow-up (days, months)</b>	Up to 14 days
<b>Sponsor/ lead institution</b>	Shanghai Public Health Clinical Center

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

**Table 4-3. Summary of safety from observational studies (AE and SAE) of Darunavir**

<b>Author, year</b>	<b>Moschini, 2020</b>	<b>Nicolini, 2020</b>
<b>Country</b>	Italy	Italy
<b>Sponsor / lead institution</b>	Non commercial	University of Genoa, Genoa, Italy
<b>Intervention/Product (drug name)</b>	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 <ul style="list-style-type: none"> <li>hydroxychloroquine (HY): 400 mg, bid for 5–20 days</li> <li>short-term initial antibiotic coverage, dosage not reported</li> <li>anti-inflammatory treatment with tocilizumab and/or methylprednisolone, dosage not reported</li> </ul>
<b>Dosage</b>	DRV/r: 800/100 mg qid; HY: 200 mg bid; AZ: 500 mg qid	<ul style="list-style-type: none"> <li>DRV/r : 800/100 mg once daily for 5–10 days</li> <li>HY: 400 mg, bid for 5–20 days</li> <li>short-term initial antibiotic coverage: dosage not reported</li> <li>anti-inflammatory treatment with tocilizumab and/or methylprednisolone: dosage not reported</li> </ul>

Author, year	Moschini, 2020	Nicolini, 2020
<b>Comparator</b>	None	None
<b>Study design</b>	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‡
<b>Setting</b>	Hospital	Hospital
<b>Number of pts</b>	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)
<b>Inclusion criteria</b>	<ul style="list-style-type: none"> <li>- patients with confirmed clinical and radiological diagnosis of SARS-CoV-2 pneumoni admitted to hospital</li> <li>- positive RT-PCR assay for SARS-Cov-2 in respiratory tract sample</li> <li>- ECG recording at baseline, , 3 and 7 days after start of treatment</li> <li>- Full treatment for 7 days of HY/ DRV/r (March 2 to 8, 2020)</li> <li>- Full treatment for 7 days of HY/AZ (March 9 to 15, 2020 when hospital treatment protocol had changed)</li> </ul>	<ul style="list-style-type: none"> <li>- HIV negative adult patients consecutively hospitalized for COVID-19 between February 28 and March 29, 2020 who received standard of care</li> </ul>
<b>Exclusion criteria</b>	<ul style="list-style-type: none"> <li>- QTc&gt;500 ms on baseline ECG</li> <li>- History of severe systolic dysfunction</li> <li>- History of arrhythmias, bradycardia &lt;50bpm</li> <li>- Concomitant medication that could cause QTc prolongation or early interruption of the medical therapy due to side effects</li> </ul>	<ul style="list-style-type: none"> <li>- None reported</li> </ul>
<b>Age of patients (yrs)</b>	HY & DRV/r: 67 HY & AZ: 68	Overall: mean 68 (± 13.79)
<b>Disease severity</b>	not reported	Overall: 223 (68%) had severe disease; “328 adults with COVID-19, most of whom had severe pneumonia”
<b>Follow-up (months)</b>	HY & DRV/r: 7 days HY & AZ: 7 days	Overall: median 21 (IQR 11–29) days
<b>Loss to follow-up, n (%)</b>	Overall 11 of 124 (8.9%) eligible patients excluded due to appearance of drug-related side effects	Not reported



Author, year	Moschini, 2020	Nicolini, 2020
<b>RoB*</b>	Relating to the HY & DRV/r arm: methodological limitations detected† related to <ul style="list-style-type: none"> <li>• small sample size</li> <li>• unclear sampling</li> <li>• suboptimal statistical analyses</li> <li>• inadequate response rate.</li> </ul>	Relating to the HY & DRV/r arm: methodological limitations detected† related to <ul style="list-style-type: none"> <li>• small sample size</li> <li>• insufficient coverage of the identified sample.</li> </ul>
<b>Safety – Outcomes*</b>		
<b>Overall AEs, n (%)</b>	-	86‡ (57%) in the SoC + DRV/r cohort §
<b>Serious AE (SAE), n (%)</b>	-	Grade 4/5 AE: n=21‡ (13.9%) in the SoC + DRV/r cohort #
<b>Most frequent AEs n (%)</b>	-	In the SoC + DRV/r cohort #: <ul style="list-style-type: none"> <li>- Liver enzyme elevations: 61‡ (40.4%)</li> <li>- Creatinine increase: 14‡ (9.3%)</li> <li>- Microbiologically documented bloodstream, pulmonary, or urinary infections: 30‡ (19.9%)</li> <li>- Cardiovascular disorders: 20‡ (13.2%)</li> <li>- Mild diarrhea: 11 (7.3%)</li> </ul>
<b>Most frequent SAEs, n (%)</b>	-	-
<b>AEs of special interest, n (%)</b>	Malignant ventricular arrhythmias HY & DRV/r: N=1 (1.6%) #	-
<b>Death as SAE, n (%)</b>	HY & DRV/r: 7 (11%) #	-
<b>Withdrawals due AEs, n (%)</b>	-	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]; ‡ from own calculations; § the authors reported the multiple 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: [9, 13]

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

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

<b>Trial Identifier/registry ID(s)/contact</b>	ClinicalTrials.gov identifier: NCT04435587 Trial acronym: IDRA-COVID19 Contact: Yupin Suputtamongkol, <a href="mailto:ysuputtamongkol@gmail.com">ysuputtamongkol@gmail.com</a> ; 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 Kongsangdao <a href="mailto:skhongsa@gmail.com">skhongsa@gmail.com</a> ; Rajavithi Hospital, Bangkok, Thailand; Tel. +66818180890
<b>Study design, study phase</b>	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
<b>Recruitment status</b>	Not yet recruiting (last update posted at trial registry at 23 June 2020)	Recruiting (last update posted at trial registry 1 Sept. 2020)
<b>Number of Patients, Disease severity*</b>	80 Asymptomatic or Afebrile COVID-19 Infection	320 Mild to critical COVID-19
<b>Setting (hospital, ambulatory,..)</b>	Hospital	In- and outpatients
<b>Intervention (generic drug name and dosage)</b>	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 (this is the control trial arm as described by the principal investigator)	Darunavir / ritonavir & favipiravir & chloroquine or Darunavir / ritonavir & oseltamivir ± chloroquine  Details: <ul style="list-style-type: none"> <li>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</li> <li>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</li> </ul>
<b>Comparator (standard care or generic drug name and dosage)</b>	oral ivermectin, 600 mcg/kg/day once daily for 3 days (this is the experimental trial arm as described by the principal investigator)	<ul style="list-style-type: none"> <li>Oseltamivir plus Chloroquine in Mild COVID19: Oseltamivir 300mg ( or 4-6 mg/kg) per day plus Hydroxychloroquine 800 mg per day In mild COVID19</li> <li>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</li> <li>Lopinavir and Ritonavir plus Oseltamivir in mild COVID19: Lopinavir 800 mg ( or 10 mg/kg ) per day and Ritonavir 200</li> </ul>

		<p>mg ( or 2.5 mg/kg ) per day plus Oseltamivir 300 mg ( or 4-6 mg /kg ) per day In mild COVID19</p> <ul style="list-style-type: none"> <li>• 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</li> <li>• 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</li> </ul> <p>Conventional Quarantine: “Patient who unwilling to treatment and willing to quarantine in mild COVID19”</p>
<b>Primary Outcome(s)</b>	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 ]
<b>Sponsor/ lead institution, country (also country of recruitment if different)</b>	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 4-5. Ongoing trials of combination therapies including Darunavir/ Cobicistat**

<b>Trial Identifier/registry ID(s)/contact</b>	Clinicaltrials.gov ID: NCT04304053 / EudraCT ID: 2020-001031-27; Sponsor's Protocol Code Number: HCQ4COV19 (previously CQ4COV19); Trial acronym: PEP CoV-2 Study Contact: Oriol Mitja, Prof (Ass) Infectious Disease and Global Health, Fundacio Lluita Contra la SIDA	Chinese Clinical Trial registry ID: ChiCTR2000029541 Trial acronym: not reported Contact: <a href="mailto:wangxinghuan@whu.edu.cn">wangxinghuan@whu.edu.cn</a> ; 169 Donghu Road, Wuchang District, Wuhan, Hubei, China; Tel. +86 18971387168 / +86 15729577635
<b>Study design, study phase</b>	Study 1: cluster randomised trial evaluating effects in contacts of infected individuals, focusing on prevention; 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. Laboratory technicians were blinded throughout the trial [7] Phase 3	Single center randomised three-arm controlled trial with parallel group assignment. Blinding not described. Block randomisation method using software. Phase not reported
<b>Recruitment status</b>	Completed (last update posted at clinicaltrials.gov at 30 June 2020). Study 1 [14] and study 2 are published [7, 8].	Not yet recruiting (last update posted at trial registry at 12 Feb. 2020)
<b>Number of Patients, Disease severity*</b>	Total 3040 planned; 2300 actual Study 2: 168 in experimental, 184 in control (actual) Study 1: Asymptomatic to moderate for contacts of confirmed cases Study 2: Mild to moderate for confirmed cases	100 Non-severe, non-critical, with 2019-nCoV pneumonia
<b>Setting (hospital, ambulatory,..)</b>	Outpatients	Hospitalised
<b>Intervention (generic drug name and dosage)</b>	Darunavir & cobicistat & hydroxychloroquine Details: Study 1 <ul style="list-style-type: none"> <li>prophylactic regimen of hydroxychloroquine once daily (200 mg tablets) 800 mg on day 1, and 400 mg on days 2-7.</li> </ul> Study 2 <ul style="list-style-type: none"> <li>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 &amp; cobistat boosted darunavir (DRV/c, Rezolsta), once daily, consisting of 800 mg Darunavir &amp; 150 mg cobicistat for 7 days</li> </ul> As of 4 April 2020, a protocol modification occurred to use HCQ alone after findings of no benefit of the protease inhibitor lopinavirritonavir. Ninety received HCQ & DRV/c, 79 received HCQ only.	Darunavir & cobicistat & thymosin Details: <ul style="list-style-type: none"> <li>DRV/c group (n=40): DRV/c (800mg/150mg QD) + Conventional treatment containing thymosin (1.6 mg SC QOD)</li> <li>LPV/r group (n=40): LPV/r (400mg/100mg bid) + Conventional treatment containing thymosin (1.6 mg SC QOD)</li> </ul> Both intervention groups also receive standard of care as described below.
<b>Comparator (standard care or generic drug name and dosage)</b>	no intervention: standard SARS-CoV-2 surveillance	Standard of care (n=20): Conventional treatment containing thymosin (1.6 mg SC QOD)
<b>Primary Outcome(s)</b>	Study 1 up to 14 days after start of treatment	Time to conversion of 2019-nCoV RNA result from RI sample

	<ul style="list-style-type: none"> <li>• Ring prophylaxis effectiveness to reduce development of disease assessed by Incidence of secondary cases (basic case reproduction number) among contacts of a case</li> <li>• Ring prophylaxis effectiveness to reduce transmissibility assessed by PCR conversion to positive of contacts that are negative at baseline</li> </ul> <p>Study 2</p> <ul style="list-style-type: none"> <li>• Virological outcome in index cases [Time Frame: Up to 7 days after start of treatment]: reduction of viral RNA load in nasopharyngeal swabs at days 3, and 7 after treatment start.</li> <li>• 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</li> </ul> <p>At EudraCT, primary outcome was originally described as: Symptom type, duration and severity among SARS-CoV-2 positive cases</p>	
<b>Sponsor/ lead institution, country (also country of recruitment if different)</b>	Fundacio Lluita Contra la SIDA, Spain	Zhongnan Hospital of Wuhan University, Hubei, China

\*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

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

<b>Trial Identifier/registry ID(s)/contact</b>	EudraCT ID: 2020-001528-32 Other ID: ARCO-Home study Contact: <a href="mailto:simone.janini@inmi.it">simone.janini@inmi.it</a> ; Istituto Nazionale per le Malattie Infettive Lazzaro Spallanzani; Dipartimento di Epidemiologia Digno, Via Portuense, Roma, 00149, Italy
<b>Study design, study phase</b>	Multicenter, 5-arm randomized open label controlled trial with adaptive design Phase 3
<b>Recruitment status</b>	Ongoing (last update at registry on 24 June 2020, at AIFA 23 November 2020)
<b>Number of Patients, Disease severity*</b>	Minimal 175 to maximal 435 (adaptive design) Symptomatic, not meeting criteria for immediate hospitalization (national early warning score-NEWS = 2 criteria)
<b>Setting (hospital, ambulatory,..)</b>	Outpatients
<b>Intervention (generic drug name and dosage)</b>	Darunavir & cobicistat Details: <ul style="list-style-type: none"> <li>• Trial arm darunavir/cobicistat (Rezolsta, Janssen-Cilag) 800/150 mg SID for 14 days</li> <li>• Trial arm idrossiclorochina (plaquenil, Sanofi-Aventis) 400 mg BID on day 1, 200 mg BID on day 2 to 10</li> <li>• Trial arm lopinavir/ritonavir (Kaletra, AbbVie) 400/100 mg BID for 14 days</li> <li>• Trial arm favipiravir (avigan, Fujifilm) 1.800 mg BID on day 1, 800 mg BID on day 2 to 10</li> </ul>
<b>Comparator (standard care or generic drug name and dosage)</b>	<ul style="list-style-type: none"> <li>• Trial arm: no antiviral treatment</li> </ul>
<b>Primary Outcome(s)</b>	<ul style="list-style-type: none"> <li>• Proportion of participants with undetectable SARS-CoV-2 gene E and gene M at day 7 after randomization.</li> <li>• Proportion of participants who need not hospitalization (NEWS = 2) by day 14 after randomization.</li> </ul>
<b>Sponsor/ lead institution, country (also country of recruitment if different)</b>	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 = cobicistat-boosted darunavir; LPV/r = lopinavir/ritonavir; BID = twice daily

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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 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](http://www.clinicaltrials.gov)) and World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) ([www.who.int/ictcp/en/](http://www.who.int/ictcp/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 coronavirus*[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*[Title/Abstract] OR ((corona*[Title/Abstract] OR corono*[Title/Abstract] AND (virus*[Title/Abstract] OR viral*[Title/Abstract] OR virinae*[Title/Abstract])) AND ((((((randomized controlled trial [Higgins JPT, #1]) OR (controlled clinical trial [Higgins JPT, #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])	10/12/2020

Database	URL	Search line / Search terms	Date of search
Ovid MEDLINE(R) ALL)	ovidsp.dc2.ovid.com	<ol style="list-style-type: none"> <li>1. exp coronavirus/</li> <li>2. ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw.</li> <li>3. (coronavirus* or coronavirus* or coronavirinae* or Coronavirus* or Coronavirus* 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.</li> <li>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.</li> <li>5. ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (China* or Chinese* or Huanan*)).ti,ab,kw.</li> <li>6. "severe acute respiratory syndrome*".ti,ab,kw.</li> <li>7. or/1-6</li> <li>8. randomized controlled trial.pt.</li> <li>9. controlled clinical trial.pt.</li> <li>10. random*.ab.</li> <li>11. placebo.ab.</li> <li>12. clinical trials as topic.sh.</li> <li>13. random allocation.sh.</li> <li>14. trial.ti.</li> <li>15. or/8-14</li> <li>16. exp animals/ not humans.sh.</li> <li>17. 15 not 16</li> <li>18. 7 and 17</li> <li>19. limit 18 to yr="2019 -Current"</li> </ol>	10/12/2020
OVID EMBASE	ovidsp.dc2.ovid.com	<ol style="list-style-type: none"> <li>1. exp Coronavirinae/ or exp Coronavirus/</li> <li>2. exp Coronavirus infection/</li> <li>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.</li> <li>4. or/1-3</li> <li>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/</li> <li>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.</li> <li>7. 5 or 6</li> <li>8. 4 and 7</li> <li>9. limit 8 to yr="2019 -Current"</li> </ol>	10/12/2020
<b>Additional search strategy as executed by SNHTA</b>			
Citation screening	-	10. Citation screening of all systematic reviews evaluating darunavir, identified in NIH LitCovid and NIPH (n=2 systematic reviews)	10/09/'20
Google	scholar.google.com & google.com	11. Performed on all identified ongoing studies: google and google scholar search using trial registry ID or acronym as search term (1 RCT with outcome data)	13/12/'20
PubMed	pubmed.ncbi.nlm.nih.gov	12. Performed on all identified ongoing studies: PubMed search using trial registry ID or acronym as search terms (1 RCT with outcome data)	13/12/'20

## 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. We receive studies that [EPPI Centre](#) has screened after searching weekly in Medline and Embase. We supplement these studies with a weekly search in Scopus. The retrieved hits were imported into an Endnote database and combined with generic names of the 15 included COVID-19 drugs.

Table 6-2 depicts the search strategy executed by NIPHNO and the search run by SNHTA up to 30 November 2020.

**Table 6-2 Search strategy to identify observational studies**

Database	URL	Search terms / Search modality	Date of search	Hits
<b>Search strategy as executed by NIPHNO for version 4 of the report</b>				
FHI Live COVID-19 Evidence Map	<a href="https://www.fhi.no/en/qk/systematic-reviews-hta/map/">https://www.fhi.no/en/qk/systematic-reviews-hta/map/</a>	Endnote file of hits retrieved in Medline + Embase + Scopus, combined with generic drug names	27/09/'20 until 25/10/'20	317
OVID Medline	Imported from EPPI Centre	<ol style="list-style-type: none"> <li>1. exp Coronavirus/</li> <li>2. exp Coronavirus Infections/</li> <li>3. (coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*).mp.</li> <li>4. (or/1-3) and ((20191* or 202*).dp. or 20190101:20301231.(ep).)</li> <li>5. 4 not (SARS or SARS-CoV or MERS or MERS-CoV or Middle East respiratory syndrome or camel* or dromedar* or equine or coronary or coronal or covidence* or covidien or influenza virus or HIV or bovine or calves or TGEV or feline or porcine or BCoV or PED or PEDV or PDCoV or FIPV or FCoV or SADS-CoV or canine or CCov or zoonotic or avian influenza or H1N1 or H5N1 or H5N6 or IBV or murine corona*).mp.</li> <li>6. ((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.</li> <li>7. (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 on 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.</li> <li>8. COVID-19.rx,px,ox. or severe acute respiratory syndrome coronavirus 2.os.</li> <li>9. ("32240632" or "32236488" or "32268021" or "32267941" or "32169616" or "32267649" or "32267499" or "32267344" or "32248853" or "32246156" or "32243118" or "32240583" or "32237674" or "32234725" or "32173381" or "32227595" or "32185863" or "32221979" or "32213260" or "32205350" or "32202721" or "32197097" or "32196032" or "32188729" or "32176889" or "32088947" or "32277065" or "32273472" or "32273444" or "32145185" or "31917786" or "32267384" or "32265186" or "32253187" or "32265567" or "32231286" or "32105468" or "32179788" or "32152361" or "32152148" or "32140676" or "32053580" or "32029604" or "32127714" or "32047315" or "32020111" or "32267950" or "32249952" or "32172715").ui.</li> <li>10. or/6-9</li> <li>11. 5 or 10</li> </ol>	26/10/'20 until 30/11/'20  And from 1/09/'20 until 30/11/'20 for the new compounds Regeneron, Bamlanivimab, Baricitinib, Molnupiravir	

Database	URL	Search terms / Search modality	Date of search	Hits
OID EMBASE		<ol style="list-style-type: none"> <li>exp Coronavirus Infections/</li> <li>exp coronavirinae/</li> <li>(coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*).mp.</li> <li>or/1-3</li> <li>4 not (SARS or SARS-CoV or MERS or MERS-CoV or Middle East respiratory syndrome or camel* or dromedar* or equine or coronary or coronal or covidence* or covidien* or influenza virus or HIV or bovine or calves or TGEV or feline or porcine or BCoV or PED or PEDV or PDCoV or FIPV or FCoV or SADS-CoV or canine or CCov or zoonotic or avian influenza or H1N1 or H5N1 or H5N6 or IBV or murine corona*).mp.</li> <li>((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.</li> <li>(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 on 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.</li> <li>6 or 7</li> <li>5 or 8</li> </ol>	26/10/20 until 30/11/20  and from 1/09/20 until 30/11/20 for the new compounds Regeneron, Bamlanivimab, Baricitinib, Molnupiravir	
Scopus		TITLE-ABS-KEY(((pneumonia OR covid* OR coronavirus* OR "corona virus*" OR ncov* OR 2019-ncov OR sars*) AND Wuhan) 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) W/1 (CoV OR nCoV OR covid OR coronavirus* OR "corona virus*" OR pandemi*)) OR ((covid OR covid19 OR covid-19) AND pandemic*) OR ((coronavirus* OR "corona virus*" AND pneumonia)) AND ORIG-LOAD-DATE > 20200920[date changes from week to week] AND ORIG-LOAD-DATE < 20200928 [date changes from week to week] AND NOT INDEX(medline)	26/10/20 until 30/11/20  and from 1/09/20 until 30/11/20 for the new compounds Regeneron, Bamlanivimab, Baricitinib, Molnupiravir	
<b>Search by SNHTA performed for this version of the report</b>				
Cochrane COVID-19 Register	<a href="https://covid-19.cochrane.org">https://covid-19.cochrane.org</a>	Filtered by "darunavir"	13/12/20	15 0 new
<b>Search by NIPHO performed for version 4 of this report</b>				
FHI Live COVID-19 Evidence Map	<a href="https://www.fhi.no/en/qk/systematic-reviews-hta/map/">https://www.fhi.no/en/qk/systematic-reviews-hta/map/</a>	Endnote file of hits retrieved in Medline + Embase + Scopus, combined with generic drug names	27/09/20 until 25/10/20	378
<b>Search by NIPHO performed for version 3 of this report</b>				
FHI Live COVID-19 Evidence Map	<a href="https://www.fhi.no/en/qk/systematic-reviews-hta/map/">https://www.fhi.no/en/qk/systematic-reviews-hta/map/</a>	Endnote file of hits retrieved in Medline + Embase + Scopus, combined with generic drug names	24/08/20& 27/09/20	460
<b>Search Strategy as executed by SNHTA for version 1 and 2 of this report</b>				
NIH LitCovid	<a href="https://www.ncbi.nlm.nih.gov/research/coronavirus/">https://www.ncbi.nlm.nih.gov/research/coronavirus/</a>	Darunavir* or prezista OR tmc114 or "tmc-114" or DRV or Prezcoibx	10/09/20	36
NIPH	<a href="https://www.fhi.no/en/qk/systematic-reviews-hta/map/">https://www.fhi.no/en/qk/systematic-reviews-hta/map/</a>	Searching "Interventions to treat the infected patient" Ticking "darunavir" and "darunavir & cobicistat" and "Any population"	10/09/20	11
Citation screening	-	Citation screening of all systematic reviews evaluating darunavir, identified in NIH LitCovid and NIPH (n = 2 systematic reviews)	10/09/20	1
Google	<a href="https://scholar.google.com/">scholar.google.com/</a> & <a href="https://www.google.com/">google.com</a>	Performed on all identified ongoing studies: google and google scholar search using trial registry ID or acronym as search term	15/09/20	2

\* all hits retrieved with search term darunavir

### 6.3 Search strategy to identify ongoing studies

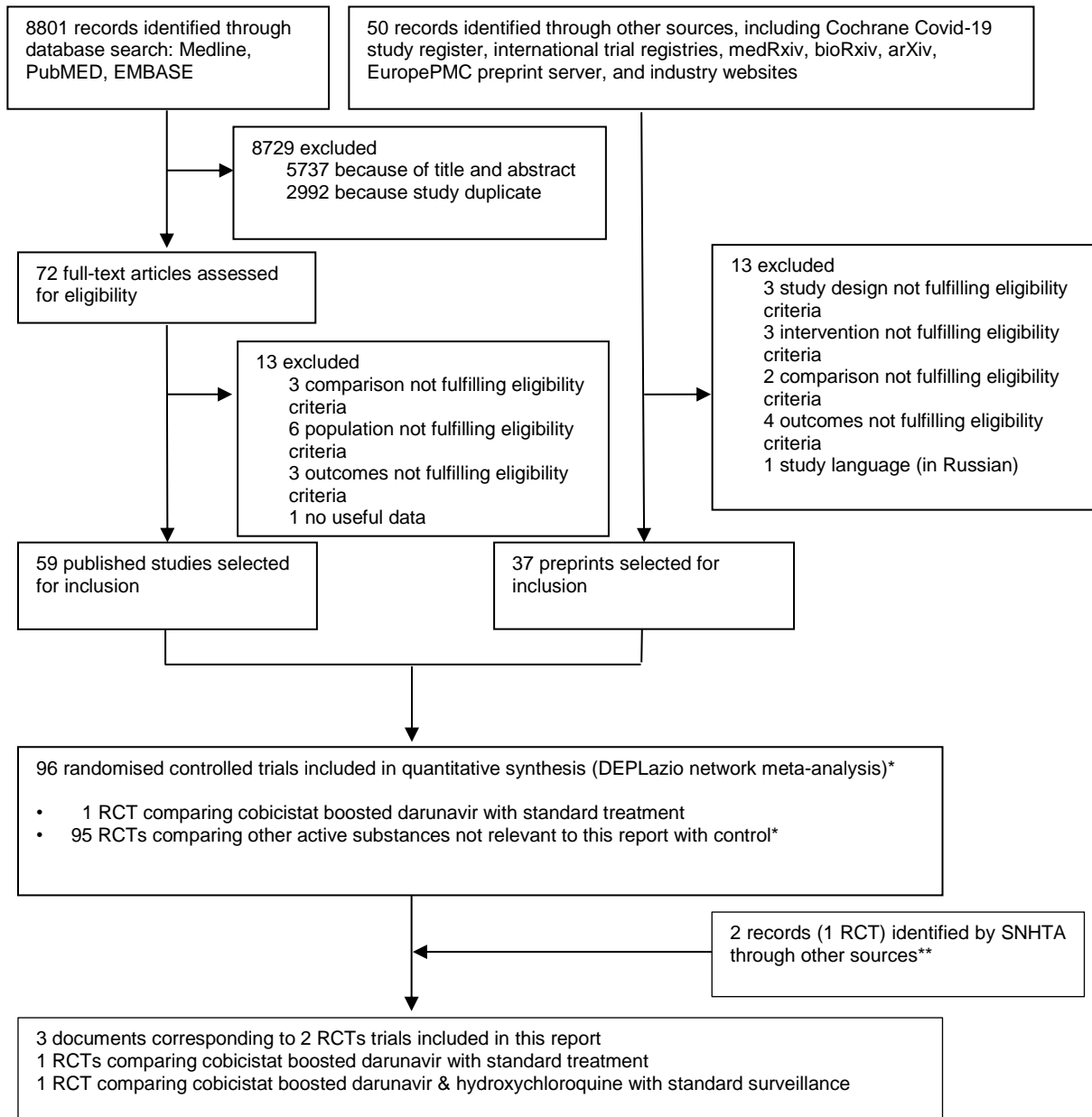
SNHTA is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and darunavir are described in Table 6-3.

**Table 6-3 Search strategy to identify ongoing studies**

Database	URL	Search terms / Search modality	Date of search	Hits retrieved
ClinicalTrials.gov	<a href="https://clinicaltrials.gov/">https://clinicaltrials.gov/</a>	Basic search mode* Terms used at “condition or disease”: <ul style="list-style-type: none"> <li>• covid-19</li> <li>• SARS</li> </ul> Terms used at “other terms”: <ul style="list-style-type: none"> <li>• Darunavir</li> <li>• Rezolsta</li> </ul> Synonyms for COVID-19 and darunavir are automatically searched	13/12/20	10 0 new
ISRCTN	<a href="https://www.isrctn.com/">https://www.isrctn.com/</a>	Basic search mode Search terms: <ul style="list-style-type: none"> <li>• covid-19 and darunavir</li> <li>• covid-19 and Prezista</li> <li>• covid-19 and tmc-114</li> <li>• covid-19 and tmc114</li> <li>• covid-19 and drv</li> <li>• covid-19 and Rezolsta</li> </ul> The same intervention terms were combined with the term «SARS», giving identical hits	13/12/20	0 0 new
European Clinical Trials Registry	<a href="https://www.clinicaltrialsregister.eu/">https://www.clinicaltrialsregister.eu/</a>	Basic search mode Search terms: <ul style="list-style-type: none"> <li>• covid-19 and darunavir</li> <li>• covid-19 and prezista</li> <li>• covid-19 and «TMC-114»</li> <li>• covid-19 and TMC114</li> <li>• covid-19 and Rezolsta</li> <li>• SARS and darunavir</li> <li>• SARS and prezista</li> <li>• SARS and «TMC-114»</li> <li>• SARS and TMC114</li> <li>• SARS and Rezolsta</li> </ul>	13/12/20	3 0 new
Cochrane COVID-19 Register	<a href="https://covid-19.cochrane.org">https://covid-19.cochrane.org</a>	Filtered by “darunavir”	13/12/20	15 0 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

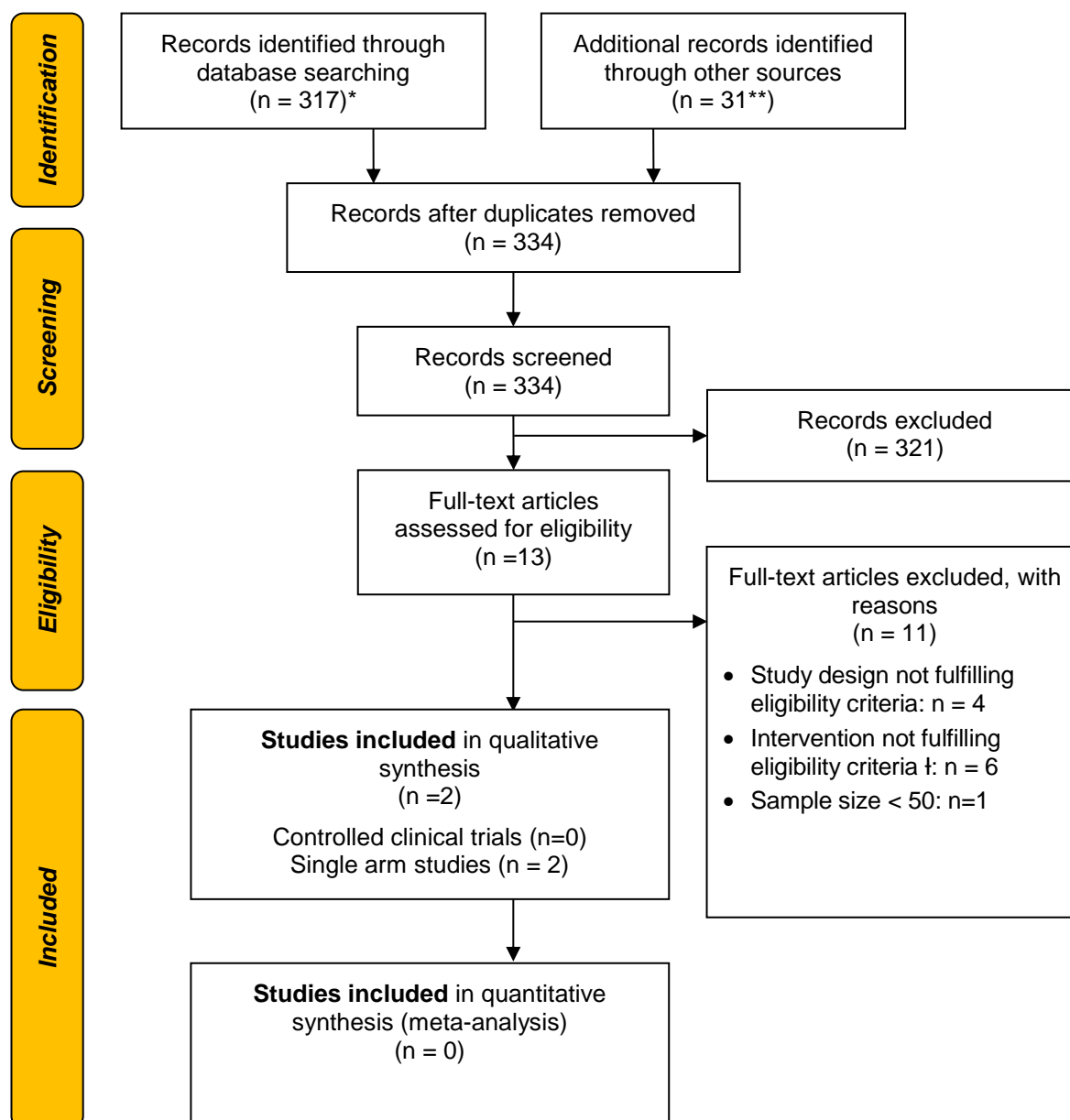
\* In Basic Search mode, one term was added to the field “condition or disease” and one term in the field “other terms”.

## 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](https://www.prospero.com/CRD42020176914); the single trial identified by DePlazio is considered in the summary of findings tables in this report. \*\* the recently identified trial with outcome data was identified by searches in PubMed and Google Scholar, using trial registry identification numbers and trial acronyms. This trial will be considered in the summary of findings tables in the next version of this report [7, 8].



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

\* Hits from searches executed by NIPHNO in the period 26 October 2020 to 30 November 2020;

\*\* including 2 studies included in previous versions of this report

† studies evaluating active substances relevant to other EUnetHTA rolling collaborative reviews