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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DOCUMENT HISTORY AND CONTRIBUTORS

Version	Date	Description of changes
V 1.0	**17/08/2020**	First version
V 1.1	**10/09/2020**	Literature searches, Literature screening, Data extraction
V 1.2	**15/09/2020**	Data extraction and analysis complete
V 1.3	**17/09/2020**	Check of data extraction and analysis
V 2.0	**22/09/2020**	Second version

Major changes from previous version

Chapter, page no.	Major changes from version 1.0
Methods, p. 8-10 **Summary, p. 13**	The description of the search methods for observational and ongoing studies is expanded: • Search methods are described in Appendix Tables 1-2 • A flow diagram was added
About the treatment, p. 10 **Summary, p. 11-12**	The pool of included studies has changed. • One previously ongoing RCT with EudraCT number: 2020-001031-27 has been published in part [1, 2] • One single arm observational study was added [3] • Two ongoing studies evaluating darunavir as part of a combination therapy (Chinese Clinical Trials registry ID ChiCTR2000029541 and EudraCT ID 2020-001528-32)
Summary, p. 17-21	The structure of the tables describing ongoing studies has changed: • at outcome, we now focus on the description of primary outcomes • we no longer list trial collaborators
Summary, p. 17-21	Actual status of all ongoing trials listed in Tables 4 are verified and updated when indicated.

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.

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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).

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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 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. (1) **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:

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

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

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

- medRxiv Health Sciences
- bioRxiv Biology

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

Data extraction, Risk of bias assessment, data synthesis:

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

Risk of bias is assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [4].

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 [5]. Network meta-analysis (NMA) is performed for the primary outcome. For rating the certainty of the evidence, the GRADE approach is being used [6].

- 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/
- https://www.ncbi.nlm.nih.gov/research/coronavirus/docsum?filters=topics.General%20Info

Search methods are described in more detail in Appendix Table 1.

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
Comparison	Any active treatment, placebo, or standard of care.
Outcomes	See project Scope
Study design	Prospective non-randomised controlled trials, prospective case series, registries Exclusion criteria: retrospective case series, case studies

One researcher carries out title and abstract screening and assesses the full texts of all potentially eligible studies. One researcher extracts the data and assesses the risk of bias using Robins-I (https://training.cochrane.org/handbook/current/chapter-25).

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/

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

Inclusion criteria: Randomised controlled trials, Controlled trials

One researcher is searching and extracting the data for the eligible studies. The process of study selection is depicted in the a flow diagram.

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 [7].

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 [7]. 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 [7].

The flow diagram depicts the screening process to identify eligible studies on darunavir as treatment modality for COVID-19 (Figure 4-1). The combined search on completed and ongoing studies resulted in 63 hits, of which 24 were screened on full text basis). Of the 12 citations excluded during full text screening, four concerned retrospective study designs [8-11], one case-reports [12] and the remainder did not evaluate darunavir. In this update, ten unique studies (11 reports) were included, concerning two completed RCTs, two observational studies and six 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 [13]. 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. In this update, two reports describing the RCT "PEP COV-2" were identified [1, 2]. 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).

As of September 10th, 2020, one additional observational study was identified. The two available studies, both conducted in Italy, are described in Table 4.2. Both concerned uncontrolled designs, that aimed to evaluate a combination therapy including darunavir. In both studies, a protocol modification occurred 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 newly included and larger 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. 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 [13].

With regard to the Spanish trial, we only address outcome data for the two arms as described in the original protocol. 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 Log10 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 [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 larger 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 4-2.

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

Five ongoing randomised trials of interest were identified in the register of clinicaltrials.gov, the EU Clinical Trial register and through citation checking (Figure 4-1). 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/rr 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” [1, 2]. Two ongoing trials were added in this update. 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.[16]

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

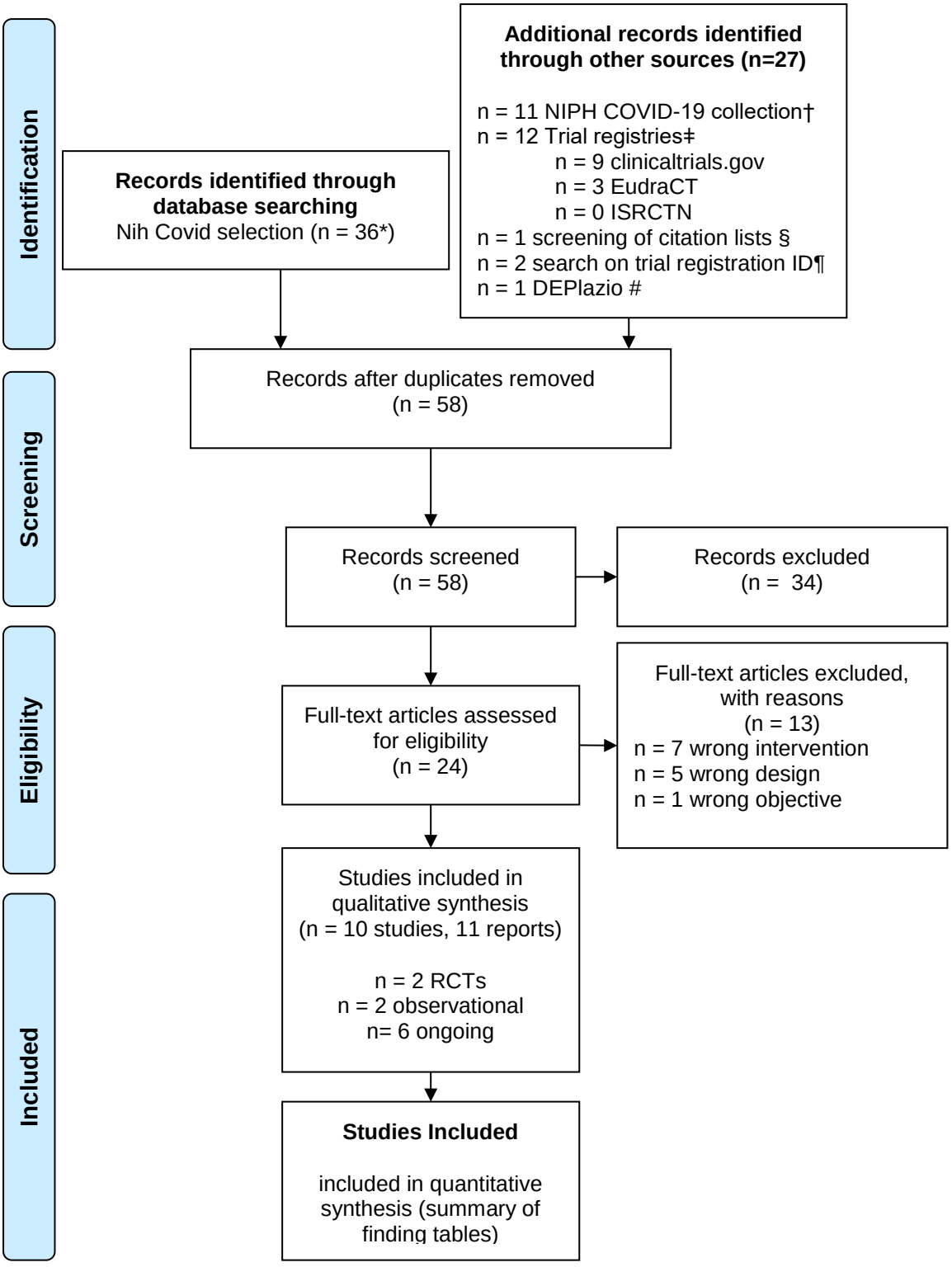

Figure 4-1 Flow Diagram

* from https://www.ncbi.nlm.nih.gov/research/coronavirus/docsum?filters=topics.General%20Info, 9 added in update 1; † from www.nornesk.no/forskningskart/NIPH_interventionsTreatMap.html, 9 added in update 1; ‡ 1 added in this update; § citation screening of 2 systematic reviews; ¶ 1 completed and 2 ongoing RCTs; # DEPLazio provided 1 citation, the systematic search by DEPlazio is described elsewhere; RCT = randomised controlled trial; DEPLazio = the department of Epidemiology Lazio Regional Health Service, Italy

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)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with Darunavir / Cobicistat	Risk with standard care[a]				
All-cause mortality at 14 days			Not estimable	30 (1)	very low[b]	No death
SARS-CoV-2 clearance at 7 days	468 per 1000	600 per 1000	RR 0.78 (0.39 to 1.54)	(1)	very low[b]	
Time to SARS-CoV-2 clearance (follow up duration of maximally 25 days)	Not estimable	Not estimable	HR 0.82 (0.36 to 1.88)	30 (1)	very low[b]	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[b]	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)	30 (1)	very low[b]	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)	30 (1)	very low[b]	
Number of patients with severe adverse events	-	-	Not estimable	30 (1)	very low[b]	All adverse events were mild
Withdrawals due to AEs	-	-	Not estimable	30 (1)	very low[b]	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 small sample size (<200)

Source: based on publication by Chen et al, 2020 [13] & ClinicalTrials.gov NCT04252274. Outcome data and GRADE assessment from the department of Epidemiology Lazio Regional Health Service (DEPLazio), Italy [17]; 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. Summary of safety from observational studies (AE and SAE) of Darunavir

Author, year	Moschini, 2020	Nicolini, 2020
Country	Italy	Italy
Sponsor	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	RD: 100/800 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/RD: 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)

Author, year	Moschini, 2020	Nicolini, 2020
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/RD (March 2 to 8, 2020) - Full treatment for 7 days of HY/AZ (March 9 to 15, 2020 when hospital treatment protocol had changed) Excluded: - QTc>500 ms on baseline ECG - History of sever 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	- HIV negative adult patients consecutively hospitalized for COVID-19 between February 28 and March 29, 2020
Age of patients (yrs)	HY/RD: 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/RD: 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*	Not assessed†	Not assessed†
Safety – Outcomes*		
Overall AEs, n (%)	-	86ǂ (57%) in the SoC + DRV/r cohort §
Serious AE (SAE), n (%)	-	Grade 4/5 AE: n=21ǂ (13.9%) in the SoC + DRV/r cohort #
Most frequent AEs n (%)	-	In the SoC + DRV/r cohort #: - Liver enzyme elevations: 61ǂ (40.4%) - Creatinine increase: 14ǂ (9.3%) - Microbiologically documented bloodstream, pulmonary, or urinary infections: 30ǂ (19.9%) - Cardiovascular disorders: 20ǂ (13.2%) - Mild diarrhea: 11 (7.3%)
Most frequent SAEs, n (%)	-	-

Author, year	Moschini, 2020	Nicolini, 2020
AEs of special interest, n (%)	Malignant ventricular arrhythmias HY/RD: N=1 (1.6%) #	-
Death as SAE, n (%)	HY/RD: 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, no generally accepted risk of bias tool exists for uncontrolled studies; 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: [3, 14]

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

Table 4-3. Ongoing trials of combination therapies including Darunavir/ Ritonavir

Active substance	Darunavir/ritonavir & hydroxychloroquine	Darunavir / ritonavir & favipiravir & chloroquine Darunavir / ritonavir & oseltamivir ± chloroquine
Sponsor	Mahidol University, Thailand	Rajavithi Hospital
Trial Identifier	ClinicalTrials.gov identifier: NCT04435587 Trial acronym: IDRA-COVID19	ClinicalTrials.gov Identifier: NCT04303299 Acronym: previously THDMS-COVID-19; currently fight COVID-19
Phase & Intention	Phase 4, treatment Title: Comparative Efficacy of Ivermectin Versus Combination of Hydroxychloroquine Plus Darunavir/ Ritonavir for Shortening Duration of SARS-CoV2 Detection From Respiratory Secretion Among Asymptomatic or Afebrile COVID-19 Infection	Phase 3, treatment Title (new title): Favipiravir, Protease Inhibitors, Oseltamivir -Gpo, Hydroxychloroquine for Treatment of COVID-19 (FIGHT-COVID-19)
Study design	Open label two-arm randomised controlled study with parallel group design. Outcome assessors are masked for allocation status.	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.
Status of trial	Not yet recruiting (last update posted at trial registry at 23 June 2020)	Recruiting (last update posted at trial registry 1 Sept. 2020)
Duration/End of Study	Estimated Primary Completion Date: June 2021 Estimated Study Completion Date: November 2021	Estimated Primary Completion Date: 31 December 2021 Estimated Study Completion Date: 31 December 2021
Study details		
Number of Patients	80	320
Disease severity	Asymptomatic or Afebrile COVID-19 Infection	Mild to critical COVID-19
Setting	Hospital	In- and outpatients
Location/Centres	Thailand, Bangkok, 1 center	Thailand, Bangkok
Intervention drug name and dosage	• Combined hydroxychloroquine (Vermectin), 400 mg bid on day 1, then 200 mg bid on Day 2-5 plus darunavir/ ritonavir 400/100	• 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

Active substance	Darunavir/ritonavir & hydroxychloroquine	Darunavir / ritonavir & favipiravir & chloroquine Darunavir / ritonavir & oseltamivir ± chloroquine
	mg every 12 hours for 5 days (this is the control trial arm as described by the principal investigator)	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 (drug name and dosage)	• oral ivermectin, 600 mcg/kg/day once daily for 3 days (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”
Duration of observation/ Follow-up	Up to 28 days of follow-up	Up to 24 weeks
Primary Outcomes Secondary Outcomes	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]
Results/Publication	None, status 15 September 2020	None, status 15 Sept. 20

Abbreviations: bid=twice per day; mg = milligram.

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

Active substance	Darunavir & cobicistat & hydroxychloroquine	Darunavir & cobicistat & thymosin
Sponsor	Fundacio Lluita Contra la SIDA	Zhongnan Hospital of Wuhan University
Trial Identifier	Clinicaltrials.gov ID: NCT04304053 EudraCT ID: 2020-001031-27 Sponsor's Protocol Code Number: HCQ4COV19 (previously CQ4COV19) Trial acronym: PEP CoV-2 Study	Chinese Clinical Trial registry ID: ChiCTR2000029541 Trial acronym: not reported
Phase & Intention	Phase 3, Study 1: prevention Study 2: treatment Title: Treatment of non-severe confirmed cases of COVID-19 and chemoprophylaxis of their contacts as prevention strategy: a Cluster Randomized Clinical Trial	Phase not reported Treatment Title: A randomised, open, controlled trial for darunavir/cobicistat or Lopinavir/ritonavir combined with thymosin a1 in the treatment of novel coronavirus pneumonia (COVID-19)
Study design	NCT04304053 described two studies. Study 1:cluster randomised trial evaluating effects in contacts of infected individuals Study 2: randomised two-arm open label controlled trial with parallel group assignment on confirmed cases. Independent randomisation using a computer generated random-number list. Laboratory technicians were blinded throughout the trial [1]	Single center randomised three-arm controlled trial with parallel group assignment. Blinding not described. Block randomisation method using software.
Status of trial	Completed (last update posted at clinicaltrials.gov at 30 June 2020)	Not yet recruiting (last update posted at trial registry at 12 Feb. 2020)
Duration/End of Study	15th of June 2020 (actual)	Planned end of study: 1 Dec. 2020
Study details		
Number of Patients	Total 3040 planned; 2300 actual Study 2: 168 in experimental, 184 in control (actual)	100
Disease severity	Study 1: Asymptomatic to moderate for contacts of confirmed cases Study 2: Mild to moderate for confirmed cases	Non-severe, non-critical, with 2019-nCoV pneumonia
Setting	Outpatients	Hospitalised
Location/Centres	Spain, three health regions	China, Hubei, single center
Intervention drug name and dosage	Study 1 • prophylactic regimen of hydroxychloroquine once daily (200 mg tablets) 800 mg on day 1, and 400 mg on days 2-7. Study 2 • 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	• 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.

Active substance	Darunavir & cobicistat & hydroxychloroquine	Darunavir & cobicistat & thymosin
	As of 4 April 2020, a protocol modification occured to use HCQ alone after findings of no benefit of the protease inhibitor lopinavirritonavir. Ninety received HCQ & DRV/c, 79 received HCQ only.	
Comparator (drug name and dosage)	• no intervention: standard SARS-CoV-2 surveillance	• Standard of care (n=20): Conventional treatment containing thymosin (1.6 mg SC QOD)
Duration of observation/ Follow-up	Up to 28 days	Not reported
Primary Outcomes	Study 1 up to 14 days after start of treatment: • Ring prophylaxis effectiveness to reduce development of disease assessed by Incidence of secondary cases (basic case reproduction number) among contacts of a case • Ring prophylaxis effectiveness to reduce transmissibility assessed by PCR conversion to positive of contacts that are negative at baseline Study 2 • 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. • 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	Time to conversion of 2019-nCoV RNA result from RI sample
Results/Publication	Study 1: none, status 15 September 2020 Study 2: published [1, 2]	None, status 15 September 2020

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 4-5. Ongoing trials of combination therapies including Darunavir/ Cobicistat, continued

Active substance	**Darunavir & cobicistat**
Sponsor	Istituto Nazionale Per Le Malattie Infettive "Lazzaro Spallanzani"
Trial Identifier	EudraCT ID: 2020-001528-32 Other ID: ARCO-Homestudy
Phase & Intention	Treatment Phase 3 Title: Adaptive Randomized trial for therapy of COrona virus disease 2019 at home with oral antivirals (ARCO-Home study)
Study design	Multicenter, 5-arm randomized open label controlled trial with adaptive design
Status of trial	Ongoing (last update at registry on 24 June 2020)
Duration/End of Study	3 month duration
Study details	
Number of Patients	Minimal 175 to maximal 435 (adaptive design)
Disease severity	Symptomatic, not meeting criteria for immediate hospitalization (national early warning score-NEWS = 2 criteria)
Setting	outpatients
Location/Centres	Italy, 5 sites
Intervention drug name and dosage	• 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 (drug name and dosage)	• Trial arm: no antiviral treatment
Duration of observation/ Follow-up	Up to day 14
Primary Outcomes	• 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.
Results/Publication	None, status 17 Sept. 2020

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 APPENDIX

Appendix Table 1. Search strategy to identify observational studies

Database	URL	Search terms / Search modality	Date of search	Hits retrieved
NIH LitCovid	https://www.ncbi.nlm.nih.gov/research/coronavirus/	Darunavir* or prezista OR tmc114 or "tmc-114" or DRV or Prezcobix	10 August 2020	27
NIH LitCovid	https://www.ncbi.nlm.nih.gov/research/coronavirus/	Darunavir* or prezista OR tmc114 or "tmc-114" or DRV or Prezcobix	10 September 2020	36, including 27 previously identified
NIPH	https://www.fhi.no/en/qk/systematic-reviews-hta/map/	Seaching “Interventions to treat the infected patient” Ticking “darunavir” and “darunavir & cobicistat” and “Any population”	10 August 2020	2
NIPH	https://www.fhi.no/en/qk/systematic-reviews-hta/map/	Seaching “Interventions to treat the infected patient” Ticking “darunavir” and “darunavir & cobicistat” and “Any population”	10 September 2020	11, including 2 previously identified
Citation screening	-	Citation screening of all systematic reviews evaluating darunavir, identified in NIH LitCovid and NIPH	10 September 2020	2 systematic reviews (1 ongoing RCT identified)
Google		Performed on all identified ongoing studies: google search using trial registry ID or acronym as search term	15 September 2020	2 reports identified

***** all hits retrieved with search term darunavir

Appendix Table 2. Search strategy to identify ongoing studies

Database	URL	Search terms / Search modality	Hits retrieved	Date of search
ClinicalTrials.gov	https://clinicaltrials.gov/	Basic search mode* Terms used at Condition or disease: • covid-19 • SARS Terms used at “other terms”: • Darunavir • Prezista • tmcT-114 • tmc114	Overall: 9	10 August 2020
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 now automatically searched	Overall: 9, 9 identifed in previous search	10 September 2020
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	Overall: 0 0 0 0 0 0	10 August 2020

Database	URL	Search terms / Search modality	Hits retrieved	Date of search
ISRCTN	https://www.isrctn.com/	Basic search mode Search terms: • covid-19 and darunavir • covid-19 and Prezista • covid-19 and T-705 • 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	Overall: 0 0 0 0 0 0	10 September 2020
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	Overall: 2 2 0 0 0	10 August 2020
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	Overall: 3 2, 2 identifed in previous search 0 0 0 1, 1 identified in previous search 2, 1 identified in previous search 0 0 0 2, 1 identified in previous search	10 September 2020
Citation screening	-	Citation screening of all systematic reviews evaluating darunavir, identified in NIH LitCovid and NIPH, see Appendix Table 1	10 September 2020	2 systematic reviews (1 additional ongoing trials identified)

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

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