EUnetHTA Joint Action 3 WP4

"Rolling Collaborative Review" of Covid-19 treatments

CASIRIVIMAB AND IMDEVIMAB (REGN-COV2) FOR THE TREATMENT OF COVID-19

Project ID: RCR16
Monitoring Report

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DOCUMENT HISTORY AND CONTRIBUTORS

Version	Date	Description of changes
V 1.0	15/12/2020	First version
V 2.0	20/01/2021	Second version
V 2.1	08/02/2021	Literature searches, Literature screening, Data extraction
V 2.2	10/02/2021	Data extraction and analysis complete
V 2.3	11/02/2021	Check of data extraction and analysis
V 3.0	15/02/2021	Third version

Major changes from previous version

Chapter, page no.	Major changes from version 2.0
Chapter 3, p. 11 p.12	• Regulatory data: EMA's human medicines committee (CHMP) has started a 'rolling review' and a review, to provide a harmonised scientific opinion at EU level to support national decision making on the possible use of the antibodies before a formal authorisation is issued • In vitro data related to new SARS-CoV-2 variants
Chapter 4, p.	• One new ongoing RCT 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
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/)

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	• 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	Casirivimab and imdevimab (REGN-COV2): combination of neutralising monoclonal antibodies
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.

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

Population	See project Scope
Intervention	Casirivimab and imdevimab (REGN-COV2): combination of neutralising monoclonal antibodies
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

Neutralising monoclonal antibodies to SARS-CoV-2 have the potential to be used for both prevention and treatment of infection. They can help to guide vaccine design and development as well. The main target of SARS-CoV-2 neutralizing monoclonal antibodies is the surface spike glycoprotein that mediates viral entry into host cells. Some products will include of a combination of 2 monoclonal antibodies targeting different sites on the spike protein. Due to long half-life of most monoclonal antibodies (approximately 3 weeks for IgG1), a single infusion should be sufficient. A potential limitation of monoclonal antibodies for treatment of COVID-19 is the unknown bioavailability of passively infused IgG in tissues affected by the disease, especially the lungs, which serve as a key target of SARS-CoV-2 infection. Due to the effect of viral diversity it will be important to monitor for the emergence of resistant viral mutations under selective pressure of monoclonal antibody treatment [4, 5].

Casirivimab and imdevimab (REGN-COV2) is a combination of two monoclonal antibodies (previously REGN10933 and REGN10987) which bind non-competitively to the critical receptor binding domain of the virus's spike protein, which diminishes the ability of mutant viruses to escape treatment and protects against spike variants that have arisen in the human population.

3.2 Regulatory Status

The combination of casirivimab and imdevimab is not authorised in Covid-19 patients (EMA, FDA).

On November 21, 2020, the U.S. Food and Drug Administration issued an **emergency use authorization (EUA)** for casirivimab and imdevimab to be administered together for the **treatment** of **mild to moderate COVID-19** in adults and pediatric patients (12 years of age or older weighing at least 40 kilograms [about 88 pounds]) with positive results of direct SARS-CoV-2 viral testing and who are **at high risk for progressing to severe COVID-19**. This includes those who are 65 years of age or older or who have certain chronic medical conditions.

High risk is defined as patients who meet at least one of the following criteria: have a body mass index (BMI) ≥35, chronic kidney disease, diabetes, immunosuppressive disease (immunocompromised), are currently receiving immunosuppressive treatment, are ≥65 years of age, are ≥55 years of age AND have cardiovascular disease or hypertension or chronic obstructive pulmonary disease/other chronic respiratory disease, are 12 – 17 years of age AND have a BMI ≥85th percentile for their age and gender based on CDC growth charts, or sickle cell disease or congenital or acquired heart disease or neurodevelopmental disorders (e.g. cerebral palsy) or a medical-related technological dependence (e.g. tracheostomy, gastrostomy, or positive pressure ventilation [not related to COVID-19]), or asthma, reactive airway or other chronic respiratory disease that requires daily medication for control.

The dosage in adults and in pediatric patients (12 years of age and older weighing at least 40 kg) is 1,200 mg of casirivimab and 1,200 mg of imdevimab administered together as a single intravenous infusion over at least 60 minutes. Casirivimab and imdevimab solutions must be diluted prior to administration. Casirivimab and imdevimab should be given together as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 10 days of symptom onset.

There are limited clinical data available for casirivimab and imdevimab. Serious and unexpected adverse events may occur that have not been previously reported with casirivimab and imdevimab use, hypersensitivity including anaphylaxis and Infusion-related reactions.

Casirivimab and imdevimab are not authorised for patients who are hospitalised due to COVID-19 or require oxygen therapy due to COVID-19. A benefit of casirivimab and imdevimab treatment has not been shown in patients hospitalised due to COVID-19. Monoclonal antibodies, such as casirivimab and imdevimab, may be associated with worse clinical outcomes when administered to hospitalised patients with COVID-19 requiring high flow oxygen or mechanical ventilation [6].

On February 1st, 2021, EMA's human medicines committee (CHMP) has started a 'rolling review' of data on REGN-COV2 antibody combination (casirivimab / imdevimab), based on preliminary results from a study that indicate a beneficial effect of the medicine in reducing the amount of virus in the nose and throat of non-hospitalised patients with COVID-19. The CHMP will evaluate all data on this medicine, including evidence from a study in hospitalised patients with COVID-19 and other clinical trials as they become available [7].

On February 4, 2021, EMA stated that the CHMP is reviewing available data on the use of the monoclonal antibodies, as two separate reviews, one for the casirivimab/imdevimab combination and another for bamlanivimab/etesevimab, to provide a harmonised scientific opinion at EU level to support national decision making on the possible use of the antibodies before a formal authorisation is issued. The Committee will also look at the use of bamlanivimab alone based on a study which indicated that bamlanivimab monotherapy can reduce viral load and provide clinical benefit [8].

Regeneron is collaborating with Roche to increase global supply of REGEN-COV2. Regeneron is responsible for development and distribution of the treatment in the U.S., and Roche is primarily responsible for development and distribution outside the U.S.

US COVID-19 Treatment Guidelines

The US COVID-19 Treatment Guidelines Panel issued new recommendations on pharmacological treatment for patients with COVID-19 (as of December 3, 2020) [9]:

At this time, there are insufficient data to recommend either for or against the use of casirivimab plus imdevimab for the treatment of outpatients with mild to moderate COVID-19. The casirivimab plus imdevimab combination should not be considered the standard of care for the treatment of patients with COVID-19. Patients who are hospitalised for COVID-19 should not receive casirivimab plus imdevimab outside of a clinical trial.

There are currently no comparative data to determine whether there are differences in clinical efficacy or safety between casirivimab plus imdevimab and bamlanivimab.

3.3   Level of Evidence

Currently, only one scientific publication related to interim results of an RCT was found. No scientific publications related to prospective observational studies of casirivimab and imdevimab combination treatment in COVID-19 patients were found.

Outpatient setting

On December 17, 2020, Weinreich et al. [10] published **preliminary** positive results of the phase 1-2 portion of an ongoing double-blind, phase 1–3 trial (NCT04425629) involving non-hospitalised patients with Covid-19, randomly assigned (1:1:1) to receive placebo, 2.4 g of REGN-COV2, or 8.0 g of REGN-COV2 and were prospectively characterized at baseline for endogenous immune response against SARS-CoV-2 (serum antibody–positive or serum antibody–negative).

In this interim analysis, data from 275 patients are reported: the REGN-COV2 antibody cocktail reduced viral load, with a greater effect in patients whose immune response had not yet been initiated or who had a high viral load at baseline: The least-squares mean difference (combined REGN-COV2 dose groups vs. placebo group) in the time-weighted average change in viral load from day 1 through day 7 was −0.56 log10 copies per milliliter (95% confidence interval −1.02 to −0.11) among patients who were serum antibody–negative at baseline and −0.41 log10 copies per milliliter (95% CI, −0.71 to −0.10) in the overall trial population. In the overall trial population, 6% of the patients in the placebo group and 3% of the patients in the combined REGN-COV2 dose groups reported at least one medically attended visit; among patients who were serum antibody–negative at baseline, the corresponding percentages were 15% and 6% (difference, −9 percentage points; 95% CI, −29 to 11). The percentages of patients with hypersensitivity reactions, infusion-related reactions, and other adverse events were similar in the combined REGN-COV2 dose groups and the placebo group [10].

On October 28, 2020, Regeneron Pharmaceuticals, Inc. announced positive results from an ongoing

phase 2/3 RCT (NCT04425629) in the COVID-19 outpatient setting (ambulatory patients, n=799) on their website; the trial met the primary and key secondary endpoints. REGN-COV2 significantly reduced viral load and patient medical visits (hospitalisations, emergency room, urgent care visits and/or physician office/telemedicine visits), by 57% through day 29 (2.8% combined dose groups; 6.5% placebo; p=0.024) and by 72% in patients with one or more risk factor (including being over 50 years of age; body mass index greater than 30; cardiovascular, metabolic, lung, liver or kidney disease; or immunocompromised status) (combined dose groups; nominal p=0.0065) [11].

Serious adverse events were numerically more frequent with placebo than REGN-COV2 treatment (0.8% high dose, 1.6% low dose; 2.3% placebo). Numerically more infusion reactions occurred with the REGN-COV2 high dose compared to placebo (1.5% high dose; 0% low dose; 0.4% placebo) [11].

Safety issue in hospitalised patients

On October 30, 2020, Regeneron Pharmaceuticals, Inc. received a recommendation from the independent data monitoring committee (IDMC) for the REGN-COV2 antibody cocktail treatment trials for COVID-19 that the current hospitalised patient trial to be modified. Specifically, based on a potential safety signal and an unfavourable risk/benefit profile at this time, the IDMC recommends further enrolment of patients requiring high-flow oxygen or mechanical ventilation to be placed on hold, pending collection and analysis of further data on patients already enrolled. The IDMC also recommends continuing enrolment of hospitalised patients requiring either no or low-flow oxygen as the risk/benefit remains acceptable in these cohorts. Finally, the IDMC recommends continuation of the outpatient trial without modification [12].

New SARS-CoV-2 Variants B.1.351 and B.1.1.7

On January 27, 2021, Regeneron Pharmaceuticals, Inc. announced that researchers in Columbia University lab [13] and Regeneron scientists have independently confirmed that REGEN-COVTM (casirivimab and imdevimab antibody cocktail) successfully neutralizes the circulating SARS-CoV-2 variants first identified in the UK (B.1.1.7) and South Africa (B.1.351), in preclinical research [14].

Both antibodies retaining their potency against the B.1.1.7 variant; against the B.1.351 variant, imdevimab retained its potency and, while the casirivimab potency was reduced, it was still comparable to the potency that other single antibodies in development have against the original virus.
Regeneron is conducting additional preclinical research against the variant first identified in Brazil (1.1.248).

4 SUMMARY

4.1 Effectiveness and Safety evidence from RCTs

Currently, only one scientific publication related to interim results of an RCT on the casirivimab and imdevimab combination treatment in COVID-19 non-hospitalised patients was found.

4.2 Safety evidence from observational studies

No publications related to prospective observational studies of the casirivimab and imdevimab combination treatment in COVID-19 patients were found.

4.3 Ongoing studies

One new ongoing RCT was found; four RCTs related to the casirivimab and imdevimab combination treatment are currently ongoing and are described in Table 4-1 below. One is the RECOVERY (Randomised Evaluation of COVid-19 thERapY) trial, led by the University of Oxford.

4.4 Scientific conclusion about status of evidence generation

At the moment, effectiveness and safety of the casirivimab and imdevimab combination treatment from RCTs in COVID-19 patients could not be assessed because there are no published final results in scientific journals. The same is true for safety from prospective observational studies.

Based on published **preliminary (interim) results** of the phase 1-2 portion of an ongoing double-blind, phase 1–3 trial (NCT04425629), involving non-hospitalised patients with Covid-19, the REGN-COV2 antibody cocktail reduced viral load, with a greater effect in patients whose immune response had not yet been initiated or who had a high viral load at baseline. The same is true for medically attended visit, with a greater effect among patients who were serum antibody–negative at baseline. The percentages of patients with hypersensitivity reactions, infusion-related reactions, and other adverse events were similar in the combined REGN-COV2 dose groups and the placebo group.

Based on **unpublished preliminary results**, related to a randomised controlled phase 2/3 trial including 799 non-hospitalised adults with mild to moderate COVID-19 that compared the combination of two monoclonal antibodies, casirivimab and imdevimab, at two different doses (2400 and 8000 mg total doses) with placebo, both doses significantly reduced viral loads more than placebo, and significantly reduced COVID-19-related hospitalisation or emergency room visits in patients at high risk for disease progression within 28 days after treatment when compared to placebo.

The safety and effectiveness of this investigational therapy for use in the treatment of COVID-19 continues to be evaluated.

High quality evidence from ongoing RCTs is expected to assess effectiveness and safety of casirivimab and imdevimab combination treatment in COVID-19 patients.

On November 21, 2020, the U.S. Food and Drug Administration issued an **emergency use authorization** (EUA) for casirivimab and imdevimab to be administered together for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age or older weighing at least 40 kilograms [about 88 pounds]) with positive results of direct SARS-CoV-2 viral testing and who are at high risk for progressing to severe COVID-19. This includes those who are 65 years of age or older or who have certain chronic medical conditions.

On February 1st, 2021, EMA's human medicines committee (CHMP) has started a 'rolling review' of data on REGN-COV2 antibody combination. On February 4, 2021, the EMA stated that the CHMP is reviewing available data on the use of the monoclonal antibodies, as two separate reviews, one for the casirivimab/imdevimab combination and another for bamlanivimab/etesevimab, to provide a harmonised scientific opinion at EU level to support national decision making on the possible use of the antibodies before a formal authorisation is issued.

Table 4-1. Ongoing trials of agent casirivimab and imdevimab (REGN-COV2) (previously REGN10933+REGN10987)

Trial Identifier/registry ID(s)/contact	NCT04425629, EudraCT 2020-003690-21	NCT04426695 EudraCT 2020-002537-15	NCT04381936 RECOVERY EudraCT 2020-001113-21 ISRCTN50189673	NCT04666441
Study design, study phase	RCT, phase 1/2	RCT, phase 1/2	RCT, phase 2/3	RCT, phase 2
Recruitment status	Recruiting	Recruiting	Recruiting	Recruiting
Number of Patients, Disease severity*	2104, Mild	2970, Mixed (Severe and Critical): Cohort 1, On Low-Flow Oxygen; Cohort 1A, with COVID-19 symptoms but not requiring supplemental O2; Cohort 2, High O2 no Mechanical ventilation; Cohort 3, on Mechanical ventilation	20000, Mixed	1400; Mixed (mild to moderate)
Setting (hospital, ambulatory,)	Ambulatory	Hospitalised	Hospitalised	Ambulatory
Intervention (generic drug name and dosage)	REGN10933+REGN10987 combination therapy intravenously (IV) single dose High dose Low dose	REGN10933+REGN10987 combination therapy intravenously (IV) single dose	Lopinavir-Ritonavir, Hydroxychloroquine, Corticosteroids, Azithromycin, Colchicine, IV Immunoglobulin (children only), Convalescent plasma, Synthetic neutralizing antibodies (REGN-COV2) single dose of REGN10933 + REGN10987 8 g, Tocilizumab or Aspirin, Colchicine	REGN10933+REGN10987 combination therapy, different intravenously and subcutaneous doses, single dose
Comparator (standard care or generic drug name and dosage)	Placebo IV Single Dose	Placebo	Standard care	Placebo iv or sc, single dose
Primary Outcome(s)	Proportion of patients with treatment-emergent serious adverse events (SAEs) [Through Day 29]; Proportion of patients with infusion-related reactions [Through Day 4]; Proportion of patients with hypersensitivity reactions [through Day 29]; Time-weighted average change from baseline in viral shedding as measured by quantitative reverse	Proportion of patients with treatment-emergent Serious Adverse Events (SAEs) [Through Day 169]; Proportion of patients with infusion-related reactions [Through Day 4]; Proportion of patients with hypersensitivity reactions [Through Day 29]; Time-weighted average change from baseline in viral shedding as measured by quantitative reverse transcription polymerase chain reaction (RT-qPCR) in	All-cause mortality [Within 28 days after randomisation]	Time-weighted average daily change from baseline in viral load (log10 copies/mL), as measured by reverse transcription quantitative polymerase chain reaction (RT-qPCR) in nasopharyngeal (NP) swab samples [Time Frame: Baseline to day 7]

	transcription quantitative polymerase chain reaction (RT-qPCR) in nasopharyngeal (NP) swab samples up to Day 22; Proportion of patients with at least one COVID-19 related medically attended visit [Through Day 29]	nasopharyngeal (NP) swab samples Baseline up to Day 22]; Proportion of patients with at least 1-point improvement on a 7-Point Ordinal Scale in clinical status [From Day 1 up to Day 29]		
Sponsor/ lead institution, country (also, country of recruitment if different)	Regeneron Pharmaceuticals, Romania, United States	Regeneron Pharmaceuticals, Brazil, Chile, Moldova, Republic of, Romania, United States	University of Oxford United Kingdom	Regeneron Pharmaceuticals, United States

*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 [1]) OR (controlled clinical trial [1])) OR (randomized [tiab])) OR (placebo [tiab])) OR (clinical trials as topic [mesh: noexp])) OR (randomly [tiab])) OR (trial [ti]))) NOT (animals [mh] NOT humans [mh]) AND (2019/10/01:2020[dp])	05/02/2020

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

Rolling Collaborative Review - Living Report
RCR16 - Casirivimab and Imdevimab (REGN-COV2) for the treatment of COVID-19

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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 [15, 16]. The retrieved hits were imported to a reference management tool, Endnote (Clarivate Analytics), for deduplication. We then searched the EndNote database using the generic names and synonyms for the included COVID-19 drugs.

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

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

Table 6-2. Search strategy to identify observational studies

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

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 REGN-COV-2/ or bamlanivimab/ or baricitinib/ or molnupiravir/ or Aspirin/ or mavrilimumab/ or exp Vitamin D/dt or Vitamin D Deficiency/dt or Ivermectin/) use medall [MeSH-terms for drugs in MEDLINE]

4   (Hyperimmune globulin/dt or tocilizumab/ or camostat/ or camostat mesilate/ or nafamstat/ or solnatide/ or anakinra/ or darunavir/ or favipiravir/ or sarilumab/ or exp Interferon/ or gimsilumab/ or canakinumab/ or baricitinib/ or acetylsalicylic acid/ or mavrilimumab/ or exp Vitamin D/dt or Vitamin D Deficiency/dt or ivermectin/) use oemezd [Emtree-terms for drugs in Embase]

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

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

6.3 Search strategy to identify ongoing studies

AIHTA is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and REGN-COV2 are described in Appendix Table 6-3.
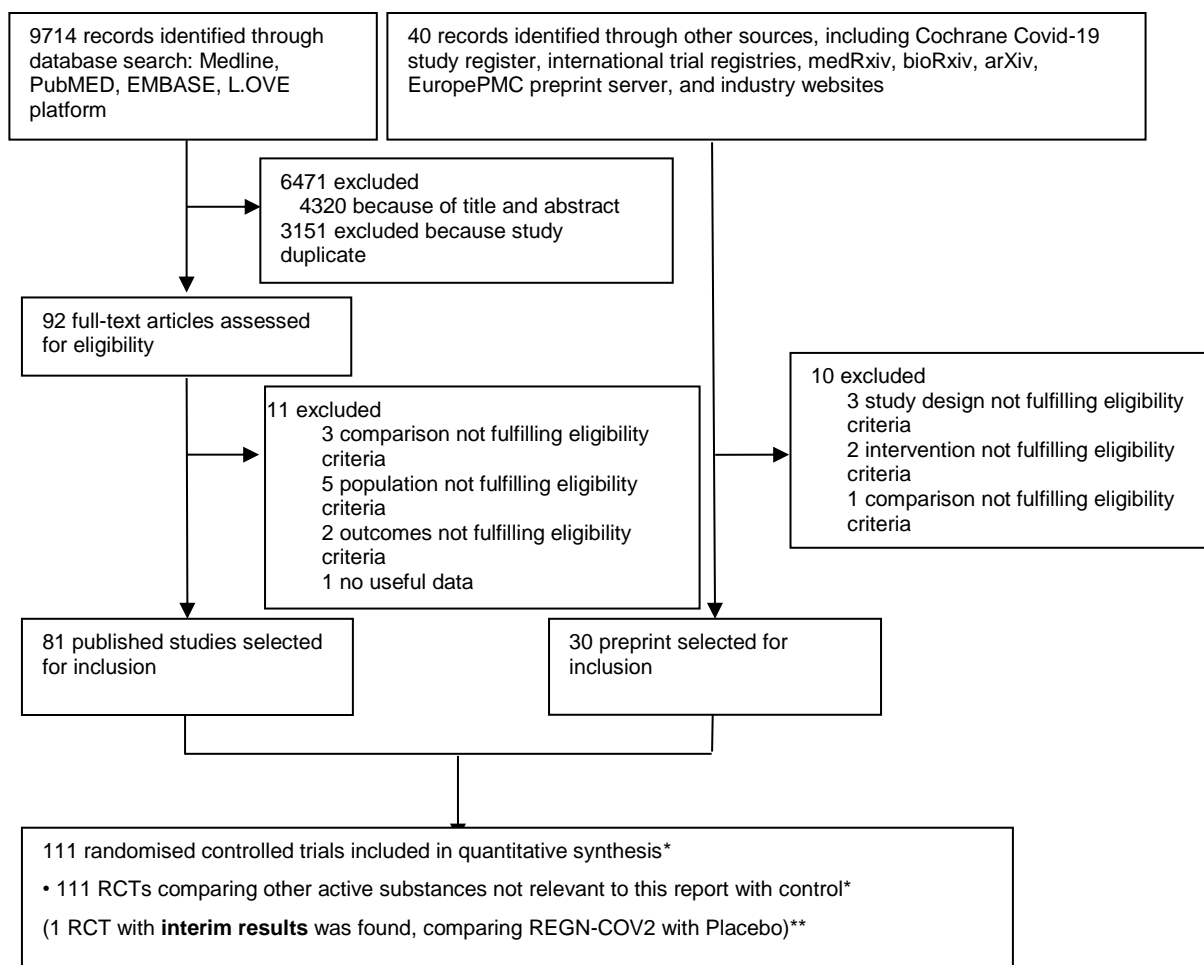
Table 6-3. Search strategy to identify ongoing studies

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 Terms used at "other terms": • REGN10933 and REGN10987 • REGN-COV2	08/02/2021	6 1 new
ISRCTN	https://www.isrctn.com/	Basic search mode Search terms: 1. covid-19 and REGN-COV2 2. covid-19 and REGN10933 and REGN10987 3. SARS-CoV-2 and REGN-COV2 4. SARS-CoV-2 REGN10933 and REGN10987	08/02/2021	1 0 new
European Clinical Trials Registry	https://www.clinicaltrialsregister.eu/	Basic search mode Search terms: 1. covid-19 and REGN-COV2 2. covid-19 and REGN10933 and REGN10987 3. SARS-CoV-2 and REGN-COV2 4. SARS-CoV-2 and REGN10933 and REGN10987	08/02/2021	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

```
┌─────────────────────────────┐   ┌──────────────────────────────────────────────┐
│ 9714 records identified      │   │ 40 records identified through other sources,   │
│ through database search:     │   │ including Cochrane Covid-19 study register,    │
│ Medline, PubMED, EMBASE,     │   │ international trial registries, medRxiv,        │
│ L.OVE platform               │   │ bioRxiv, arXiv, EuropePMC preprint server,     │
│                              │   │ and industry websites                          │
└─────────────────────────────┘   └──────────────────────────────────────────────┘
```

6471 excluded
  4320 because of title and abstract
3151 excluded because study duplicate

92 full-text articles assessed for eligibility

11 excluded
  3 comparison not fulfilling eligibility criteria
  5 population not fulfilling eligibility criteria
  2 outcomes not fulfilling eligibility criteria
  1 no useful data

10 excluded
  3 study design not fulfilling eligibility criteria
  2 intervention not fulfilling eligibility criteria
  1 comparison not fulfilling eligibility criteria

81 published studies selected for inclusion

30 preprint selected for inclusion

111 randomised controlled trials included in quantitative synthesis*

• 111 RCTs comparing other active substances not relevant to this report with control*

(1 RCT with **interim results** was found, comparing REGN-COV2 with Placebo)**

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.
** The RCT with **interim results** included in this report has been identified through the NEJM Published alerts
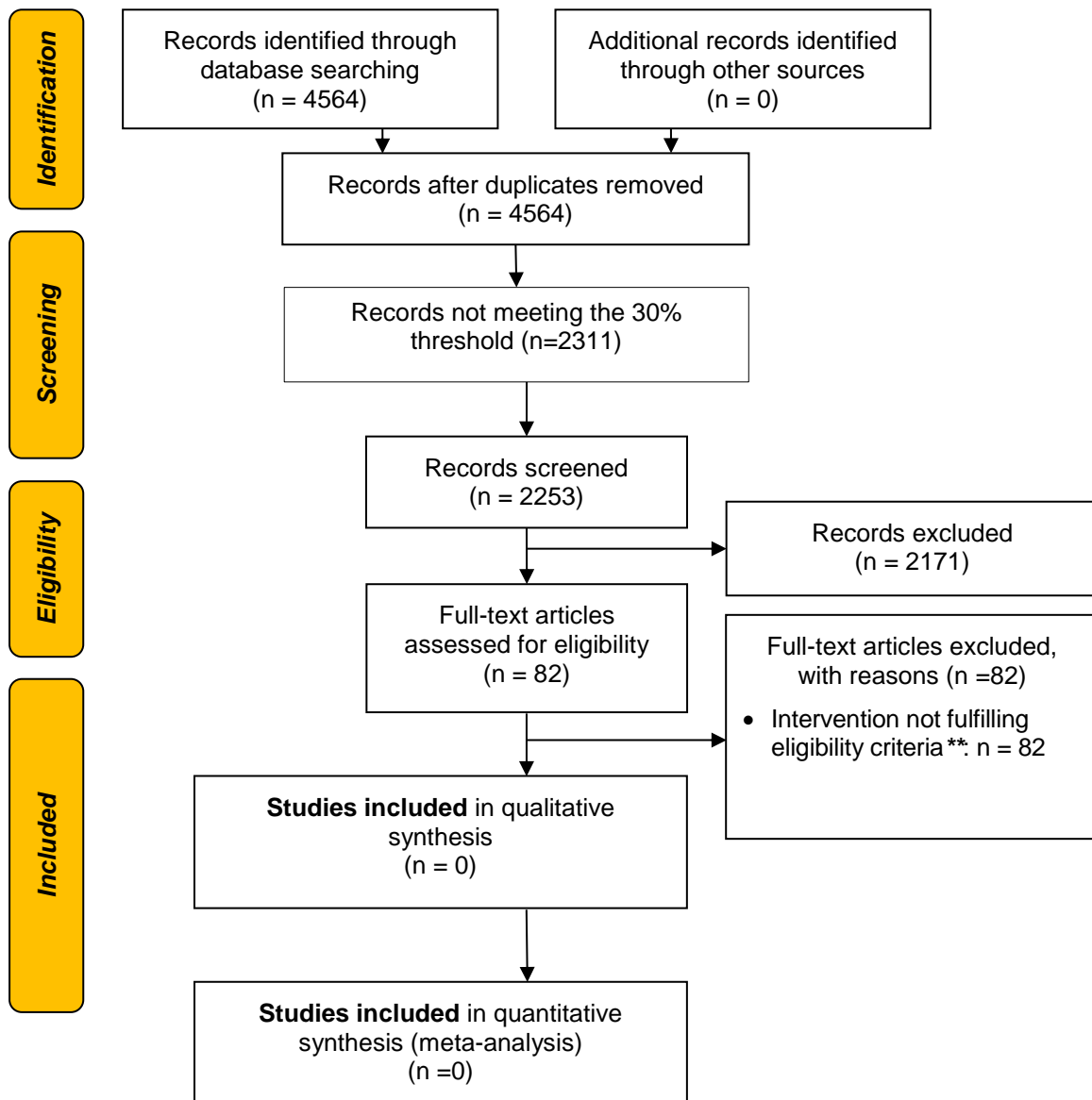
Appendix Figure 6-2. Flow diagram depicting the selection process of observational studies

** studies evaluating active substances relevant to other EUnetHTA rolling collaborative reviews