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"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 2.0	**20/01/2021**	Second version
V 3.0	**15/02/2021**	Third version
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V 5.0	**20/04/2021**	Fifth version
V 6.0	**17/05/2021**	Sixth version
V 7.0	**15/06/2021**	Seventh version
V 8.0	**15/07/2021**	Eight version
V 9.0	**16/08/2021**	Ninth version
V 9.1	**September 2021**	Literature searches, Literature screening, Data extraction
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V 9.3	**11/09/2021**	Check of data extraction and analysis
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Major changes from previous version

Chapter, page no.	Major changes from version 9.0
Chapter 3 and 4	US COVID-19 Treatment Guidelines Panel update Additional data from published article related to COV-BARRIER trial added

Disclaimer

The content of this "Rolling Collaborative Review" (RCR) represents a consolidated view based on the consensus within the Authoring Team; it cannot be considered to reflect the views of the European Network for Health Technology Assessment (EUnetHTA), EUnetHTA's participating institutions, the European Commission and/or the Consumers, Health, Agriculture and Food Executive Agency or any other body of the European Union. The European Commission and the Agency do not accept any responsibility for use that may be made of the information it contains.

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Conflict of interest

All authors and co-authors involved in the production of this living document have declared they have no conflicts of interest in relation to the technology and comparator(s) assessed according to the EUnetHTA declaration of interest (DOI) form. Conflict of Interest was evaluated following the EUnetHTA Procedure Guidance for handling DOI form (https://eunethta.eu/doi).

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LIST OF ABBREVIATIONS

AE	Adverse Event
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) - not mandatory from June 2021

2.2 Sources of information

According to the project plan, this Rolling Collaborative Review is based on two main mandatory sources and one optional source of information, as described below:

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

From June 2021, AIHTA has updated the SoF table monthly with the use of covid-nma.com (COVID-NMA initiative: find the living review protocol here).

In addition, from June 2021, the literature search is used from COVID-NMA initiative according living review protocol [1-3] or is conducted by authors of this RCR 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.

Data extraction, Risk of bias assessment, data synthesis:

The search results are screened, full texts of studies are assessed and study characteristics and outcome data are extracted according to pre-defined criteria.

Risk of bias is assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [4] or reused from one living SR/MA source [2]. Each study was presented with the Cochrane Risk of bias 2 (RoB 2) tool for RCTs [5].

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 [6]. Network meta-analysis (NMA) is performed for the primary outcome. For rating the certainty of the evidence, the GRADE approach is being used [7].

From June 2021, if new RCTs are published, certainty of evidence has been reused from already published living systematic reviews/meta-analysis (SRs/MA) source from the international COVID-NMA initiative.

- Sources: https://covid-nma.com/ for SoF

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

From June 2021, only RCTs are used for assessment of safety.

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 6-1.

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 [8].

3.2 Regulatory Status

Baricitinib (Olumiant, Eli Lilly Nederland B.V.) 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 [8].

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

On July 28, 2021 the FDA issued revision to Emergency Use Authorization (EUA) for the distribution and emergency use of baricitinib to be used alone for the treatment of COVID-19 in hospitalised adults and pediatric patients two years of age or older requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) [9]. The EUA for baricitinib no longer requires baricitinib be used in combination with remdesivir. The use of baricitinib in combination with remdesivir is not contraindicated under the terms and conditions of this authorization. Previous EUA [10] was based on a 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 [11].

This July revision to the EUA for baricitinib was supported by data from the clinical trial of hospitalised patients with COVID-19, where baricitinib showed a reduction in the proportion of patients who died through 28 days of follow-up compared to patients treated with the standard of care for COVID-19 alone (COV-BARRIER, NCT04421027); details can be found below [12]. 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.

On April 29, 2021, EMA started evaluating an application to extend the use of baricitinib (Olumiant) to include treatment of COVID-19 in hospitalised patients from 10 years of age who require supplemental oxygen [13].

US COVID-19 Treatment Guidelines

The US COVID-19 Treatment Guidelines Panel (last update August 25, 2021), for hospitalised and requires oxygen delivery through a high-flow device or non-invasive ventilation, recommends **using** either **baricitinib (BIIa)** or **tocilizumab (BIIa)** (listed alphabetically) in combination with **dexamethasone** alone or **dexamethasone plus remdesivir** for the treatment of COVID-19 patients who were recently hospitalised with rapidly increasing oxygen needs and systemic inflammation. The Panel recommends **tofacitinib** as an alternative to **baricitinib** only when baricitinib is not available or not feasible to use **(BIIa)**.

The Panel **recommends against** the use of **baricitinib** in combination with **tocilizumab** for the treatment of COVID-19 **(AIII)**. Because both baricitinib and tocilizumab are potent immunosuppressants, there is the potential for an additive risk of infection [14].

3.3 Level of Evidence

Baricitinib plus remdesivir compared with remdesivir alone in hospitalised adults with COVID-19

On December 11, 2020, Kalil et al. [11] 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 4-2.

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 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).

Baricitinib monotherapy + standard treatment compared to placebo + standard treatment

Marconi et al. 2021 [12] published as **pre-print** and on September 3, 2021 **in scientific journal [15]** results from phase 3, global, double-blind, randomized, placebo-controlled trial **COV-BARRIER** (**NCT04421027**). 1525 **hospitalised adults** with COVID-19 **receiving standard of care (SOC)** were randomly assigned (1:1) to once-daily **baricitinib 4-mg** (n=764) or **placebo** (n=761) for up to 14 days. **SOC included systemic corticosteroids in ~79% of participants (dexamethasone ~90%).** The primary endpoint was the proportion who progressed to high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation, or death by day 28. A key secondary endpoint was all-cause mortality by day 28. All-cause mortality by day 60 was an exploratory endpoint.

Participants were stratified according to the following baseline factors: disease severity, age, region, and use of corticosteroids for COVID-19. Baseline demographics and disease characteristics were balanced among treatment groups. The mean age of the participants was 57.6 years (SD 14.1), 63.1% were male, and enrollment was global. Countries contributing >10% of enrollment included Brazil (21%), United States (21%), Mexico (18.4%), and Argentina (13.6%); participants were also enrolled in Europe, India, Japan, Korea and Russia. Overall, 61.6% of participants were white, 11.7% were Asian, and 5.0% were black or African American (with 10.3% of US participants of black or African American race). The majority (83.3%) of participants had symptoms ≥7 days prior to enrollment. Clinical status at baseline was OS 4 (hospitalised, not requiring supplemental oxygen) for 12.3%, OS 5 (hospitalised, requiring supplemental oxygen) for 63.4% and OS 6 (hospitalised, receiving noninvasive ventilation or high-flow oxygen devices) for 24.4% of participants. At baseline, the majority (79.3%) of participants received systemic corticosteroids, of which 91.3% received dexamethasone; 18.9% of participants received remdesivir. Of the participants that received remdesivir, 91.6% also received corticosteroids. The majority of participants (99.7%) had ≥1 pre-existing comorbid condition [12]. Detailed characteristics of the study can be found in Table 4-2.

27.8% of participants receiving baricitinib vs 30.5% receiving placebo progressed (primary endpoint, odds ratio 0.85, 95% CI 0.67-1.08; p=0.18). The 28-day all-cause mortality was 8% (n=62) for baricitinib and 13% (n=100) for placebo (hazard ratio [HR] 0.57 [95% CI 0.41–0.78]; nominal p=0.0018), a 38.2% relative reduction in mortality; one additional death was prevented per 20 baricitinib-treated participants. Reduction in mortality was significant for participants on high-flow oxygen/non-invasive ventilation at baseline [17.5%, baricitinib vs 29.4%, placebo; HR 0.52, 95% CI 0.33-0.80; nominal p=0.007]). A significant reduction in mortality was observed with baricitinib compared with placebo for the pre-specified subgroups of participants treated at baseline with systemic corticosteroids (9.3% vs 13.9%; HR 0.63, 95% CI 0.45-0.89; nominal p=0.017), without systemic corticosteroids (3.3% vs 11.0%; HR 0.28, 95% CI 0.10-0.77; nominal p=0.011), or without remdesivir (8.0% vs 13.8%; HR 0.52, 95% CI 0.36-0.74; nominal p=0.001); for the 18.9% of participants with concomitant remdesivir treatment at baseline (91.6% also with corticosteroids) a numerical reduction in mortality was observed [12]. The 60-day all-cause mortality was 10% (n=79) for baricitinib and 15% (n=116) for placebo (HR 0.62 [95% CI 0.47–0.83]; p=0.0050) [15].

The frequency of adverse events, serious adverse events, serious infections, and venous thromboembolic events was similar between groups [12].

334 (45%) of 750 participants in the baricitinib group and 334 (44%) of 752 in the placebo group had at least one treatment-emergent adverse event, and serious adverse events were observed in 110 (15%) participants in the baricitinib group and 135 (18%) in the placebo group. The frequencies of deaths reported as being due to adverse events (ie, rather than disease progression, 12 [2%] participants in the baricitinib group *vs* 31 [4%] in the placebo group) and of discontinuation of study treatment due to adverse events (56 [7%] *vs* 70 [9%]) were numerically lower with baricitinib than placebo. Serious infections were reported in 64 (9%) baricitinib-treated participants and 74 (10%) placebo-treated participants. Among participants using corticosteroids at baseline, serious infections occurred at a similar frequency between groups (58 [10%] of 605 *vs* 63 [11%] of 590. There were similar distributions of positively adjudicated venous thromboembolic events (20 [3%] *vs* 19 [3%]) and major adverse cardiovascular events (eight [1%] *vs* nine [1%]) in the baricitinib and placebo groups and no reports of gastrointestinal perforations [15].

On August 3, 2021 Eli Lilly and Company announced results from an additional cohort of 101 adult critical COVID-19 patients from the above mentioned COV-BARRIER trial. In this sub-study, patients with COVID-19 on mechanical ventilation or extracorporeal membrane oxygenation (ECMO) who received baricitinib plus standard of care were 46 percent less likely to die by Day 28 compared to patients who received placebo plus standard of care (nominal p-value=0.0296; hazard ratio [HR] [95% CI] = 0.54 [0.31, 0.96]; analysis not adjusted for multiplicity). The cumulative proportion of patients who died by Day 28 was 39.2 percent (n/N: 20/51) in the baricitinib arm versus 58 percent in the placebo arm (n/N: 29/50). Similar mortality benefit was observed by Day 60 (HR [96% CI] = 0.56 [0.33, 0.97]) with a cumulative proportion of death of 45.1 percent (n/N: 23/51) for baricitinib compared to 62.0 percent for placebo (n/N: 31/50). These findings are consistent with the reduction in mortality observed in the overall COV-BARRIER patient population. By Day 28, the frequency of adverse events, serious adverse events and serious infections were similar in the baricitinib group (88%, 50% and 44%, respectively) compared to placebo (95.9%, 71.4% and 53.1%, respectively). Venous thromboembolic events were reported in 6% of patients treated with baricitinib and 6.1% of patients treated with placebo. No new safety signals were identified [16].

From June 2021, only RCTs are used for assessment of safety. Previous evidence from prospective observational studies, can be found in EUnetHTA JA3 version, May 2021.

4 SUMMARY

4.1 Effectiveness and Safety evidence from RCTs

Baricitinib plus remdesivir compared with remdesivir alone in hospitalised adults with COVID-19

High certainty evidence from one 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), and does not increase 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 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 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).

Baricitinib monotherapy (in addition to standard care) compared to placebo (in addition to standard care) in hospitalised adults with COVID-19

Results from COVID-NMA Meta-analysis show that baricitinib monotherapy compared to placebo significantly reduced COVID-19 related all-cause mortality at day 28 (Risk ratio 0.62, 95% CI 0.46 to 0.83).

Baricitinib monotherapy compared to placebo does not significantly increase clinical improvement (Risk ratio 1.00, 95% CI 0.95 to 1.05), adverse events (Risk ratio 1.00, 95% CI 0.89 to 1.12) and serious adverse events (Risk ratio 0.81, 95% CI 0.64 to 1.02).

Summary of finding table and certainty of evidence will be provided in the next versions of this report.

Unpublished new results from phase 3 COV-BARRIER sub-study in critical COVID-19 patients, announced by manufacturer in August 2021, showed 46% risk reduction in mortality by Day 28 and 44% risk reduction in mortality by Day 60 for baricitinib-treated patients on mechanical ventilation or ECMO, compared to placebo.

4.2 Safety evidence from observational studies

From June 2021, only RCTs are used for assessment of safety. Previous evidence from prospective observational studies can be found in EUnetHTA JA3 RCR18 version 6.0, May 2021.

4.3 Ongoing studies

There are several ongoing RCTs, evaluating baricitinib alone (7 RCTs and 1 nRCT) or in combination with other pharmaceuticals (4 RCTs), in Covid-19 hospitalised patients, in ClinicalTrials.gov, ISRCTN and EUdraCT registers (details listed in Table 4-3, Table 4-4,

Table **4-5**). One is the RECOVERY (Randomised Evaluation of COVid-19 thERapY) trial, led by the University of Oxford [17].

4.4 Scientific conclusion about status of evidence generation

Baricitinib in combination with remdesivir
High certainty evidence from one published RCT, ACTT-2 trial, showed that baricitinib in combination with remdesivir does not reduce all-cause mortality, and does not increase the number of patients with any adverse events as well as the number of patients with serious adverse events in hospitalised COVID-19 patients.

Combination of baricitinib and remdesivir significantly reduced the 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 significantly lower in the combination of baricitinib and remdesivir vs remdesivir alone, as was the incidence of progression to death or invasive ventilation.

Baricitinib monotherapy in addition to standard treatment (predominantly dexamethasone)
Evidence from one new published RCT, COV-BARRIER trial, showed that baricitinib monotherapy in addition to standard treatment (predominantly dexamethasone) compared to placebo significantly reduced COVID-19 related all-cause mortality in hospitalised patients by day 28 and day 60. Reduction in mortality was the most prominent for participants on high-flow oxygen/non-invasive ventilation at baseline). Baricitinib compared to placebo does not significantly increase clinical improvement, adverse events and serious adverse events.

Unpublished new results from phase 3 COV-BARRIER sub-study in critical COVID-19, announced by manufacturer in August 2021, showed significant risk reduction in mortality by Day 28 and by Day 60 for baricitinib-treated patients on mechanical ventilation or ECMO, compared to placebo.

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 July 28, 2021 the FDA issued revision to Emergency Use Authorization (EUA) for the distribution and emergency use of baricitinib to be used alone for the treatment of COVID-19 in hospitalised adults and pediatric patients two years of age or older requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

On April 29, 2021, EMA started evaluating an application to extend the use of baricitinib (Olumiant) to include treatment of COVID-19 in hospitalised patients from 10 years of age who require supplemental oxygen.

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) [11]	⊕⊕⊕⊕ 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) [11]	⊕⊕⊕⊕ 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) [11]	⊕⊕⊕⊕ HIGH	Baricitinib in combination with remdesivir reduces the risk of serious AE

Source: [18]
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, [11], NCT04401579 (ACTT-2)	Marconi et al. 2021 [12], NCT04421027 (COV-BARRIER)
Study design, study phase	RCT, phase 3	RCT, phase 3
Centres (single centre or multicentre), country, setting	Multicentre (67 trial sites), 8 countries worldwide, Hospital	Multicenter / Argentina, Brazil, Germany, India, Italy, Japan, Mexico, Russia, South Korea, Spain, UK, USA (including Puerto Rico), 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]).	Randomized 1525 participants (n_1=764 / n_2= 761) Mean age: 57.7 963 males Severity: Mild: n=186 / Moderate: n=962/ Severe: n=370 Critical: n=0
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	≥18 years of age; hospitalized with laboratory confirmed SARS-CoV-2 infection; had evidence of pneumonia or active, symptomatic COVID-19; had ≥1 elevated inflammatory marker (C reactive protein, D-dimer, lactate dehydrogenase, ferritin); participants requiring baseline oxygen support (later protocol amenendment implemented after enrollment had started)
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.	Requiring invasive mechanical ventilation (National Institute of Allergy and Infectious Disease Ordinal Scale [NIAID-OS] 7) at study entry; receiving immunosuppressants (high dose corticosteroids, biologics, T cell or B cell-targeted therapies, interferon, or JAK inhibitors); received convalescent plasma or intravenous immunoglobulin for COVID-19
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	Baricitinib 4 mg orally once daily for 14 days or until discharge from hospital

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	Placebo
Primary Outcome(s)	Time to recovery	Proportion of participants who progressed to high-flow oxygen or non-invasive ventilation, invasive mechanical ventilation or extracorporeal membrane oxygenation, or death by day 28
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.	Key secondary outcomes were adjusted for multiplicity and included the following (evaluated at days 1-28, unless otherwise specified): all-cause mortality day 28 and day 60, proportion of participants with ≥1-point improvement on NIAID-OS or discharge from hospital at days 4, 7, 10, and 14; number of ventilator-free days; time to recovery (NIAID-OS 1-3); overall improvement on the NIAID-OS evaluated at days 4, 7, 10, and 14; duration of hospitalization; proportion of participants with a change in oxygen saturation from < 94% to ≥94% from baseline to days 4, 7, 10, and 14. Adverse events were recorded days 1-28, coded by the Medical Dictionary for Regulatory Activities (version 23.1).
Follow-up (days, months)	29 days	28 days to 60 days
Sponsor/ lead institution	National Institute of Allergy and Infectious Diseases, US	Private (Eli Lilly and Company (Incyte Corporation licence))

Table 4-3 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	**Completed**
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 4-4 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)	NCT04381936 (RECOVERY) EudraCT 2020-001113-21 ISRCTN50189673	EudraCT 2021-000541-41, NCT04891133 (SolidAct)
Study design, study phase	nRCT, phase 2	RCT, phase 2/3	RCT, phase 3	RCT, phase 2/3	RCT, phase 3
Recruitment status	Recruiting	Ongoing	Ongoing	Recruiting	Ongoing
Number of Patients, Disease severity*	800, Mixed (Moderate to severe)	1000, Severe and critical	800, Hospitalised	20000, Mixed	2000, Part A: moderate; Part B severe and critical disease
Setting (hospital, ambulatory...)	Hospital	Hospital	Hospital	Hospital	Hospital
Intervention (generic drug name and dosage)	Baricitinib 2 mg	Immune modulatory drugs, baricitinib, sarilumab, tocilizumab, anakinra, eculizumab, secukinumab, bevacizumab...	Baricitinib Remdesivir	Lopinavir-Ritonavir, Hydroxychloroquine, Corticosteroids, Azithromycin, IV Immunoglobulin (children >44 weeks gestational age with PIMS-TS only), Convalescent plasma, Synthetic neutralizing antibodies (REGN-COV2) single dose of REGN10933 + REGN10987 8 g, Tocilizumab, Aspirin, Colchicine, Baricitinib 4mg, Anakinra (children with PIMS-TS only)	Baricitinib 4 mg
Comparator (standard care or generic drug name and dosage)	Standard of care	See above	Placebo	Standard care	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	Day of recovery (defined as the first day on which the subject satisfies one of the three categories from the ordinal scale)	All-cause mortality [Within 28 days after randomisation]	Part B: occurrence of death within 60 days; Part A is occurrence of disease progression,

Trial Identifier/registry ID(s)/contact	NCT04321993	EUdraCT 2020-001246-18 (CORIMUNO-19)	EudraCT 2020-001052-18 (ACTT/EU/UK)	NCT04381936 (RECOVERY) EudraCT 2020-001113-21 ISRCTN50189673	EudraCT 2021-000541-41, NCT04891133 (SolidAct)
Study design, study phase	nRCT, phase 2	RCT, phase 2/3	RCT, phase 3	RCT, phase 2/3	RCT, phase 3
Recruitment status	Recruiting	Ongoing	Ongoing	Recruiting	Ongoing
		incidence of successful tracheal extubation (defined as duration extubation > 48h) at day 14; Early end point: OMS progression scale >7 at day 4			defined as a progression of disease state from moderate (WHO score 4-5) to severe/critical (WHO score 6-9) or death (WHO score 10); Part A and B is to explore the effect of the intervention on respiratory dysfunction assessed by SpO2/FiO2-ratio at day
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	University of Oxford United Kingdom	Oslo University Hospital; Belgium, France, Germany, Hungary, Ireland, Italy, Luxembourg, Norway, Spain, Turkey

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

Table 4-5 Ongoing trials of combination therapies with baricitinib

Trial Identifier/registry ID(s)/contact	NCT04640168 (ACTT-4)	NCT04373044	EudraCT 2020-001854-23, NCT04832880 (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	**Terminated****	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; **after the release of results of ACTT-2 (NCT04401579)

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6 APPENDIX

6.1 Search strategy to identify randomised controlled trials

From June 2021, literature search strategy and results from COVID-NMA initiative were used, according living review protocol [1] [3]. 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 were included. Early-phase clinical trials, single-arm trials, non-randomized studies or modelling studies of interventions for COVID-19 were excluded, as well as studies about prognosis, systematic reviews and meta-analyses and diagnostic test accuracy studies. Details can be found in COVID-NMA Protocol [2].

6.2 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 6-1.

Table 6-1 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	10/09/2021	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	10/09/2021	3 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	10/09/2021	11 0 new

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