EUnetHTA Joint Action 3 WP4

"Rolling Collaborative Review" of Covid-19 treatments

MOLNUPIRAVIR FOR THE TREATMENT OF COVID-19

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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
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://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	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	Main outcome: • All-cause Mortality (Survival) Additional Outcomes: Efficacy: • Length of hospital stay, • Viral burden (2019-nCoV RT-PCR negativity), • Clinical progression (WHO Clinical Progression Scale measured daily over the course of the study), • Rates of hospitalization and of patients entering ICU, • Duration of mechanical ventilation, • Quality of life. Safety: • Adverse events (AE), • Severe adverse events (SAE), • Withdrawals due to AEs, • Most frequent AEs, • Most frequent SAEs. **Rationale:** We will give priority according to the Core Outcome Set for Clinical Trials on Coronavirus Disease 2019 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102592/pdf/main.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 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 May 10, 2021, 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.

On March 6, 2021, Merck and Ridgeback Biotherapeutics announced preliminary findings from their phase 2a randomized, double-blind, placebo-controlled trial (NCT04405570, completed February 21, 2021), reporting findings on one secondary objective. The study enrolled 202 non-hospitalised adults with signs or symptoms of Covid-19 within 7 days and confirmed active SARS-CoV-2 infection. Preliminary data show a reduction in time to negativity of infectious virus isolation in nasopharyngeal swabs from participants with symptomatic SARS-CoV-2 infection, as determined by isolation in Vero cell line culture. At day 5, there was a reduction (nominal p=0.001, not controlled for multiplicity) in positive viral culture in subjects who received Molnupiravir (all doses) compared to placebo: 0% (0/47) for Molnupiravir and 24% (6/25) for placebo. Of 202 treated participants, no safety signals have been identified; of the 4 serious adverse events reported, none were considered to be related to the intervention. The full study results will be shared later [12].

On April 15, 2021, Merck and Ridgeback Biotherapeutics provided an update on the clinical development program for Molnupiravir. Based on a planned interim analysis of data from NCT04575584 and NCT04575597, and from a previously completed Phase 2a dose-ranging study in outpatients (NCT04405570), the companies decided to proceed with Phase 3 of NCT04575597 in outpatients with COVID-19, evaluating the 800 mg dose of Molnupiravir twice daily. Data from NCT04575584 indicate that Molnupiravir is unlikely to demonstrate a clinical benefit in hospitalized patients; therefore, the companies decided not to proceed to Phase 3. The percentage of patients who were hospitalized and/or

died in Phase 2 of NCT04575597 was lower in the combined molnupiravir-treated groups versus the placebo group; the number of events reported are not sufficient to provide a meaningful measure of clinical effect. In both studies (NCT04575597, NCT04575584), the analysis of SARS-CoV-2 in nasopharyngeal and oropharyngeal swabs indicates that Molnupiravir inhibits the replication of the virus, as demonstrated by a greater decrease from baseline in viral RNA compared to placebo at Day 5 and Day 10, and by a larger proportion of participants with undetectable viral RNA at Day 10 and Day 15 following the end of treatment. The largest overall magnitude of antiviral effect was observed in the 800 mg dose compared with the 200 mg and 400 mg doses. Among 299 patients treated in NCT04575597, 6.2% in the Molnupiravir group and 6.8% in the placebo group reported drug-related adverse events. In NCT04575584, 11% in the Molnupiravir group and 21.3% in the placebo group reported drug-related adverse events. In both trials, no deaths were considered drug-related by the investigators, and there were no drug-related adverse events that led to discontinuation in participants who received Molnupiravir. Based on subgroup analysis, Merck will amend the inclusion criteria for NCT04575597 (allowable symptom duration for enrollment < 5 days, at least one risk factor for progression to severe disease). Final data of NCT04575597 Phase 3 will be available in September/October 2021. The earliest possible submission for an Emergency Use Authorization for Molnupiravir is estimated to be in the second half of 2021 [13].

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.

Preliminary results from one phase 2a trial and information regarding the interim analysis of data from NCT04575584 and NCT04575597 are described in section 3.3.

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, 10 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, and one completed study (NCT04405570) with available preliminary results, 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 and one completed RCT 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
Study design, study phase	RCT, phase 2/3	RCT, phase 2/3
Recruitment status	Active, **not recruiting** (last update May 7)	Recruiting (last update April 19)
Number of Patients, Disease severity*	1300 participants Actual enrolment: 304 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
Setting (hospital, ambulatory,..)	hospital	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)
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)
Primary Outcome(s)	• 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]	• 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]
Sponsor/ lead institution, country (also country of recruitment if different)	Merck Sharp & Dohme Corp., USA Recruitment: USA, Brazil, Chile, Columbia, France, Israel, Poland, Russia, Spain, Ukraine, UK	Merck Sharp & Dohme Corp., USA Recruitment: USA, Chile, Columbia, France, Israel, Russia, Spain, Ukraine, UK

*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 Clinicaltrials.gov Identifier: NCT04746183 Contact: agile.accord@nhs.net https://www.agiletrial.net/	**NCT04405739** Contact: Laura Szewczyk EIDD2801@ridgebackbio.com	**NCT04746183** ISRCTN27106947 EudraCT number: 2020-001860-27 Contact: Helen E Reynolds livagile@liv.ac.uk
Study design, study phase	RCT, phase I/IIa platform trial	RCT, phase 2	Phase I/II Bayesian randomised platform trial
Recruitment status	Recruiting (last update May 4)	Recruiting (last update Feb 21)	Recruiting (last update April 13)
Number of Patients, Disease severity*	180 participants Adults (≥18 years) with laboratory-confirmed SARS-CoV-2 infection	80 participants Newly hospitalized adults with polymerase chain reaction (PCR)-Confirmed COVID-19	600 participants Male or female ≥ 60 years old or ≥50 years old with at least one well controlled comorbidity with laboratory confirmed SARS-CoV-2 infection (PCR); severe, mild-moderate
Setting (hospital, ambulatory,..)	hospital	hospital	hospital, ambulatory
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	Phase Ib: EIDD-2801 will be administered orally, twice daily (BID) for 10 doses (5 or 6 days) Phase II: As per Phase Ib, with the dose determined by the recommended phase II dose
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	Phase 1b: standard of care Phase II: Placebo will be administered orally, twice daily (BID) for 10 doses (5 or 6 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	• 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	• Phase I: To determine the safety and tolerability of multiple ascending doses of EIDD-2801 to recommend dose for phase II. [Time Frame: 7 days from randomisation] Dose limiting toxicity (DLT) using CTCAE version 5 (grades 3 and above) over 7 days.

	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	polymerase chain reaction (qPCR) after administration with EIDD-2801 • 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]	• Phase II: To determine the ability of EIDD-2801 to reduce serious complications of COVID-19 including hospitalization, reduction in SAO2<92%, or death. [Time Frame: 29 days from randomisation] Progression of disease (SpO2<92% based on at least 2 consecutive recordings on the same day) or hospitalization or death up to day 29
Sponsor/ lead institution, country (also country of recruitment if different)	Sponsor: Ridgeback Biotherapeutics, USA Lead institution: University of Liverpool Recruitment: South Africa, UK	Ridgeback Biotherapeutics, LP, USA	University of Liverpool University of Southampton Liverpool School of Tropical Medicine Lancaster University Liverpool University Hospitals NHS Foundation Trust

*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/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])	03/05/2021

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"	03/05/2021
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"	03/05/2021

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 [14, 15]. 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.

As a supplement we used Microsoft Academics Graph (MAG) to identify further relevant research. We used articles previously included in the EUnetHTA rolling collaborative review until last search and ran the Bring up-to-date function in EPPI Reviewer. Bring up-to-date uses the neural networks of MAG to identify publications similar to input articles, added to the MAG database.

Table 6-2 Search strategy to identify observational studies

Database	URL	Search terms / Search modality	Date of search	Hits retrieved
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	From 06/04/2021 until 03/05/2021	1032

		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 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 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 (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 (20210406 OR 20210407 OR 20210408 OR 20210409 OR 2021041* OR 2021042* OR 2021043* OR 202105*).dt. use medall [time limits in MEDLINE] 7 (20210406 OR 20210407 OR 20210408 OR 20210409 OR 2021041* OR 2021042* OR		

		2021043* OR 202105*).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

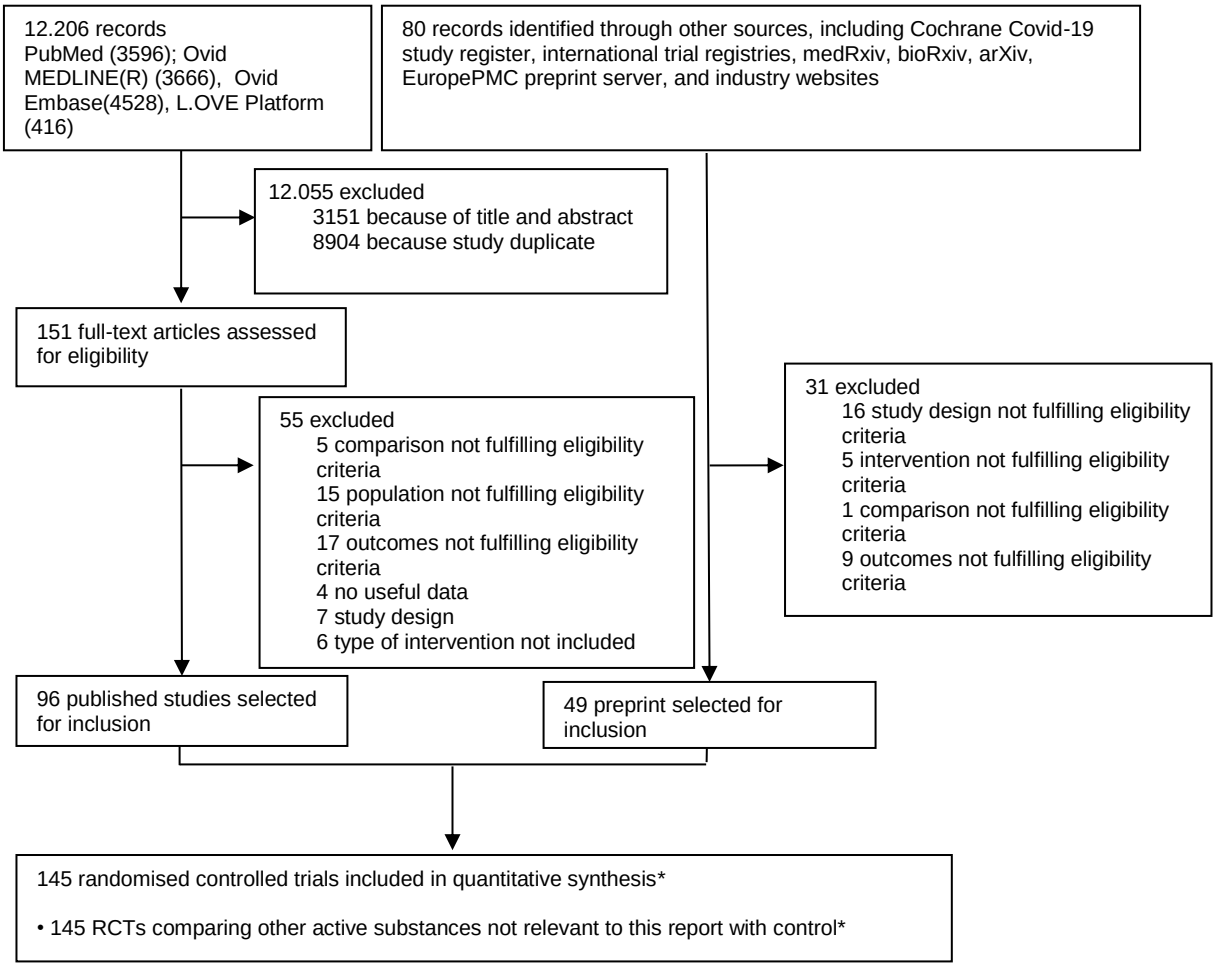
AIHTA is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and Molnupiravir are described in Appendix Table 6-3.

Table 6-3 Search strategy to identify ongoing studies

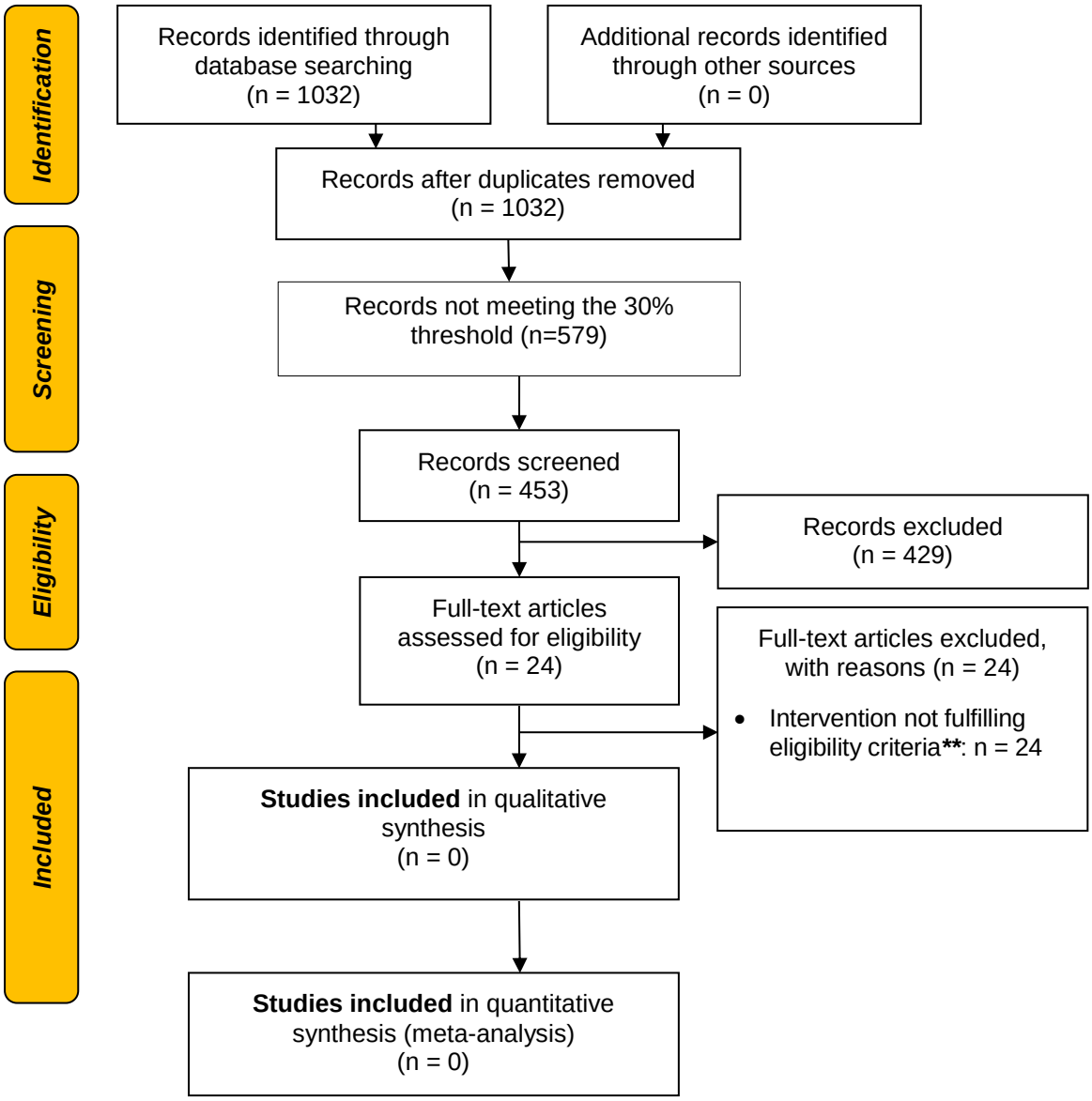
Database	URL	Search line / search terms	Date of search	Hits retrieved
ClinicalTrials.gov	https://clinicaltrials.gov/	"Basic search mode* Terms used at Condition or disease: • Covid-19, • SARS-CoV-2, • Coronavirus Terms used at "other terms": • Molnupiravir • EIDD-2801 • MK-4482	10/05/2021	6 0 new
ISRCTN	https://www.isrctn.com/	Basic search mode Search terms: 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	10/05/2021	1 0 new
European Clinical Trials Registry	https://www.clinicaltrialsregister.eu/	Basic search mode Search terms: 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	10/05/2021	3 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