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 |
|---|---|---|
| **V0.1** | **July 2020** | Literature searches, Literature screening, Data extraction |
| **V0.2** | **10/08/2020** | Data extraction complete |
| **V0.3** | **13/08/2020** | Check of data extraction |
| **V1.0** | **17/08/2020** | First version |

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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 |
| 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 |
| MD | Mean Difference |
| MeSH | Medical Subject Headings |
| NA | Not applicable |
| NR | Not reported |
| OR | Odds Ratio |
| PP | Per Protocol |
| qid | Four times a day |
| RCT | Randomized Controlled Trial |
| REA | Relative Effectiveness Assessment |
| RR | Relative Risk |
| RT-PCR | Reverse transcription polymerase chain reaction |
| SAE | Serious Adverse Event |
| SD | Standard Deviation |
| SMD | Standardized Mean Difference |
| SmPC | Summary of product characteristics |
| 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, aiming at critical appraisal of the clinical evidence based on the Submission Dossier submitted by the 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**<br><br>• 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.<br><br>**ICD-Codes** (https://www.who.int/classifications/icd/covid19/en)<br><br>• 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.<br>• 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.<br>• 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.<br>• 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.<br><br>**MeSH-terms**<br><br>• COVID-19, Coronavirus Disease 2019 |

| | |
|---|---|
| | **Target population**<br>(https://www.covid19treatmentguidelines.nih.gov/overview/management-of-covid-19/)<br><br>• 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.<br>• 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.<br>• 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.<br>• 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%.<br>• 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.<br><br>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)<br><br>**MESH Terms**<br><br>• Darunavir |
| **Comparison** | Any active treatment, placebo, or standard of care.<br><br>**Rationale**: Since there is no gold standard treatment any comparator is acceptable as well as the above listed interventions. |
| **Outcomes** | Main outcome:<br><br>• All-cause Mortality (Survival)<br><br>Additional Outcomes:<br><br>Efficacy:<br><br>• Length of hospital stay,<br>• Viral burden (2019-nCoV RT-PCR negativity),<br>• Clinical progression (WHO Clinical Progression Scale measured daily over the course of the study),<br>• Rates of hospitalization and of patients entering ICU,<br>• Duration of mechanical ventilation,<br>• Quality of life.<br><br>Safety:<br><br>• Adverse events (AE),<br>• Severe adverse events (SAE),<br>• Withdrawals due to AEs,<br>• Most frequent AEs,<br>• 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.pdf)<br><br>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)<br>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. **Table 1 - Summary of findings (SoF) 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 table1 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.<br><br>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<br><br>Additional outcomes: Length of hospital stay, 2019-nCoV RT-PCR negativity, PaO2/FiO2, Duration of mechanical ventilation, radiological Worsening as measured on CT, 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 (Higgins et al., 2019).

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 (DerSimonian 1986).Network meta-analysis (NMA) is performed for the primary outcome. For rating the certainty of the evidence, the GRADE approach is being used.

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

**2. Table 2 - 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

| | |
|---|---|
| **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.<br>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)<br>MeSH terms<br>• Darunavir |
| **Comparison** | Any active treatment, placebo, or standard of care. |
| **Outcomes** | See project Scope |
| **Study design** | Observational studies (comparative or single-arm prospective studies and registries)<br>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 3 - 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 is searching and extracting the data for the eligible studies.

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 [1].

## *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 [1]. 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 [1].

# 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*

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 [2]. All participants also received interferon alpha 2b and standard of care 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. 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.

### *4.2 Safety evidence from observational studies*

As of August 13th, 2020, one single-arm prospective observational study is completed that evaluated darunavir co-administered with low dose ritonavir in combination with hydroxychloroquine to assess safety endpoints in 61 hospitalised COVID-19 patients with pneumonia [3]. During the 7 day follow-up, the combination therapy increased the corrected QT interval, while 1 out of 61 (1.6%) patients experienced malignant ventricular arrhythmia . Seven (11%) of the patients died in hospital.

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 [4].

### *4.3 Ongoing studies*

Three ongoing randomised trials of interest were identified in the register of clinicaltrials.gov and the EU Clinical Trial register. All three trials evaluated combination therapies. One moderate sized multi-arm trial (n=320) in Thailand is evaluating various combinations of agent, including the combination of

- Darunavir plus ritonavir plus Oseltamivir plus Hydroxychloroquine in persons with mild to critically illness in COVID-19 and

- Favipiravir plus Darunavir plus Ritonavir 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 darunavir/ritonavir in asymptomatic carrier of SARS-CoV2. A large single center randomised open label controlled trial with parallel group assignment is evaluating darunavir & cobicistat (Rezolsta) & Hydroxychloroquine (Dolquine) in 3040 persons that are diagnosed with mild to moderate COVID-19, or a contact of cases. This trial is focusing on both prevention and 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.[5]

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 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 |

**Source**: based on publication by Chen et al, 2020 [2] & ClinicalTrials.gov NCT04252274. Outcome data and GRADE assessment from the department of Epidemiology Lazio Regional Health Service (DEPLazio), Italy [6]; 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.

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)

**Table 4-2. Summary of safety from observational studies (AE and SAE) of darunavir**

| Author, year | Moschini, 2020 |
|---|---|
| **Country** | Italy |
| **Sponsor** | Non commercial |
| **Intervention/Product (drug name)** | Ritonavir/darunavir & hydroxychloroquine (HY/RD)<br>Or<br>Hydroxychloroquine & azithromycin (HY/AZ) |
| **Dosage** | RD: 100/800 mg qid;<br>HY: 200 mg bid;<br>AZ: 500 mg qid |
| **Comparator** | None |
| **Study design** | Two single arm observational studies with prospective and consecutive enrollment of patients<br>Uncontrolled design |
| **Setting** | Hospital |
| **Number of pts** | HY/RD: n=61<br>HY/AZ n=52 |
| **Inclusion criteria** | - patients with confirmed clinical and radiological diagnosis of SARS-CoV-2 pneumoni admitted to hospital<br>- postive RT-PCR assay for SARS-Cov-2 in respiratory tract sample<br>- ECG recording at baseline, , 3 and 7 days after start of treatment<br>- Full treatment for 7 days of HY/RD (March 2 to 8, 2020)<br>- Full treatment for 7 days of HY/AZ (March 9 to 15, 2020 when hospital treatment protocol had changed)<br>Excluded:<br>- QTc>500 ms on baseline ECG<br>- History of sever systolic dysfunction<br>- History of arrhythmias, bradycardia <50bpm<br>- Concomitant medication that could cause QTc prolongation or early interruption of the medical therapy due to side effects |
| **Age of patients (yrs)** | HY/RD: 67<br>HY/AZ: 68 |
| **Disease severity** | HY/RD: not reported<br>HY/AZ: not reported |
| **Follow-up (months)** | HY/RD: 7 days<br>HY/AZ: 7 days |
| **Loss to follow-up, n (%)** | Overall 11 of 124 (8.9%) eligible patients excluded due to appearance of drug-related side effects<br>HY/RD: not reported<br>HY/AZ: not reported |
| **RoB** | HY/RD: High<br>HY/RD: High |
| **Overall AEs, n (%)** | - |
| **Serious AE (SAE), n (%)** | - |
| **Most frequent AEs n (%)** | - |
| **Most frequent SAEs, n (%)** | - |
| **AEs of special interest, n (%)** | Malignant ventricular arrhythmias<br>HY/RD: N=1 (1.6%)<br>HY/AZ N=1 (1.9%) |

| Author, year | Moschini, 2020 |
|---|---|
| **Death as SAE, n (%)** | HY/RD: 7 (11%)<br>HY/AZ: 2 (4%) |
| **Withdrawals due AEs, n (%)** | - |

*** by arms, if available, (Robins-I): https://training.cochrane.org/handbook/current/chapter-25**

**Source:** [3]

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

| **Active substance** | **Darunavir/ritonavir & hydroxychloroquine** | **Favipiravir lopinavir /Ritonavir Darunavir /ritonavir favipiravir chloroquine** |
|---|---|---|
| **Sponsor/Collaborator** | Mahidol University, Thailand | Rajavithi Hospital |
| **Trial Identifier** | ClinicalTrials.gov identifier: NCT04435587<br>Trial acronym: IDRA-COVID19 | ClinicalTrials.gov Identifier: NCT04303299<br>Trial acronym: THDMS-COVID-19 |
| **Phase & Intention** | Phase 4, treatment<br>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<br>Title: A 6 Week Prospective, Open Label, Randomized, in Multicenter Study of, Oseltamivir Plus Hydroxychloroquine Versus Lopipinavir/ Ritonavir Plus Oseltamivir Versus Darunavir/ Ritonavir Plus Oseltamivir Plus Hydroxychloroquine in Mild COVID-19 AND Lopipinavir/ Ritonavir Plus Oseltamivir Versus Favipiravir Plus Lopipinavir / Ritonavir Versus Darunavir/ Ritonavir Plus Oseltamivir Plus Hydroxychloroquine Versus Favipiravir Plus Darunavir and Ritonavir Plus Hydroxychloroquine in Moderate to Critically Ill COVID-19 |
| **Study design** | Open label two-arm randomised controlled study with parallel group design. Outcome assessors are masked for allocation status. | Open label two-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, started July 2020 | Not yet recruiting, started July 15, 2020 |
| **Duration/End of Study** | Estimated Primary Completion Date: June 2021<br>Estimated Study Completion Date: November 2021 | Estimated Primary Completion Date: December 31, 2020<br>Estimated Study Completion Date: March 30, 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), 400mg bid on day 1, then 200mg bid on Day 2-5 plus darunavir/ ritonavir 400/100mg every 12 hours for 5 days (this is the control trial arm as described by the principal investigator) | Favipiravir lopinavir /Ritonavir for mod. To severe:<br>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<br><br>Darunavir /ritonavir favipiravir chloroquine mod-severe:<br>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<br><br>Darunavir and Ritonavir plus oseltamivir in Mild COVID19: Darunavir 400 mg every 8 hours Ritonavir 200 mg (or 2.5 mg/kg ) per day plus plus Oseltamivir 300mg ( or 4-6 |

| Active substance | Darunavir/ritonavir & hydroxychloroquine | Favipiravir lopinavir /Ritonavir Darunavir /ritonavir favipiravir chloroquine |
|---|---|---|
| | | mg/kg) per day plus Hydroxychloroquine 400mg per day<br><br>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<br><br>Lopinavir and Ritonavir Oseltamivir moderate to critically ill 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<br><br>Darunavir /ritonavir oseltamivir chloroquine moderate to critically ill COVID-19: 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<br><br>Conventional Qurantine: 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 |
| **Endpoints**<br>**Primary Outcomes**<br>**Secondary Outcomes** | Primary outcome:<br>Adverse event rates [Time Frame: after first dose until day 28 of follow up]<br>Secondary outcome:<br>Antibody detection rates [Time Frame: weekly after treatment until 4th week] | Primary outcome:<br>SARS-CoV-2 eradication time<br>[ Time Frame: Up to 24 weeks ]<br>Secondary outcomes:<br><br>• Number of patient with Death [ Time Frame: Up to 24 weeks ]<br>• Number of patient with Recovery adjusted by initial severity in each arm [ Time Frame: Up to 24 weeks ]<br>• Number of day With ventilator dependent adjusted by initial severity in each arm [ Time Frame: Up to 24 weeks ]<br>• Number of patient developed Acute Respiratory Distress Syndrome After treatment [ Time Frame: Up to 24 weeks ]<br>• Number of patient with Acute Respiratory Distress Syndrome Recovery [ Time Frame: Up to 24 weeks ] |
| **Results/Publication** | None, status 13 August 2020 | None, status 13 Aug. 2020 |

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

| Active substance | Rezolsta (darunavir & cobicistat) & Dolquine | |
|---|---|---|
| **Sponsor/Collaborator** | AEMPS: Fundación Fls De Lucha Contra El Sida, Las Enfermedades Infecciosas Y La Promoción De La Salud Y La Ciencia, Spain | |
| **Trial Identifier** | EudraCT number: 2020-001031-27<br>Sponsor's Protocol Code Number: CQ4COV19<br>Trial acronym: PEP CoV-2 Study | |

| | | |
|---|---|---|
| **Active substance** | **Rezolsta (darunavir & cobicistat) & Dolquine** | |
| **Phase & Intention** | Phase 3,<br>• to evaluate the transmissibility of SARS-CoV-2 and reduction of disease progression within the study population over the course of the outbreak<br>• Explore the effect of the intervention on patient individual parameters<br>• Feasibility of implementation of treatment strategy<br>• Cost effectiveness of test-and-treat intervention<br>Title: Treatment of non-severe confirmed cases of COVID-19 and chemoprophylaxis of their contacts as prevention strategy: a Cluster Randomized Clinical Trial | |
| **Study design** | Single center randomised two-arm open label controlled trial with parallel group assignment | |
| **Status of trial** | Ongoing | |
| **Duration/End of Study** | 3 months | |
| **Study details** | | |
| **Number of Patients** | Total 3040<br>18 to 64 years: n=2432<br>Age 65 and older: n=608 | |
| **Disease severity** | Mild to moderate for confirmed cases<br>Asymptomatic to moderate for contacts of confirmed cases | |
| **Setting** | Not described, including outpatients | |
| **Location/Centres** | Spain, single center | |
| **Intervention drug name and dosage** | Rezolsta, oral use, consisting of Darunavir, 800 mg & cobicistat 150 mg plus Dolquine, oral use, consising of Hydroxychloroquine 200 mg | |
| **Comparator (drug name and dosage)** | Placebo / no intervention: standard SARS-CoV-2 surveillance | |
| **Duration of observation/ Follow-up** | Up to 5 months | |
| **Endpoints**<br>**Primary Outcomes**<br>**Secondary Outcomes** | Primary outcome up to 14 days after start of treatment:<br>• Ring prophylaxis effectiveness to reduce development of disease assessed by Incidence of secondary cases (basic case reproduction number) among contacts of a case<br>• Ring prophylaxis effectiveness to reduce transmissibility assessed by PCR conversion to positive of contacts that are negative at baseline<br>• Symptom type, duration and severity among SARS-CoV-2 positive cases<br><br>Secondary outcomes:<br>• Feasibility of implementation of treatment strategy up to 6 months<br>• Cost effectiveness of test-and-treat intervention up to 6 months<br>• The virological clearance rate of throat swabs, sputum, or lower respiratory tract secretions at days 3<br>• The mortality rate of subjects at weeks 2<br>• Proportion of participants that drop out of study<br>• Proportion of participants that show non-compliance with study drug | • |

| | | |
|---|---|---|
| **Active substance** | **Rezolsta (darunavir & cobicistat) & Dolquine** | |
| | • Proportion of participants that show non-compliance with public health measures<br>• Drug levels and biomarkers of severity of infection | |
| **Results/Publication** | None, status 13 August 2020 | |

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