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“Rolling Collaborative Review” of Covid-19 treatments

MOLNUIPIRAVIR FOR THE TREATMENT OF COVID-19

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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 \(https://eunetha.eu/doi\)](https://eunetha.eu/doi).

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LIST OF ABBREVIATIONS

AE	Adverse Event
CI	Confidence Interval
DOI	Declaration of interest
EUnetHTA	European Network of Health Technology Assessment
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HR	Hazard Ratio
ICD	International Classification of Diseases
MD	Mean Difference
MeSH	Medical Subject Headings
NA	Not applicable
NR	Not reported
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
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://eunetha.eu/services/covid-19/>) and on the EUnetHTA Rolling Collaborative Review Sharepoint page each 15th of the month.

2.1 Scope

Table 2-1 Scope of the RCR

Description	Project Scope
Population	<p>Disease</p> <ul style="list-style-type: none"> • 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. <p>ICD-Codes (https://www.who.int/classifications/icd/covid19/en)</p> <ul style="list-style-type: none"> • 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. <p>MeSH-terms</p> <ul style="list-style-type: none"> • COVID-19, Coronavirus Disease 2019 <p>Target population (https://www.covid19treatmentguidelines.nih.gov/overview/management-of-covid-19/)</p>

	<ul style="list-style-type: none"> 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	Molnupiravir (EIDD-2801/MK-4482), an orally administered prodrug of the direct acting antiviral agent EIDD-1931
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	<p><u>Main outcome:</u></p> <ul style="list-style-type: none"> All-cause Mortality (Survival) <p><u>Additional Outcomes:</u></p> <p>Efficacy:</p> <ul style="list-style-type: none"> 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. <p>Safety:</p> <ul style="list-style-type: none"> Adverse events (AE), Severe adverse events (SAE), Withdrawals due to AEs, Most frequent AEs, Most frequent SAEs. <p>Rationale: We will give priority according to the Core Outcome Set for Clinical Trials on Coronavirus Disease 2019 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102592/pdf/main.pdf) and A minimal common outcome measure set for COVID-19 clinical research from the WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection.</p>
Study design	Efficacy: randomised controlled trials (RCT) Safety: observational studies (comparative or single-arm prospective studies and registries)

2.2 Sources of information

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

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

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

The literature search is conducted in the following databases:

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

Population	<p>People affected by COVID-19, as defined by the authors of the studies. No limits in terms of gender or ethnicity.</p> <p>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.</p>
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	<p>All-cause mortality</p> <p>Additional outcomes: Length of hospital stay, 2019-nCoV RT-PCR negativity, PaO₂/FiO₂, Duration of mechanical ventilation, radiological imaging, Adverse events, Severe adverse events.</p>
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/farmacicoindex.html> for SoF (or <https://covid-nma.com/>)

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

The literature search is conducted on a monthly basis using the following sources:

- <https://www.fhi.no/en/gk/systematic-reviews-hta/map/>

Search methods are described in more detail in Appendix Table 6-2.

Population	See project Scope
Intervention	Molnupiravir (EIDD-2801/MK-4482), an orally administered prodrug of the direct acting antiviral agent EIDD-1931.
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 Table 6-3.

Data are presented in tabular form.

3 ABOUT THE TREATMENT

3.1 *Mode of Action*

Molnupiravir (development codes MK-4482 and EIDD-2801) is an investigational antiviral drug, which is the orally-bioavailable prodrug of the ribonucleoside analog N4-hydroxycytidine (NHC, EIDD-1931) that inhibits the replication of multiple RNA viruses, including SARS-CoV-2, by introducing copying errors during viral RNA replication. EIDD-1931 has broad spectrum antiviral activity against influenza virus and coronaviruses, such as MERS-CoV, and SARS-CoV [4-6].

Molnupiravir attacks the same viral enzyme as Gilead's Remdesivir, but it can be taken orally. This would allow an administration at home and, therefore, earlier in the course of the disease [7]. According to Ridgeback Biotherapeutics, Molnupiravir has an extremely high barrier to resistance [8].

According to MSD [9], Molnupiravir is aimed at the treatment of Covid-19 in

- patients hospitalized due to mild, moderate or severe disease,
- non-hospitalized patients with mild or moderate disease.

3.2 *Regulatory Status*

Molnupiravir (as EIDD-2801) was developed at Drug Innovation Ventures at Emory (DRIVE), a not-for-profit biotechnology company owned by Emory University, Atlanta. It was then licensed by Ridgeback Biotherapeutics, and is now developed further in cooperation with Merck & Co. (in Europe: Merck Sharp & Dohme/ MSD) [10].

Molnupiravir is not approved by the European Medicines Agency (EMA) or the American Food and Drug Administration (FDA).

3.3 *Level of Evidence*

In April 2020, the FDA and the UK Medicines and Healthcare Products Regulatory Agency allowed phase I human testing which started with April in the UK and demonstrated that the compound is generally safe and well-tolerated [8, 11].

As of December 15, 2020, 5 ongoing studies related to Molnupiravir in COVID-19 patients were found in trial registries. No publications related to RCTs or prospective observational studies of Molnupiravir in COVID-19 patients were identified.

4 SUMMARY

4.1 *Effectiveness and Safety evidence from RCTs*

No published results of RCTs investigating the safety and efficacy of Molnupiravir for the treatment of Covid-19 could be identified.

4.2 *Safety evidence from observational studies*

No published results of observational studies investigating the safety and efficacy of Molnupiravir for the treatment of Covid-19 could be identified.

4.3 Ongoing studies

Overall, 9 hits were retrieved through database search (see Table 6-3). After deduplication and the exclusion of one completed first-in-human study investigating the safety, tolerability, and pharmacokinetics of Molnupiravir in healthy volunteers (NCT04392219) for which no published results were available, 5 ongoing studies, mainly phase 2 and 2/3, were included in Table 4-1 and Table 4-2.

4.4 Scientific conclusion about status of evidence generation

Based on the available evidence, the effectiveness and safety of Molnupiravir in COVID-19 patients cannot be assessed.

Results from 5 ongoing RCTs are expected in the coming months.

Table 4-1 Ongoing trials of single agent Molnupiravir

Trial Identifier/registry ID(s)/contact	NCT04575584 EudraCT Number: 2020-003367-26 Contact: Trialsites@merck.com	NCT04575597 EudraCT Number: 2020-003368-24 Contact: Trialsites@merck.com	NCT04405570 Contact: Laura Szewczyk EIDD2801@ridgebackbio.com
Study design, study phase	RCT, phase 2/3	RCT, phase 2/3	RCT, phase 2
Recruitment status	Recruiting (update Dec 2)	Recruiting (update Dec 2)	Recruiting (update Nov 27)
Number of Patients, Disease severity*	1300 participants Hospitalized adults with mild, moderate or severe COVID-19, require medical care in the hospital for ongoing clinical manifestations of COVID-19	1450 participants Non-Hospitalized adults with mild or moderate COVID-19	108 participants Adult outpatients with COVID-19
Setting (hospital, ambulatory,..)	hospital	ambulatory	ambulatory
Intervention (generic drug name and dosage)	Molnupiravir 200mg/ 400mg/ 800mg administered orally every 12 hours for 5 days (10 doses total)	Molnupiravir 200mg/ 400mg/ 800mg administered orally every 12 hours for 5 days (10 doses total)	Oral capsule of EIDD-2801 twice daily (BID) for 5 days
Comparator (standard care or generic drug name and dosage)	Placebo matching molnupiravir administered orally every 12 hours for 5 days (10 doses total)	Placebo matching molnupiravir administered orally every 12 hours for 5 days (10 doses total)	Placebo oral capsule (PBO) twice daily (BID) for 5 days
Primary Outcome(s)	<ul style="list-style-type: none"> • Time-to-sustained recovery [Time Frame: Up to 29 days] Sustained recovery is defined as: the participant is alive and not hospitalized; or the participant is alive and medically ready for discharge as determined by the investigator. • Percentage of participants with an adverse event (AE) [Time Frame: Up to 19 days] • Percentage of participants who discontinued study intervention due to an AE [Time Frame: Up to 6 days] 	<ul style="list-style-type: none"> • Percentage of participants who are hospitalized and/or die [Time Frame: Up to 29 days] Hospitalization (all cause) is ≥ 24 hours of acute care in a hospital or similar acute care facility. Death is due to any cause. • Percentage of participants with an adverse event (AE) [Time Frame: Up to 19 days] • Percentage of participants who discontinued study intervention due to an AE [Time Frame: Up to 6 days] 	<ul style="list-style-type: none"> • Virologic Efficacy [Time Frame: 28 days] The distribution of days until first non-detectable SARS-CoV-2 in nasopharyngeal (NP) swabs will be estimated for each randomized arm (drug versus placebo) • Number of Participants with any Adverse Events (AEs) as Assessed by Kaplan Meier Approach [Time Frame: 28 days]
Sponsor/ lead institution, country	Merck Sharp & Dohme Corp., USA	Merck Sharp & Dohme Corp., USA	Ridgeback Biotherapeutics, LP, USA

(also country of recruitment if different)	Recruitment: USA, Brazil, Chile, Columbia, France, Israel, Poland, Russia, Spain, Ukraine, UK	Recruitment: USA, Chile, Columbia, France, Israel, Russia, Spain, Ukraine, UK	
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*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

Table 4-2 Ongoing trials of single agent Molnupiravir, continued

Trial Identifier/registry ID(s)/contact	ISRCTN27106947 EudraCT number: 2020-001860-27 Contact: agile.accord@nhs.net https://www.agiletrial.net/	NCT04405739 Contact: Laura Szewczyk EIDD2801@ridgebackbio.com
Study design, study phase	RCT, phase I/IIa platform trial	RCT, phase 2
Recruitment status	Recruiting (update Dec 7)	Recruiting (update Oct 22)
Number of Patients, Disease severity*	180 participants Adults (≥18 years) with laboratory-confirmed SARS-CoV-2 infection	89 participants Newly hospitalized adults with polymerase chain reaction (PCR)-Confirmed COVID-19
Setting (hospital, ambulatory,..)	hospital	hospital
Intervention (generic drug name and dosage)	Phase I: EIDD-2801 administered orally, twice daily (BID) for 10 doses (5 or 6 days) Phase II: EIDD-2801 and SOC; EIDD-2801 administered orally, twice daily (BID) for 10 doses (5 or 6 days)	Oral capsule of EIDD-2801 twice daily (BID) for 5 days
Comparator (standard care or generic drug name and dosage)	Phase I: standard of care (SOC) Phase II: Placebo and SOC; placebo administered orally, twice daily (BID) for 10 doses (5 or 6 days)	Oral placebo capsule (PBO) twice daily (BID) for 5 days
Primary Outcome(s)	Phase I: 1. Dose-limiting toxicity (DLT) using CTCAE version 5 (grades 3 and above) over 7 days 2. CTCAE grading related to platelets and/or lymphocytes	<ul style="list-style-type: none"> Number of Participants that achieve Virologic Clearance after oral administration of EIDD-2801 [Time Frame: 28 days] Achievement of undetectable SARS-CoV-2 RNA by Day 5 in nasopharyngeal (NP) swabs by quantitative reverse transcription

	<p>Phase II: 1. Time to negative PCR measured using SARS-CoV-2 nose/throat swab at screening, Days 1, 3, 5, 8, 11, 15, 22 and 29</p>	<p>polymerase chain reaction (qPCR) after administration with EIDD-2801</p> <ul style="list-style-type: none"> • Number of Participants With any Serious Adverse Events(SAEs) as assessed by DAIDS [Time Frame: 28 days] • Number of Participants With any Adverse Events(AEs) as assessed by DAIDS [Time Frame: 28 days]
<p>Sponsor/ lead institution, country (also country of recruitment if different)</p>	<p>Sponsor: Ridgeback Biotherapeutics, USA Lead institution: University of Liverpool Recruitment: South Africa, UK</p>	<p>Ridgeback Biotherapeutics, LP, USA</p>

*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 (Appendix 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/ictcp/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	<p>1. ((((((("Coronavirus"[Mesh]) OR (coronavirus*[Title/Abstract] OR coronavirus*[Title/Abstract] OR coronavirinae*[Title/Abstract] OR Coronavirus*[Title/Abstract] OR Coronavirus*[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 [1]) OR (controlled clinical trial [1])) OR (randomized [tiab])) OR (placebo [tiab])) OR (clinical trials as topic [mesh: noexp])) OR (randomly [tiab])) OR (trial [8])))) NOT (animals [mh] NOT humans [mh]) AND (2019/10/01:2020[dp])</p>	10/12/2020

Database	URL	Search line / Search terms	Date of search
Ovid MEDLINE(R) ALL)	ovidsp.dc2.ovid.com	<ol style="list-style-type: none"> 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" 	10/12/2020
OVID EMBASE	ovidsp.dc2.ovid.com	<ol style="list-style-type: none"> 1. exp Coronavirinae/ or exp Coronavirus/ 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" 	10/12/2020

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. We receive studies that [EPPI Centre](#) has screened after searching weekly in Medline and Embase. We supplement these studies with a weekly search in Scopus. The retrieved hits were imported into an Endnote database and combined with generic names of the 17 included COVID-19 drugs.

Table 6-2 Search strategy to identify observational studies

Database	URL	Search terms / Search modality	Date of search
<p>OVID Medline</p>	<p>Imported from EPPI Centre</p>	<p>1 exp Coronavirus/ 2 exp Coronavirus Infections/ 3 (coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*).mp. 4 (or/1-3) and ((2019* or 202*).dp. or 20190101:20301231.(ep.) 5 4 not (SARS or SARS-CoV or MERS or MERS-CoV or Middle East respiratory syndrome or camel* or dromedar* or equine or coronary or coronal or covidence* or covidien or influenza virus or HIV or bovine or calves or TGEV or feline or porcine or BCoV or PED or PEDV or PDCoV or FIPV or FCoV or SADS-CoV or canine or CCov or zoonotic or avian influenza or H1N1 or H5N1 or H5N6 or IBV or murine corona*).mp. 6 ((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp. 7 (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 on 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. 8 COVID-19.rx,px,ox. or severe acute respiratory syndrome coronavirus 2.os. 9 ("32240632" or "32236488" or "32268021" or "32267941" or "32169616" or "32267649" or "32267499" or "32267344" or "32248853" or "32246156" or "32243118" or "32240583" or "32237674" or "32234725" or "32173381" or "32227595" or "32185863" or "32221979" or "32213260" or "32205350" or "32202721" or "32197097" or "32196032" or "32188729" or "32176889" or "32088947" or "32277065" or "32273472" or "32273444" or "32145185" or "31917786" or "32267384" or "32265186" or "32253187" or "32265567" or "32231286" or "32105468" or "32179788" or "32152361" or "32152148" or "32140676" or "32053580" or "32029604" or "32127714" or "32047315" or "32020111" or "32267950" or "32249952" or "32172715").ui. 10 or/6-9 11 5 or 10</p>	<p>26/10/2020 until 30/11/2020</p> <p>And from 1/09/2020 until 30/11/2020 for the new compounds Regeneron, Bamlanivimab, Baricitinib, Molnupiravir</p>
<p>OVID EMBASE</p>		<p>1 exp Coronavirus Infections/ 2 exp coronavirinae/ 3 (coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*).mp. 4 or/1-3 5 4 not (SARS or SARS-CoV or MERS or MERS-CoV or Middle East respiratory syndrome or camel* or dromedar* or equine or coronary or coronal or covidence* or covidien or influenza virus or HIV or bovine or calves or TGEV or feline or porcine or BCoV or PED or PEDV or PDCoV or FIPV or FCoV or SADS-CoV or canine or CCov or zoonotic</p>	<p>26/10/2020 until 30/11/2020</p> <p>And from 1/09/2020 until 30/11/2020 for the new compounds Regeneron, Bamlanivimab, Baricitinib, Molnupiravir</p>

		<p>or avian influenza or H1N1 or H5N1 or H5N6 or IBV or murine corona*).mp. 6 ((pneumonia or covid* or coronavirus* or corona virus* or nCoV* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp. 7 (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 on 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. 8 6 or 7 9 5 or 8</p>	
Scopus		<p>TITLE-ABS-KEY(((pneumonia OR covid* OR coronavirus* OR "corona virus*" OR nCoV* OR 2019-ncov OR sars*) AND Wuhan) 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) W/1 (CoV OR nCoV OR covid OR coronavirus* OR "corona virus*" OR pandemi*)) OR ((covid OR covid19 OR covid-19) AND pandemic*) OR ((coronavirus* OR "corona virus*" AND pneumonia) AND ORIG-LOAD-DATE > 20200920[date changes from week to week] AND ORIG-LOAD-DATE < 20200928 [date changes from week to week] AND NOT INDEX(medline)</p>	<p>26/10/2020 until 30/11/2020</p> <p>And from 1/09/2020 until 30/11/2020 for the new compounds Regeneron, Bamlanivimab, Baricitinib, Molnupiravir</p>

6.3 Search strategy to identify ongoing studies

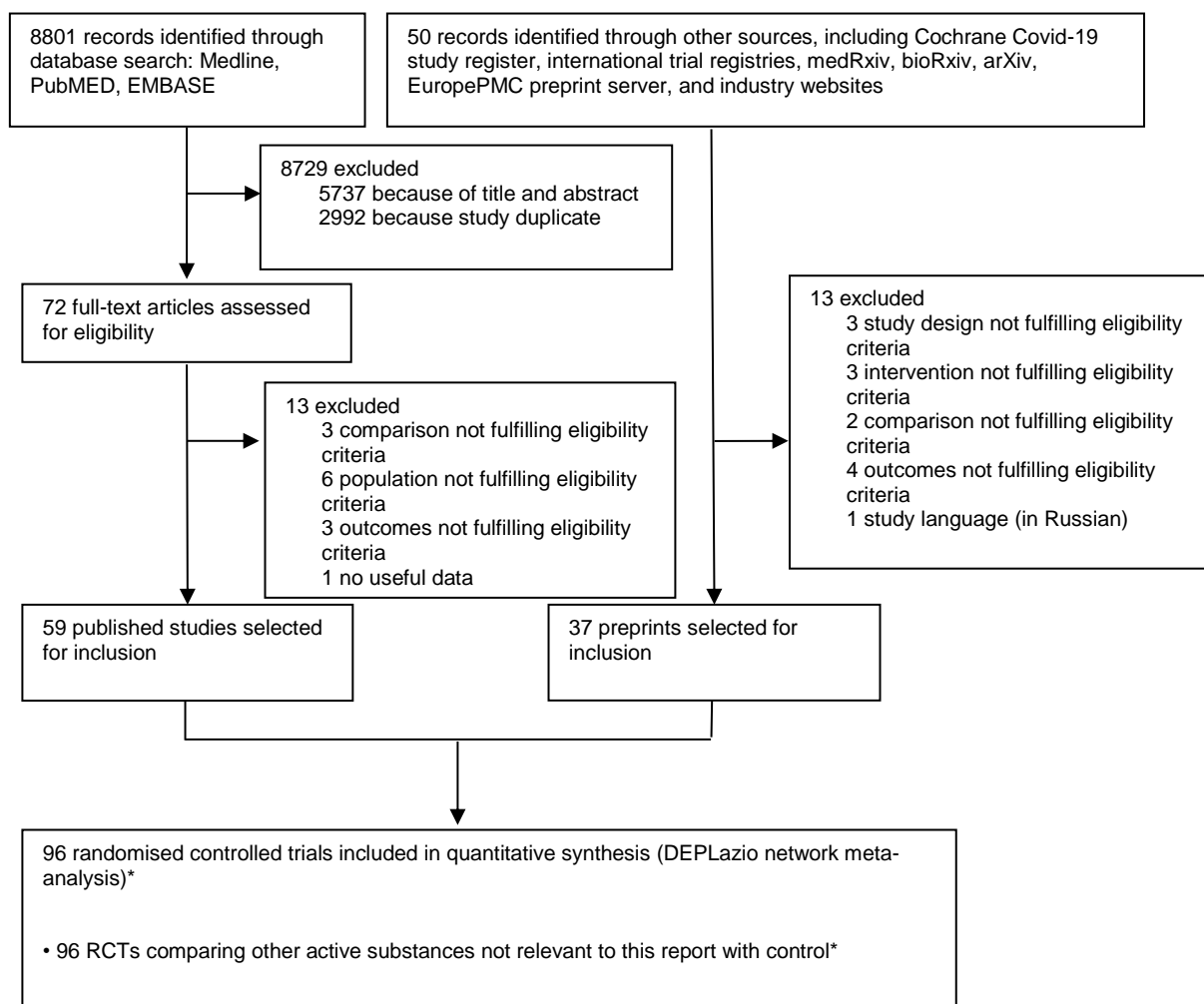
AIHTA is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and Molnupiravir are described in Appendix Table 6-3.

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" Terms used at Condition or disease: <ul style="list-style-type: none"> • Covid-19, • SARS-CoV-2, • Coronavirus Terms used at "other terms": <ul style="list-style-type: none"> • Molnupiravir • EIDD-2801 • MK-4482 	10/12/2020	5 5 new
ISRCTN	https://www.isrctn.com/	Basic search mode Search terms: <ol style="list-style-type: none"> 1. covid-19 and Molnupiravir 2. covid-19 and EIDD-2801 3. covid-19 and MK-4482 4. SARS-CoV-2 and Molnupiravir 5. SARS-CoV-2 and EIDD-2801 6. SARS-CoV-2 and MK-4482 	10/12/2020	1 1 new
European Clinical Trials Registry	https://www.clinicaltrialsregister.eu/	Basic search mode Search terms: <ol style="list-style-type: none"> 1. covid-19 and Molnupiravir 2. covid-19 and EIDD-2801 3. covid-19 and MK-4482 4. SARS-CoV-2 and Molnupiravir 5. SARS-CoV-2 and EIDD-2801 6. SARS-CoV-2 and MK-4482 	10/12/2020	3 3 new

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

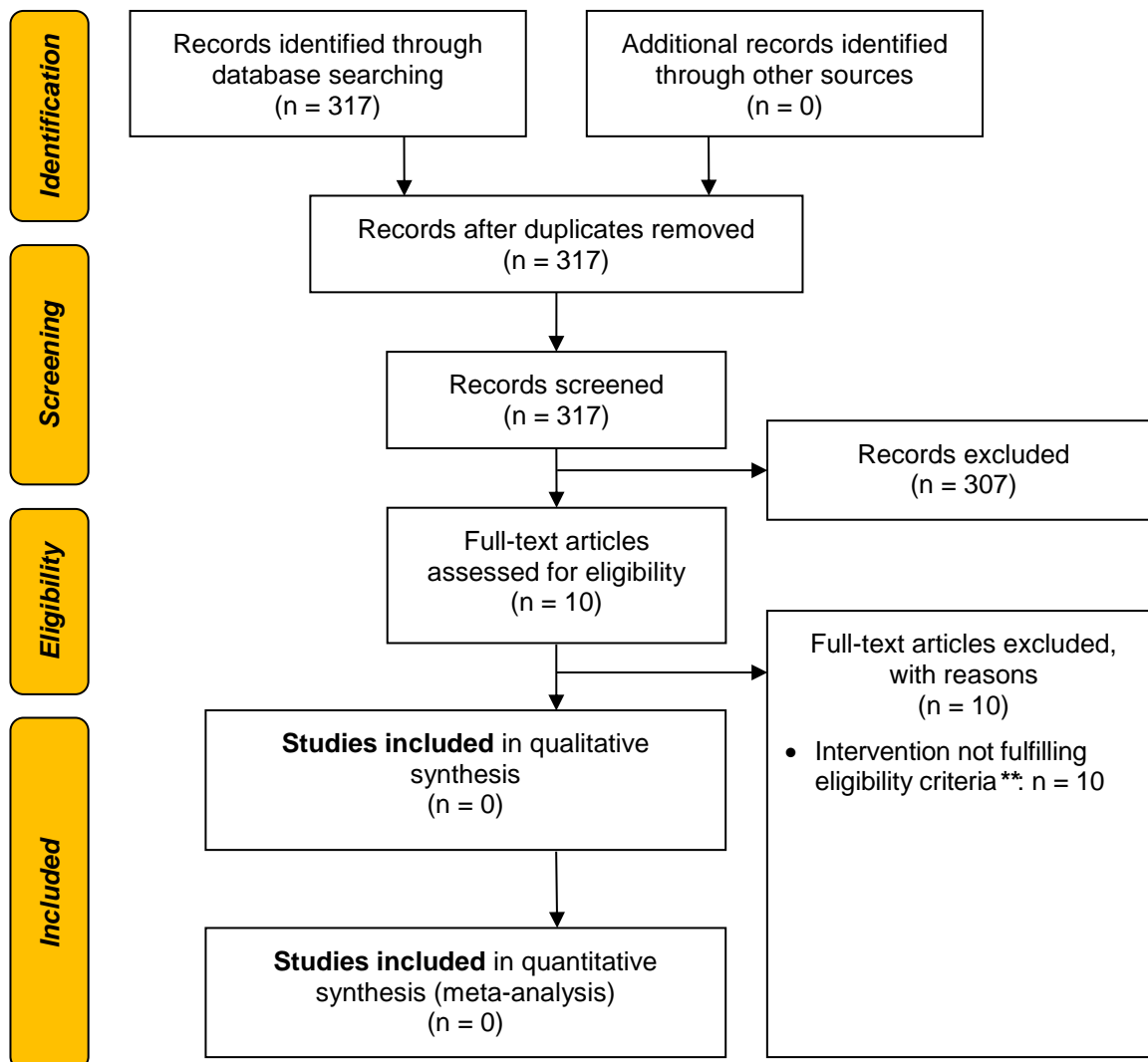
6.4 Flow diagrams



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