EUnetHTA Joint Action 3 WP4

"Rolling Collaborative Review" of Covid-19 treatments

LOPINAVIR AND RITONAVIR FOR THE TREATMENT OF COVID-19

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Monitoring Report

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Disclaimer

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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
ARR	Absolute Risk Reduction
ATC	Anatomical Therapeutic Chemical [Classification System]
ATMP	Advanced therapy medicinal product
CI	Confidence Interval
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
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
RCT	Randomized Controlled Trial
REA	Relative Effectiveness Assessment
RR	Relative Risk
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** • 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	Lopinavir - HIV protease inhibitor used in a fixed-dose combination with ritonavir - provides the antiviral activity of Kaletra. Lopinavir is an inhibitor of the HIV-1 and HIV-2 proteases. Ritonavir is an HIV protease inhibitor that works by interfering with the reproductive cycle of HIV. Inhibition of HIV protease prevents cleavage of the gag-pol polyprotein resulting in the production of immature, non-infectious virus. It is also an inhibitor of cytochrome P-450 CYP3A.
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	Main outcome: • All-cause Mortality (Survival) Additional Outcomes: 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.pdf) 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. 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. 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 (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	Lopinavir-ritonavir as a mono- or combination therapy
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) 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

Lopinavir provides the antiviral activity of Kaletra. Lopinavir is an inhibitor of the HIV-1 and HIV-2 proteases. Inhibition of HIV protease prevents cleavage of the gag-pol polyprotein resulting in the production of immature, non-infectious virus.

Lopinavir/ritonavir (ATC-code: J05AR10) is indicated by the EMA in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infected adults, adolescents and children aged from 14 days and older.

The safety of lopinavir/ritonavir has been investigated in over 2600 HIV patients in Phase II-IV clinical trials, of which over 700 have received a dose of 800/200 mg (6 capsules or 4 tablets) once daily. Along with nucleoside reverse transcriptase inhibitors (NRTIs), in some studies, lopinavir/ritonavir was used in combination with efavirenz or nevirapine.

4 SUMMARY

The combination of lopinavir and ritonavir has been suggested as a possible treatment in the context of the COVID-19 pandemic recently.

The effectiveness and safety of lopinavir and ritonavir has been studied in a number of clinical trials. A moderate-sized, randomized trial failed to find a virologic or clinical benefit of lopinavir/ritonavir over SOC. Another study of lopinavir and ritonavir (combined with ribavirin) neither supports nor refutes the use of lopinavir/ritonavir with or without ribavirin in patients with COVID-19. Trials usually report their findings on low sample sizes.

There is extensive experience with the use of lopinavir/ritonavir in pregnant women with HIV, and generally, the drug has a good safety profile.

According to the database of *clinicaltrials.gov*, there are currently 61 studies (including in other indications than COVID-19) ongoing with lopinavir and ritonavir.

As of August 13th, 2020, no observational studies were completed with the combination of lopinavir and ritonavir to assess safety endpoints.

The conclusion is that based on the latest clinical data AbbVie recommends withdrawing Kaletra (lopinavir/ritonavir) from the EUnetHTA RCR list.

The University of Oxford, the World Health Organization and INSERM publicly announced that the Kaletra arms of the RECOVERY, SOLIDARITY and DISCOVERY studies in adults hospitalized with severe COVID-19 will be stopped given the data showed no beneficial effect.

Table 4-1 Summary of findings table for published RCTs related to effectiveness and safety of lopinavir-ritonavir

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with lopinavir-ritonavir	Risk with umifenovir				
Number of patients with any adverse events	238 per 1000	0 per 1000	RR 8.50 (0.50 to 143.32)	37	Low	
Number of patients with severe adverse events	48 per 1000	0 per 1000	RR 2.32 (0.10 to 53.42)	37	Low	

Source: [1].

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with Lopinavir+ritonavir+ ribavirina+ interferone beta-1b	Risk with lopinavir+ ritonavir				
All-cause mortality	0 per 1000	0 per 1000	-	127	Moderate	
Length of hospital stay, days	9 days (7 to 13)	14.5 days (9.3 to 16)	HR 2.72 (1.2 to 6.13)	127	Moderate	
Time to negative viral load, days (nasopharyngeal swab)	7 days (5 to 11)	12 days (8 to 15)	HR 4.37 (1.86 to 10.24)	127	Moderate	
Number of patients with any adverse events	477 per 1000	488 per 1000	RR 0.98 (0.67 to 1.43)	127	Moderate	
Number of patients with severe adverse events	0 per 1000	24 per 1000	RR 2.32 (0.10 to 53.42)	127	Moderate	

Source: [2].

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with Lopinavir+ritonavir	Risk with SoC				
All-cause mortality	214 per 1000	214 per 1000	RR 1,00 (0,83 to 1,21)	5127	Moderate	
Number of patients with any adverse events	467 per 1000	462 per 1000	RR 1,01 (0,68 to 1,49)	222	Low	
Number of patients with severe adverse events	190 per 1000	302 per 1000	RR 0,63 (0,39 to 1,02)	222	Low	
Clinical progression of COVID-19	381 per 1000	143 per 1000	RR 2,67 (0,40 to 17,74)	28	Low	

Source: [3, 4].

Table 4-2 Ongoing trials of single agents Lopinavir + Ritonavir

Active substance	**Lopinavir+ Ritonavir**	**Lopinavir + Ritonavir**	**Lopinavir + Ritonavir**	**Lopinavir + Ritonavir**
Sponsor/Collaborator	Tongji Hospital		Darrell Tan	
Trial Identifier	NCT04255017	NCT04315948	NCT04321174	ChiMCTR2000002940
Phase & Intention	Phase 4 study to Compare the Efficacy of Three Antiviral Drugs (Abidol Hydrochloride (Umifenovir), Oseltamivir and Lopinavir/Ritonavir) in the Treatment of 2019-nCoV Pneumonia.			
Study design	Single blinded, Prospective, Randomised Controlled Cohort Study	Adaptive, randomised open clinical trial to one of 4 treatments	Open label randomised trial	
Status of trial	Recruiting	Recruiting	Not yet recruiting	Not Recruiting
Duration/End of Study	Estimated study completion: July 1, 2020	Estimated study completion: March 2023	Estimated Primary Completion: March 31, 2021	Estimated study completion: Dec 31, 2020
Study details				
Number of Patients	N=400 patients with CT manifestation of viral pneumonia + mCoV positive randomised to Abidol hydrochloride, Oseltamivir, or Lopinavir/ritonavir	N=3200	N=1220	N=60 randomised to traditional Chinese medicine, Lopinavir/ritonavir, or traditional Chinese medicine + lopinavir/ritonavir
Disease severity			High risk close contact with a confirmed COVID-19 case	
Setting			Post exposure prophylaxis	
Location/Centres	Tongji Hospital, Hubei, China	EU: France, Spain, UK, Germany, Belgium, Netherlands, Luxembourg, Norway	Canada, Ontario	Wuhan, China
Intervention drug name and dosage				
Comparator (drug name and dosage)				
Duration of observation/ Follow-up				
Endpoints **Primary Outcomes** **Secondary Outcomes**	Rate of disease remission (Time Frame: two weeks) Time for lung recovery (Time Frame: two weeks)	Subject clinical status (on a 7-point ordinal scale) on Day 15	Microbiologic evidence of infection [Time Frame: 14 days]	The rate of remission
Results/Publication				
Active substance	Lopinavir+ Ritonavir	Lopinavir + Ritonavir	Lopinavir + Ritonavir	Lopinavir + Ritonavir
Sponsor/Collaborator			First Affiliated Hospital of Zhejiang University	
Trial Identifier	NCT04252885	NCT04276688	NCT04261907 ChiCTR2000029603	
Phase & Intention				

Active substance	Lopinavir+ Ritonavir	Lopinavir + Ritonavir	Lopinavir + Ritonavir	Lopinavir + Ritonavir
Study design	Open label	Phase 2 study Open-label randomised controlled trial	Randomised, Open-label, Multi-centre Clinical Trial	
Status of trial	Recruiting	Recruiting;	Recruiting (according to Chinese website that was updated)	
Duration/End of Study	Estimated study completion: July 31, 2020	Estimated study completion: July 31,2022	Estimated study completion: June 30, 2020	
Study details				
Number of Patients	125 patients Randomised 2:2:1 to Lopinavir /Ritonavir Tablets, Arbidol, or ordinary treatment	N=70 hospitalised patients with confirmed covid 19 infection randomised to Lopinavir/ritonavir, Ribavirin, or Interferon Beta-1B	N=160 patients with pneumonia caused by covid-19 randomised to ASC09/ritonavir or lopinavir/ritonavir	
Disease severity				
Setting				
Location/Centres	Guangdong, China	Hong Kong	Zhejiang University, China	
Intervention drug name and dosage				
Comparator (drug name and dosage)		Ribavirin, or Interferon Beta-1B		
Duration of observation/ Follow-up				
Endpoints Primary Outcomes Secondary Outcomes	The rate of virus inhibition	Time to negative nasopharyngeal swab (NPS) 2019-n-CoV coronavirus viral RT- PCR	The incidence of composite adverse outcome (time frame 14 days)	
Results/Publication				

Table 4-3 Ongoing trials of combination therapies Lopinavir + Ritonavir

Active substance	**Lopinavir + Ritonavir** in combination with Interferon-beta	**Lopinavir + Ritonavir vs Interferon 1β vs Low-dose Corticosteroids vs Hydroxychloroquine.**		
Sponsor/Collaborator		University of Oxford		
Trial Identifier	NCT04315948	EudraCT 2020-001113-21		
Phase & Intention				
Study design	Adaptive, randomised open clinical trial to one of 4 treatments	Adaptive, open label randomised controlled trial.		
Status of trial	Recruiting	Ongoing		
Duration/End of Study	Estimated study completion: March 2023	Estimated Primary Completion: March 31, 2021		
Study details				
Number of Patients	EU: France, Spain, UK, Germany, Belgium, Netherlands, Luxembourg, Norway	N=2000 hospitalised patients with covid-19 are randomised to 1 of 5 treatment arms in addition to usual standard of care:		

Active substance	**Lopinavir + Ritonavir** in combination with Interferon-beta	**Lopinavir + Ritonavir vs Interferon 1β vs Low-dose Corticosteroids vs Hydroxychloroquine.**		
	N=3200			
Disease severity				
Setting				
Location/Centres		UK		
Intervention drug name and dosage		Lopinavir-Ritonavir		
Comparator (drug name and dosage)		No additional treatment, Interferon 1β, Low-dose Corticosteroids, or Hydroxychloroquine.		
Duration of observation/ Follow-up				
Endpoints **Primary Outcomes** **Secondary Outcomes**	Subject clinical status (on a 7-point ordinal scale) on Day 15	In-hospital death, discharge, and need for ventilation. Time frame 28 days		
Results/Publication				

5 REFERENCES

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