EUnetHTA Joint Action 3 WP4

“Rolling Collaborative Review” of Covid-19 treatments

SARILUMAB FOR THE TREATMENT OF COVID-19

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Monitoring Report

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V 1.0	**14/08/2020**	First version
V 2.0	**15/09/2020**	Second version
V 3.0	**14/10/2020**	Third version
V 4.0	**12/11/2020**	Fourth version
V 5.0	**15/12/2020**	Fifth version
V 6.0	**19/01/2021**	Sixth version
V 7.0	**15/02/2021**	Seventh version
V 8.0	**15/03/2021**	Eighth version
V 9.0	**20/04/2021**	Ninth version
V 10.0	**18/05/2021**	Tenth version

Major changes from previous version

Chapter, page no.	Major changes from version 9.0
4.1, page 10	• One new RCT has been included
4.3, page 11	• Status of some ongoing trials has been updated
6.4, page 32	• Flow diagrams have been updated

Disclaimer

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Conflict of interest

All authors and co-authors involved in the production of this living document have declared they have no conflicts of interest in relation to the technology and comparator(s) assessed according to the EUnetHTA declaration of interest (DOI) form. Conflict of Interest was evaluated following the EUnetHTA Procedure Guidance for handling DOI form (https://eunethta.eu/doi).

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TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical [Classification System]
ATMP	Advanced therapy medicinal product
CI	Confidence Interval
COVID-19	Corona Virus Disease - 19
CT	Controlled trial
DMARD	Disease-modifying anti-rheumatic drug
DOI	Declaration of interest
EMA	European Medicines Agency
EUnetHTA	European Network of Health Technology Assessment
FDA	Food and Drug Administration
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HR	Hazard Ratio
ICD	International Classification of Diseases
IL	Interleukin
MD	Mean Difference
MeSH	Medical Subject Headings
NA	Not applicable
NR	Not reported
OR	Odds Ratio
RCT	Randomized Controlled Trial
RCR	Rolling Collaborative Review
REA	Relative Effectiveness Assessment
RR	Relative Risk
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome - Corona Virus - 2
SD	Standard Deviation
SMD	Standardized Mean Difference
SoF	Summary of Findings
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://eunethta.eu/covid-19-treatment/) and on the EUnetHTA Rolling Collaborative Review Sharepoint page each 15th of the month.

2.1 Scope

Table 2-1 Scope of the RCR

Description	Project Scope
Population	**Disease** • SARS-CoV-2 is a novel coronavirus causing a respiratory illness termed Covid-19. The full spectrum of Covid-19 ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multi-organ failure, and death. **ICD-Codes** (https://www.who.int/classifications/icd/covid19/en) • An emergency ICD-10 code of 'U07.1 COVID-19, virus identified' is assigned to a disease diagnosis of COVID-19 confirmed by laboratory testing. • An emergency ICD-10 code of 'U07.2 COVID-19, virus not identified' is assigned to a clinical or epidemiological diagnosis of COVID-19 where laboratory confirmation is inconclusive or not available. • Both U07.1 and U07.2 may be used for mortality coding as cause of death. See the International guidelines for certification and classification (coding) of COVID-19 as cause of death following the link below. • In ICD-11, the code for the confirmed diagnosis of COVID-19 is RA01.0 and the code for the clinical diagnosis (suspected or probable) of COVID-19 is RA01.1. **MeSH-terms** • COVID-19, Coronavirus Disease 2019 **Target population** (https://www.covid19treatmentguidelines.nih.gov/overview/management-of-covid-19/)

	• Asymptomatic or pre-symptomatic Infection: Individuals who test positive for SARS-CoV-2 by virologic testing using a molecular diagnostic (e.g., polymerase chain reaction) or antigen test, but have no symptoms. • Mild Illness: Individuals who have any of the various signs and symptoms of COVID 19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnoea, or abnormal chest imaging. • Moderate Illness: Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO2) ≥94% on room air at sea level. • Severe Illness: Individuals who have respiratory frequency >30 breaths per minute, SpO2 <94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mmHg, or lung infiltrates >50%. • Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.
Intervention	Sarilumab (Kevzara®), Sarilumab (Kevzara®) in combination with other treatment(s) or standard of care
Comparison	Any active treatment, placebo, or standard of care. **Rationale**: Since there is no gold standard treatment any comparator is acceptable as well as the above listed interventions.
Outcomes	Main outcome: • All-cause Mortality (Survival) Additional Outcomes: Efficacy: • Length of hospital stay, • Viral burden (2019-nCoV RT-PCR negativity), • Clinical progression (WHO Clinical Progression Scale measured daily over the course of the study), • Rates of hospitalization and of patients entering ICU, • Duration of mechanical ventilation, • Quality of life. Safety: • Adverse events (AE), • Severe adverse events (SAE), • Withdrawals due to AEs, • Most frequent AEs, • Most frequent SAEs. **Rationale:** We will give priority according to the Core Outcome Set for Clinical Trials on Coronavirus Disease 2019 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102592/pdf/main.pdfc) and A minimal common outcome measure set for COVID-19 clinical research from the WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection.
Study design	Efficacy: randomised controlled trials (RCT) Safety: observational studies (comparative or single-arm prospective studies and registries)

2.2 Sources of information

According to the project plan, this Rolling Collaborative Review is based on three main sources of information, as described below:

2.2.1 Summary of findings(SoF) table for published RCTs related to effectiveness and safety:

This table is based on the living systematic review and Network Meta-Analysis (NMA) created by the partnering institute of DEPLazio: find the PROSPERO protocol here. DEPLazio provides updates for the SoF table on a monthly basis to the EUnetHTA partners authoring the respective Rolling CR documents who are integrating this information accordingly.

The literature search is conducted in the following databases:

- PubMed
- MEDLINE, accessed via OVID
- Embase, accessed via OVID

Population	People affected by COVID-19, as defined by the authors of the studies. No limits in terms of gender or ethnicity. SARS-CoV-2 is a novel coronavirus causing a respiratory illness termed Covid-19. It started spreading in December 2019 and was declared a pandemic by the World Health Organisation on 11th March 2020. The full spectrum of Covid-19 ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multi-organ failure, and death.
Intervention	Interventions for the treatment of people affected by COVID-19, including pharmacological interventions (e.g. antibiotics, antibodies, antimalarial, antiviral, antiretroviral, immune-suppressors/modulators, kinase inhibitors) and their combinations.
Comparison	Any active treatment, placebo, or standard of care.
Outcomes	All-cause mortality Additional outcomes: Length of hospital stay, 2019-nCoV RT-PCR negativity, PaO2/FiO2, Duration of mechanical ventilation, radiological imaging, Adverse events, Severe adverse events.
Study design	Randomised controlled trials (RCT); no restriction on language of publication

To identify preprints of preliminary reports of work that have not been peer-reviewed, the following sources are searched:

- medRxiv Health Sciences
- bioRxiv Biology

In addition to the sources and strategies described above, registers of ongoing studies are screened. Key conferences and conference proceedings are considered. Appendix Table 6-1 describes in detail the sources searched, the search terms used and the dates at which the searches are executed.

Data extraction, Risk of bias assessment, data synthesis:

Two reviewers from DEPLazio are screening search results, assessing full texts of studies and extract study characteristics and outcome data according to pre-defined criteria. The process of study selection is depicted as a flow diagram in Appendix Figure 6-1.
Risk of bias is assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [1].

Dichotomous outcomes are analysed by calculating the relative risk (RR) for each trial with the uncertainty in each result being expressed by its 95% confidence interval (CI).Continuous outcomes are analysed by calculating the mean difference (MD) with the relative 95% CI when the study used the same instruments for assessing the outcome.

The standardised mean difference (SMD) is applied when studies used different instruments. Pairwise meta-analyses is performed for primary and secondary outcomes using a random-effects model in RevMan for every treatment comparison [2]. Network meta-analysis (NMA) is performed for the primary outcome. For rating the certainty of the evidence, the GRADE approach is being used [3].

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

2.2.2 Table(s) on published (peer reviewed) observational studies for safety results:

The literature search is conducted on a monthly basis.

The sources and search methods are described in more detail in Appendix Table 6-2.

Population	See project Scope
Intervention	Sarilumab (Kevzara®), Sarilumab (Kevzara®) in combination with other treatment(s) or standard of care
Comparison	Any active treatment, placebo, or standard of care.
Outcomes	See project Scope
Study design	Inclusion criteria: Prospective non-randomised controlled trials, prospective case series (i.e. comparative or single-arm prospective studies), registries Exclusion criteria: retrospective studies, case studies/ case reports, observational studies that do not report safety data

Two researchers from NIPHNO carry out title and abstract screening and assess the full texts of all potentially eligible studies. The study selection process is depicted in a flow diagram (Appendix Figure 6-2).
One researcher of NIPHNO extracts the data and assesses the risk of bias using Robins-I (https://training.cochrane.org/handbook/current/chapter-25). For prospective single arm studies, the Johanna Briggs tool for prevalence studies is used to assess the methodological rigor and applicability.

Results are presented in tabular form for all included studies.

2.2.3 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 NIPHNO 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

Circulating IL-6 levels are closely linked to the severity of COVID-19/SARS-CoV-2 infection [4-6]. In severe cases the massive release of vasoactive mediators (cytokine storm or cytokine release syndrome) is repeatedly observed [4-6]. High interleukin 6 (IL-6) levels have been identified as a potential predictor of a fatal outcome of COVID-19 disease as an increase in IL-6 levels results in pronounced vasodilatation and membrane leakage, and ultimately refractory vasoplegia and multiple organ failure [6, 7]. Some of the therapeutic approaches against SARS-CoV-2 are based on the involvement of the cytokine IL-6. This cytokine can be blocked with monoclonal antibodies targeting IL-6 itself or its receptor (IL6R). Sarilumab is a fully human IgG1 monoclonal antibody that targets both soluble and membrane-bound IL-6R, thus inhibiting both IL-6-mediated inflammatory pathways [8]. At present, IKL6R-antagonists such as Tocilizumab, Sarilumab, and Siltuximab are primarily utilized in the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, and Castleman's disease [9].

3.2 Regulatory Status

Sarilumab (trade name Kevzara®) is a human monoclonal antibody against the interleukin-6 receptor [8, 9]. Regeneron Pharmaceuticals and Sanofi developed the drug for the treatment of rheumatoid arthritis (RA), for which it received US FDA approval on 22 May 2017 [10] and European Medicines Agency approval on 23 June 2017 [11]. Kevzara® (Sarilumab) injection, for subcutaneous use is an interleukin-6 (IL-6) receptor antagonist indicated for treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more disease-modifying antirheumatic drugs (DMARDs) [12]. In the ATC classification system, Sarilumab is an immunosuppressant (L04) and an interleukin inhibitor (L04A) with ATC code = L04AC14 [13].

3.3 Level of Evidence

One international, multifactorial, adaptive platform trial constitutes the only experimental evidence regarding the effects and safety of Sarilumab in adult patients with COVID-19 [14]. The trial has found that Sarilumab is related to lower mortality and fewer adverse events than either standard treatments or Tocilizumab. The certainty on the evidence is moderate. In addition, one randomised, double-blind, placebo-controlled, multinational trial in 420 adult patients with severe COVID-19 did not demonstrate efficacy of Sarilumab in patients hospitalised with COVID-19 and receiving supplemental oxygen [15].

Furthermore, one observational study with more than 50 patients evaluating the safety of treatment with Sarilumab has been published so far. This study had no control group and therefore provide little evidence for comparison alone, though the authors conclude that "IL-6 inhibition leads to good clinical outcome in patients with severe SARS-CoV-2 pneumonia and Sarilumab is a valid and safe alternative in the therapeutic armamentarium of this disease without defined standardized treatment algorythms" [16]. More evidence is needed in order to evaluate the safety and effect of Sarilumab in the treatment of SARS-CoV-2.

4 SUMMARY

4.1 Effectiveness and Safety evidence from RCTs

Two RCTs have addressed the effects of Sarilumab in hospitalized patients with COVID 19 [14, 15].
It is uncertain whether Sarilumab has an effect on all-cause mortality compared to standard treatment. The quality of the evidence was rated as very low due to high risk of performance bias in one study and unclear risk of attrition and reporting bias in the other study. Besides, the comparison showed high inconsistency (I^2=88%). For the same comparison, data from one ongoing RCT suggests that Sarilumab reduces the number of patients with any adverse event (high quality evidence). Finally, moderate quality evidence indicates that Sarilumab probably reduces the number of patients with serious adverse events, the duration of hospitalization in intensive care, and the length of stay. The quality of the evidence was downgraded due to study limitations. Based on one RCT, Sarilumab probably reduces all-cause mortality compared with Tocilizumab (Moderate quality evidence), whereas low quality evidence suggests no difference in the number of patients with serious adverse events.

Source: http://deplazio.net/farmacicovid/index.html [17].

4.2 Safety evidence from observational studies

One observational study [16] including 53 patients evaluating the safety of treatment with Sarilumab has been published so far. This study had no control group. Adverse events were reported in 42% of the participants and include mild and severe neutropenia, increased liver enzymes, mild thrombocytopenia, pulmonary embolism and deep venous thrombosis. The authors report no drug-related serious adverse events and conclude that “IL-6 inhibition leads to good clinical outcome in patients with severe SARS-CoV-2 pneumonia and Sarilumab is a valid and safe alternative in the therapeutic armamentarium of this disease without defined standardized treatment algorithms”. (See Table 4-3). Risk of bias in this study was appraised as high due to the small sample size and a mainly male study population (90%).

An Italian cohort study addressed the association of interleukin-1 and interleukin-6 inhibition compared with standard management in mortality and safety outcomes in patients with COVID-19 and hyperinflammation [18]. The study included 392 patients; 275 were allocated to the control group (no interleukin inhibition); 62 patients received the IL-1 inhibitor anakinra, and the remaining 55 received an IL-6 inhibitor (39 received tocilizumab and 26 received Sarilumab). Separate data for those receiving Sarilumab were not reported. Hence, we excluded this study due to the small number of participants that received Sarilumab (26, 22% of the exposed group). The authors concluded that IL-1, but not IL-6 inhibition, was associated with reductions in mortality. IL-6 inhibitors were effective in patients with high C-reactive protein concentrations and in patients with low lactate dehydrogenase concentrations. No evidence of a different adverse clinical outcome risk was found in patients treated with IL-1 inhibition or IL-6 inhibition compared to those in the control group.

Sources:https://www.ncbi.nlm.nih.gov/research/coronavirus/docsum?filters=topics.General%20Info [19] and https://www.fhi.no/en/qk/systematic-reviews-hta/map/.

4.3 Ongoing studies

There are currently 11 ongoing mainly Phase II and III trials registered as randomized controlled, evaluating the clinical efficacy of Sarilumab (see Table 4-4, Table 4-5, Table 4-6).

4.4 Scientific conclusion about status of evidence generation

Two RCTs have addressed the effects of Sarilumab for hospitalized patients with COVID 19. It is uncertain whether Sarilumab has an effect on all-cause mortality compared to standard treatment (Very low-quality evidence). For the same comparison, data from one ongoing RCT suggests that Sarilumab reduces the number of patients with any adverse event (high quality evidence). Finally, moderate quality evidence indicates that Sarilumab probably reduces the number of patients with serious adverse events, duration of hospitalization in intensive care, and length of stay. Further well-conducted trials are needed to confirm these findings. Several clinical trials are underway.

Table 4-1 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of Sarilumab

Sarilumab vs standard treatment

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute effect (95% CI)	Number of participants (studies)	Certainty of evidence
	Risk with Sarilumab	Risk with Standard treatment				
All-cause mortality	109 per 1000	307 per 1000	**RR 0.68** (0.43 to 1.10)	**98 fewer per 1.000** (from 175 fewer to 31 more)	707 (2 RCTs)	Very low
Number of patients with any adverse events	699 per 1000	655 per 1000	**RR 1.07** (0.89 to 1.28)	**46 more per 1.000** (from 72 fewer to 183 more)	257 (1 RCT)	High
Number of patients with serious adverse events	231 per 1000	64 per 1000	**RR 1.20** (0.77 to 1.87)	**13 more per 1.000** (from 15 fewer to 55 more)	707 (2 RCTs)	Moderate
Duration of hospitalization in intensive care	-	-	**HR 1.64** (1.21 to 2.45)	**-**	-	Moderate
Length of stay in hospital	-	-	**HR 1.60** (1.17 to 2.19)	-	-	Moderate

Explanations of GRADE: Level of certainty was downgraded for high risk of performance bias in one study and unclear risk of attrition and reporting bias in the other study. Besides, this was further downgraded by two levels for inconsistency (high heterogeneity I^2=88%)

Source:

1. Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, Arabi YM, et al The REMAP-CAP Investigators. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19 – Preliminary report. medRxiv. 2021:2021.01.07.21249390 [14]
2. Lescure F-X, Honda H, Fowler RA, Lazar JS, Shi G, Wung P, et al. Sarilumab treatment of hospitalised patients with severe or critical COVID-19: a multinational, randomised, adaptive, phase 3, double-blind, placebo-controlled trial. medRxiv. 2021:2021.02.01.21250769 [15]

Tocilizumab vs Sarilumab

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute effect (95% CI)	Number of participants (studies)	Certainty of evidence
	Risk with Tocilizumab	Risk with Sarilumab				
All-cause mortality	280 per 1000	222 per 1000	**RR 1.26** (0.71 to 2.23)	**58 more per 1.000** (from 64 fewer to 273 more)	395	Moderate [a]
Number of patients with serious adverse events	25 per 1000	0 per 1000	**RR 2.63** (0.16 to 44.48)	**0 fewer per 1.000** (from 0 fewer to 0 fewer)	401	Low [a,b]

Explanations of GRADE: Level of certainty was downgraded for: a) high risk of performance bias, and b) wide confidence interval (imprecision)

Source: Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, Arabi YM, et al The REMAP-CAP Investigators. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19 – Preliminary report. medRxiv. 2021:2021.01.07.21249390. [14]

Table 4-2 Study characteristics of included RCTs

Author, year, reference number/Study name/Study ID	**Gordon et al. 2021 [14]** **The REMAP-CAP Investigators**
Study design, study phase	Randomized-controlled trial. The trial is overseen by a blinded International Trial Steering Committee (ITSC) and an unblinded independent Data and Safety Monitoring Board (DSMB).
Centres (single centre or multicentre), country, setting	Multicentre study: REMAP-CAP is an international, adaptive platform trial designed to determine best treatment strategies for patients with severe pneumonia in both pandemic and non-pandemic settings.
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	Tocilizumab: n=353, mean age: 61 (SD 12) years, male 74%, severe Sarilumab: n=48, mean age 63 (SD 13) years, male 81%, severe Control: n=402, mean age 61 (SD 12) years, male 70, severe
Inclusion criteria	Critically ill patients, aged >18 years, with suspected or confirmed Covid-19, admitted to an intensive care unit (ICU) and receiving respiratory or cardiovascular organ support.
Exclusion criteria	Presumption that death was imminent with lack of commitment to full support, and prior participation in REMAP-CAP within 90 days.
Intervention **(generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)**	Tocilizumab: dose of 8mg/kg of actual body weight (up to a maximum of 800mg), administered as an intravenous infusion over one hour; this dose could be repeated 12-24 hours later at the discretion of the treating clinician. Sarilumab: 400mg, administered as an intravenous infusion once only.
Comparator(s) **(standard care or generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)**	Control: standard care, which included corticosteroids in most patients (>80%)
Primary Outcome(s)	Respiratory and cardiovascular organ support-free days up to day 21, in which all deaths within hospital were assigned the worst outcome (-1)
Patient-relevant secondary outcome(s)	90-day Survival (time to event) Respiratory/Cardiovascular support-free days Time to ICU discharge WHO scale at day 14 Progression to invasive mechanical ventilation, ECMO or death, restricted to those not intubated at baseline Serious adverse events
Follow-up (days, months)	21 days
Sponsor/ lead institution	The REMAP-CAP Investigators, Imperial College London, London, United Kingdom. The full list of funders is provided in the full text.

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

Author, year, reference number/Study name/Study ID	Lescure et al. 2021 [15]
Study design, study phase	Multinational, randomised, adaptive, phase 3, double-blind, placebo-controlled trial
Centres (single centre or multicentre), country, setting	45 sites in Argentina, Brazil, Canada, Chile, France, Germany, Israel, Italy, Japan, Russia, and Spain. Hospital
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	Sarilumab 200mg: n=159, mean age 58 (51-67) years, male 68%, severe 58% Sarilumab 400mg: n=173, mean age 58 (48-67) years, male 57%, severe 61% Placebo: n=84, mean age 60 (53-69) years, male 54%, severe 65%
Inclusion criteria	Patients aged 18 years or older at the time of signing informed consent who had been hospitalised for laboratory-confirmed SARS-CoV-2 infection in any specimen within 2 weeks prior to randomisation and with evidence of pneumonia by chest imaging or chest auscultation and no alternative explanation for current clinical presentation. Patients also had to meet criteria for severe disease (defined as administration of supplemental oxygen by nasal cannula, simple face mask, or another similar device) or critical disease (defined as need for supplemental oxygen delivered by nonrebreather mask or high-flow nasal cannula, use of invasive or non-invasive ventilation, or treatment in an intensive care unit).
Exclusion criteria	In the investigator's opinion, a low probability of surviving 48 hours or remaining at the investigational site beyond 48 hours, or dysfunction of ≥2 organ systems or need for extracorporeal life support or renal replacement therapy at screening; absolute neutrophil count <2000/mm3; aspartate aminotransferase or alanine aminotransferase (ALT) exceeding 5-fold upper limit of normal (ULN) at screening; platelets <50,000/mm3 at screening; known active, incompletely treated, suspected or known extrapulmonary tuberculosis; prior or concurrent use of immunosuppressants at screening, including, but not limited to, IL-6 inhibitors or Janus kinase inhibitors within 30 days of baseline; anti-CD20 agents without evidence of B-cell recovery to baseline levels or IL-1 receptor antagonist (anakinra) within 1 week of baseline; abatacept within 8 weeks of baseline; tumor necrosis factor α inhibitors within 2–8 weeks of baseline; alkylating agents, including cyclophosphamide, within 6 months of baseline; cyclosporine, azathioprine, mycophenolate mofetil, leflunomide, or methotrexate within 4 weeks of baseline; or intravenous (IV) immunoglobulin within 5 months of baseline; use of systemic chronic (eg, oral) corticosteroids for a condition not related to COVID-19 at doses higher than prednisone 10 mg/day or equivalent at screening; or suspected or known active systemic bacterial or fungal infections within 4 weeks of screening.
Intervention (generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	After confirming the randomisation number accessed via IRT, the hospital pharmacist added the contents of prefilled syringes (PFS) of Sarilumab 200 mg solution for subcutaneous injection supplied by the sponsor into a specified volume of locally sourced 0• 9% NaCl solution for IV infusion (two syringes for the 400-mg dose, one syringe for the 200-mg dose, and 0• 9% NaCl solution for the placebo dose) to produce an IV bag containing a colourless solution to be administered by blinded hospital staff as a single IV infusion.
Comparator(s) (standard care or generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	Control: placebo
Primary Outcome(s)	Clinical improvement of ≥2 points on a 7-point ordinal scale, with numerical values defined as follows: 1—Death; 2—Hospitalised, on invasive mechanical ventilation or extracorporeal membrane oxygenation; 3—Hospitalised, on non-invasive ventilation or high-flow oxygen devices; 4—Hospitalised, requiring supplemental oxygen; 5—Hospitalised, not requiring supplemental oxygen –requiring ongoing medical care (COVID-19 related or otherwise);

Author, year, reference number/Study name/Study ID	**Lescure et al. 2021 [15]**
Study design, study phase	Multinational, randomised, adaptive, phase 3, double-blind, placebo-controlled trial
Centres (single centre or multicentre), country, setting	45 sites in Argentina, Brazil, Canada, Chile, France, Germany, Israel, Italy, Japan, Russia, and Spain. Hospital
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	Sarilumab 200mg: n=159, mean age 58 (51-67) years, male 68%, severe 58% Sarilumab 400mg: n=173, mean age 58 (48-67) years, male 57%, severe 61% Placebo: n=84, mean age 60 (53-69) years, male 54%, severe 65%
	6—Hospitalised, not requiring supplemental oxygen – no longer requiring ongoing medical care; 7—Not hospitalised.
Patient-relevant secondary outcome(s)	Discharge prior to day 29 was considered as a 2-point improvement. The key secondary efficacy endpoint was the proportion of patients alive at day 29. Other secondary efficacy endpoints included differences in time-to-event endpoints by treatment (eg, time to improvement of ≥1 point on the 7-point scale, fever resolution, or discharge from hospital), score changes at specific time points (eg, proportion with 1-point improvement/worsening), and event durations (eg, mechanical ventilation, hospitalisation).
Follow-up (days, months)	60 days
Sponsor/ lead institution	Sanofi and Regeneron Pharmaceuticals, Inc.

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

Table 4-3 Summary of safety from observational studies (AE and SAE) of Sarilumab

Author, year	Gremese et al. (2020) [16]
Country	Italy
Sponsor/ lead institution	No funding was used for the conduction of the study.
Intervention/Product (drug name)	Sarilumab
Dosage	400 mg intravenously on day 1, 33% of medical ward patients and 93% of ICU patients received a second dose.
Comparator	None
Study design	Observational clinical study
Setting	Hospital, medical wards and ICU
Number of pts	53
Inclusion criteria	Hospitalized patients with severe SARS-CoV-2 pneumonia unless contraindicated
Exclusion criteria	Septic state, total neutrophil count <1500/mm3, serum levels of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) more than five times the ULN, diverticulitis/diverticulosis or pregnancy
Age of patients (yrs)	40-95 (median 66)
Disease severity	Severe, defined as SARS-CoV2 infection confirmed by RT-PCR assay, interstitial pneumonia at imaging (chest X-Ray or CT scan), impairment of respiratory function (PaO2/FiO2 ratio<300), rapid worsening of the respiratory condition or need for ICU admission
Follow-up (days)	Up to 14 days
Loss to follow-up, n (%)	0
RoB	High
Overall AEs, n (%)	22(41.5%)
Serious AE (SAE), n (%)	No drug-related SAE registered
Most frequent AEs n (%)	Increased liver enzymers (4 UNL) 6(18.8%)
Most frequent SAEs, n (%)	n.a.
AEs of special interest, n (%)	n.a.
Death as SAE, n (%)	3 (5.7%) (not registered as drug-related)
Withdrawals due AEs, n (%)	-

Table 4-4 Ongoing trials of single agent Sarilumab

Trial Identifier/registry ID(s)/contact	NCT04357808 EudraCT 2020-001634-36 (SARCOVID)	NCT04315298 EudraCT 2020-001162-12	NCT04359901	NCT04357860 EudraCT 2020-001531-27 (SARICOR)
Study design, study phase	RCT, Randomised, open-label, comparative trial. Phase II	RCT, Randomized, Double-Blind, Placebo-Controlled Study, quadruple masking (participant, care provider, investigator, outcomes assessor), parallel assignment, Phase II	RCT, Randomised (open-labelled) controlled trial, parallel assignment, Phase II	RCT, Randomised (open-labelled) controlled trial, parallel assignment, Phase II
Recruitment status	Completed	Completed	Active, not recruiting	Not yet recruiting
Number of Patients, Disease severity*	n = 30 (>18 years)	n = 1912 (originally estimated: 400) (18 years and older)	n = 120 (18 years and older), Moderate	n = 120 (Age ≥ 18 years and <75 years)
Setting (hospital, ambulatory,..)				
Intervention (generic drug name and dosage)	Sarilumab 200 mg, 2 sc injections in pre-filled syringe or pen, single dose plus standard of care	Single or multiple intravenous (IV) doses of sarilumab. Additional doses may be administered if the patient meets protocol defined criteria.	Standard of care as directed by the treating clinicians, plus sarilumab 400 mg subcutaneous injection. Sarilumab is provided in prefilled syringes/pens containing 200 mg each as is used clinically, and both injections will be given as soon as is convenient after the patient has decided to enroll.	Arm 1: Sarilumab 200 MG/1.14 ML Subcutaneous Solution [KEVZARA] Best available treatment up to 14 days plus Sarilumab 200 mg Arm 2: Subjects treated with the best available treatment up to 14 days plus Sarilumab 400 mg single dose. Intervention: Drug: Sarilumab 400 MG/2.28 ML Subcutaneous Solution [KEVZARA]
Comparator (standard care or generic drug name and dosage)	Standard of care (treatment with drugs or procedures in routine clinical practice)	Single or multiple intravenous (IV) doses of placebo to match sarilumab administration	Standard of care as directed by the treating clinicians.	Treatment with the best available treatment up to 14 days.
Primary Outcome(s)	- Time to become afebrile for a minimum period of 48 hours, without antipyretics - Average change in the ordinal scale of 7 points from the inclusion in the study until day 7 (after randomization): 1. Death 2. Hospitalized, with mechanical ventilation or extracorporeal	Percent change in C-reactive protein (CRP) levels in patients with serum IL-6 level greater than the upper limit of normal [Time Frame: Day 4] Proportion of patients with at least 1-point improvement in clinical status using the 7-point ordinal scale in patients with critical COVID-19 receiving mechanical ventilation at	Intubation or death [Time Frame: within 14 Days of enrollment] Composite outcome of intubation or death	Ventilation requirements [Time Frame: At day 28 or when the subject is discharged (whichever occurs first)] Proportion of patients requiring or time (in days) until required:

	membrane oxygenation (ECMO). 3. Hospitalized, with non-invasive mechanical ventilation, a mask with a reservoir or oxygen with high flow nasal goggles. 4. Hospitalized with oxygen supplement 5. Hospitalized, without oxygen supplement, but in need of continued medical care (related or not with COVID) 6. Hospitalized, without oxygen supplement and without the need for continued medical care 7. Not hospitalized - Duration of hospitalization (days) - Death	baseline [Time Frame: Up to day 22] (Score ranges 1-7 = Death (1); Hospitalized, requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) (2); Hospitalized, requiring non-invasive ventilation or high flow oxygen devices (3); Hospitalized, requiring supplemental oxygen (4); Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise) (5); hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care (6); Not hospitalized (7) Proportion of patients with at least 1-point improvement in clinical status using the 7-point ordinal scale in patients with COVID-19 receiving mechanical ventilation at baseline [Time Frame: Up to day 22		-High flow nasal oxygenation (HFNO) -Non-invasive mechanical ventilation type BiPAP -Non-invasive mechanical ventilation type CPAP -Invasive mechanical ventilation
Sponsor/ lead institution, country (also country of recruitment if different)	Maria del Rosario Garcia de Vicuña Pinedo/Instituto de Investigación Sanitaria Hospital Universitario de la Princesa, Spain	Regeneron Pharmaceuticals/Sanofi, USA	Westyn Branch-Elliman, VA Boston Healthcare System, USA	Maimónides Biomedical Research Institute of Córdoba Consejería de Salud y Familias - Junta de Andalucía Red Andaluza de Ensayos Clínicos en Enfermedades Infecciosas (Red ANCRAID), Spain

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

Table 4-5 Ongoing trials of single agent Sarilumab, continued

Trial Identifier/registry ID(s)/contact	EudraCT 2020-002037-15	EudraCT 2020-001290-74 (SARCOVID)	EudraCT 2020-001390-76 (ESCAPE)	EudraCT 2020-001854-23 (AMMURAVID)
Study design, study phase	RCT, randomized, open-label study, parallel groups, Phase II	RCT, randomized, open-label study, not parallel groups, Phase III	RCT, randomized, (open-labeled) trial, not parallel groups, Phase III	RCT, randomised (open labelled), parallel groups, Phase II and III
Recruitment status	Ongoing	Completed	Ongoing	Ongoing
Number of Patients, Disease severity*	n = 200 (18 years and older)	n = 216 (18 years and older)	n = 171 (18 years and older)	n = 1400 (≥18 years of age)
Setting (hospital, ambulatory,..)				
Intervention (generic drug name and dosage)	Standard care + sarilumab (200 mg)	Sarilumab (200 mg)	Sarilumab (200 mg) + standard of care	Various immunomodulating compounds (arms). Among these Sarilumab administered 150 mg (in addition to hydroxicloroquine)
Comparator (standard care or generic drug name and dosage)	Standard care	Standard of care (including azithromycin, hydroxychloroquine)	Standard of care	No information
Primary Outcome(s)	Proportion of patients progressing to severe respiratory failure (Brescia-COVID Scale ≥2), ICU admission, or death (From baseline up to Day-15)	Time to clinical improvement, defined as the time from randomization to a two-point improvement (from randomization status) on an ordinal scale of seven categories or hospital discharge, whichever occurs first	Time to clinical improvement, defined as the time from receiving the first dose of drug to an improvement of two points (from the status at baseline) on a 7-point category ordinal scale. The 7-point category ordinal scale consisted of the following categories: 1. not hospitalized with resumption of normal activities; 2. not hospitalized, but unable to resume normal activities; 3. hospitalized, not requiring supplemental oxygen; 4. hospitalized, requiring supplemental oxygen; 5. hospitalized, requiring noninvasive mechanical ventilation (CPAP or NIV);	Proportion of patients with PaO2/FiO2 <200 mmHg at day 10 in each intervention arm as compared to the control arm

			6. hospitalized, requiring ECMO, invasive mechanical ventilation, or both; 7. death.	
Sponsor/ lead institution, country (also country of recruitment if different)	Cristina Avendaño Sola, Spain	Consorci Parc de Salut Mar (PSMAR), Spain	ISTITUTO NAZIONALE PER LE MALATTIE INFETTIVE "LAZZARO SPALLANZANI", Italy	SOCIETA' ITALIANA MALATTIE INFETTIVE E TROPICALI, Italy

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

Table 4-6 Ongoing trials of single agent Sarilumab, continued

Trial Identifier/registry ID(s)/contact	NCT04324073 (CORIMUNO-SARI) EudraCT 2020-001246-18	NCT02735707 EudraCT 2015-002340-14 (REMAP-CAP)	NCT04327388
Study design, study phase	RCT, randomised (Bayesian open-label) trial, parallel assignment, Phase II and III	RCT, randomised (open-labelled), factorial assignment, Phase IV	RCT, Randomised controlled trial, quadruple masked participant, care provider, investigator, outcomes assessor), parallel assignment, Phase III
Recruitment status	Active, not recruiting	Recruiting	Completed
Number of Patients, Disease severity*	N=239 (18 years and older), moderate and severe	n = 7100 (18 years and older)	n = 409 (18 years and older)
Setting (hospital, ambulatory,..)	Hospital	Hospital	
Intervention (generic drug name and dosage)	Sarilumab (an IV dose of 400 mg of sarilumab in a 1 hour-infusion at D1).	Various compounds (arms). Among these, Sarilumab administered as a single dose of 400 mg, via IV infusion through peripheral or central line over a one-hour period.	Arm 1: Sarilumab Dose 1 given intravenously one time on Day 1. Patients may receive a second dose with Sarilumab Dose 1 24 to 48 hours after the first dose. Arm 2: Sarilumab Dose 2 given intravenously one time on Day 1. Patients may receive a second dose with Sarilumab Dose 2 24 to 48 hours after the first dose.
Comparator (standard care or generic drug name and dosage)	Standard of care	Not indicated	Matching placebo given intravenously one time on Day 1. Patients may receive a second dose with matching placebo 24 to 48 hours after the first dose.
Primary Outcome(s)	-Survival without needs of ventilator utilization at day 14 -WHO progression scale <=5 at day 4 -Cumulative incidence of successful tracheal extubation (defined as duration extubation > 48h) at day 14 -WHO progression scale at day 4	All-cause mortality [Time Frame: Day 90] Days alive and not receiving organ support in ICU [Time Frame: Day 21]	Time to improvement of 2 points in clinical status assessment from baseline using the 7-point ordinal scale [Time Frame: Baseline to Day 29]
Sponsor/ lead institution, country (also country of recruitment if different)	Assistance Publique - Hôpitaux de Paris, France	University of Pittsburgh Medical Center, Australia, Belgium, Canada, Croatia, Germany, Hungary, Ireland, Netherlands, New Zealand, Portugal, Romania, Spain, UK, USA	Sanofi/ Regeneron Pharmaceuticals, Argentina, Brazil, Canada, Chile, France, Germany, Israel, Italy, Japan, Russian Federation, Spain

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

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6 APPENDIX

6.1 Search strategy to identify randomised controlled trials

DEPLazio, the Department of Epidemiology of the Regional Health Service Lazio in Rome, Italy is responsible for setting up the search strategy to identify randomised controlled trials (RCTs). DEPLazio performed a search in Medline, PubMed, and Embase, which has been updated weekly from March 2020 (Appendix Table 6-1). DEPLazio searched medRxiv.org (https://www.medrxiv.org/), bioRxiv.org (https://www.bioRxiv.org/), and arXiv.org (https://www.arXiv.org/) for preprints of preliminary reports of randomised trials. The Cochrane Covid-19 Study Register (https://covid-19.cochrane.org/), ClinicalTrials.gov (www.clinicaltrials.gov) and World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en/) were search in addition. Other sources included journal alerts, contact with researchers, websites such as Imperial College, London School of Hygiene and Tropical Medicine, and Eurosurveillance. We applied no restriction on language of publication.

We included randomised controlled trials (RCTs) comparing any pharmacological intervention against another pharmacological intervention or placebo or standard care (SC), for the treatment of individuals with Covid-19. We excluded studies comparing two dosages of the same pharmacological agent. We did not exclude studies on individuals with a comorbid disorder.

Four authors independently screened the references retrieved by the search, selected the studies, and extracted the data, using a predefined data-extraction sheet. The same reviewers discussed any uncertainty regarding study eligibility and data extraction until consensus was reached; conflicts of opinion were resolved with other members of the review team. Two authors independently assessed the risk of bias of the included studies with the Cochrane tool. Three authors used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, to evaluate the strength of evidence.

The methods described above are part of a living review of pharmacological agents for the treatment of Covid-19 conducted by the Department of Epidemiology of the Regional Health Service Lazio, Italy, to inform national regulatory agencies and clinicians, available at https://www.deplazio.net/farmacicovid. The review is registered on Prospero (CRD42020176914).

Table 6-1 Search strategy to identify randomised controlled studies

Database	URL	Search line / Search terms	Date of search
Pubmed	pubmed.ncbi.nlm.nih.gov	1. (((((((("Coronavirus"[Mesh]) OR (coronavirus*[Title/Abstract] OR coronovirus*[Title/Abstract] OR coronavirinae*[Title/Abstract] OR Coronavirus*[Title/Abstract] OR Coronovirus*[Title/Abstract] OR Wuhan*[Title/Abstract] OR Hubei*[Title/Abstract] OR Huanan[Title/Abstract] OR "2019-nCoV"[Title/Abstract] OR 2019nCoV[Title/Abstract] OR nCoV2019[Title/Abstract] OR "nCoV-2019"[Title/Abstract] OR "COVID-19"[Title/Abstract] OR COVID19[Title/Abstract] OR "CORVID-19"[Title/Abstract] OR CORVID19[Title/Abstract] OR "WN-CoV"[Title/Abstract] OR WNCoV[Title/Abstract] OR "HCoV-19"[Title/Abstract] OR HCoV19[Title/Abstract] OR CoV[Title/Abstract] OR "2019 novel*"[Title/Abstract] OR Ncov[Title/Abstract] OR "n-cov"[Title/Abstract] OR "SARS-CoV-2"[Title/Abstract] OR "SARSCoV-2"[Title/Abstract] OR "SARSCoV2"[Title/Abstract] OR "SARS-CoV2"[Title/Abstract] OR SARSCov19[Title/Abstract] OR "SARS-Cov19"[Title/Abstract] OR "SARSCov-19"[Title/Abstract] OR "SARS-Cov-19"[Title/Abstract] OR Ncovor[Title/Abstract] OR Ncorona*[Title/Abstract] OR Ncorono*[Title/Abstract] OR NcovWuhan*[Title/Abstract] OR NcovHubei*[Title/Abstract] OR NcovChina*[Title/Abstract] OR NcovChinese*[Title/Abstract])) OR ((((respiratory*[Title/Abstract] AND (symptom*[Title/Abstract] OR disease*[Title/Abstract] OR illness*[Title/Abstract] OR condition*))[Title/Abstract] OR "seafood market*"[Title/Abstract] OR "food market*")[Title/Abstract] AND (Wuhan*[Title/Abstract] OR Hubei*[Title/Abstract] OR China*[Title/Abstract] OR Chinese*[Title/Abstract] OR Huanan*))[Title/Abstract])) OR ("severe acute respiratory syndrome*")) OR ((corona*[Title/Abstract] OR corono*)[Title/Abstract] AND (virus*[Title/Abstract] OR viral*[Title/Abstract] OR virinae*)[Title/Abstract])) AND (((((((randomized controlled trial [pt]) OR (controlled clinical trial [pt])) OR (randomized [tiab])) OR (placebo [tiab])) OR (clinical trials as topic [mesh: noexp])) OR (randomly [tiab])) OR (trial [ti]))) NOT (animals [mh] NOT humans [mh]) AND (2019/10/01:2020[dp])	03/05/2021

Database	URL	Search line / Search terms	Date of search
Ovid MEDLINE(R) ALL)	ovidsp.dc2.ovid.com	1. exp coronavirus/ 2. ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw. 3. (coronavirus* or coronovirus* or coronavirinae* or Coronavirus* or Coronovirus* or Wuhan* or Hubei* or Huanan or "2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCoV or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese*).ti,ab,kw. 4. (((respiratory* adj2 (symptom* or disease* or illness* or condition*)) or "seafood market*" or "food market*") adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw. 5. ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (China* or Chinese* or Huanan*)).ti,ab,kw. 6. "severe acute respiratory syndrome*".ti,ab,kw. 7. or/1-6 8. randomized controlled trial.pt. 9. controlled clinical trial.pt. 10. random*.ab. 11. placebo.ab. 12. clinical trials as topic.sh. 13. random allocation.sh. 14. trial.ti. 15. or/8-14 16. exp animals/ not humans.sh. 17. 15 not 16 18. 7 and 17 19. limit 18 to yr="2019 -Current"	03/05/2021
OVID EMBASE	ovidsp.dc2.ovid.com	1. exp Coronavirinae/ or exp Coronavirus/ 2. exp Coronavirus infection/ 3. ((("Corona virinae" or "corona virus" or Coronavirinae or coronavirus or COVID or nCoV) adj4 ("19" or "2019" or novel or new)) or (("Corona virinae" or "corona virus" or Coronavirinae or coronavirus or COVID or nCoV) and (wuhan or china or chinese)) or "Corona virinae19" or "Corona virinae2019" or "corona virus19" or "corona virus2019" or Coronavirinae19 or Coronavirinae2019 or coronavirus19 or coronavirus2019 or COVID19 or COVID2019 or nCOV19 or nCOV2019 or "SARS Corona virus 2" or "SARS Coronavirus 2" or "SARS-COV-2" or "Severe Acute Respiratory Syndrome Corona virus 2" or "Severe Acute Respiratory Syndrome Coronavirus 2").ti,ab,kw. 4. or/1-3 5. Clinical-Trial/ or Randomized-Controlled-Trial/ or Randomization/ or Single-Blind-Procedure/ or Double-Blind-Procedure/ or Crossover-Procedure/ or Prospective-Study/ or Placebo/ 6. (((clinical or control or controlled) adj (study or trial)) or ((single or double or triple) adj (blind$3 or mask$3)) or (random$ adj (assign$ or allocat$ or group or grouped or patients or study or trial or distribut$)) or (crossover adj (design or study or trial)) or placebo or placebos).ti,ab. 7. 5 or 6 8. 4 and 7 9. limit 8 to yr="2019 -Current"	03/05/2021

6.2 Search strategy to identify observational studies

As of October 2020, NIPHNO is responsible for setting up the search strategy to identify observational studies.

From September to December 2020, we received records that EPPI Centre has screened after searching weekly in Medline and Embase (until beginning of November 2020), from November onwards Microsoft Academics Graph (MAG). We supplemented these studies with a weekly search in Scopus (Elsevier). Detailed descriptions of the EPPI and NIPHNO searches are given at their websites [20, 21]. The retrieved hits were imported to a reference management tool, Endnote (Clarivate Analytics), for deduplication. We then searched the EndNote database using the generic names and synonyms for the included COVID-19 drugs.

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

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

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

Table 6-2 Search strategy to identify observational studies

Database	URL	Search terms / Search modality	Date of search	Hits retrieved
Embase 1974 to 2021 Ovid MEDLINE(R) ALL 1946 to 2021		Lines 1 and 2 are copies of Ovid's Expert searches for covid-19 in MEDLINE and Embase 1 ((((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.) or (2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus* or corona virus or pandemi*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp. or COVID-19.rx,px,ox,sh. or severe acute respiratory syndrome coronavirus 2.os.) use medall [COVID-19 in MEDLINE] 2 ((((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.) or (coronavirus disease 2019 or 2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or severe acute respiratory syndrome coronavirus 2 or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus* or corona virus or pandemi*2))	From 06/04/2021 until 03/05/2021	1032

		or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp. or (coronavirus disease 2019 or severe acute respiratory syndrome coronavirus 2).sh,dj.) use oemezd [COVID-19 in Embase] 3 (COVID-19 serotherapy/ or Immunization, Passive/ or tocilizumab/ or camostat/ or nafamostat/ or AP301 peptide/ or Interleukin 1 Receptor Antagonist Protein/ or alunacedase alfa/ or darunavir/ or favipiravir/ or sarilumab/ or exp Interferons/ or gimsilumab/ or canakinumab/ or baricitinib/ or molnupiravir/ or Aspirin/ or mavrilimumab/ or exp Vitamin D/dt or Vitamin D Deficiency/dt or Ivermectin/) use medall [MeSH-terms for drugs in MEDLINE] 4 (Hyperimmune globulin/dt or tocilizumab/ or camostat/ or camostat mesilate/ or nafamstat/ or solnatide/ or anakinra/ or darunavir/ or favipiravir/ or sarilumab/ or exp Interferon/ or gimsilumab/ or canakinumab/ or baricitinib/ or acetylsalicylic acid/ or mavrilimumab/ or exp Vitamin D/dt or Vitamin D Deficiency/dt or ivermectin/) use oemezd [Emtree-terms for drugs in Embase] 5 ((convalescent adj (plasma or sera or serum)) or serotherap* or ((atoxin or hyperimmunoglobulin or hyperimmune globulin or hyperimmune gammaglobulin) adj therap*) or passive immuni?ation or (tocilizumab or atlizumab or (MRA adj monoclonal antibod*) or MSB-11456 or MSB11456 or R-1569 or R1569 or RO-4788533 or RO4788533 or Actemra or Roactemra) or (camostat* or FOY-305 or FOY305 or FOY S 980) or (nafamostat or nafamstat or FUT-175 or FUT175) or (solnatide or AP301 or AP-301 or (TIP adj peptide)) or (anakinra or ((interleukin 1 or IL1 or IL-1) adj2 (antagonist or block* or inhibitor*)) or IL-1Ra or Kineret) or (alunacedase or APN01 or APN-01 or rhACE2 or recombinant human angiotensin converting enzyme 2 or GSK-2586881 or GSK2586881) or (darunavir or prezista or TMC-114 or TMC114 or UIC-94017 or UIC94017) or (favipi?avir or T-705 or T705 or Avigan or Olumiant) or (sarilumab or REGN-88 or REGN88 or SAR-153191 or SAR153191 or Kevzara) or (interferon* or (IFN adj1 (alpha* or beta* or gamma*)) or novaferon or CL-884 or CL884) or (gimsilumab or KIN-1901 or KIN1901 or morab-022 or morab022) or (canakinumab or ACZ-885 or ACZ885 or immunoglobulin G1 or Ilaris) or (baricitinib or LY-3009104 or LY3009104 or INCB-028050 or INCB028050 or INCB-28050 or INCB28050 or Olumiant) or (molnupiravir or MK-4482 or MK4482 or EIDD-2801 or EIDD2801) or (aspirin or acetylsalicylic acid) or (mavrilimumab or immunoglobulin G4 or CAM-3001 or CAM3001) or ((vitamin? D? or D?-vitamin?) adj4 (high-dose* or highdose* or supplement*)) or (ivermect* or MK-933 or MK933)).mp,bt,ot,du,dy,tn,nm. [other terms (title, abstract, author keywords and more) in MEDLINE and Embase] 6 (20210406 OR 20210407 OR 20210408 OR 20210409 OR 2021041* OR 2021042* OR 2021043* OR 202105*).dt. use medall [time limits in MEDLINE] 7 (20210406 OR 20210407 OR 20210408 OR 20210409 OR 2021041* OR 2021042* OR 2021043* OR 202105*).dc. use oemezd [time limits in Embase]		

		8	(1 and (3 or 5) and 6) use medall		
		9	(2 and (4 or 5) and 7) use oemezd		

6.3 Search strategy to identify ongoing studies

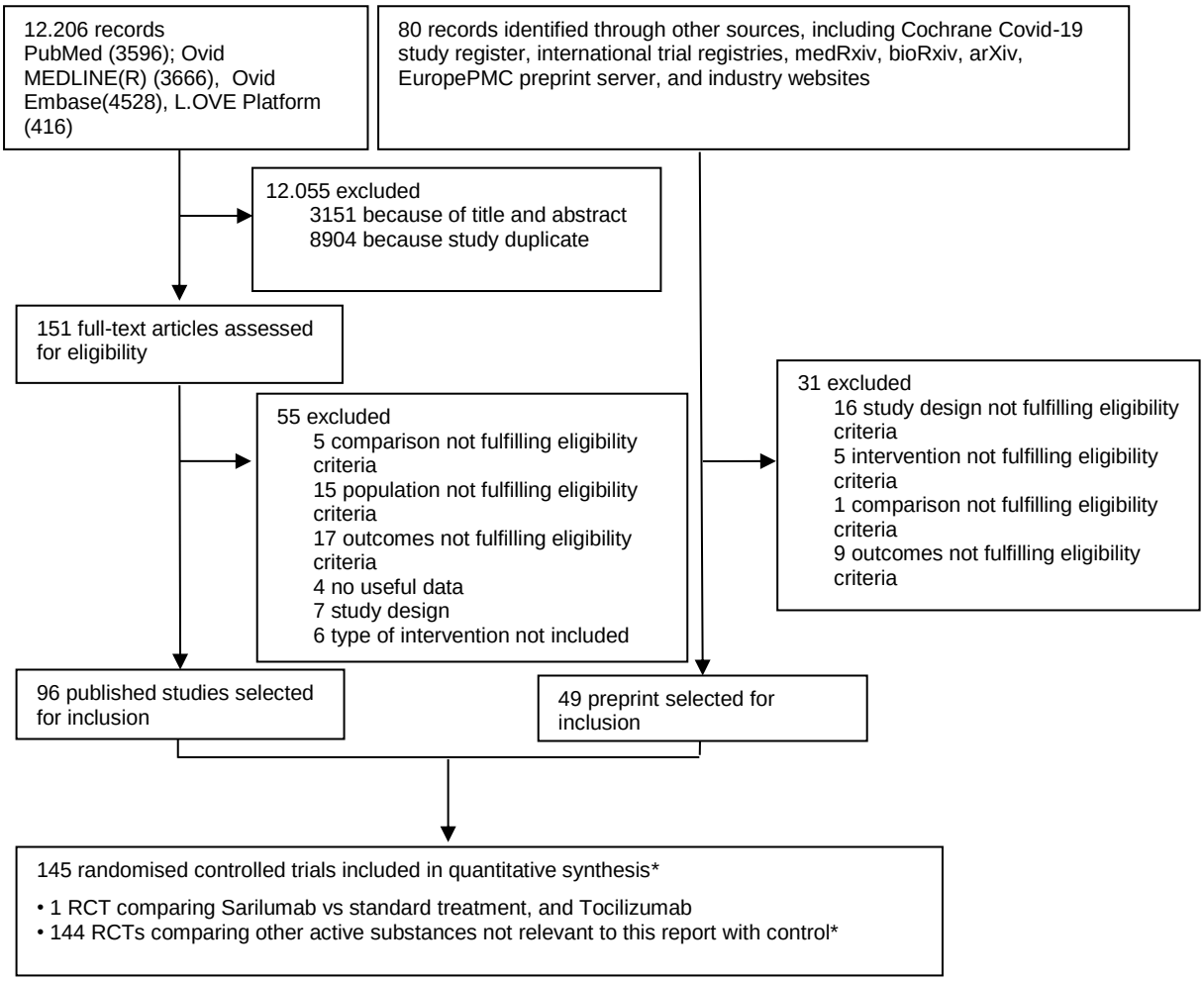
NIPHNO is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and Sarilumab are described in Appendix Table 6-3.

Table 6-3 Search strategy to identify ongoing studies

Database	URL	Search line / search terms	Date of search	Hits retrieved
ClinicalTrials.gov	https://clinicaltrials.gov/	"Basic search mode*" Terms used at Condition or disease: • covid-19 Terms used at "other terms": • Sarilumab	10/05/2021	17 0 new
ISRCTN	https://www.isrctn.com/	Basic search mode Search terms: 1. covid-19 and Sarilumab	10/05/2021	3 0 new
European Clinical Trials Registry	https://www.clinicaltrialsregister.eu/	Basic search mode Search terms: 1. covid-19 and Sarilumab	10/05/2021	14 0 new

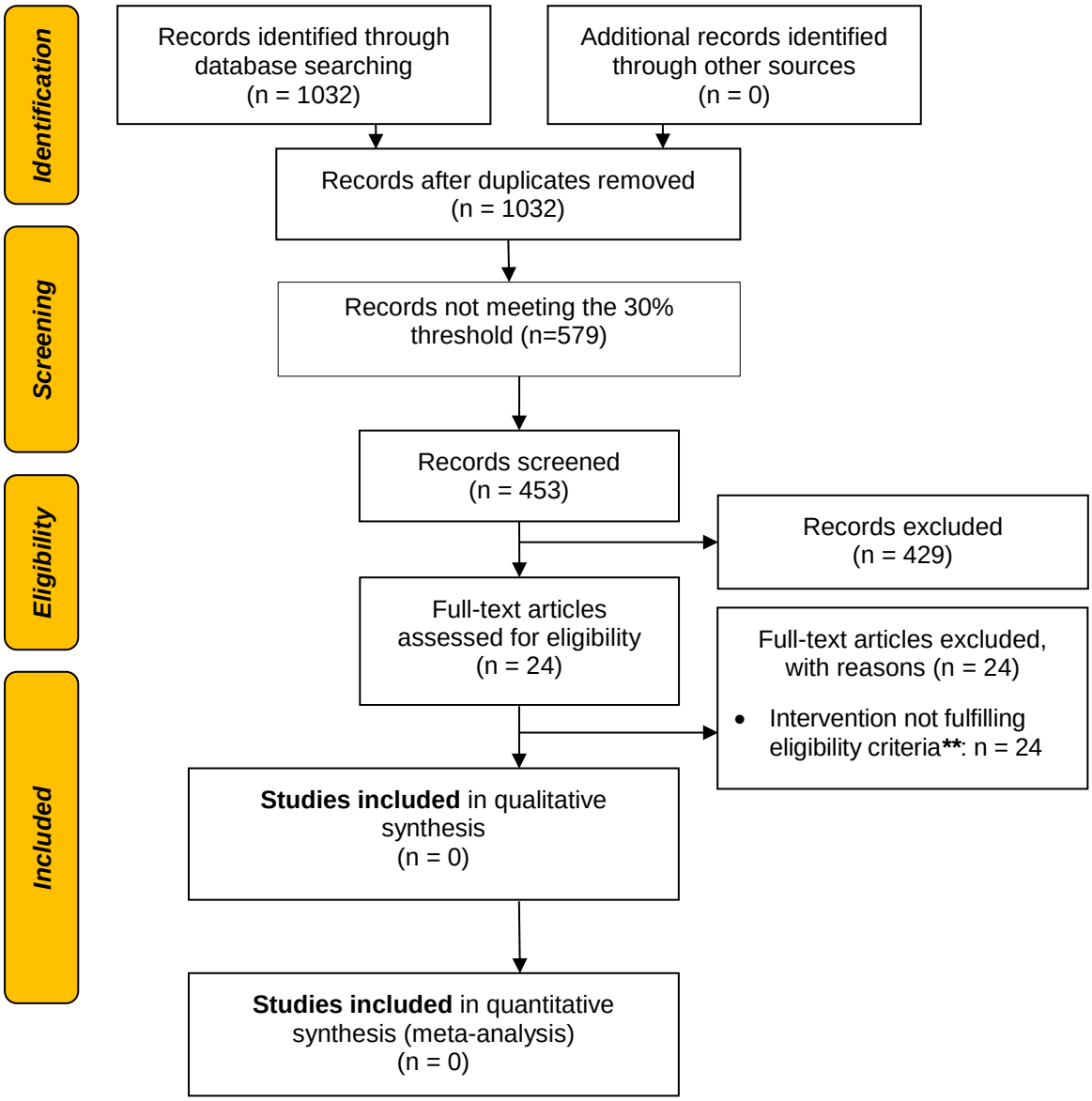
***** In Basic Search mode, one term was added to the field "condition or disease" and one term in the field "other terms".

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.