EUnetHTA Joint Action 3 WP4

“Rolling Collaborative Review” of Covid-19 treatments

BARICITINIB FOR THE TREATMENT OF COVID-19

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Monitoring Report

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V 2.1	**February 2021**	Literature searches, Literature screening, Data extraction
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Major changes from previous version

Chapter, page no.	Major changes from version 2.0
Chapter 3	1 new prospective observational study published
Chapter 4	Summary of safety from observational studies (AE and SAE) of baricitinib added
Chapter 6	New search strategy for observational studies added

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
CI	Confidence Interval
DOI	Declaration of interest
ECMO	extracorporeal membrane oxygenation
EMA	European Medicines Agency
EUA	Emergency Use Authorisation
EUnetHTA	European Network of Health Technology Assessment
FDA	Food and Drug Administration
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HR	Hazard Ratio
ICD	International Classification of Diseases
JAK	Janus kinase
MD	Mean Difference
MAH	Marketing Authorization Holder
MeSH	Medical Subject Headings
NA	Not applicable
NIAID	National Institute of Allergy and Infectious Diseases
NMA	Network Meta-Analysis
NR	Not reported
nRCT	Non-RCT
OR	Odds Ratio
RCT	Randomized Controlled Trial
RCR	Rolling Collaborative Review
REA	Relative Effectiveness Assessment
RR	Relative Risk
SAE	Serious Adverse Event
SD	Standard Deviation
SMD	Standardized Mean Difference
SoF	Summary of Findings
STAT	Signal transducers and activators of transcription
WP4	Work Package 4

1 OBJECTIVE

The aim of this EUnetHTA Rolling Collaborative Review is

- to inform health policy at the national/regional and at the European level at an early stage in the life-cycle of therapies which interventions are currently undergoing clinical trials,
- to monitor (ongoing studies and their results) permanently - in the format of a Living Document - potential therapies against covid-19,
- to present comparative data on effectiveness and safety of potential therapies and
- to support preparations for an evidence-based purchasing of regional/ national health politicians, if necessary.

To avoid redundancies and duplication, the EUnetHTA Rolling Collaborative Review will reuse sources from international initiatives to collect information and data on Covid-19 treatments.

The scope of the Rolling Collaborative Review is of descriptive nature. These **EUnetHTA Rolling Collaborative Reviews are not meant to substitute a joint Relative Effectiveness Assessment (REA)** adhering to the agreed procedures and aiming at critical appraisal of the clinical evidence based on the Submission Dossier submitted by the (prospective) Marketing Authorization Holder (MAH).

2 METHODS

This Rolling Collaborative Review is prepared according to the project plan ("Rolling Collaborative Review (RCR) on Covid-19 treatments: Project description and planning", published on the EUnetHTA website) and will be updated monthly. Monthly updates are published on the EUnetHTA Covid-19 Website (https://eunethta.eu/covid-19-treatment/) and on the EUnetHTA Rolling Collaborative Review Sharepoint page each 15th of the month.

2.1 Scope

Table 2-1 Scope of the RCR

Description	Project Scope
Population	**Disease** • SARS-CoV-2 is a novel coronavirus causing a respiratory illness termed Covid-19. The full spectrum of Covid-19 ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multi-organ failure, and death. **ICD-Codes** (https://www.who.int/classifications/icd/covid19/en) • An emergency ICD-10 code of 'U07.1 COVID-19, virus identified' is assigned to a disease diagnosis of COVID-19 confirmed by laboratory testing. • An emergency ICD-10 code of 'U07.2 COVID-19, virus not identified' is assigned to a clinical or epidemiological diagnosis of COVID-19 where laboratory confirmation is inconclusive or not available. • Both U07.1 and U07.2 may be used for mortality coding as cause of death. See the International guidelines for certification and classification (coding) of COVID-19 as cause of death following the link below. • In ICD-11, the code for the confirmed diagnosis of COVID-19 is RA01.0 and the code for the clinical diagnosis (suspected or probable) of COVID-19 is RA01.1. **MeSH-terms** • COVID-19, Coronavirus Disease 2019 **Target population** (https://www.covid19treatmentguidelines.nih.gov/overview/management-of-covid-19/)

	• Asymptomatic or pre-symptomatic Infection: Individuals who test positive for SARS-CoV-2 by virologic testing using a molecular diagnostic (e.g., polymerase chain reaction) or antigen test, but have no symptoms. • Mild Illness: Individuals who have any of the various signs and symptoms of COVID 19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnoea, or abnormal chest imaging. • Moderate Illness: Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO2) ≥94% on room air at sea level. • Severe Illness: Individuals who have respiratory frequency >30 breaths per minute, SpO2 <94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mmHg, or lung infiltrates >50%. • Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.
Intervention	Baricitinib is a selective and reversible inhibitor of Janus kinase (JAK)1 and JAK2
Comparison	Any active treatment, placebo, or standard of care. **Rationale**: Since there is no gold standard treatment any comparator is acceptable as well as the above listed interventions.
Outcomes	<u>Main outcome:</u> • All-cause Mortality (Survival) <u>Additional Outcomes:</u> Efficacy: • Length of hospital stay, • Viral burden (2019-nCoV RT-PCR negativity), • Clinical progression (WHO Clinical Progression Scale measured daily over the course of the study), • Rates of hospitalization and of patients entering ICU, • Duration of mechanical ventilation, • Quality of life. Safety: • Adverse events (AE), • Severe adverse events (SAE), • Withdrawals due to AEs, • Most frequent AEs, • Most frequent SAEs. **Rationale:** We will give priority according to the Core Outcome Set for Clinical Trials on Coronavirus Disease 2019 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102592/pdf/main.pdfc) and A minimal common outcome measure set for COVID-19 clinical research from the WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection.
Study design	Efficacy: randomised controlled trials (RCT) Safety: observational studies (comparative or single-arm prospective studies and registries)

2.2 Sources of information

According to the project plan, this Rolling Collaborative Review is based on three main sources of information, as described below:

1. Summary of findings (SoF) table for published RCTs related to effectiveness and safety:

This table is based on the living systematic review and Network Meta-Analysis (NMA) created by the partnering institute of DEPLazio: find the PROSPERO protocol here. DEPLazio provides updates for the SoF table on a monthly basis to the EUnetHTA partners authoring the respective Rolling CR documents who are integrating this information accordingly.

The literature search is conducted in the following databases:

- PubMed
- MEDLINE, accessed via OVID
- Embase, accessed via OVID

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

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

- medRxiv Health Sciences
- bioRxiv Biology

In addition to the sources and strategies described above, registers of ongoing studies are screened. Key conferences and conference proceedings are considered. Appendix Table 6-1 describes in detail the sources searched, the search terms used and the dates at which the searches are executed.

Data extraction, Risk of bias assessment, data synthesis:

Two reviewers from DEPLazio are screening search results, assessing full texts of studies and extract study characteristics and outcome data according to pre-defined criteria. The process of study selection is depicted as a flow diagram in Appendix Figure 6-1.

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

Dichotomous outcomes are analysed by calculating the relative risk (RR) for each trial with the uncertainty in each result being expressed by its 95% confidence interval (CI). Continuous outcomes are analysed by calculating the mean difference (MD) with the relative 95% CI when the study used the same instruments for assessing the outcome.

The standardised mean difference (SMD) is applied when studies used different instruments. Pairwise meta-analyses is performed for primary and secondary outcomes using a random-effects model in RevMan for every treatment comparison [2]. Network meta-analysis (NMA) is performed for the primary outcome. For rating the certainty of the evidence, the GRADE approach is being used [3].

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

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

The literature search is conducted on a monthly basis.

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

Population	See project Scope
Intervention	Baricitinib is a selective and reversible inhibitor of Janus kinase (JAK)1 and JAK2
Comparison	Any active treatment, placebo, or standard of care.
Outcomes	See project Scope
Study design	Inclusion criteria: Prospective non-randomised controlled trials, prospective case series (i.e. comparative or single-arm prospective studies), registries Exclusion criteria: retrospective studies, case studies/ case reports, observational studies that do not report safety data

Two researchers from NIPHNO carry out title and abstract screening and assess the full texts of all potentially eligible studies. The study selection process is depicted in a flow diagram (Appendix Figure 6-2).

One researcher of AIHTA 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/

Inclusion criteria: Randomised controlled trials, Controlled trials

One researcher of AIHTA is searching and extracting the data for the eligible studies. At the drafting stage of each update, the author team verifies whether the status of previously identified studies has changed. This is done by verifying the date of the last update posted in the trial registers. In addition, trial register IDs of all previously identified studies are entered in both PubMed and Google (google.com) to verify if previously identified studies have been published since the last update. In Google, the first 10 hits are screened for this purpose.

Search methods are described in more detail in Appendix Table 6-3.

Data are presented in tabular form.

3 ABOUT THE TREATMENT

3.1 Mode of Action

Baricitinib is a selective and reversible inhibitor of Janus kinase (JAK)1 and JAK2. Janus kinases (JAKs) are enzymes that transduce intracellular signals from cell surface receptors for a number of cytokines and growth factors involved in haematopoiesis, inflammation and immune function. Within the intracellular signalling pathway, JAKs phosphorylate and activate signal transducers and activators of transcription (STATs), which activate gene expression within the cell. Baricitinib modulates these signalling pathways by partially inhibiting JAK1 and JAK2 enzymatic activity, thereby reducing the phosphorylation and activation of STATs [4].

3.2 Regulatory Status

Baricitinib (Olumiant) is indicated in the EU for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to or who are intolerant to one or more disease-modifying anti-rheumatic drugs. Baricitinib may be used as monotherapy or in combination with methotrexate. It is also indicated for the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy [4].

Baricitinib (Olumiant) has not been approved by the European Medicines Agency (EMA) or the American Food and Drug Administration (FDA) for COVID-19.

On November 19, 2020, the FDA issued an Emergency Use Authorization (EUA) for the distribution and emergency use of baricitinib to be used in combination with remdesivir in hospitalised adult and paediatric patients two years of age or older with suspected or laboratory confirmed COVID-19 who require supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) [5].

EUA was based on review of the data from the randomised, double-blind, placebo-controlled trial conducted by the National Institute of Allergy and Infectious Diseases (NIAID) comparing baricitinib in combination with remdesivir to remdesivir alone (ACTT-2 study, NCT04401579), details can be found below [6].

The recommended dosage of baricitinib under the EUA is: Adults and paediatric patients 9 years of age and older: 4 mg once daily; Paediatric patients 2 years to less than 9 years of age: 2 mg once daily. The optimal duration of treatment is unknown. The recommended total treatment duration of baricitinib is 14 days or until hospital discharge, whichever comes first. Serious Side Effects: serious venous thrombosis, including pulmonary embolism, and serious infections have been observed in COVID-19 patients treated with baricitinib and are known adverse drug reactions of baricitinib.

US COVID-19 Treatment Guidelines
The US COVID-19 Treatment Guidelines Panel stated that there are **insufficient data** to recommend either **for or against** baricitinib in combination with remdesivir therapy in hospitalised patients with COVID-19 disease, in cases where corticosteroids can be used instead [7]:

In the rare circumstances where corticosteroids cannot be used, the Panel recommends using baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalised, non-intubated patients who require oxygen supplementation **(BIIa)**.

The Panel **recommends against** the use of baricitinib in the absence of remdesivir, except in a clinical trial **(AIII)**.

There are insufficient data for the Panel to recommend either for or against the use of baricitinib in combination with corticosteroids for the treatment of COVID-19. Since both agents are potent immunosuppressants, there is potential for an additive risk of infection.

3.3 Level of Evidence

On December 11, 2020, Kalil et al. [6] published results from the Adaptive COVID-19 Treatment Trial (**ACTT-2**) (**NCT NCT04401579**), a multicentre, double-blind, randomized, placebo-controlled trial evaluating baricitinib plus remdesivir with remdesivir alone in hospitalised adults with Covid-19 in eight countries. All the patients received remdesivir (≤10 days) and either baricitinib (≤14 days) or placebo (control). The primary outcome was the time to recovery. The key secondary outcome was clinical status at day 15. Detailed characteristics of the study can be found in Table 4-1.

A total of 1033 patients underwent randomisation (with 515 assigned to combination treatment and 518 to control). The intention-to-treat population included 706 patients with moderate disease (ordinal score of 4 or 5 [not receiving ventilation]) and 327 with severe disease (ordinal score of 6 or 7 [receiving non-invasive or invasive ventilation]). A total of 498 patients in the combination group and 495 in the control group completed the trial through day 29, recovered, or died.

Patients receiving baricitinib had a median time to recovery of 7 days (95% confidence interval 6 to 8), as compared with 8 days (95% CI, 7 to 9) with control (rate ratio for recovery, 1.16; 95% CI, 1.01 to 1.32; p=0.03), and 30% higher odds of improvement in clinical status at day 15 (odds ratio, 1.3; 95% CI, 1.0 to 1.6). When analysed according to the severity entered at the time of randomisation (moderate vs. severe), the hazard ratio was 1.15 (95% CI, 1.00 to 1.31; p=0.047). Patients receiving high-flow oxygen or non-invasive ventilation at enrolment had a time to recovery of 10 days with combination treatment and 18 days with control (rate ratio for recovery, 1.51; 95% CI, 1.10 to 2.08). Among patients with a baseline score of 4 (no oxygen) and 5 (supplemental oxygen), the rate ratio for recovery was 0.88 (95% CI, 0.63 to 1.23) and 1.17 (95% CI, 0.98 to 1.39), respectively. For those receiving mechanical ventilation or ECMO at enrolment (baseline ordinal score of 7), the rate ratio for recovery was 1.08 (95% CI, 0.59 to 1.97).

The odds of improvement in clinical status at day 15 as assessed with the ordinal scale were greater in the combination group than in the control group (odds ratio for improvement, 1.3; 95% CI, 1.0 to 1.6). Patients with a baseline ordinal score of 6 who received combination treatment were most likely to have clinical improvement at day 15 (odds ratio, 2.2; 95% CI, 1.4 to 3.6).

The 28-day mortality was 5.1% in the combination group and 7.8% in the control group (hazard ratio for death, 0.65; 95% CI, 0.39 to 1.09).

The median time to an improvement by one category on the ordinal scale was 6 days in the combination group and 8 days in the control group (rate ratio, 1.21; 95% CI, 1.06 to 1.39), and the median time to discharge or a National Early Warning Score of 2 or less for 24 hours was 6 days and 7 days in the respective groups (rate ratio, 1.24; 95% CI, 1.07 to 1.44).

The incidence of new use of oxygen was lower in the combination group than in the control group (22.9% vs. 40.3%; difference, -17.4 percentage points; 95% CI, -31.6 to -2.1), as was the incidence of new use of mechanical ventilation or ECMO (10.0% vs. 15.2%; difference, -5.2 percentage points; 95% CI, -9.5 to -0.9).

The median number of days of receipt of mechanical ventilation or ECMO among the 128 patients in whom these interventions were started after enrolment or who died with no observed new use was 16 days in the combination group and 27 days in the control group (difference, -11.0; 95% CI, -18.3 to -3.7). The incidence of progression to death or non-invasive or invasive ventilation was lower in the combination group than in the control group (22.5% vs. 28.4%; rate ratio, 0.77; 95% CI, 0.60 to 0.98), as was the incidence of progression to death or invasive ventilation (12.2% vs. 17.2%; rate ratio, 0.69; 95% CI, 0.50 to 0.95).

Grade 3 or 4 adverse events occurred in 207 patients (40.7%) in the combination group and 238 (46.8%) in the control group. The most common grade 3 or 4 adverse events occurring in at least 5% of all patients were hyperglycaemia, anaemia, decreased lymphocyte count, and acute kidney injury. The incidence of these adverse events was similar in the two treatment groups. Serious adverse events were less frequent in the combination group than in the control group (16.0% vs. 21.0%; difference, -5.0 percentage points; 95% CI, -9.8 to -0.3; p=0.03), as were new infections (5.9% vs. 11.2%; difference, -5.3 percentage points; 95% CI, -8.7 to -1.9; p=0.003).

Hasan et al. 2021 [8] published results from a prospective observational control study conducted on COVID-19 hospitalised patients with moderate-to-severe COVID-19 pneumonia in Bangladesh.

Seventeen patients in the “no loading dose (LND) group” (control) received baricitinib 4 mg daily orally for 2 weeks, whereas 20 patients in the “loading dose (LD) group” (case) received baricitinib 8mg single dose orally as a loading dose on day 1 and then 4 mg daily orally from days 2 to 14. All patients in both groups tolerated baricitinib therapy well with no mild-to-serious adverse events (AEs) during the study period. No bacterial or fungal or any other opportunistic infections, hepatic or haematological toxicity were observed in the groups.

4 SUMMARY

4.1 Effectiveness and Safety evidence from RCTs

High certainty evidence from one recently published RCT showed that baricitinib in combination with remdesivir does not reduce All-cause mortality (RR 0.65, 95% CI 0.40 to 1.07; 25 fewer per 1.000, 95% CI from 43 fewer to 5 more), but reduces the Number of patients with any adverse events (RR 0.85, 95% CI 0.73 to 0.99; 65 fewer per 1.000, 95% CI from 117 fewer to 4 fewer) as well as the Number of patients with serious adverse events (RR 0.76, 95% CI 0.59 to 0.99; 50 fewer per 1.000, 95% CI from 86 fewer to 2 fewer) (Table 4-1). The most common grade 3 or 4 adverse events occurring in at least 5% of all patients were hyperglycaemia, anaemia, decreased lymphocyte count, and acute kidney injury, with the incidence similar in the two treatment groups.

Patients treated with baricitinib in combination with remdesivir had a significant reduction in median time to recovery from 8 to 7 days compared to remdesivir. Patients receiving high-flow oxygen or non-invasive ventilation at enrolment had a time to recovery of 10 days with combination treatment and 18 days with remdesivir alone (rate ratio for recovery, 1.51; 95% CI, 1.10 to 2.08). Patients treated with baricitinib in combination with remdesivir were more likely to have a better clinical status at Day 15 compared to patients treated with remdesivir. Patients with a baseline ordinal score of 6 who received combination treatment were most likely to have clinical improvement at day 15 (odds ratio, 2.2; 95% CI, 1.4 to 3.6).

The incidence of new use of oxygen was statistically significantly lower in the combination group than in the remdesivir group (22.9% vs. 40.3%; difference, -17.4 percentage points; 95% CI, -31.6 to -2.1), as was the incidence of new use of mechanical ventilation or ECMO (10.0% vs. 15.2%; difference, -5.2 percentage points; 95% CI, -9.5 to -0.9). The incidence of progression to death or non-invasive or invasive ventilation was statistically significantly lower in the combination group than in the remdesivir group (22.5% vs. 28.4%; rate ratio, 0.77; 95% CI, 0.60 to 0.98), as was the incidence of progression to death or invasive ventilation (12.2% vs. 17.2%; rate ratio, 0.69; 95% CI, 0.50 to 0.95).

4.2 Safety evidence from observational studies

One publication related to a prospective observational study of baricitinib treatment in COVID-19 patients was found, but without an additional control group of patients with standard care/placebo. No mild-to-serious adverse events were observed, as well as bacterial or fungal or any other opportunistic infections, hepatic or hematological toxicity, in baricitinib groups with or without a high oral loading dose.

4.3 Ongoing studies

There are several ongoing RCTs, evaluating baricitinib alone (6 RCTs and one nRCT) or in combination with other pharmaceuticals (5 RCTs), in Covid-19 hospitalised patients, in ClinicalTrials.gov, ISRCTN and EUdraCT registers (details listed in Table 4-4, Table 4-5, Table 4-6).

4.4 Scientific conclusion about status of evidence generation

High certainty evidence from one published RCT, ACTT-2 trial, showed that baricitinib in combination with remdesivir does not reduce All-cause mortality, but reduces the Number of patients with any adverse events as well as the Number of patients with serious adverse events.

Combination of baricitinib and remdesivir significantly reduced median time to recovery in hospitalised COVID-19 patients from eight days to seven days, compared to remdesivir treatment alone. Patients who required high-flow oxygen or non-invasive ventilation during hospitalisation appeared to have had the largest benefit: their median time to recovery was shortened from eighteen days to ten days. Participants' conditions at day 15 was significantly improved when they received the two therapeutics combined. The incidence of progression to death or non-invasive or invasive ventilation was statistically significantly lower in the combination of baricitinib and remdesivir vs remdesivir alone, as was the incidence of progression to death or invasive ventilation.

Further RCTs examining baricitinib alone or in combination with other pharmaceuticals for the treatment of COVID-19 hospitalised patients are under way. Published, peer-reviewed, high-quality evidence from ongoing RCTs are awaited, to further assess the effectiveness and safety of baricitinib in COVID-19 patients.

On November 19, 2020, the FDA issued an Emergency Use Authorization (EUA) for the distribution and emergency use of baricitinib to be used in combination with remdesivir in hospitalised adult and paediatric patients two years of age or older with suspected or laboratory confirmed COVID-19 who require supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

Table 4-1 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of baricitinib + remdesivir

Question: Should Baricitinib-Remdesivir compared to Standard treatment (placebo/remdesivir) be used for COVID-19 patients?
Setting: Inpatient

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with placebo+remdesivir	Risk with baricitinib+remdesivir					
All-cause mortality	71 per 1000	46 per 1000	**RR 0.65** (0.40 to 1.07)	**25 fewer per 1.000** (from 43 fewer to 5 more)	1033 (1 RCT) [6]	⊕⊕⊕⊕ HIGH	Baricitinib in combination with remdesivir does not reduce All-cause mortality
Number of patients with any adverse event	432 per 1000	367 per 1000	**RR 0.85** (0.73 to 0.99)	**65 fewer per 1.000** (from 117 fewer to 4 fewer)	1016 (1 RCT) [6]	⊕⊕⊕⊕ HIGH	Baricitinib in combination with remdesivir reduces the risk of AE
Number of patients with serious adverse events	210 per 1000	159 per 1000	**RR 0.76** (0.59 to 0.99)	**50 fewer per 1.000** (from 86 fewer to 2 fewer)	1013 (1 RCT) [6]	⊕⊕⊕⊕ HIGH	Baricitinib in combination with remdesivir reduces the risk of serious AE

Source: [9]
Abbreviations: RR=Risk ratio; CI=Confidence interval; AE=Adverse event; SAE=Serious adverse event

Table 4-2 Study characteristics of included RCTs

Author, year, reference number/Study name/Study ID	Kalil 2020, [6], NCT04401579 (ACTT-2)
Study design, study phase	RCT, phase 3
Centres (single centre or multicentre), country, setting	Multicentre (67 trial sites), 8 countries worldwide, Hospital
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	A total of 1033 patients underwent randomization. Mean age of the patients was 55.4 years, and 63.1% were male. 706 patients with moderate disease (ordinal score of 4 or 5 [not receiving ventilation]) and 327 with severe disease (ordinal score of 6 or 7 [receiving non-invasive or invasive ventilation]).
Inclusion criteria	Radiographic infiltrates by imaging study, peripheral oxygen saturation (SpO2) ≤94% on room air, or requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO); a laboratory-confirmed SARS-CoV-2 infection as determined by a positive reverse transcription, polymerase-chain-reaction (RT-PCR) assay result from any respiratory specimen collected; agreeing not to participate in another COVID-19 treatment clinical trial through Day 29 and practicing heterosexual abstinence or using study-specified contraception through Day 29 for women of childbearing potential
Exclusion criteria	Alanine aminotransferase (ALT) or an aspartate aminotransferase (AST) > 5 times the upper limit of the normal range; impaired renal function as determined by calculating an estimated glomerular filtration rate (eGFR), or need for haemodialysis or hemofiltration; allergy to study product; pregnancy or breast-feeding; and anticipated discharge from the hospital or transfer to another hospital within 72 hours of enrolment.
Intervention (generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	Baricitinib (a 4-mg daily dose (either orally [two 2-mg tablets] or through a nasogastric tube) for 14 days or until hospital discharge) + Remdesivir (intravenously as a 200-mg loading dose on day 1, followed by a 100-mg maintenance dose administered daily on days 2 through 10 or until hospital discharge or death); 515 assigned to combination treatment baricitinib plus remdesivir
Comparator(s) (standard care or generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	Remdesivir (intravenously as a 200-mg loading dose on day 1, followed by a 100-mg maintenance dose administered daily on days 2 through 10 or until hospital discharge or death) + matching oral placebo; 518 assigned to remdesivir and placebo
Primary Outcome(s)	Time to recovery
Patient-relevant secondary outcome(s)	Clinical status at day 15; time to improvement by one or two categories from the ordinal score at baseline; clinical status, as assessed on the ordinal scale at days 3, 5, 8, 11, 15, 22, and 29; mean change in the ordinal score from day 1 to days 3, 5, 8, 11, 15, 22, and 29; time to discharge or to a National Early Warning Score of 2 or less (on a scale from 0 to 20, with higher scores indicating greater clinical risk) that was maintained for 24 hours, whichever occurred first; change in the National Early Warning Score from day 1 to days 3, 5, 8, 11, 15, 22, and 29; number of days of receipt of supplemental oxygen, non-invasive ventilation or high-flow oxygen, and invasive ventilation or extracorporeal membrane oxygenation (ECMO) up to day 29 (if these were being used at baseline); the incidence and duration of new use of oxygen, new use of non-invasive ventilation or high-flow oxygen, and new use of invasive ventilation or ECMO; duration of hospitalization up to day 29 (patients who remained hospitalized at day 29 had a value of 28 days); and mortality at 14 and 28 days after enrolment. Secondary safety outcomes: grade 3 and 4 adverse events and serious adverse events that occurred through day 29, discontinuation or temporary suspension of trial-product administration for any reason, and changes in assessed laboratory values over time.

Follow-up (days, months)	29 days
Sponsor/ lead institution	National Institute of Allergy and Infectious Diseases, US

Table 4-3 Summary of safety from observational studies (AE and SAE) of baricitinib

Author, year	**Hasan, 2021 [8]**
Country	Bangladesh
Sponsor/ lead institution	Square Hospitals Ltd., Dhaka, Bangladesh
Intervention/Product (drug name)	Baricitinib 8mg single dose orally as a loading dose on day 1 and then 4 mg daily orally from days 2 to 14
Dosage	See above
Comparator	Baricitinib 4 mg daily orally for 2 weeks
Study design	Prospective observational study
Setting	Hospital
Number of pts	37 (17 in no loading dose group -NLD and 20 in loading dose group-LD)
Inclusion criteria	Presence of SARS-CoV 2 in the nasal/oral swabs; no previous history of COVID-19 infection; having at least 3 of the following symptoms: fever, cough, tiredness, sore throat, anosmia, respiratory distress, and myalgia; evidence of pneumonia in radiological diagnosis
Exclusion criteria	More than 10 days from onset of symptoms; patient with pregnancy; any history of trauma or surgical procedure within the last 3 months of admission; any history of acute/chronic autoimmune disease; evidence of bacterial or fungal coinfection
Age of patients (yrs)	NLD group 52 (50.5–62) vs LD group 59 (49.8–69)
Disease severity	Patients with moderate-to-severe COVID-19 pneumonia
Follow-up (months)	14 days
Loss to follow-up, n (%)	None
RoB	High
Overall AEs, n (%)	None observed
Serious AE (SAE), n (%)	None observed
Most frequent AEs n (%)	See above
Most frequent SAEs, n (%)	See above
AEs of special interest, n (%)	See above
Death as SAE, n (%)	See above
Withdrawals due AEs, n (%)	See above

Table 4-4 Ongoing trials of single agent baricitinib

Trial Identifier/registry ID(s)/contact	NCT04346147 (Covid19COVINIB)	NCT04390464 EudraCT 2020-001354-22, ISRCTN 11188345 (TACTIC-R)	NCT04393051 (BARICIVID-19)	NCT04421027, EudraCT 2020-001517-21 (COV-BARRIER)
Study design, study phase	RCT, phase 2	RCT, phase 4	RCT, phase 2	RCT, phase 3
Recruitment status	Recruiting	Recruiting	Recruiting	Recruiting
Number of Patients, Disease severity*	165, COVID-19 pneumonia	1167, Pre-ICu patients	126, Hospitalised	1400, Hospitalised
Setting (hospital, ambulatory...)	Hospital	Hospital	Hospital	Hospital
Intervention (generic drug name and dosage)	Baricitinib 4 mg alone Imatinib 400 mg alone	Baricitinib + Standard of care Ravulizumab + Standard of care	Baricitinib 2 mg	Baricitinib 4 mg
Comparator (standard care or generic drug name and dosage)	Supportive treatment	Standard of care	Standard treatment	Placebo
Primary Outcome(s)	Time to clinical improvement [Time Frame: baseline to day 14]	Time to incidence of the composite endpoint of: Death, Mechanical ventilation, ECMO, Cardiovascular organ support, or Renal failure [Time Frame: up to Day 14]	Need of invasive mechanical ventilation [Time Frame: after 7 and 14 days of treatment]	Percentage of Participants who Die or Require Non-Invasive Ventilation/High-Flow Oxygen or Invasive Mechanical Venti extracorporeal membrane oxygenation [ECMO]) [Time Frame: Day 1 to Day 28]
Sponsor/ lead institution, country (also, country of recruitment if different)	Hospital Universitario de Fuenlabrada, Spain	Cambridge University Hospitals NHS Foundation Trust, UK	Azienda Ospedaliero, Universitaria Pisana, Italy	Eli Lilly and Company, Argentina, Brazil, Germany, India, Italy, Japan, Korea, Republic of, Mexico, Puerto Rico, Russian Federation, Kingdom, United States

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

Table 4-5 Ongoing trials of single agent baricitinib, continued

Trial Identifier/registry ID(s)/contact	NCT04321993	EUdraCT 2020-001246-18 (CORIMUNO-19)	EudraCT 2020-001052-18 (ACTT/EU/UK)
Study design, study phase	nRCT, phase 2	RCT, phase 2/3	RCT, phase 3
Recruitment status	Recruiting	Ongoing	Ongoing
Number of Patients, Disease severity*	800, Mixed (Moderate to severe)	1000, Severe and critical	800, Hospitalised
Setting (hospital, ambulatory...)	Hospital	Hospital	Hospital
Intervention (generic drug name and dosage)	Baricitinib 2 mg	Immune modulatory drugs, baricitinib, sarilumab, tocilizumab, anakinra, eculizumab, secukinumab, bevacizumab...	Baricitinib Remdesivir
Comparator (standard care or generic drug name and dosage)	Standard of care	See above	Placebo
Primary Outcome(s)	Clinical status of subject at day 15 (on a 7 point ordinal scale). [Time Frame: Up to 15 days]	For the group 1 of patients not requiring ICU: Survival without needs of ventilator utilization (including Non invasive ventilation) at day 14; Early end point : OMS progression scale < or = 5 at day 4, For the group 2 of patients requiring ICU: Cumulative incidence of successful tracheal extubation (defined as duration extubation > 48h) at day 14; Early end point: OMS progression scale >7 at day 4	Day of recovery (defined as the first day on which the subject satisfies one of the three categories from the ordinal scale)
Sponsor/ lead institution, country (also, country of recruitment if different)	Lisa Barrett, Nova Scotia Health Authority, Canada	Assistance Publique - Hôpitaux de Paris, France	Regents of the University of Minnesota, US; EU/UK

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

Table 4-6 Ongoing trials of combination therapies with baricitinib

Trial Identifier/registry ID(s)/contact	NCT04640168 (ACTT-4)	NCT04373044	EudraCT 2020-001854-23 (AMMURAVID)	EudraCT 2020-001321-31	NCT04693026
Study design, study phase	RCT, phase 3	RCT, phase 2	RCT, phase 2/3	RCT, phase 2	RCT, phase 3
Recruitment status	Recruiting	Recruiting	Ongoing	Ongoing	Recruiting
Number of Patients, Disease severity*	1500, Hospitalised	144, Mixed (Moderate to severe)	1400, Moderate	165, Severe	150, Severe
Setting (hospital, ambulatory...)	Hospital	Hospital	Hospital	Hospital	Hospital
Intervention (generic drug name and dosage)	Baricitinib + Remdesivir; Remdesivir + Dexamethasone	Baricitinib plus Hydroxychloroquine	Baricitinib, Tocilizumab, Sarilumab, Situximab, Canakinumab, Metilpredisolone, in addition to Hydroxychloroquine	Hydroxychloroquine together with baricitinib, imatinib or early lopinavir / ritonavir	Baricitinib+Remdesivir
Comparator (standard care or generic drug name and dosage)	Remdesivir + Placebo	Hydroxychloroquine plus placebo	See above	See above	Remdesivir+Tocilizumab
Primary Outcome(s)	The proportion of subjects not meeting criteria for one of the following two ordinal scale categories at any time: 8) Death; 7) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) [Time Frame: Day 1 through Day 29]	Proportion of patients requiring invasive mechanical ventilation or dying [Time Frame: Up to 14 days]	Proportion of patients with PaO2/FiO2 <200 mmHg at day 10 in each intervention arm as compared to the control arm	Different laboratory parameters, Microbiological parameters, Clinical variables, Clinical management variables	Time to Clinical Improvement (TTCI) [Time Frame: Following randomization 30 days]
Sponsor/ lead institution, country (also, country of recruitment if different)	National Institute of Allergy and Infectious Diseases (NIAID), US	University of Southern California, US	Italian Medicine Agency, Italy	Hospital Universitario de Fuenlabrada, Spain	M Abdur Rahim Medical College and Hospital, Bangladesh

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

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6 APPENDIX

6.1 Search strategy to identify randomised controlled trials

DEPLazio, the Department of Epidemiology of the Regional Health Service Lazio in Rome, Italy is responsible for setting up the search strategy to identify randomised controlled trials (RCTs). DEPLazio performed a search in Medline, PubMed, and Embase, which has been updated weekly from March 2020 (Table 6-1). DEPLazio searched medRxiv.org (https://www.medrxiv.org/), bioRxiv.org (https://www.bioRxiv.org/), and arXiv.org (https://www.arXiv.org/) for preprints of preliminary reports of randomised trials. The Cochrane Covid-19 Study Register (https://covid-19.cochrane.org/), ClinicalTrials.gov (www.clinicaltrials.gov) and World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en/) were search in addition. Other sources included journal alerts, contact with researchers, websites such as Imperial College, London School of Hygiene and Tropical Medicine, and Eurosurveillance. We applied no restriction on language of publication.

We included randomised controlled trials (RCTs) comparing any pharmacological intervention against another pharmacological intervention or placebo or standard care (SC), for the treatment of individuals with Covid-19. We excluded studies comparing two dosages of the same pharmacological agent. We did not exclude studies on individuals with a comorbid disorder.

Four authors independently screened the references retrieved by the search, selected the studies, and extracted the data, using a predefined data-extraction sheet. The same reviewers discussed any uncertainty regarding study eligibility and data extraction until consensus was reached; conflicts of opinion were resolved with other members of the review team. Two authors independently assessed the risk of bias of the included studies with the Cochrane tool. Three authors used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, to evaluate the strength of evidence.

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

Table 6-1 Search strategy to identify randomised controlled studies

Database	URL	Search line / Search terms	Date of search
Pubmed	pubmed.ncbi.nlm.nih.gov	1. (((((((("Coronavirus"[Mesh]) OR (coronavirus*[Title/Abstract] OR coronovirus*[Title/Abstract] OR coronavirinae*[Title/Abstract] OR Coronavirus*[Title/Abstract] OR Coronovirus*[Title/Abstract] OR Wuhan*[Title/Abstract] OR Hubei*[Title/Abstract] OR Huanan[Title/Abstract] OR "2019-nCoV"[Title/Abstract] OR 2019nCoV[Title/Abstract] OR nCoV2019[Title/Abstract] OR "nCoV-2019"[Title/Abstract] OR "COVID-19"[Title/Abstract] OR COVID19[Title/Abstract] OR "CORVID-19"[Title/Abstract] OR CORVID19[Title/Abstract] OR "WN-CoV"[Title/Abstract] OR WNCoV[Title/Abstract] OR "HCoV-19"[Title/Abstract] OR HCoV19[Title/Abstract] OR CoV[Title/Abstract] OR "2019 novel*"[Title/Abstract] OR Ncov[Title/Abstract] OR "n-cov"[Title/Abstract] OR "SARS-CoV-2"[Title/Abstract] OR "SARSCoV-2"[Title/Abstract] OR "SARSCoV2"[Title/Abstract] OR "SARS-CoV2"[Title/Abstract] OR SARSCov19[Title/Abstract] OR "SARS-Cov19"[Title/Abstract] OR "SARSCov-19"[Title/Abstract] OR "SARS-Cov-19"[Title/Abstract] OR Ncovor[Title/Abstract] OR Ncorona*[Title/Abstract] OR Ncorono*[Title/Abstract] OR NcovWuhan*[Title/Abstract] OR NcovHubei*[Title/Abstract] OR NcovChina*[Title/Abstract] OR NcovChinese*[Title/Abstract])) OR ((((respiratory*[Title/Abstract] AND (symptom*[Title/Abstract] OR disease*[Title/Abstract] OR illness*[Title/Abstract] OR condition*))[Title/Abstract] OR "seafood market*"[Title/Abstract] OR "food market*")[Title/Abstract] AND (Wuhan*[Title/Abstract] OR Hubei*[Title/Abstract] OR China*[Title/Abstract] OR Chinese*[Title/Abstract] OR Huanan*))[Title/Abstract])) OR ("severe acute respiratory syndrome*")) OR ((corona*[Title/Abstract] OR corono*)[Title/Abstract] AND (virus*[Title/Abstract] OR viral*[Title/Abstract] OR virinae*)[Title/Abstract])) AND (((((((randomized controlled trial [pt]) OR (controlled clinical trial [pt])) OR (randomized [tiab])) OR (placebo [tiab])) OR (clinical trials as topic [mesh: noexp])) OR (randomly [tiab])) OR (trial [ti]))) NOT (animals [mh] NOT humans [mh]) AND (2019/10/01:2020[dp])	05/02/2020

Database	URL	Search line / Search terms	Date of search
Ovid MEDLINE(R) ALL)	ovidsp.dc2.ovid.com	1. exp coronavirus/ 2. ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw. 3. (coronavirus* or coronovirus* or coronavirinae* or Coronavirus* or Coronovirus* or Wuhan* or Hubei* or Huanan or "2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCoV or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese*).ti,ab,kw. 4. (((respiratory* adj2 (symptom* or disease* or illness* or condition*)) or "seafood market*" or "food market*") adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw. 5. ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (China* or Chinese* or Huanan*)).ti,ab,kw. 6. "severe acute respiratory syndrome*".ti,ab,kw. 7. or/1-6 8. randomized controlled trial.pt. 9. controlled clinical trial.pt. 10. random*.ab. 11. placebo.ab. 12. clinical trials as topic.sh. 13. random allocation.sh. 14. trial.ti. 15. or/8-14 16. exp animals/ not humans.sh. 17. 15 not 16 18. 7 and 17 19. limit 18 to yr="2019 -Current"	05/02/2020
OVID EMBASE	ovidsp.dc2.ovid.com	1. exp Coronavirinae/ or exp Coronavirus/ 2. exp Coronavirus infection/ 3. ((("Corona virinae" or "corona virus" or Coronavirinae or coronavirus or COVID or nCoV) adj4 ("19" or "2019" or novel or new)) or (("Corona virinae" or "corona virus" or Coronavirinae or coronavirus or COVID or nCoV) and (wuhan or china or chinese)) or "Corona virinae19" or "Corona virinae2019" or "corona virus19" or "corona virus2019" or Coronavirinae19 or Coronavirinae2019 or coronavirus19 or coronavirus2019 or COVID19 or COVID2019 or nCOV19 or nCOV2019 or "SARS Corona virus 2" or "SARS Coronavirus 2" or "SARS-COV-2" or "Severe Acute Respiratory Syndrome Corona virus 2" or "Severe Acute Respiratory Syndrome Coronavirus 2").ti,ab,kw. 4. or/1-3 5. Clinical-Trial/ or Randomized-Controlled-Trial/ or Randomization/ or Single-Blind-Procedure/ or Double-Blind-Procedure/ or Crossover-Procedure/ or Prospective-Study/ or Placebo/ 6. (((clinical or control or controlled) adj (study or trial)) or ((single or double or triple) adj (blind$3 or mask$3)) or (random$ adj (assign$ or allocat$ or group or grouped or patients or study or trial or distribut$)) or (crossover adj (design or study or trial)) or placebo or placebos).ti,ab. 7. 5 or 6 8. 4 and 7 9. limit 8 to yr="2019 -Current"	05/02/2020

6.2 Search strategy to identify observational studies

As of October 2020, NIPHNO is responsible for setting up the search strategy to identify observational studies.

From September to December 2020, we received records that EPPI Centre has screened after searching weekly in Medline and Embase (until beginning of November 2020), from November onwards Microsoft Academics Graph (MAG). We supplemented these studies with a weekly search in Scopus (Elsevier). Detailed descriptions of the EPPI and NIPHNO searches are given at their websites [10, 11]. The retrieved hits were imported to a reference management tool, Endnote (Clarivate Analytics), for deduplication. We then searched the EndNote database using the generic names and synonyms for the included COVID-19 drugs.

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

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

Table 6-2 Search strategy to identify observational studies

Database	URL	Search terms / Search modality	Date of search
Embase 1974 to 2021 Ovid MEDLINE(R) ALL 1946 to 2021		Lines 1 and 2 are copies of Ovid's Expert searches for covid-19 in MEDLINE and Embase 1 ((((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.) or (2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus* or corona virus or pandemi*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp. or COVID-19.rx,px,ox,sh. or severe acute respiratory syndrome coronavirus 2.os.) use medall [COVID-19 in MEDLINE] 2 ((((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.) or (coronavirus disease 2019 or 2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or severe acute respiratory syndrome coronavirus 2 or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus* or corona virus or pandemi*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp. or (coronavirus disease 2019 or	From 1/9/2020 until 3/2/2021 Covering publication dates 01. September 2020

		severe acute respiratory syndrome coronavirus 2).sh,dj.) use oemezd [COVID-19 in Embase] 3 (COVID-19 serotherapy/ or Immunization, Passive/ or tocilizumab/ or camostat/ or nafamostat/ or AP301 peptide/ or Interleukin 1 Receptor Antagonist Protein/ or alunacedase alfa/ or darunavir/ or favipiravir/ or sarilumab/ or exp Interferons/ or gimsilumab/ or canakinumab/ or REGN-COV-2/ or bamlanivimab/ or baricitinib/ or molnupiravir/ or Aspirin/ or mavrilimumab/ or exp Vitamin D/dt or Vitamin D Deficiency/dt or Ivermectin/) use medall [MeSH-terms for drugs in MEDLINE] 4 (Hyperimmune globulin/dt or tocilizumab/ or camostat/ or camostat mesilate/ or nafamstat/ or solnatide/ or anakinra/ or darunavir/ or favipiravir/ or sarilumab/ or exp Interferon/ or gimsilumab/ or canakinumab/ or baricitinib/ or acetylsalicylic acid/ or mavrilimumab/ or exp Vitamin D/dt or Vitamin D Deficiency/dt or ivermectin/) use oemezd [Emtree-terms for drugs in Embase] 5 ((convalescent adj (plasma or sera or serum)) or serotherap* or ((atoxin or hyperimmunoglobulin or hyperimmune globulin or hyperimmune gammaglobulin) adj therap*) or passive immuni?ation or (tocilizumab or atlizumab or (MRA adj monoclonal antibod*) or MSB-11456 or MSB11456 or R-1569 or R1569 or RO-4788533 or RO4788533 or Actemra or Roactemra) or (camostat* or FOY-305 or FOY305 or FOY S 980) or (nafamostat or nafamstat or FUT-175 or FUT175) or (solnatide or AP301 or AP-301 or (TIP adj peptide)) or (anakinra or ((interleukin 1 or IL1 or IL-1) adj2 (antagonist or block* or inhibitor*)) or IL-1Ra or Kineret) or (alunacedase or APN01 or APN-01 or rhACE2 or recombinant human angiotensin converting enzyme 2 or GSK-2586881 or GSK2586881) or (darunavir or prezista or TMC-114 or TMC114 or UIC-94017 or UIC94017) or (favipi?avir or T-705 or T705 or Avigan or Olumiant) or (sarilumab or REGN-88 or REGN88 or SAR-153191 or SAR153191 or Kevzara) or (interferon* or (IFN adj1 (alpha* or beta* or gamma*)) or novaferon or CL-884 or CL884) or (gimsilumab or KIN-1901 or KIN1901 or morab-022 or morab022) or (canakinumab or ACZ-885 or ACZ885 or immunoglobulin G1 or Ilaris) or (REGN-CoV-2 or REGN-CoV2 or antibody cocktail or ((casirivimab or REGN-10933 or REGN10933) and (imdevimab or REGN-10987 or REGN10987))) or (bamlanivimab or LY-CoV555 or LYCoV555 or LY-3819253 or LY3819253) or (baricitinib or LY-3009104 or LY3009104 or INCB-028050 or INCB028050 or INCB-28050 or INCB28050 or Olumiant) or (molnupiravir or MK-4482 or MK4482 or EIDD-2801 or EIDD2801) or (aspirin or acetylsalicylic acid) or (mavrilimumab or immunoglobulin G4 or CAM-3001 or CAM3001) or ((vitamin? D? or D?-vitamin?) adj4 (high-dose* or highdose* or supplement*)) or (ivermect* or MK-933 OR MK933)).mp,bt,ot,du,dy,tn,nm. [other	

		terms (title, abstract, author keywords and more) in MEDLINE and Embase] 6 (202009* or 202010* or 202011 or 202012* or 202101* or 202102*).dt. use medall [time limits in MEDLINE] 7 (202009* or 202010* or 202011 or 202012* or 202101* or 202102*).dc. use oemezd [time limits in Embase] 8 (1 and (3 or 5) and 6) use medall 9 (2 and (4 or 5) and 7) use oemezd	

6.3 Search strategy to identify ongoing studies

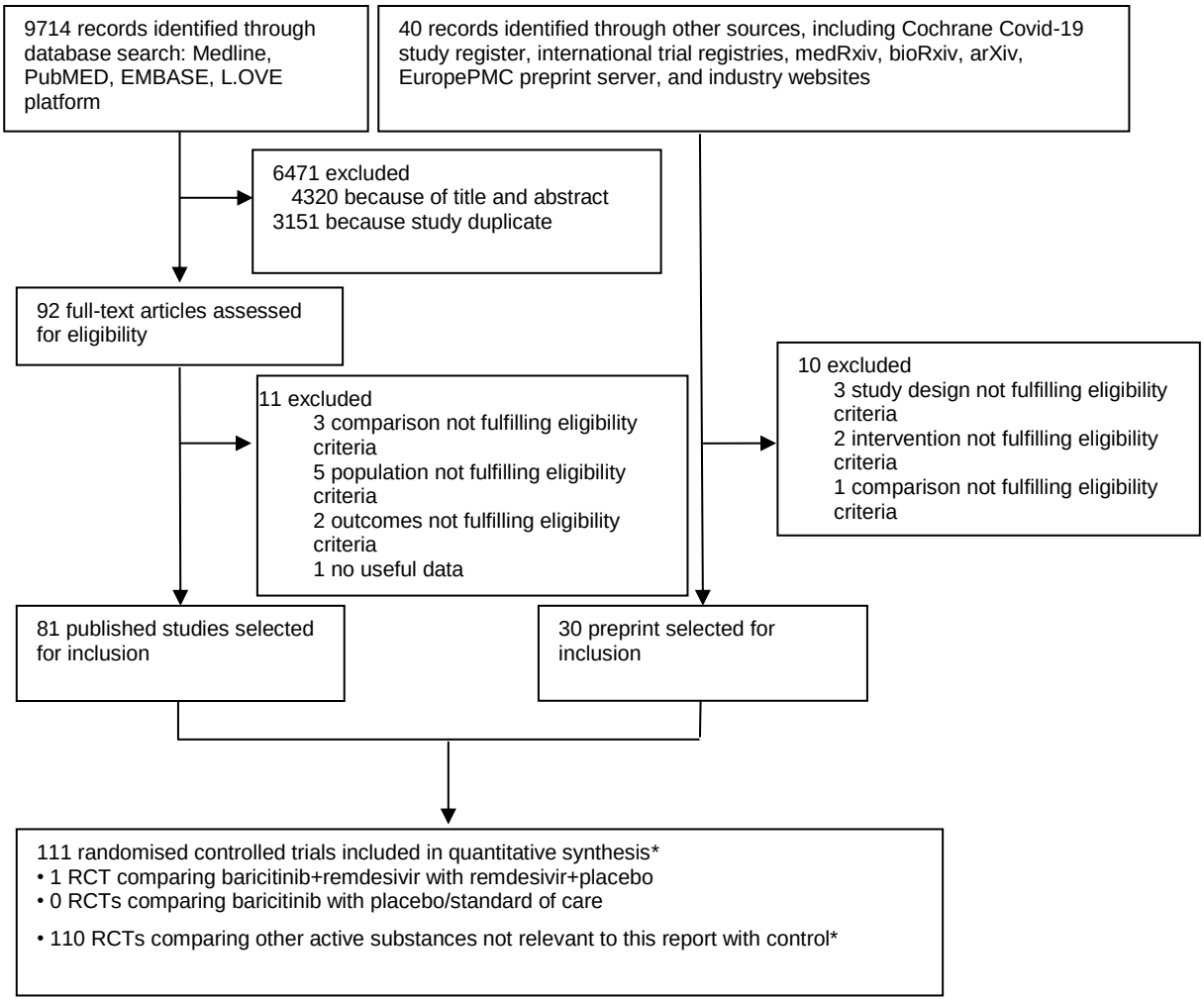
AIHTA is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and baricitinib are described in Appendix Table 6-3.

Table 6-3 Search strategy to identify ongoing studies

Database	URL	Search line / search terms	Date of search	Hits retrieved
ClinicalTrials.gov	https://clinicaltrials.gov/	"Basic search mode*" [adapt if you used "Advanced search mode"] Terms used at Condition or disease: • covid-19 Terms used at "other terms": • baricitinib • Olumiant	10/02/2021	15 0 new
ISRCTN	https://www.isrctn.com/	Basic search mode [adapt if you used "Advanced search mode"] Search terms: 1. covid-19 and baricitinib 2. covid-19 and Olumiant 3. SARS-CoV-2 and baricitinib 4. SARS-CoV-2 and Olumiant	10/02/2021	2 0 new
European Clinical Trials Registry	https://www.clinicaltrialsregister.eu/	Basic search mode [adapt if you used "Advanced search mode"] Search terms: 1. covid-19 and baricitinib 2. covid-19 and Olumiant 3. SARS-CoV-2 and baricitinib 4. SARS-CoV-2 and Olumiant	10/02/2021	10 0 new

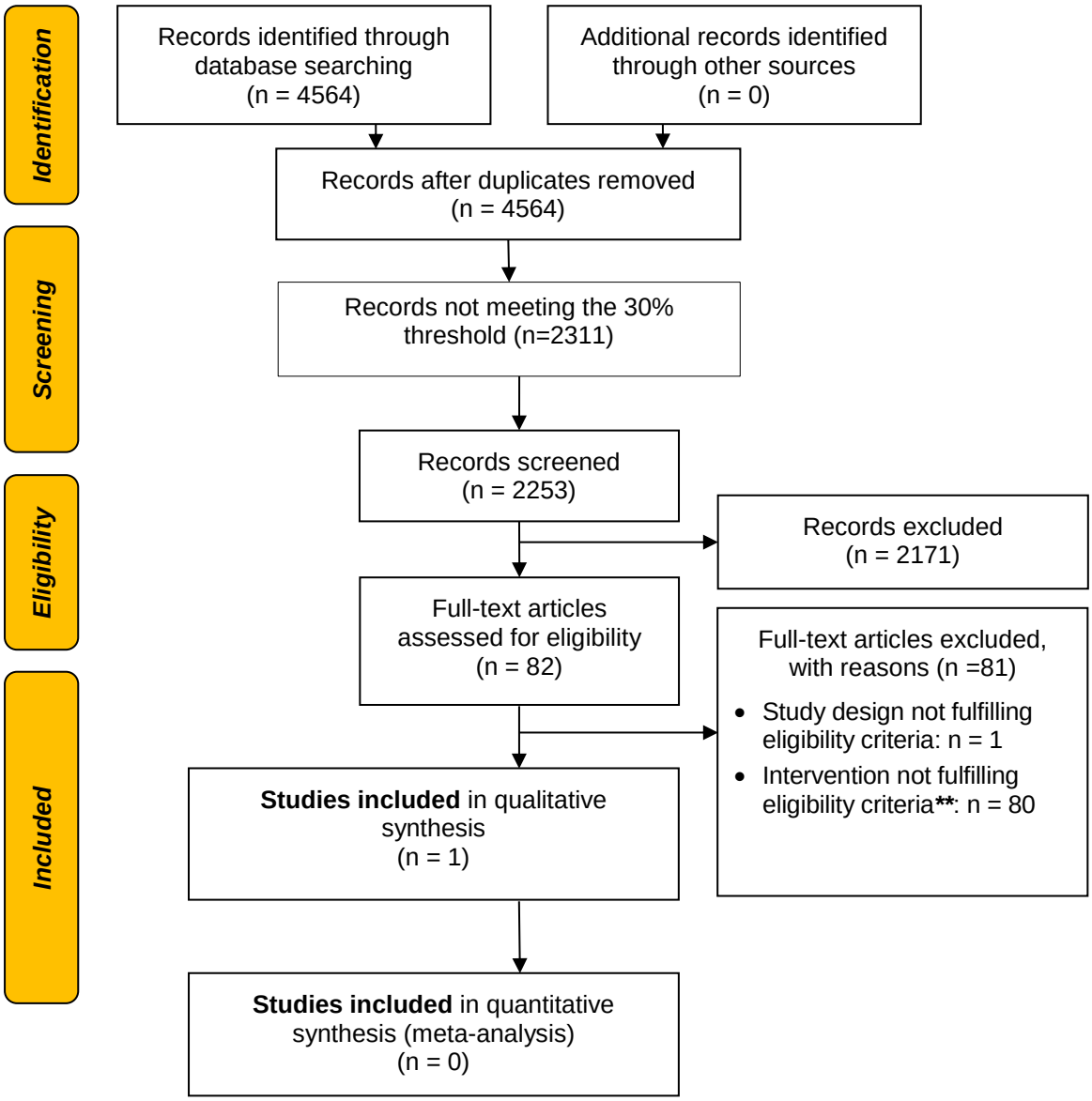
***** In Basic Search mode, one term was added to the field "condition or disease" and one term in the field "other terms".

6.4 Flow diagrams



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

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



Appendix Figure 6-2. Flow diagram depicting the selection process of observational studies
****** studies evaluating active substances relevant to other EUnetHTA rolling collaborative reviews