



**eunethta**  
EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

EUnetHTA Joint Action 3 WP4

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

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

**Project ID: RCR07**  
Monitoring Report

**Version 4.0, November 2020**

Template version October 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	November 2020	Literature searches, Literature screening, Clinical Trials Registries search, Data extraction
V 3.2	11/11/2020	Data extraction complete
V 3.3	12/11/2020	Check of data extraction
V 4.0	15/11/2020	Fourth version

### Major changes from previous version

Chapter, page no.	Major changes from version 3.0
Summary, p.13	One RCT was suspended – ANACONDA (NCT04364009) – due to efficiency and safety reasons, after enrolment of 71 hospitalized COVID-19 patients in France. The intermediate review of data from this clinical trial showed early excess mortality in the group of patients treated with anakinra plus standard optimized care vs standard optimized care alone.

### 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>	Austrian Institute for Health Technology Assessment (AIHTA), Austria
<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 (RCR07) Authoring Team. Anakinra for the treatment of COVID-19. Diemen (The Netherlands): EUnetHTA; 2020. [date of citation]. 32 pages. Report No.: RCR07. Version 4.0, November 2020. Available from: <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</b> .....	<b>4</b>
<b>LIST OF 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> .....	8
<b>3 ABOUT THE TREATMENT</b> .....	<b>11</b>
3.1 <i>MODE OF ACTION</i> .....	11
3.2 <i>REGULATORY STATUS</i> .....	11
3.3 <i>LEVEL OF EVIDENCE</i> .....	11
<b>4 SUMMARY</b> .....	<b>13</b>
4.1 <i>EFFECTIVENESS AND SAFETY EVIDENCE FROM RCTs</i> .....	13
4.2 <i>SAFETY EVIDENCE FROM OBSERVATIONAL STUDIES</i> .....	13
4.3 <i>ONGOING STUDIES</i> .....	13
4.4 <i>SCIENTIFIC CONCLUSION ABOUT STATUS OF EVIDENCE GENERATION</i> .....	13
<b>5 REFERENCES</b> .....	<b>23</b>
<b>6 APPENDIX</b> .....	<b>24</b>
6.1 <i>SEARCH STRATEGY TO IDENTIFY RANDOMISED CONTROLLED TRIALS</i> .....	24
6.2 <i>SEARCH STRATEGY TO IDENTIFY OBSERVATIONAL STUDIES</i> .....	27
6.3 <i>SEARCH STRATEGY TO IDENTIFY ONGOING STUDIES</i> .....	29
6.4 <i>FLOW DIAGRAMS</i> .....	30

## LIST OF TABLES

Table 2-1 Scope of the RCR .....	6
Table 4-1 Summary of safety from observational studies (AE and SAE) of anakinra.....	14
Table 4-2 Ongoing trials of single agent anakinra.....	16
Table 4-3 Ongoing trials of single agent anakinra (continued).....	18
Table 4-4 Ongoing trials of single agent anakinra (continued).....	19
Table 4-5 Ongoing trials of single agent anakinra (continued) and combination therapies.....	21
Table 6-1 Search strategy to identify randomised controlled studies.....	25
Table 6-2 Search strategy to identify observational studies.....	27
Table 6-3 Search strategy to identify ongoing studies .....	29

## LIST OF FIGURES

Appendix Figure 6-1. Flow diagram depicting the selection process of RCTs.....	30
Appendix Figure 6-2. Flow diagram depicting the selection process of observational studies .....	31
Appendix Figure 6-3. Flow diagram depicting the selection process of ongoing studies .....	32

## LIST OF ABBREVIATIONS

AE	Adverse Event
ARR	Absolute Risk Reduction
ATC	Anatomical Therapeutic Chemical [Classification System]
ATMP	Advanced therapy medicinal product
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
HRQOL	Health-related Quality of Life
ICD	International Classification of Diseases
ITT	Intention-to-treat
MD	Mean Difference
MeSH	Medical Subject Headings
NA	Not applicable
NR	Not reported
OR	Odds Ratio
PP	Per Protocol
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
SmPC	Summary of product characteristics
SOP	Standard Operating Procedure
WP4	Work Package 4

## 1 OBJECTIVE

The aim of this EUnetHTA Rolling Collaborative Review is

- to inform health policy at the national/regional and at the European level at an early stage in the life-cycle of therapies which interventions are currently undergoing clinical trials,
- to monitor (ongoing studies and their results) permanently - in the format of a Living Document - potential therapies against covid-19,
- to present comparative data on effectiveness and safety of potential therapies and
- to support preparations for an evidence-based purchasing of regional/ national health politicians, if necessary.

To avoid redundancies and duplication, the EUnetHTA Rolling Collaborative Review will reuse sources from international initiatives to collect information and data on Covid-19 treatments.

The scope of the Rolling Collaborative Review is of descriptive nature. These **EUnetHTA Rolling Collaborative Reviews are not meant to substitute a joint Relative Effectiveness Assessment (REA)** adhering to the agreed procedures and aiming at critical appraisal of the clinical evidence based on the Submission Dossier submitted by the (prospective) Marketing Authorization Holder (MAH).

## 2 METHODS

This Rolling Collaborative Review is prepared according to the project plan (“Rolling Collaborative Review (RCR) on Covid-19 treatments: Project description and planning”, published [on the EUnetHTA website](#)) and will be updated monthly. Monthly updates are published on the EUnetHTA Covid-19 Website (<https://eunetha.eu/services/covid-19/>) and on the EUnetHTA Rolling Collaborative Review Sharepoint page each 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>	Anakinra (Kineret®): immunosuppressive medicine, a copy of a natural human protein - 'human interleukin 1 receptor antagonist' (r-metHuIL-1ra, produced in Escherichia coli cells by recombinant DNA technology); it neutralises the biologic activity of interleukin-1α (IL-1α) and interleukin-1β (IL-1β) by competitively inhibiting their binding to interleukin-1 type I receptor (IL-1RI). Interleukin-1 (IL-1) is a pivotal pro-inflammatory cytokine mediating many cellular responses including those important in synovial inflammation.
<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/qk/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>	Anakinra (Kineret®): immunosuppressive medicine, a copy of a natural human protein - 'human interleukin 1 receptor antagonist' (r-metHuIL-1ra, produced in Escherichia coli cells by recombinant DNA technology); it neutralises the biologic activity of interleukin-1 $\alpha$ (IL-1 $\alpha$ ) and interleukin-1 $\beta$ (IL-1 $\beta$ ) by competitively inhibiting their binding to interleukin-1 type I receptor (IL-1RI). Interleukin-1 (IL-1) is a pivotal pro-inflammatory cytokine mediating many cellular responses including those important in synovial inflammation.
<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, 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. The process of study selection is depicted in a flow diagram (Appendix Figure 6-3). 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

Anakinra (Kineret®) is an immunosuppressive medicine, a copy of a natural human protein - 'human interleukin 1 receptor antagonist' (r-metHuIL-1ra, produced in *Escherichia coli* cells by recombinant DNA technology). Anakinra neutralises the biologic activity of interleukin-1 $\alpha$  (IL-1 $\alpha$ ) and interleukin-1 $\beta$  (IL-1 $\beta$ ) by competitively inhibiting their binding to interleukin-1 type I receptor (IL-1RI). Interleukin-1 (IL-1) is a pivotal pro-inflammatory cytokine mediating many cellular responses including those important in synovial inflammation [4]. Boehringer Ingelheim RCV GmbH & Co KG, Austria and Pfizer Health AB, Sweden, are listed as manufacturers of the biological active substance, and Swedish Orphan Biovitrum AB, Sweden, as Marketing Authorisation Holder, responsible for batch release.

#### 3.2 Regulatory Status

Anakinra is authorised in the EU for Rheumatoid Arthritis (RA), Cryopyrin-Associated Periodic Syndromes (CAPS), Familial Mediterranean Fever (FMF) and Still's Disease [4, 5]. Kineret® received a marketing authorisation valid throughout the European Union on 8 March 2002; Anakinra received the FDA approval in November 2001. It is available as a solution for injection under the skin.

Anakinra is not authorised in Covid-19 patients (EMA, FDA) [5].

#### 3.3 Level of Evidence

As of November 11, 2020, no publications related to RCTs evaluating anakinra treatment in COVID-19 patients were found.

Related to safety evidence from prospective observational studies, one prospective cohort study was found: the Ana-COVID study, with 52 consecutive severe Covid-19 patients who received subcutaneous anakinra at dose of 100 mg twice daily for 72 h, followed by 100 mg daily for 7 days, in addition to the standard treatment and supportive care (with a historical comparison group, n=44 patients, who received standard care), published by Huet et al. 2020 [6].

Safety outcomes measured were an increase in liver aminotransferase enzymes (more than three times the upper limit of normal), thromboembolic events (confirmed by a CT pulmonary angiogram for pulmonary embolism and by a venous doppler for deep vein thrombosis of the lower limbs), bacteraemia (confirmed when the patient had a recognised pathogen cultured from one or more blood cultures), and premature discontinuation of treatment. Authors reported an increase in liver aminotransferases occurred in seven (13%) patients in the anakinra group and four (9%) patients in the historical group. Ten (19%) patients in the anakinra group and five (11%) in the historical group developed a thromboembolic event during the hospital stay. Among the anakinra group, seven (13%) had a pulmonary embolism, three (6%) had deep vein thrombosis of the lower limbs, and one (2%) had arterial thrombosis. None of the patients in the anakinra group had a documented bacterial infection during the hospital stay [6]. Summary of safety can be found in Table 4-1.

Several ongoing RCTs and one interventional nRCT are registered in EudraCT, ISRCTN and ClinicalTrials.gov registers, including 30 to 342 COVID-19 patients per study. Seven RCTs evaluate anakinra alone, as well as one interventional nRCT; two RCTs evaluate anakinra alone and in combination with ruxolitinib, and one RCT evaluates anakinra alone and in combination with siltuximab or tocilizumab. Details can be found in Table 4-2, Table 4-3, Table 4-4 and Table 4-5.

One RCT was found in ClinicalTrials.gov and EudraCT registers – ANACONDA (NCT04364009) – which was suspended due to efficiency and safety reasons, after enrolment of 71 hospitalized COVID-19 patients in France. On October 29, 2020, the French National Agency for Medicines and Health Products Safety (ANSM) announced that inclusions in clinical trials evaluating anakinra (Kineret®) in the treatment of COVID-19 are suspended due to safety information regarding the ANACONDA-COVID-19

clinical trial, <https://ansm.sante.fr/S-informer/Actualite/Suspension-des-inclusions-en-France-dans-les-essais-clinique-évaluant-l-anakinra-dans-la-prise-en-charge-de-la-COVID-19-Point-d-information>.

The intermediate review of data from this clinical trial showed early excess mortality in the group of patients treated with anakinra combined with standard optimized care, compared to the group of patients treated with standard optimized care alone. A deleterious effect of anakinra (Kinere<sup>®</sup>) cannot be ruled out, as the information available at this stage does not explain this difference between the two treatment arms. In this context, the CHRU de Tours, sponsor of this clinical trial, suspended inclusions in the ANACONDA-COVID-19 trial. Inclusions are also suspended in other clinical trials conducted with anakinra and authorized in France under the COVID-19 indication. These clinical trials had already stopped or had not yet begun.

The US COVID-19 Treatment Guidelines Panel stated that there are insufficient data to recommend either for or against anakinra therapy in patients with COVID-19 disease [7].

## **4 SUMMARY**

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

Currently, no publications related to RCTs of anakinra treatment in COVID-19 patients were found.

### **4.2 Safety evidence from observational studies**

In one prospective cohort study with high risk of bias, an increase in liver aminotransferases occurred in similar frequency in both groups. More patients in the anakinra group developed a thromboembolic event (pulmonary embolism, deep vein thrombosis of the lower limbs, and arterial thrombosis). None of the patients had a documented bacterial infection during the hospital stay.

### **4.3 Ongoing studies**

Several RCTs and one interventional nRCT related to anakinra alone or in combination therapy are currently ongoing. One RCT– ANACONDA (NCT04364009) – was suspended due to efficiency and safety reasons, after enrolment of 71 hospitalized COVID-19 patients. On October 29, 2020, the French National Agency for Medicines and Health Products Safety (ANSM) announced that inclusions in clinical trials evaluating anakinra (Kineret®) in the treatment of COVID-19 in France are suspended due to safety information regarding the ANACONDA-COVID-19 clinical trial.

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

At the moment, effectiveness and safety of anakinra treatment from RCTs in COVID-19 patients could not be assessed. The same is true for safety from prospective observational studies because only one prospective cohort study with high risk of bias was found.

High quality evidence from ongoing RCTs are expected to assess effectiveness and safety of anakinra in COVID-19 patients.

**Table 4-1 Summary of safety from observational studies (AE and SAE) of anakinra**

Author, year	Huet, 2020
Country	France
Sponsor	Groupe Hospitalier Paris Saint-Joseph
Intervention/Product (drug name)	Anakinra
Dosage	100 mg twice a day for 72 h, then 100 mg daily for 7 days
Comparator	Standard treatments and supportive care
Study design	Observational prospective cohort study with historical control
Setting	Hospital
Number of pts	52 in anakinra group and 44 in historical control
Inclusion criteria	Aged 18 years or older and admitted to Groupe Hospitalier Paris Saint-Joseph with severe COVID-19-related bilateral pneumonia on chest x-ray or lung CT scan; either laboratory-confirmed SARS-CoV-2 or typical lung infiltrates on a lung CT scan, and either an oxygen saturation of 93% or less under oxygen 6 L/min or more, or aggravation (saturation $\leq$ 93% under oxygen 3 L/min) with a loss of 3% of oxygen saturation in ambient air over the previous 24 h.
Age of patients (yrs)	71.0 in anakinra group vs 71.1 in historical group
Disease severity	Severe COVID-19-related bilateral pneumonia requiring oxygen therapy
Follow-up (months)	Until discharge from hospital or death
Loss to follow-up, n (%)	None
RoB	High
<b>Safety – Outcomes*</b>	
Overall AEs, n (%)	Increase in liver aminotransferases:  Seven (13%) patients in the anakinra group vs four (9%) patients in the historical group  Thromboembolic event:  Ten (19%) patients in the anakinra group vs five (11%) in the historical group  (among the anakinra group, seven (13%) had a pulmonary embolism, three (6%) had deep vein thrombosis of the lower limbs, and one (2%) had arterial thrombosis)
Serious AE (SAE), n (%)	Not reported as such (see above)
Most frequent AEs n (%)	See above

Author, year	Huet, 2020
Most frequent SAEs, n (%)	Not reported as such (see above)
AEs of special interest, n (%)	Not reported as such (see above)
Death as SAE, n (%)	Not reported
Withdrawals due AEs, n (%)	Not reported

**Abbreviations:** RoB=Risk of Bias (Robins-I: <https://training.cochrane.org/handbook/current/chapter-25>)

*\*by arms*

**Table 4-2 Ongoing trials of single agent anakinra**

Active substance	Anakinra	Anakinra	Anakinra
<b>Sponsor</b>	Fundacion Miguel Servet	Karolinska University Hospital	University Hospital, Tours
<b>Trial Identifier</b>	NCT04443881, EudraCT 2020-001825-29 (ANA-COVID-GEAS)	NCT04412291, EudraCT 2020-001748-24 (ImmCoVA) Study	NCT04364009, EudraCT 2020-001734-36 (ANACONDA)
<b>Phase &amp; Intention</b>	Phase 2/3, investigating the efficacy and safety of intravenous administration of anakinra, an interleukin 1 receptor antagonist (IL-1), added to standard treatment, compared to standard treatment alone, to reduce hyperinflammation and respiratory distress in patients with SARS-CoV-2 infection	Phase 2, to compare standard-of-care with anakinra and tocilizumab treatment the Immunomodulation-CoV Assessment (ImmCoVA) Study	Phase 3, to assess the efficacy of anakinra + optimized Standard of Care (oSOC) as compared to oSOC alone on the condition of patients with COVID-19 infection and worsening respiratory symptoms
<b>Study design</b>	RCT, open label, parallel group, 2-arm, multicenter study	RCT, open label, parallel group assignment	RCT, open label, parallel group assignment
<b>Status of trial</b>	Recruiting	Recruiting	<b>Suspended (Efficiency and safety reasons)</b>
<b>Duration/End of Study</b>	May 2020 - March 2021	June 2020 – February 2021	April 2020 – September 2020
<b>Study details</b>			
<b>Number of Patients</b>	180	120	240
<b>Disease severity</b>	Severe pneumonia COVID-19	Patients with COVID-19 and Respiratory Distress not requiring mechanical ventilation	Patients with COVID-19 infection and worsening respiratory symptoms
<b>Setting</b>	Hospital	Hospital	Hospital
<b>Location/Centres</b>	Spain	Sweden	France
<b>Intervention drug name and dosage</b>	Anakinra (100 mg/ 6 hours) i.v infusión during 15 days plus standard of care	Anakinra total dose of 400mg per day (divided in 4 doses of 100 mg iv every 6 hours) for 7 days + Standard of care	Anakinra 400mg from Day 1 to Day 3 (two injections of 100 mg each 12 hours) and 200mg the remaining 7 days plus Optimized Standard of Care (oSOC)
<b>Comparator (drug name and dosage)</b>	Standard of care	Tocilizumab: 8mg/kg for a single infusion iv up to max 800 mg + Standard of care  Standard of care alone	Optimized Standard of Care (oSOC)
<b>Duration of observation/ Follow-up</b>	Up to 28 days	Up to 60 days	Up to 28 days
<b>Primary Outcomes</b>	Primary: Treatment success, defined as number of patients not requiring mechanical ventilation by Day 15; Number of patients not requiring mechanical ventilation; Time to mechanical ventilation; Time to oxygen	Primary: Time to recovery [Time Frame: Day 1 through Day 29]	Primary: Treatment success [Time Frame: After 14 days of treatment]

Active substance	Anakinra	Anakinra	Anakinra
	saturation normalization; Stay in ICU and hospitalization		
<b>Results/Publication</b>	Not applicable (ongoing trial)	Not applicable (ongoing trial)	Not applicable (ongoing trial) - <b>Suspended (Efficiency and safety reasons)</b>

**Table 4-3 Ongoing trials of single agent anakinra (continued)**

Active substance	Anakinra	Anakinra	Anakinra
<b>Sponsor</b>	Swedish Orphan Biovitrum	Hellenic Institute for the Study of Sepsis	Weill Medical College of Cornell University
<b>Trial Identifier</b>	NCT04324021 EudraCT 2020-001167-93	NCT04339712, EudraCT 2020-001039-29 (ESCAPE)	NCT04603742 (SOBI)
<b>Phase &amp; Intention</b>	Phase 2/3, to assess the efficacy and safety of emapalumab or anakinra, versus standard of care (SoC)	Phase 2, to assess personalized immunotherapy in patients with SARS-CoV-2 (COVID-19) associated with organ dysfunction and with laboratory findings of macrophage activation syndrome or immune dysregulation	Phase 2, to assess efficacy of anakinra, in reducing the need for mechanical ventilation and/or 28-day mortality among patients with COVID-19 who have features of cytokine storm syndrome and severe respiratory failure
<b>Study design</b>	RCT, open label, parallel group assignment	nRCT interventional study	RCT, double-blind, placebo-controlled, parallel group assignment
<b>Status of trial</b>	Recruiting	Recruiting	Not yet recruiting
<b>Duration/End of Study</b>	April 2020 - September 2020	April 2020 - April 2022	November 2020 – February 2022
<b>Study details</b>			
<b>Number of Patients</b>	54	40	100
<b>Disease severity</b>	Patients With SARS-CoV-2 Infection	Life-threatening organ dysfunction by SARS-CoV-2	Severe COVID-19
<b>Setting</b>	Hospital	Hospital	Hospital
<b>Location/Centres</b>	Italy	Greece	US
<b>Intervention drug name and dosage</b>	Anakinra i.v infusion four times daily for 15 days. 400 mg/day in total, divided into 4 doses given every 6 hours + Standard of care  Emapalumab i.v infusion every 3rd day for a total 5 infusions. Day 1: 6mg/kg. Days 4, 7, 10 and 13: 3 mg/kg + Standard of care	Anakinra 200mg three times daily (every eight hours) for 7 days  Tocilizumab 8mg/kg body weight once up to a maximum of 800mg	Anakinra 100 mg IV 4 times a day for 7 days
<b>Comparator (drug name and dosage)</b>	Standard of care	No comparator	Normal saline IV
<b>Duration of observation/ Follow-up</b>	Up to weeks 10	Up to day 90	Up to 60 days
<b>Primary Outcomes</b>	Primary: Treatment success [Time Frame: Up to Day 15]	Primary: Change of baseline total sequential organ failure assessment (SOFA) score; Improvement of lung involvement measurements; Increase of pO <sub>2</sub> /FiO <sub>2</sub> ratio	Primary: Number of subjects alive without having required mechanical ventilation [Time Frame: 28 days post randomization]
<b>Results/Publication</b>	Not applicable (ongoing trial)	Not applicable (ongoing trial)	Not applicable (ongoing trial)

**Table 4-4 Ongoing trials of single agent anakinra (continued)**

Active substance	Anakinra	Anakinra	Anakinra
<b>Sponsor</b>	University of Alabama at Birmingham	Assistance Publique - Hôpitaux de Paris	Hospital/treatment centre
<b>Trial Identifier</b>	NCT04362111	NCT04341584 (CORIMUNO-ANA)	ISRCTN67000768; NCT02735707; EudraCT2015-002340-14 (REMAP-CAP)
<b>Phase &amp; Intention</b>	3, to determine whether early treatment with anakinra in patients admitted to the hospital with markers of Cytokine Storm Syndrome improves or prevents deterioration of respiratory dysfunction and prevents the development of respiratory failure requiring mechanical ventilation	2, to determine the therapeutic effect and tolerance of anakinra in patients with moderate, severe pneumonia or critical pneumonia associated with Coronavirus disease 2019 (COVID-19)	4, to evaluate the effect of a range of interventions to improve outcome as defined by all-cause mortality at 90 days, in patients admitted to intensive care with severe community-acquired pneumonia. During this pandemic, to identify the effect of a range for interventions to improve outcome for patients admitted to hospital with acute illness due to suspected or confirmed pandemic infection.
<b>Study design</b>	RCT, placebo controlled, parallel assignment, triple masked	RCT, parallel assignment, open label	RCT, embedded, multifactorial adaptive platform trial, open label
<b>Status of trial</b>	Recruiting	Not yet recruiting	Recruiting
<b>Duration/End of Study</b>	July 2020-March 2021	April 2020-December 2020	Original study start date: April 2016. Study protocol amended (COVID-19 added) in March 2020/ 2023
<b>Study details</b>			
<b>Number of Patients</b>	30	240	7100
<b>Disease severity</b>	Severe	Severe and critical	Severe
<b>Setting</b>	Hospital	Hospital	Hospital
<b>Location/Centres</b>	US	France	Australia, Belgium, Canada, Croatia, Germany, Hungary, Ireland, Netherlands, New Zealand, Portugal, Romania, Spain, United Kingdom
<b>Intervention drug name and dosage</b>	Anakinra 100 mg subcutaneously every 6-12 hours for a period of 10 days	Treatment includes the administration of two IV infusions / day of anakinra 200mg (total 400 mg) at day 1 (D1), D2 and D3, two IV infusions / day of anakinra 100mg (total 200 mg) at day 4 (D4), and one IV infusion of anakinra 100mg (total 100 mg) at day 5 (D5)	Anakinra (loading dose 300mg, followed by maintenance doses of 100mg administered every 6 hours) (as COVID-19 immune modulation – pandemic) (As one intervention among other drugs listed as intervention in pandemic - antivirals, immune modulation, immunoglobulin therapy, anticoagulation, simvastatin, vitamin C therapy, corticosteroids, antibiotic domain, macrolide domain...)
<b>Comparator (drug name and dosage)</b>	Normal saline placebo subcutaneously every 6-12 hours for period of 10 days	Standard of care	No immune modulation for COVID-19

<b>Active substance</b>	<b>Anakinra</b>	<b>Anakinra</b>	<b>Anakinra</b>
<b>Duration of observation/ Follow-up</b>	Up to Day 28	Up to 90 days	Up to 90 days
<b>Primary Outcomes</b>	Primary: Percentage of patients discharged from the hospital alive and without the need for mechanical ventilation [Time Frame: Variable up to Day 28]	Primary: Survival without needs of ventilator utilization at day 14 [Time Frame: 14 days]; WHO progression scale $\leq 5$ [Time Frame: 4 days]; Cumulative incidence of successful tracheal extubation; Decrease of at least one point in WHO progression scale score [Time Frame: 4 days]	Primary: All-cause mortality; Days alive and outside of ICU
<b>Results/Publication</b>	Not applicable (ongoing trial)	Not applicable (ongoing trial)	Not applicable (ongoing trial)

**Table 4-5 Ongoing trials of single agent anakinra (continued) and combination therapies**

Active substance	Anakinra alone (and Anakinra + Siltuximab and Anakinra + Tocilizumab)	Anakinra alone (and Anakinra plus Ruxolitinib)	Anakinra alone (and Anakinra plus Ruxolitinib)
<b>Sponsor</b>	University Hospital, Ghent / Belgium Health Care Knowledge Centre	Assistance Publique Hôpitaux de Marseille	Centre Hospitalier Intercommunal de Toulon La Seyne-sur-mer
<b>Trial Identifier</b>	NCT04330638, EudraCT 2020-001500-41 (COV-AID)	EudraCT 2020-001754-21, NCT04424056 (INFLAMMACOV)	EudraCT 2020-001963-10, NCT04366232 (JAKINCOV)
<b>Phase &amp; Intention</b>	Phase 3, to test the safety and effectiveness of individually or simultaneously blocking IL-6 and IL-1 versus standard of care on blood oxygenation and systemic cytokine release syndrome in patients with COVID-19 coronavirus infection and acute hypoxic respiratory failure and systemic cytokine release syndrome	Phase 3, to assess anakinra or tocilizumab alone or in combination with ruxolitinib in severe stage 2b and 3 COVID-19 disease	Phase 3, to compare clinical and biological efficacy of a therapeutic strategy using anakinra with or without ruxolitinib for serious cases of SARS-CoV-2 infection, oxygen dependent, needing or not an invasive ventilation on systemic inflammation
<b>Study design</b>	RCT, open label, factorial assignment	RCT, open label	RCT, open label
<b>Status of trial</b>	Recruiting	Ongoing	Ongoing
<b>Duration/End of Study</b>	April 2020 - December 2020	Start May 2020	Start May 2020
<b>Study details</b>			
<b>Number of Patients</b>	342	150	54
<b>Disease severity</b>	COVID-19 Patients with Acute Hypoxic Respiratory Failure and Systemic Cytokine Release Syndrome	Severe stage 2b and 3 COVID-19 disease	Serious cases of SARS-CoV-2 infection, oxygen dependent, needing or not an invasive ventilation on systemic inflammation
<b>Setting</b>	Hospital	Hospital	Hospital
<b>Location/Centres</b>	Belgium	France	France
<b>Intervention drug name and dosage</b>	Anakinra alone (as a daily subcutaneous injection of 100 mg for 28 days or until hospital discharge, whichever is first)  Siltuximab alone (via single IV infusion at a dose of 11 mg/kg)  Tocilizumab alone (via single IV infusion at a dose of 8 mg/kg with a maximum infusion of 800 mg/injection)  Anakinra + Siltuximab  Anakinra + Tocilizumab	Anakinra alone Tocilizumab alone or in combination with Ruxolitinib	Anakinra with or without Ruxolitinib

Active substance	Anakinra alone (and Anakinra + Siltuximab and Anakinra + Tocilizumab)	Anakinra alone (and Anakinra plus Ruxolitinib)	Anakinra alone (and Anakinra plus Ruxolitinib)
Comparator (drug name and dosage)	Usual care	See above	See above
Duration of observation/ Follow-up	Up to 28 days and 10-20 weeks	Up to 28 days and 12 months	Up to 28 days
Primary Outcomes	Primary: Time to Clinical Improvement [Time Frame: at day 15]	Primary: Ventilation free days at D28 (VFD28) (an increase of 5 days VFD28 is expected)	Primary: Biological criteria: validation if at least 3 parameters are met including CRP and/or Ferritin 1) CRP: decrease > 50% 2) Ferritinemia: decrease > 1/3 3) Serum creatinine: decrease > 1/3 4) AST/ALT: decrease > 50% 5) Eosinophils > 50 /mm <sup>3</sup> 6) Lymphocytes > 1000 /mm <sup>3</sup>
Results/Publication	Not applicable (ongoing trial)	Not applicable (ongoing trial)	Not applicable (ongoing trial)

## 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] The European public assessment report (EPAR). Kineret - Product Information. [updated 24/06/2020]. Available from: [https://www.ema.europa.eu/en/documents/product-information/kineret-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/kineret-epar-product-information_en.pdf).
- [5] AIHTA Policy Brief Nr.: 002\_V4 2020: Covid-19, HSS/ Horizon Scanning, Living Document July 2020, Part 1. Wien: HTA Austria – Austrian Institute for Health Technology Assessment GmbH.
- [6] Huet T, Beaussier H, Voisin O, Jouveshomme S, Dauriat G, Lazareth I, et al. Anakinra for severe forms of COVID-19: a cohort study. *The Lancet Rheumatology*. 2020;**2**(7):e393-e400. DOI: 10.1016/S2665-9913(20)30164-8.
- [7] National Institutes of Health (NIH). COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. 2020 [cited 11/11/2020]. Available from: <https://www.covid19treatmentguidelines.nih.gov/>

## 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/ictpr/en/](http://www.who.int/ictpr/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>	06/11/2020

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>	06/11/2020
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>	06/11/2020

## 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>OVID Medline</p>	<p>Imported from EPPI Centre</p>	<p>1 exp Coronavirus/ 2 exp Coronavirus Infections/ 3 (coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*).mp. 4 (or/1-3) and ((2019* or 202*).dp. or 20190101:20301231.(ep).) 5 4 not (SARS or SARS-CoV or MERS or MERS-CoV or Middle East respiratory syndrome or camel* or dromedar* or equine or coronary or coronal or covidence* or covidien or influenza virus or HIV or bovine or calves or TGEV or feline or porcine or BCoV or PED or PEDV or PDCoV or FIPV or FCoV or SADS-CoV or canine or CCov or zoonotic or avian influenza or H1N1 or H5N1 or H5N6 or IBV or murine corona*).mp. 6 ((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp. 7 (2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV on nCoV or covid or coronavirus* or corona virus or Pandemi*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp. 8 COVID-19.rx,px,ox. or severe acute respiratory syndrome coronavirus 2.os. 9 ("32240632" or "32236488" or "32268021" or "32267941" or "32169616" or "32267649" or "32267499" or "32267344" or "32248853" or "32246156" or "32243118" or "32240583" or "32237674" or "32234725" or "32173381" or "32227595" or "32185863" or "32221979" or "32213260" or "32205350" or "32202721" or "32197097" or "32196032" or "32188729" or "32176889" or "32088947" or "32277065" or "32273472" or "32273444" or "32145185" or "31917786" or "32267384" or "32265186" or "32253187" or "32265567" or "32231286" or "32105468" or "32179788" or "32152361" or "32152148" or "32140676" or "32053580" or "32029604" or "32127714" or "32047315" or "32020111" or "32267950" or "32249952" or "32172715").ui. 10 or/6-9 11 5 or 10</p>	<p>27/09/2020 until 25/10/2020</p>
<p>OVID EMBASE</p>		<p>1 exp Coronavirus Infections/ 2 exp coronavirinae/ 3 (coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*).mp. 4 or/1-3 5 4 not (SARS or SARS-CoV or MERS or MERS-CoV or Middle East respiratory syndrome or camel* or dromedar* or equine or coronary or coronal or covidence* or covidien or influenza virus or HIV or bovine or calves or TGEV or feline or porcine or BCoV or PED or PEDV or PDCoV or FIPV or FCoV or SADS-CoV or canine or CCov or zoonotic or avian influenza or H1N1 or H5N1 or H5N6 or IBV or murine corona*).mp.</p>	<p>27/09/2020 until 25/10/2020</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.  7 (2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV on nCoV or covid or coronavirus* or corona virus or Pandemi*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp.  8 6 or 7  9 5 or 8</p>	
Scopus		<p>TITLE-ABS-KEY(((pneumonia OR covid* OR coronavirus* OR "corona virus*" OR ncov* OR 2019-ncov OR sars*) AND Wuhan) OR 2019-ncov OR ncov19 OR ncov-19 OR "2019-novel CoV" OR sars-cov2 OR sars-cov-2 OR sarscov2 OR sarscov-2 OR sars-coronavirus2 OR sars-coronavirus-2 OR "SARS-like coronavirus*" OR coronavirus-19 OR covid19 OR covid-19 OR "covid 2019" OR ((novel OR new OR nouveau) W/1 (CoV OR nCoV OR covid OR coronavirus* OR "corona virus*" OR pandemi*)) OR ((covid OR covid19 OR covid-19) AND pandemic*) OR ((coronavirus* OR "corona virus*") AND pneumonia)) AND ORIG-LOAD-DATE &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>27/09/2020 until 25/10/2020</p>

### 6.3 Search strategy to identify ongoing studies

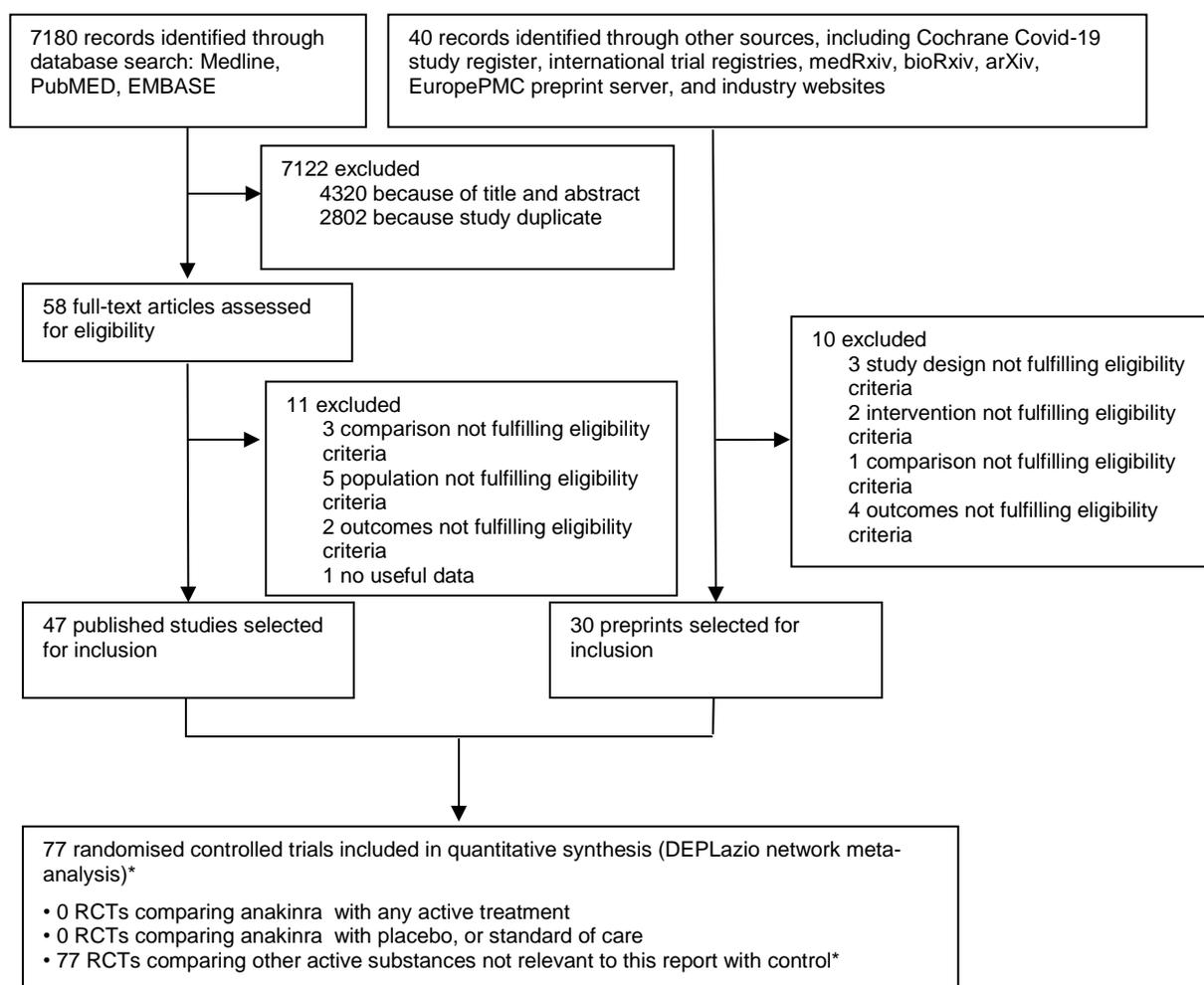
AIHTA is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and anakinra are described in Appendix Table 6-3.

**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"* 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>• Anakinra</li> <li>• IL-1RA</li> </ul>	11/11/2020	27 1 new
ISRCTN	<a href="https://www.isrctn.com/">https://www.isrctn.com/</a>	Basic search mode Search terms: <ol style="list-style-type: none"> <li>1. covid-19 and Anakinra</li> <li>2. covid-19 and Kineret</li> <li>3. covid-19 and Kinaret</li> <li>4. covid-19 and IL-1RA</li> <li>5. covid-19 and rIL-1ra</li> <li>6. SARS-CoV-2 and Anakinra</li> <li>7. SARS-CoV-2 and Kineret</li> <li>8. SARS-CoV-2 and Kinaret</li> <li>9. SARS-CoV-2 and IL-1RA</li> <li>10. SARS-CoV-2 and rIL-1ra</li> </ol>	11/11/2020	2 0 new
European Clinical Trials Registry	<a href="https://www.clinicaltrialsregister.eu/">https://www.clinicaltrialsregister.eu/</a>	Basic search mode Search terms: <ol style="list-style-type: none"> <li>1. covid-19 and Anakinra</li> <li>2. covid-19 and Kineret</li> <li>3. covid-19 and Kinaret</li> <li>4. covid-19 and IL-1RA</li> <li>5. covid-19 and rIL-1ra</li> <li>6. SARS-CoV-2 and Anakinra</li> <li>7. SARS-CoV-2 and Kineret</li> <li>8. SARS-CoV-2 and Kinaret</li> <li>9. SARS-CoV-2 and IL-1RA</li> <li>10. SARS-CoV-2 and rIL-1ra</li> </ol>	11/11/2020	14 0 new

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

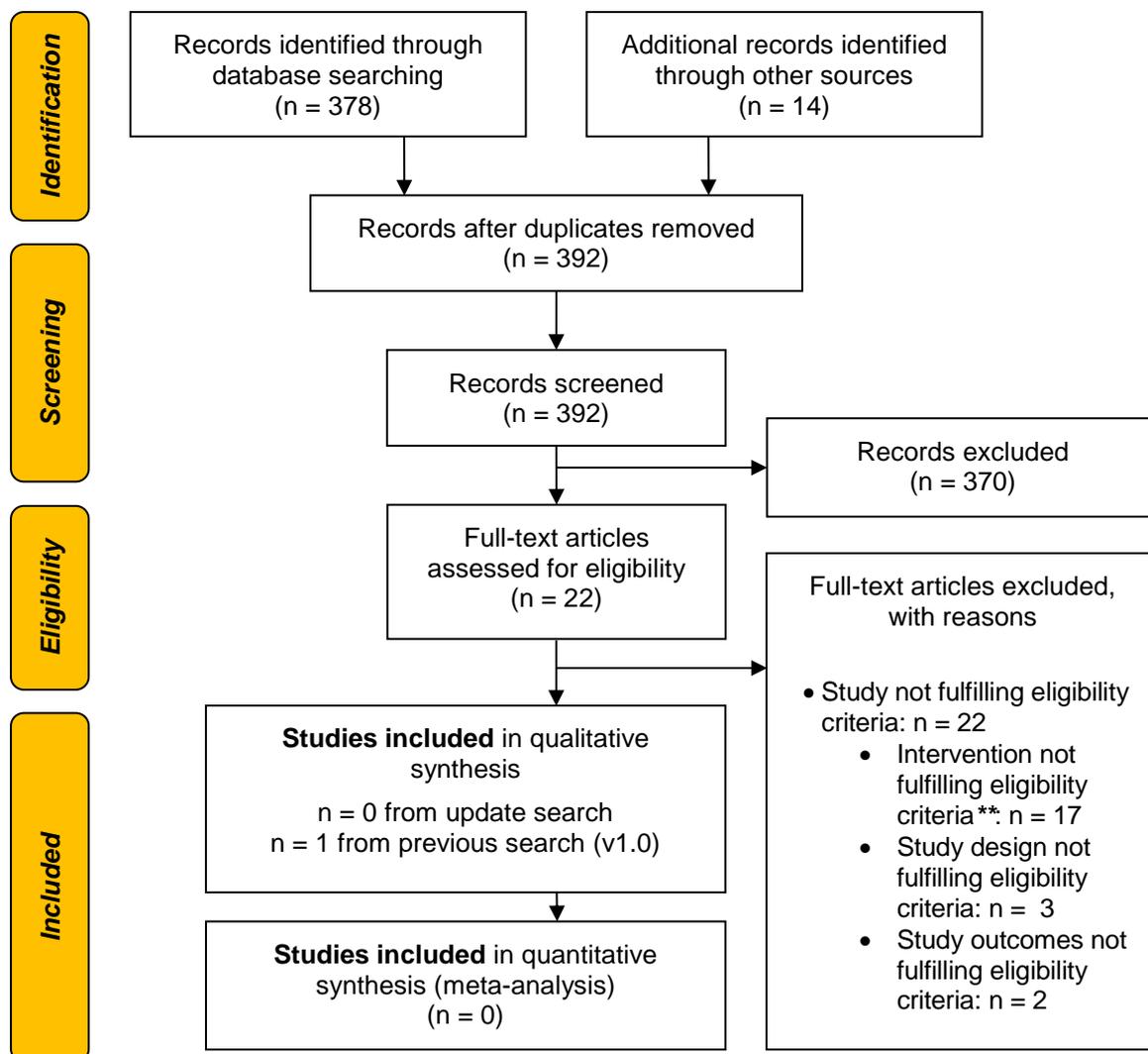
## 6.4 Flow diagrams



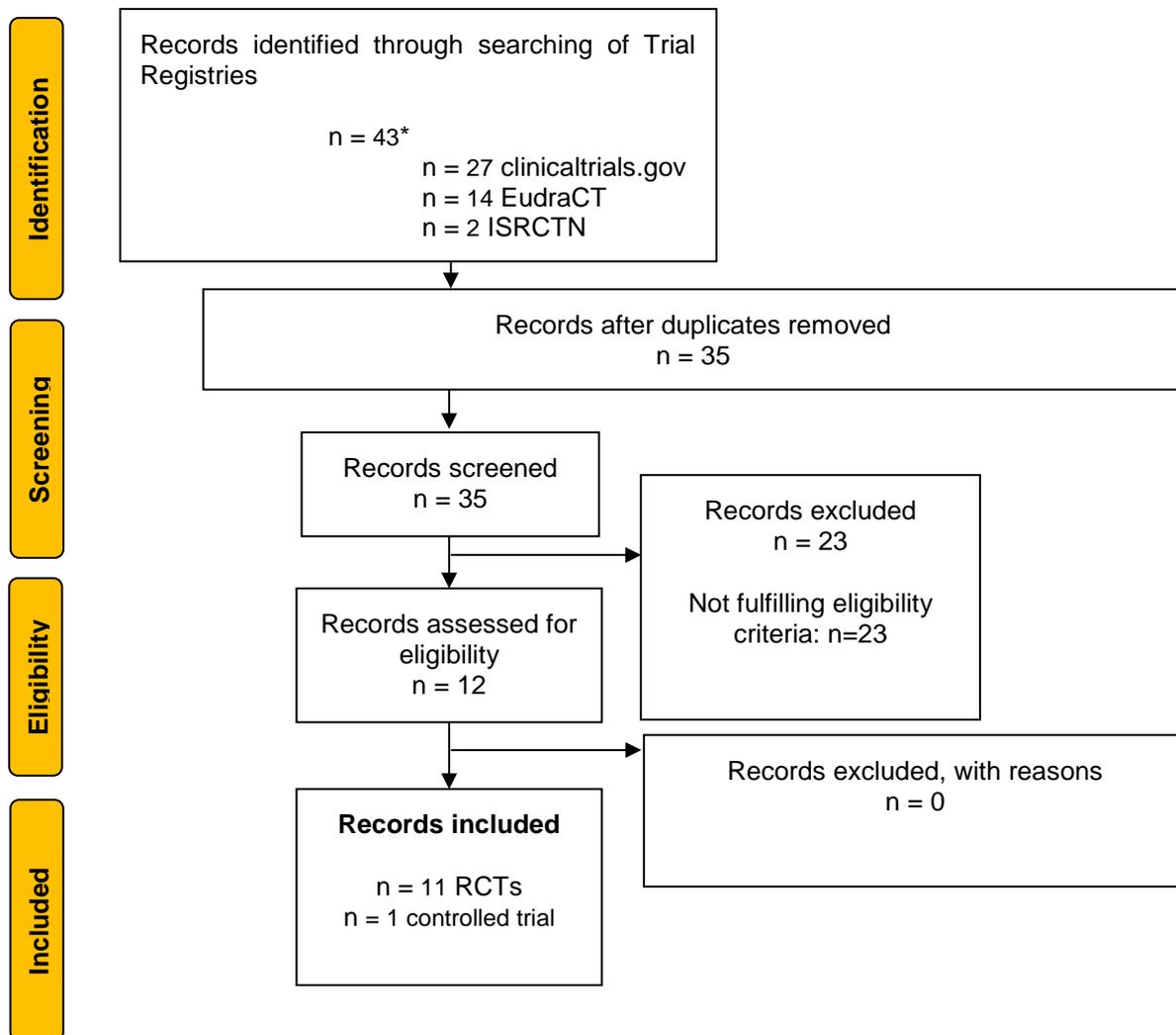
### Appendix Figure 6-1. Flow diagram depicting the selection process of RCTs

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



**Appendix Figure 6-3. Flow diagram depicting the selection process of ongoing studies**

**Abbreviation:** RCT=randomised controlled trial

\*1 added in this update