“Rolling Collaborative Review” of Covid-19 treatments

GIMSILUMAB FOR THE TREATMENT OF COVID-19

Project ID: RCR14
Monitoring Report

Version 3.0, May 2021

Template version February 2021
DOCUMENT HISTORY AND CONTRIBUTORS

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Description of changes</th>
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<tr>
<td>V 1.0</td>
<td>14/08/2020</td>
<td>First version</td>
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<tr>
<td>V 2.0</td>
<td>15/09/2020</td>
<td>Second version</td>
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<td>V 3.0</td>
<td>17/05/2021</td>
<td>Third version</td>
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Major changes from previous version

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<tr>
<th>Chapter, page no.</th>
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<tr>
<td>p. 14-15</td>
<td>Search strategy to identify randomised controlled studies (Table 6.1) was added</td>
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<tr>
<td>p. 16-18</td>
<td>Search strategy to identify observational studies (Table 6.2) was added</td>
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<td>p. 19</td>
<td>Search strategy to identify ongoing studies (Table 6.3) was added</td>
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<tr>
<td>p. 20</td>
<td>Flow diagram depicting the selection process of RCTs was added</td>
</tr>
<tr>
<td>p. 21</td>
<td>Flow diagram depicting the selection process of observational studies</td>
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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.

Rolling Collaborative Review team

<table>
<thead>
<tr>
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<th>State Medicines Control Agency of Lithuania (SMCA), Lithuania</th>
</tr>
</thead>
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<tr>
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</tbody>
</table>
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<table>
<thead>
<tr>
<th>Project Management</th>
<th>Coordination between involved parties throughout the assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zorginstituut Nederland (ZIN), Netherlands</td>
<td>Coordination of RCR</td>
</tr>
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<td>Austrian Institute for Health Technology Assessment (AIHTA), Austria</td>
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</tbody>
</table>

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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TABLE OF CONTENTS

DOCUMENT HISTORY AND CONTRIBUTORS .................................................. 2
TABLE OF CONTENTS .................................................................................. 4
LIST OF TABLES AND FIGURES .................................................................. 4
1 OBJECTIVE ............................................................................................ 6
2 METHODS .............................................................................................. 6
   2.1 SCOPE .......................................................................................... 6
   2.2 SOURCES OF INFORMATION ......................................................... 7
3 ABOUT THE TREATMENT ......................................................................... 10
   3.1 MODE OF ACTION ...................................................................... 10
   3.2 REGULATORY STATUS ............................................................... 10
   3.3 LEVEL OF EVIDENCE ................................................................. 10
4 SUMMARY ............................................................................................. 10
   4.1 EFFECTIVENESS AND SAFETY EVIDENCE FROM RCTs .......... 10
   4.2 SAFETY EVIDENCE FROM OBSERVATIONAL STUDIES ........... 10
   4.3 ONGOING STUDIES ................................................................. 10
   4.4 SCIENTIFIC CONCLUSION ABOUT STATUS OF EVIDENCE GENERATION .............................................................. 10
5 REFERENCES .......................................................................................... 12
6 APPENDIX ............................................................................................. 13
   6.1 SEARCH STRATEGY TO IDENTIFY RANDOMISED CONTROLLED TRIALS .............................................................. 13
   6.2 SEARCH STRATEGY TO IDENTIFY OBSERVATIONAL STUDIES ............................................................... 16
   6.3 SEARCH STRATEGY TO IDENTIFY ONGOING STUDIES .......... 19
   6.4 FLOW DIAGRAMS ......................................................................... 20

LIST OF TABLES AND FIGURES

Table 2-1 Scope of the RCR ........................................................................... 6
Table 4-4 Ongoing trials of single agent Gimsilumab ........................................... 11
Table 6-1 Search strategy to identify randomised controlled studies .................. 14
Table 6-2 Search strategy to identify observational studies ................................. 16
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

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>DOI</td>
<td>Declaration of interest</td>
</tr>
<tr>
<td>EUnetHTA</td>
<td>European Network of Health Technology Assessment</td>
</tr>
<tr>
<td>GRADE</td>
<td>Grading of Recommendations, Assessment, Development and Evaluation</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard Ratio</td>
</tr>
<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
</tr>
<tr>
<td>MD</td>
<td>Mean Difference</td>
</tr>
<tr>
<td>MeSH</td>
<td>Medical Subject Headings</td>
</tr>
<tr>
<td>NA</td>
<td>Not applicable</td>
</tr>
<tr>
<td>NR</td>
<td>Not reported</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized Controlled Trial</td>
</tr>
<tr>
<td>RCR</td>
<td>Rolling Collaborative Review</td>
</tr>
<tr>
<td>REA</td>
<td>Relative Effectiveness Assessment</td>
</tr>
<tr>
<td>RR</td>
<td>Relative Risk</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SMD</td>
<td>Standardized Mean Difference</td>
</tr>
<tr>
<td>WP4</td>
<td>Work Package 4</td>
</tr>
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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

<table>
<thead>
<tr>
<th>Description</th>
<th>Project Scope</th>
</tr>
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<tbody>
<tr>
<td>Population</td>
<td>Disease</td>
</tr>
<tr>
<td></td>
<td>ICD-Codes (<a href="https://www.who.int/classifications/icd/covid19/en">https://www.who.int/classifications/icd/covid19/en</a>)</td>
</tr>
<tr>
<td></td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>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.</td>
</tr>
<tr>
<td>MeSH-terms</td>
<td>COVID-19, Coronavirus Disease 2019</td>
</tr>
<tr>
<td>Target population</td>
<td>(<a href="https://www.covid19treatmentguidelines.nih.gov/overview/management-of-covid-19/">https://www.covid19treatmentguidelines.nih.gov/overview/management-of-covid-19/</a>)</td>
</tr>
</tbody>
</table>
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

Treatment with gimsilumab - human monoclonal antibody that acts on granulocyte-macrophage colony-stimulating factor (GM-CSF).

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.pdf) and A minimal common outcome measure set for COVID-19 clinical research from the WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection.

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

<table>
<thead>
<tr>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any active treatment, placebo, or standard of care.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised controlled trials (RCT); no restriction on language of publication</td>
</tr>
</tbody>
</table>

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](http://deplazio.net/farmacicovid/index.html) for SoF (or [https://covid-nma.com/](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.

<table>
<thead>
<tr>
<th>Population</th>
<th>See project Scope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Treatment with gimsilumab - human monoclonal antibody that acts on granulocyte-macrophage colony-stimulating factor (GM-CSF).</td>
</tr>
<tr>
<td>Comparison</td>
<td>Any active treatment, placebo, or standard of care.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>See project Scope</td>
</tr>
<tr>
<td>Study design</td>
<td>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</td>
</tr>
</tbody>
</table>

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 SMCA extracts the data and assesses the risk of bias using Robins-I ([https://training.cochrane.org/handbook/current/chapter-25](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/](https://clinicaltrials.gov/)
- ISRCTN: [https://www.isrctn.com/](https://www.isrctn.com/)
- European Clinical Trials Registry: [https://www.clinicaltrialsregister.eu/](https://www.clinicaltrialsregister.eu/)

Inclusion criteria: Randomised controlled trials, Controlled trials

One researcher of SMCA 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

Gimsilumab is a fully human monoclonal antibody that acts on granulocyte-macrophage colony-stimulating factor (GM-CSF) [7]; it is manufactured by Roivant Sciences Ltd. /Altasciences.

3.2 Regulatory Status

Gimsilumab – ATC-code not assigned yet. Gimsilumab belongs to anti-inflammatories, antirheumatics, monoclonal antibodies drug class and has no approval for any indication by EMA or FDA yet. It is known that studies are currently underway for these indications (excluding Covid-19): adult respiratory distress syndrome (Phase IIA) and ankylosing spondylitis (Phase IA) [7, 8].

3.3 Level of Evidence

There is one finished Phase II study of Gimsilumab. The results haven’t been published yet [6].

4 SUMMARY

4.1 Effectiveness and Safety evidence from RCTs

There are no published results from RCTs related to effectiveness and safety of Gimsilumab for Covid-19 treatment yet.

4.2 Safety evidence from observational studies

There are no published results from observational studies related to effectiveness and safety of gimsilumab for Covid-19 treatment.

4.3 Ongoing studies

There is one finished Phase II study of Gimsilumab, the results haven’t been published yet [7].

4.4 Scientific conclusion about status of evidence generation

There is RCT, the results haven’t been published yet. So far no conclusions can be drawn.
Table 4-1 Ongoing trials of single agent Gimsilumab

<table>
<thead>
<tr>
<th>Trial identifier/registry ID(s)/contact</th>
<th>NCT04351243 (KIN-1901-2001)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design, study phase</td>
<td>Phase II study. To assess the efficacy and safety of gimsilumab in subjects with lung injury or acute respiratory distress syndrome (ARDS) secondary to COVID-19.</td>
</tr>
<tr>
<td>Recruitment status</td>
<td>Completed, results are not provided yet</td>
</tr>
<tr>
<td>Number of Patients, Disease severity*</td>
<td>n = 270 (Adult, Older Adult; 18 Years and older). Disease severity – moderate and severe</td>
</tr>
<tr>
<td>Setting (hospital, ambulatory,..)</td>
<td>Hospital</td>
</tr>
<tr>
<td>Intervention (generic drug name and dosage)</td>
<td>A high dose of gimsilumab on Day 1 and a low dose of gimsilumab on Day 8. The Day 8 dose will be omitted if the subject is discharged from the hospital or is no longer in need of supplemental oxygen or ventilatory support for &gt;48 hours.</td>
</tr>
<tr>
<td>Comparator (standard care or generic drug name and dosage)</td>
<td>Placebo (saline solution) on Day 1 and on Day 8.</td>
</tr>
<tr>
<td>Primary Outcome(s)</td>
<td>Incidence of mortality [Time Frame: Day 43];</td>
</tr>
<tr>
<td>Sponsor/ lead institution, country (also country of recruitment if different)</td>
<td>Kinevant Sciences GmbH</td>
</tr>
</tbody>
</table>
5 REFERENCES


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

<table>
<thead>
<tr>
<th>Database</th>
<th>URL</th>
<th>Search line / Search terms</th>
<th>Date of search</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pubmed</td>
<td>pubmed.ncbi.nlm.nih.gov</td>
<td>1. ((((((&quot;Coronavirus&quot;[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 &quot;2019-nCoV*[Title/Abstract]) OR 2019nCoV*[Title/Abstract]) OR nCoV2019*[Title/Abstract]) OR &quot;nCoV-2019*[Title/Abstract]) OR &quot;COVID-19*[Title/Abstract]) OR COVID19*[Title/Abstract]) OR &quot;CORVID-19*[Title/Abstract]) OR CORVID19*[Title/Abstract]) OR &quot;WN-CoV*[Title/Abstract]) OR WNCov*[Title/Abstract]) OR &quot;HCoV-19*[Title/Abstract]) OR HCoV19*[Title/Abstract]) OR CoV*[Title/Abstract]) OR &quot;2019 novel*&quot;<em>[Title/Abstract]) OR Ncov</em>[Title/Abstract]) OR &quot;n-cov&quot;<em>[Title/Abstract]) OR &quot;SARS-CoV-2</em>[Title/Abstract]) OR &quot;SARSCoV2*[Title/Abstract]) OR &quot;SARS-CoV-19*[Title/Abstract]) OR &quot;SARSCov19*[Title/Abstract]) OR &quot;SARS-CoV-19*[Title/Abstract]) OR &quot;SARS-Cov-19*[Title/Abstract]) OR Ncorona*[Title/Abstract]) OR Ncorno*[Title/Abstract]) OR NcovWuhan*[Title/Abstract]) OR NcovHubei*[Title/Abstract]) OR NcovaChina*[Title/Abstract]) OR NcovaChinese*[Title/Abstract]) OR (((respiratory*[Title/Abstract]) AND (symptom*[Title/Abstract]) OR disease*[Title/Abstract]) OR illness*[Title/Abstract]) OR condition*[Title/Abstract]) OR &quot;seafood market*[Title/Abstract]) OR &quot;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 (&quot;severe acute respiratory syndrome&quot;)<em>[Title/Abstract]) OR (&quot;corona</em>[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])</td>
<td>03/05/2021</td>
</tr>
<tr>
<td>Database</td>
<td>URL</td>
<td>Search line / Search terms</td>
<td>Date of search</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
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</tbody>
</table>
| 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 coronavirus* or corona[virinae]* or Coronavirus* or Coronavirus* 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 "SARS-CoV-2" or "SARS-CoV-2" or "SARS-CoV2" or "SARS-CoV-2" or SARSCov19 or "SARS-CoV19" 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 Coronavirus2019 or coronavirus19 or coronavirus2019 or COVID19 or "COVID19" or nCOV19 or nCOV2019 or "SARS Corona virus 2" or "SARS Coronavirus 2" or "SARS-CoV-2" or "SARS-CO-V-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 (COVID-19: a living systematic map of the evidence, Live map of COVID-19 evidence). 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 along 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 EUenetHTA 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

<table>
<thead>
<tr>
<th>Database</th>
<th>URL</th>
<th>Search terms / Search modality</th>
<th>Date of search</th>
<th>Hits retrieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embase</td>
<td>1974 to 2021</td>
<td>Lines 1 and 2 are copies of Ovid's Expert searches for covid-19 in MEDLINE and Embase</td>
<td>From 06/04/2021 until 03/05/2021</td>
<td>1032</td>
</tr>
<tr>
<td>Ovid</td>
<td>MEDLINE(R) ALL 1946 to 2021</td>
<td>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-cov2 or sars-cov2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus* or corona virus or pandemic*) or ((covid or covid19 or covid-19) and pandemic*) 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]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
|            |                   | 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-cov2 or sars-cov2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or}
Rolling Collaborative Review - Living Report
RCR14- Gimsilumab for the treatment of COVID-19

May 2021
EUnetHTA Joint Action 3 WP4

Rolling Collaborative Review - Living Report
RCR14- Gimsilumab for the treatment of COVID-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 pandemic")2) or ((covid or covid19 or covid-19) and pandemic")2 or (coronavirus" and pneumonia" or pneumonia") or (coronavirus disease 2019 or severe acute respiratory syndrome coronavirus 2).sh,dj.) use oemedz [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 alunacendase alfa/ or darunavir/ or favipiravir/ or sarilumab/ or exp Interferons/ or gimsilumab/ or canakinumab/ or baricitinib/ or molnupiravir/ or Aspirin/ or mavlilumumab/ or exp Vitamin D/dt or Vitamin D Deficiency/dt or Ivermectin/) use oemedz [MeSH-terms for drugs in MEDLINE]

4 (Hyperimmune globulin/dt or tocilizumab/ or camostat/ or camostat mesilate/ or nafamostat/ or solnaitide/ or anakinra/ or darunavir/ or favipiravir/ or sarilumab/ or exp Interferon/ or gimsilumab/ or canakinumab/ or baricitinib/ or acetylsalicylic acid/ or mavlilumumab/ or exp Vitamin D/dt or Vitamin D Deficiency/dt or Ivermectin/) use oemedz [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 immun?ation or (tocilizumab or atilzumab or (MRA adj monoclonal antibody") or MSB-11456 or MSB11456 or R-1569 or R1569 or RO-4785533 or RO4785533 or Actemra or Roactemra) or (camostat* or FOY-305 or FOY305 or FOY S 980 or nafamostat or nafamostat or FUT-175 or FUT175) or (solnaitide 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 (alunacendase 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 novatferon 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 llans) or (baricitinib or LY-309104 or LY309104 or INCB-028050 or INCB028050 or INCB28050 or Olumiant) or (molnupiravir or MK-4482 or MK4482 or EIDD-2801 or EIDD2801) or (aspirin or acetylsalicylic acid) or (mavlilumumab or immunoglobulin G4 or CAM-3001 or CAM3001) or ((vitamin? D? or D?) adj4 (high-dose* or highdose* or supplement*)) or (ivermect* or MK-933 or MK933)).mp.bt,ot,du,dy,ln,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*).dt. use medall [time limits in MEDLINE]
<p>| | | |</p>
<table>
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<tbody>
<tr>
<td></td>
<td>2021043* OR 202105*).dc. use oemezd [time limits in Embase]</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>(1 and (3 or 5) and 6) use medall</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>(2 and (4 or 5) and 7) use oemezd</td>
<td></td>
</tr>
</tbody>
</table>
6.3 Search strategy to identify ongoing studies

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

Table 6-3 Search strategy to identify ongoing studies

<table>
<thead>
<tr>
<th>Database</th>
<th>URL</th>
<th>Search line / search terms</th>
<th>Date of search</th>
<th>Hits retrieved</th>
</tr>
</thead>
</table>
| ClinicalTrials.gov              | https://clinicaltrials.gov/              | "Basic search mode"**  
Terms used at Condition or disease:  
- covid-19  
- Gimsilumab  
- Anti-GM-CSF | 10/05/2021 | 1 0 new |
| ISRCTN                          | https://www.isrctn.com/                 | Basic search mode [adapt if you used “Advanced search mode”]  
Search terms:  
1. covid-19 and Gimsilumab  
2. covid-19 and KIN-1901  
3. covid-19 and KIN-1901  
4. covid-19 and Anti-GM-CSF  
5. covid-19 and Anti-GM-CSF  
6. SARS-CoV-2 and Gimsilumab  
7. SARS-CoV-2 and KIN-1901  
8. SARS-CoV-2 and KIN-1901  
9. SARS-CoV-2 and Anti-GM-CSF  
10. SARS-CoV-2 and Anti-GM-CSF | 10/05/2021 | 1 0 new |
| European Clinical Trials Registry | https://www.clinicaltrialsregister.eu/  | Basic search mode [adapt if you used “Advanced search mode”]  
Search terms:  
1. covid-19 and Gimsilumab  
2. covid-19 and KIN-1901  
3. covid-19 and KIN-1901  
4. covid-19 and Anti-GM-CSF  
5. covid-19 and Anti-GM-CSF  
6. SARS-CoV-2 and Gimsilumab  
7. SARS-CoV-2 and KIN-1901  
8. SARS-CoV-2 and KIN-1901  
9. SARS-CoV-2 and Anti-GM-CSF  
10. SARS-CoV-2 and Anti-GM-CSF | 10/05/2021 | 0 0 new |

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

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May 2021 EUnetHTA Joint Action 3 WP4 19
### 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](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