



**eunethta**  
EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

EUnetHTA Joint Action 3 WP4

**“Rolling Collaborative Review” of Covid-19 treatments**

**APN01 FOR THE TREATMENT OF COVID-19**

**Project ID: RCR09**  
Monitoring Report

**Version 4.0, December 2020**

Template version November 2020



This Rolling Collaborative Review Living Document is part of the project / joint action '724130 / EUnetHTA JA3' which has received funding from the European Union's Health Programme (2014-2020)

## DOCUMENT HISTORY AND CONTRIBUTORS

Version	Date	Description of changes
V 1.0	14/08/2020	First version
V 2.0	15/09/2020	Second version
V 3.0	15/10/2020	Third version
V 3.1	10/12/2020	Literature searches, Literature screening, Data extraction
V 4.0	15/12/2020	Fourth version

### Major changes from previous version

Chapter, page no.	Major changes from version 3.0
	<ul style="list-style-type: none"><li>No major changes...</li></ul>

### 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.

### Rolling Collaborative Review team

<b>Author(s)</b>	Spanish Agency of Medicines and Medical Devices (AEMPS), Andalusian Health Technology Assessment Unit (AETSA), Spain
<b>Co-Author(s)</b>	Department of Epidemiology Lazio Regional Health Service (DEPLazio), Italy

## Further contributors

Project Management	
Zorginstituut Nederland (ZIN), Netherlands	Coordination between involved parties throughout the assessment
Austrian Institute for Health Technology Assessment (AIHTA), Austria	Coordination of RCR

## 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).

## Copyright

EUnetHTA assessments are published under a “CC/BY/NC” [Creative Commons Licence](https://creativecommons.org/licenses/by-nc/4.0/).



## How to cite this assessment

Please cite this assessment as follows:

EUnetHTA Rolling Collaborative Review (RCR09) Authoring Team. APN01 for the treatment of COVID-19. Diemen (The Netherlands): EUnetHTA; 2020. [date of citation]. 21 pages. Report No.: RCR09. Available from: [https //www.eunetha.eu](https://www.eunetha.eu).

Contact the EUnetHTA Secretariat [EUnetHTA@zinl.nl](mailto:EUnetHTA@zinl.nl) with inquiries about this assessment.

## TABLE OF CONTENTS

<b>DOCUMENT HISTORY AND CONTRIBUTORS</b> .....	<b>2</b>
<b>TABLE OF CONTENTS</b> .....	<b>4</b>
<b>LIST OF TABLES AND FIGURES</b> .....	<b>4</b>
<b>1 OBJECTIVE</b> .....	<b>6</b>
<b>2 METHODS</b> .....	<b>6</b>
2.1 <i>SCOPE</i> .....	6
2.2 <i>SOURCES OF INFORMATION</i> .....	7
<b>3 ABOUT THE TREATMENT</b> .....	<b>10</b>
3.1 <i>MODE OF ACTION</i> .....	10
3.2 <i>REGULATORY STATUS</i> .....	10
3.3 <i>LEVEL OF EVIDENCE</i> .....	10
<b>4 SUMMARY</b> .....	<b>10</b>
4.1 <i>EFFECTIVENESS AND SAFETY EVIDENCE FROM RCTS</i> .....	10
4.2 <i>SAFETY EVIDENCE FROM OBSERVATIONAL STUDIES</i> .....	10
4.3 <i>ONGOING STUDIES</i> .....	10
4.4 <i>SCIENTIFIC CONCLUSION ABOUT STATUS OF EVIDENCE GENERATION</i> .....	11
<b>5 REFERENCES</b> .....	<b>13</b>
<b>6 APPENDIX</b> .....	<b>14</b>
6.1 <i>SEARCH STRATEGY TO IDENTIFY RANDOMISED CONTROLLED TRIALS</i> .....	14
6.2 <i>SEARCH STRATEGY TO IDENTIFY OBSERVATIONAL STUDIES</i> .....	17
6.3 <i>SEARCH STRATEGY TO IDENTIFY ONGOING STUDIES</i> .....	19
6.4 <i>FLOW DIAGRAMS</i> .....	20

## LIST OF TABLES AND FIGURES

Table 2-1 Scope of the RCR .....	6
Table 4-1 Ongoing trials of single agent APN01 .....	12
Table 6-1 Search strategy to identify randomised controlled studies.....	15
Table 6-2 Search strategy to identify observational studies.....	17
Table 6-3 Search strategy to identify ongoing studies .....	19
Appendix Figure 6-1. Flow diagram depicting the selection process of RCTs.....	20
Appendix Figure 6-2. Flow diagram depicting the selection process of observational studies.....	21

## LIST OF ABBREVIATIONS

ACE2	Angiotensin-converting Enzyme 2
AE	Adverse Event
ARDS	Acute Respiratory Distress Syndrome
CI	Confidence Interval
DOI	Declaration of interest
ECMO	Extracorporeal Membrane Oxygenation
EUnetHTA	European Network of Health Technology Assessment
FiO2	Fraction of Inspired Oxygen
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
ICD	International Classification of Diseases
ICU	Intensive Care Unit
ITT	Intention-to-treat
MAH	Marketing Authorisation Holder
MD	Mean Difference
mmHg	Millimetres of Mercury
NA	Not applicable
NMA	Network Meta-analysis
PAH	Pulmonary Arterial Hypertension
PaO2	Arterial Partial Pressure of Oxygen
RCR	Rolling Collaborative Review
RCT	Randomized Controlled Trial
REA	Relative Effectiveness Assessment
rhACE2	Recombinant Human Angiotensin-converting Enzyme 2
RR	Relative Risk
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SAE	Serious Adverse Event
SMD	Standardized Mean Difference
SoF	Summary of Findings
SOP	Standard Operating Procedure
SpO2	Saturation of Oxygen
WHO	World Health Organisation
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/services/covid-19/>) and on the EUnetHTA Rolling Collaborative Review Sharepoint page each 15<sup>th</sup> of the month.

### 2.1 Scope

**Table 2-1 Scope of the RCR**

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

	<ul style="list-style-type: none"> <li>• 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.</li> <li>• 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.</li> <li>• Moderate Illness: Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO<sub>2</sub>) ≥94% on room air at sea level.</li> <li>• Severe Illness: Individuals who have respiratory frequency &gt;30 breaths per minute, SpO<sub>2</sub> &lt;94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO<sub>2</sub>/FiO<sub>2</sub>) &lt;300 mmHg, or lung infiltrates &gt;50%.</li> <li>• Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.</li> </ul>
<b>Intervention</b>	APN01: recombinant form of the human angiotensin-converting enzyme 2 (rhACE2)
<b>Comparison</b>	Any active treatment, placebo, or standard of care.  <b>Rationale:</b> Since there is no gold standard treatment any comparator is acceptable as well as the above listed interventions.
<b>Outcomes</b>	<p><u>Main outcome:</u></p> <ul style="list-style-type: none"> <li>• All-cause Mortality (Survival)</li> </ul> <p><u>Additional Outcomes:</u></p> <p>Efficacy:</p> <ul style="list-style-type: none"> <li>• Length of hospital stay,</li> <li>• Viral burden (2019-nCoV RT-PCR negativity),</li> <li>• Clinical progression (WHO Clinical Progression Scale measured daily over the course of the study),</li> <li>• Rates of hospitalization and of patients entering ICU,</li> <li>• Duration of mechanical ventilation,</li> <li>• Quality of life.</li> </ul> <p>Safety:</p> <ul style="list-style-type: none"> <li>• Adverse events (AE),</li> <li>• Severe adverse events (SAE),</li> <li>• Withdrawals due to AEs,</li> <li>• Most frequent AEs,</li> <li>• Most frequent SAEs.</li> </ul> <p><b>Rationale:</b> We will give priority according to the Core Outcome Set for Clinical Trials on Coronavirus Disease 2019 (<a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102592/pdf/main.pdf">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102592/pdf/main.pdf</a>) 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>
<b>Study design</b>	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

<b>Population</b>	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.
<b>Intervention</b>	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.
<b>Comparison</b>	Any active treatment, placebo, or standard of care.
<b>Outcomes</b>	All-cause mortality  Additional outcomes: Length of hospital stay, 2019-nCoV RT-PCR negativity, PaO <sub>2</sub> /FiO <sub>2</sub> , Duration of mechanical ventilation, radiological imaging, Adverse events, Severe adverse events.
<b>Study design</b>	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 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.

<b>Population</b>	See project Scope
<b>Intervention</b>	APN01: recombinant form of the human angiotensin-converting enzyme 2 (rhACE2)
<b>Comparison</b>	Any active treatment, placebo, or standard of care.
<b>Outcomes</b>	See project Scope
<b>Study design</b>	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).

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 [AEMPS/AETSA] 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*

APN01 is a recombinant form of the human angiotensin-converting enzyme 2 (rhACE2), and it may have the potential to prevent the entry of SARS-CoV-2 into the host cell and reduce lung injury [4].

APN01 has a dual mode of action. APN01 imitates the human enzyme ACE2. The ACE2 receptor is expressed in human airway epithelia as well as lung parenchyma and it has been identified as the essential gateway used by SARS-CoV-19. The virus binds to soluble ACE2/APN01, instead of ACE2 on the cell surface and, therefore, the virus may no longer infect the cells. By preventing ACE2-mediated SARS-CoV-2 interaction, APN01 could prevent the harmful inflammatory reactions in the lungs and protect against acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) [4]. APN01 is administered intravenously as an infusion [5].

### 3.2 *Regulatory Status*

APN01 was developed by APEIRON biologics for the treatment of ALI, ARDS and PAH. After licensing from APEIRON in February 2010, GlaxoSmithKline (GSK) conducted several clinical trials from 2014 to 2017 to treat ALI/ARDS and PAH patients. In 2019, APEIRON obtained the APN01 licenses back from GSK for further clinical development [5].

APN01 is currently under investigation. No licenses have been granted for this product.

### 3.3 *Level of Evidence*

The safety of APN01 has been investigated in a total of 89 healthy volunteers and patients with pulmonary arterial hypertension (PAH) and ALI/ARDS in previously completed Phase I and Phase II clinical trials. The product candidate is currently in Phase II development by APEIRON Biologics for the treatment of PAH and ALI/ARDS [6].

## 4 SUMMARY

### 4.1 *Effectiveness and Safety evidence from RCTs*

The identified RCT (EudraCT Number: 2020-001172-15) is ongoing and results have not been published yet.

### 4.2 *Safety evidence from observational studies*

There are no published observational studies for APN01 on Covid-19 or ongoing studies for APN01 in combination with another agent.

### 4.3 *Ongoing studies*

The randomized, double-blind Phase II trial will compare APN01 to placebo in up to 200 patients at 10 sites in Austria, Denmark and Germany. The primary objective of the trial is to assess the clinical efficacy and safety of APN01 in severe COVID-19 patients using, among other criteria, the need for invasive mechanical ventilation. Secondary objectives include the evaluation of measurable biological biomarker changes following treatment with APN01.

#### **4.4 Scientific conclusion about status of evidence generation**

APN01 is a rhACE2 that is being studied as a treatment for patients with COVID-19 in a single RCT. The RCT is ongoing and no results have been published up to date.

**Table 4-1 Ongoing trials of single agent APN01**

<b>Trial Identifier/registry ID(s)/contact</b>	<b>NCT04335136</b> <b>APN01- 01-COVID19</b> <b>EudraCT Number: 2020-001172-15</b> <b>Sonja Höller, Dr. [<a href="mailto:sonja.hoeller@apeiron-biologics.com">sonja.hoeller@apeiron-biologics.com</a>] Tph. 43 1 865 65 77 128</b>
<b>Study design, study phase</b>	Phase 2. Randomised clinical trial,
<b>Recruitment status</b>	Recruiting
<b>Number of Patients, Disease severity*</b>	200 patients. Severity not specified but clinical condition is not deteriorating rapidly)
<b>Setting (hospital, ambulatory,..)</b>	Hospital
<b>Intervention (generic drug name and dosage)</b>	Intravenous RhACE2 APN01 twice daily
<b>Comparator (standard care or generic drug name and dosage)</b>	Placebo (physiological saline solution, twice daily)
<b>Primary Outcome(s)</b>	All Cause-death or invasive mechanical ventilation [ Time Frame: 28 days ] The primary endpoint is a composite endpoint of all cause-death or invasive mechanical ventilation up to 28 days or hospital discharge
<b>Sponsor/ lead institution, country (also country of recruitment if different)</b>	Apeiron Biologics. 22 study locations: Austria, Denmark, Germany, Russian Federation, United Kingdom <a href="https://clinicaltrials.gov/ct2/show/NCT04335136?term=apn01&amp;draw=1&amp;rank=1">https://clinicaltrials.gov/ct2/show/NCT04335136?term=apn01&amp;draw=1&amp;rank=1</a> [6]

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

## 5 REFERENCES

- [1] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from <http://www.training.cochrane.org/handbook>.
- [2] DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986; **7**: 177-188.
- [3] Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH. GRADE guidelines: 3. Rating the quality of evidence. *Journal of Clinical Epidemiology* 2011; **64**: 401-406.
- [4] Chary MA, Barbuto A, Izadmehr S, Hayes BD, Burns MM. COVID-19: Therapeutics and Their Toxicities. *J Med Toxicol.* 2020 Jul;**16**(3):284-94.
- [5] Technology Networks/ Apeiron Biologics. Phase 2 Clinical Trial of APN01 for Treatment of COVID-19 Initiated. 2020 [August 2020]; Available from: <https://www.technologynetworks.com/drug-discovery/news/phase-2-clinical-trial-of-apn01-for-treatment-of-covid-19-initiated-332897>.
- [6] ClinicalTrials.gov. NCT number: NCT04335136. 2020 [December 2020]; Available from: <https://clinicaltrials.gov/ct2/show/NCT04335136?term=apn01&draw=2&rank=1>.

## 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](http://www.clinicaltrials.gov)) and World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) ([www.who.int/ictcp/en/](http://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 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 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]))</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"> <li>1. exp coronavirus/</li> <li>2. ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw.</li> <li>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.</li> <li>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.</li> <li>5. ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (China* or Chinese* or Huanan*)).ti,ab,kw.</li> <li>6. "severe acute respiratory syndrome".ti,ab,kw.</li> <li>7. or/1-6</li> <li>8. randomized controlled trial.pt.</li> <li>9. controlled clinical trial.pt.</li> <li>10. random*.ab.</li> <li>11. placebo.ab.</li> <li>12. clinical trials as topic.sh.</li> <li>13. random allocation.sh.</li> <li>14. trial.ti.</li> <li>15. or/8-14</li> <li>16. exp animals/ not humans.sh.</li> <li>17. 15 not 16</li> <li>18. 7 and 17</li> <li>19. limit 18 to yr="2019 -Current"</li> </ol>	10/12/2020
OVID EMBASE	ovidsp.dc2.ovid.com	<ol style="list-style-type: none"> <li>1. exp Coronavirinae/ or exp Coronavirus/ exp Coronavirus infection/</li> <li>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.</li> <li>4. or/1-3</li> <li>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/</li> <li>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.</li> <li>7. 5 or 6</li> <li>8. 4 and 7</li> <li>9. limit 8 to yr="2019 -Current"</li> </ol>	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 15 included COVID-19 drugs.

**Table 6-2 Search strategy to identify observational studies**

Database	URL	Search terms / Search modality	Date of search
<p>OID 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  And from 1/09/2020 until 30/11/2020 for the new compounds Regeneron, Bamlanivimab, Baricitinib, Molnupiravir</p>
<p>OID 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</p>	<p>26/10/2020 until 30/11/2020  And from 1/09/2020 until 30/11/2020 for the new compounds Regeneron, Bamlanivimab</p>

		<p>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.</p> <p>6 ((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.</p> <p>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.</p> <p>8 6 or 7</p> <p>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 &gt; 20200920[date changes from week to week] AND ORIG-LOAD-DATE &lt; 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</p>

### 6.3 Search strategy to identify ongoing studies

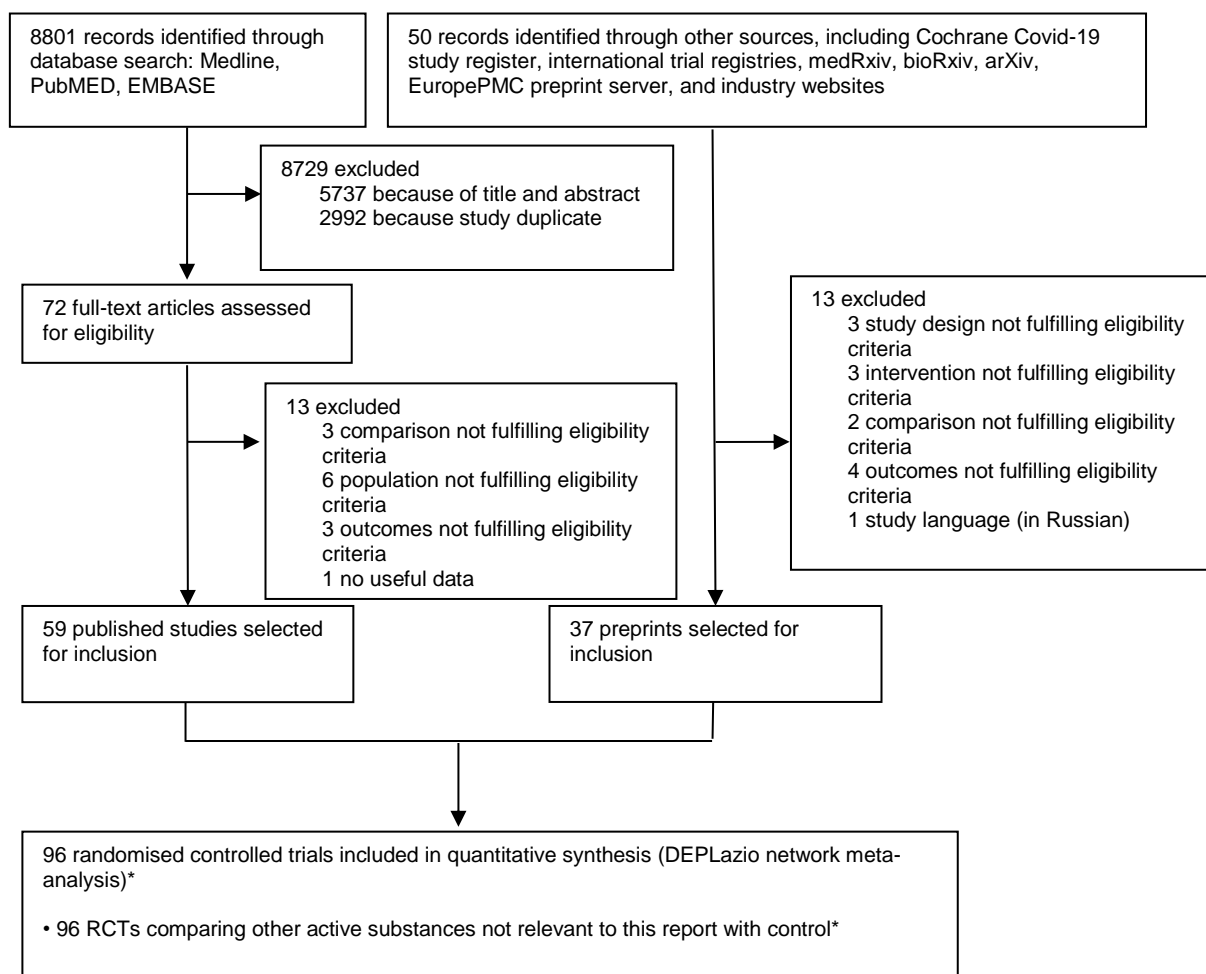
AEMPS/AETSA is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and APN01 are described in Appendix Table 6-3.

**Table 6-3 Search strategy to identify ongoing studies**

Database	URL	Search line / search terms	Date of search	Hits retrieved
ClinicalTrials.gov	<a href="https://clinicaltrials.gov/">https://clinicaltrials.gov/</a>	"Basic search mode*" [adapt if you used "Advanced search mode"] Terms used at Condition or disease: <ul style="list-style-type: none"> <li>covid-19</li> </ul> Terms used at "other terms": <ul style="list-style-type: none"> <li>APN01</li> </ul>	09/12/2020	[1] [0] new
ISRCTN	<a href="https://www.isrctn.com/">https://www.isrctn.com/</a>	Basic search mode [adapt if you used "Advanced search mode"] Search terms: 1. covid-19 and APN01	09/12/2020	[0] [0] new
European Clinical Trials Registry	<a href="https://www.clinicaltrialsregister.eu/">https://www.clinicaltrialsregister.eu/</a>	Basic search mode [adapt if you used "Advanced search mode"] Search terms: 1. covid-19 AND <b>APN01</b>	09/12/2020	[1] [0] new

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

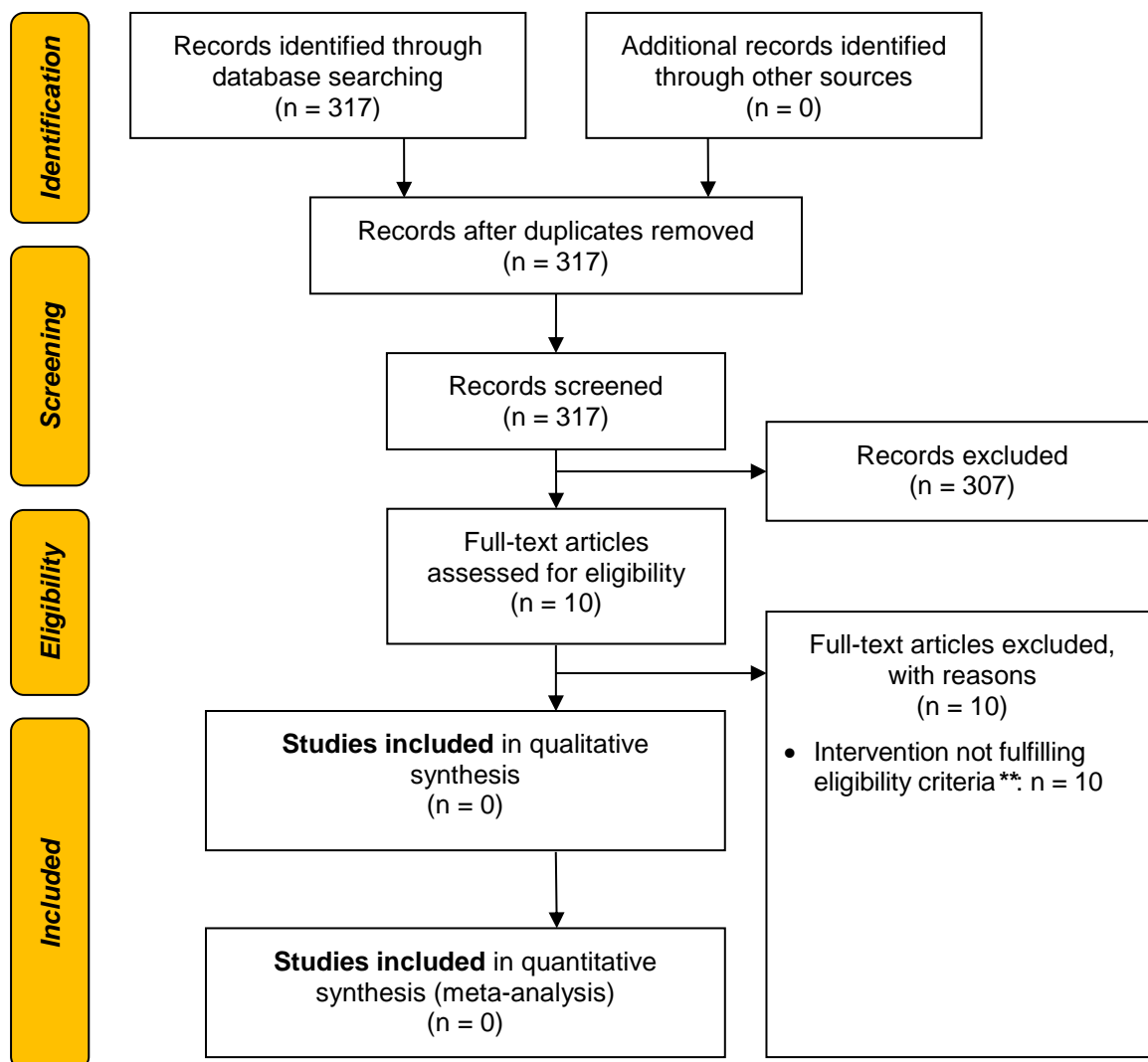
## 6.4 Flow diagrams



### 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