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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DOCUMENT HISTORY AND CONTRIBUTORS

Version	Date	Description of changes
V 0.1	**11/08/2020**	Literature searches, Literature screening
V 0.2	**12/08/2020**	Data extraction and analysis complete
V 0.3	**13/08/2020**	Check of data extraction and analysis
V 1.0	**14/08/2020**	First version
V 1.1	**10/09/2020**	Literature searches, Literature screening
V 2.0	**15/09/2020**	Second version
V 2.1	**12/10/2020**	Literature searches, Literature screening
V 3.0	**14/10/2020**	Third version
V 3.1	**05/11/2020**	Literature searches, Literature screening, Data extraction
V 3.2	**12/11/2020**	Data extraction and analysis complete
V 4.0	**12/11/2020**	Fourth version

Major changes from previous version

Chapter, page no.	Major changes from version 3.0
4.2, page 10-12	• Included one new observational study

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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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/services/covid-19/) 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	<u>Main outcome:</u> • All-cause Mortality (Survival) <u>Additional Outcomes:</u> Efficacy: • Length of hospital stay, • Viral burden (2019-nCoV RT-PCR negativity), • Clinical progression (WHO Clinical Progression Scale measured daily over the course of the study), • Rates of hospitalization and of patients entering ICU, • Duration of mechanical ventilation, • Quality of life. Safety: • Adverse events (AE), • Severe adverse events (SAE), • Withdrawals due to AEs, • Most frequent AEs, • Most frequent SAEs. **Rationale:** We will give priority according to the Core Outcome Set for Clinical Trials on Coronavirus Disease 2019 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102592/pdf/main.pdfc) and A minimal common outcome measure set for COVID-19 clinical research from the WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection.
Study design	Efficacy: randomised controlled trials (RCT) Safety: observational studies (comparative or single-arm prospective studies and registries)

2.2 Sources of information

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

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

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

The literature search is conducted in the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library
- MEDLINE, accessed via OVID
- Embase, accessed via OVID

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

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

- medRxiv Health Sciences
- bioRxiv Biology

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

Data extraction, Risk of bias assessment, data synthesis:

Two reviewers from DEPLazio are screening search results, assessing full texts of studies and extract study characteristics and outcome data according to pre-defined criteria. The process of study selection is depicted as a flow diagram in Appendix Figure 6-1.

Risk of bias is assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [1].

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

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

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

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

The literature search is conducted on a monthly basis 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.

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.

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. 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 6-2. 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

No RCTs have been published so far. Phase II and Phase III studies including RCTs to evaluate the effect of Sarilumab in COVID-19 patients are ongoing. 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"[14]. 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

No evidence from RCTs are currently available for Sarilumab (Kevzara®).

Source: http://deplazio.net/farmacicovid/index.html [15].

4.2 Safety evidence from observational studies

One observational study [14] 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 algorythms". (See Table 4-2). Risk of bias in this study was appraised as high due to the small sample size and a mainly male study population (90%).

Sources:https://www.ncbi.nlm.nih.gov/research/coronavirus/docsum?filters=topics.General%20Info [16] and https://www.fhi.no/en/qk/systematic-reviews-hta/map/ [17].

4.3 Ongoing studies

There are currently 13 ongoing mainly Phase II and III trials registered as randomized controlled, evaluating the clinical efficacy of Sarilumab (see Table 4-3).

4.4 Scientific conclusion about status of evidence generation

More evidence is needed to be able to draw conclusions on the clinical effect and safety of Sarilumab (Kevzara®) in COVID-19 patients. Several clinical trials are underway.

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

Author, year	Gremese et al. (2020) [14]
Country	Italy
Sponsor	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 (i.e. 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 4-2 Ongoing trials of single agent Sarilumab

Active substance	Sarilumab	Sarilumab	Sarilumab	Sarilumab
Sponsor	Maria del Rosario Garcia de Vicuña Pinedo/Instituto de Investigación Sanitaria Hospital Universitario de la Princesa	Regeneron Pharmaceuticals/Sanofi	Westyn Branch-Elliman, VA Boston Healthcare System	Maimónides Biomedical Research Institute of Córdoba Consejería de Salud y Familias - Junta de Andalucía Red Andaluza de Ensayos Clínicos en Enfermedades Infecciosas (Red ANCRAID)
Trial Identifier	NCT04357808 EudraCT 2020-001634-36 (SARCOVID)	NCT04315298 EudraCT 2020-001162-12	NCT04359901	NCT04357860 EudraCT 2020-001531-27 (SARICOR)
Phase & Intention	Phase II study to evaluate the efficacy of subcutaneous sarilumab in patients with moderate-severe COVID-19 infection	Phase II to evaluate the clinical efficacy of sarilumab relative to the control arm in adult patients hospitalized with COVID-19 regardless of disease severity strata, and phase III to evaluate the clinical efficacy of sarilumab relative to the control arm in adult patients hospitalized with COVID-19 (Cohort 2) and critical COVID19 (Cohort 1) receiving mechanical ventilation at baseline	Phase II to evaluate clinical efficacy of sarilumab in patients with moderate COVID-19 disease	Phase II to evaluate if early administration of sarilumab in hospitalized patients infected with COVID-19 who have pulmonary infiltrates and are at high risk of unfavorable evolution could decrease/prevent progression to acute respiratory distress syndrome (ARDS) requiring high flow nasal oxygenation (HFNO) or either invasive or non-invasive mechanical ventilation.
Study design	RCT, Randomised, open-label, comparative trial (sarilumab plus standard of care vs. standard of care in a 2:1 ratio), parallel assignment	RCT, Randomized, Double-Blind, Placebo-Controlled Study, quadruple masking (participant, care provider, investigator, outcomes assessor), parallel assignment	RCT, Randomised (open-labelled) controlled trial, parallel assignment	RCT, Randomised (open-labelled) controlled trial, parallel assignment
Status of trial	Recruiting	Active, not recruiting,	Recruiting	Not yet recruiting

Active substance	Sarilumab	Sarilumab	Sarilumab	Sarilumab
Duration/End of Study	Estimated Primary Completion Date: December 2020 Estimated Study Completion Date: December 2020 2 months	Estimated Study Completion Date: August 31, 2020 Actual Primary Completion Date: July 24, 2020 (Final data collection date for primary outcome measure) 5,5 months	Estimated Study Completion Date: April 2023 Estimated Primary Completion Date: April 2022	Estimated Primary Completion Date: July 27, 2020 Estimated Study Completion Date: July 27, 2020 6 months
Study details				
Number of Patients	n = 30 (>18 years)	n = 1912 (originally estimated: 400) (18 years and older)	n = 120 (18 years and older)	n = 120 (Age ≥ 18 years and <75 years)
Disease severity				
Setting				
Location/Centres	Spain	USA	USA	Spain
Intervention 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 (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.
Duration of observation/ Follow-up	Not indicated	Not indicated	Not indicated	Not indicated
Primary Outcomes	Mean change in clinical status assessment using the 7-point ordinal scale at day 7 after randomisation [Time Frame: 7 days from enrolment] (Score ranges 1-7 = Death (1); Hospitalized, requiring invasive mechanical ventilation or	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]	Intubation or death [Time Frame: with in 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)]

Active substance	Sarilumab	Sarilumab	Sarilumab	Sarilumab
	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) Duration of hospitalisation (days) [Time Frame: 30 days from enrolment] Number of deaths [Time Frame: 30 days from enrolment]	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 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		Proportion of patients requiring or time (in days) until required: -High flow nasal oxygenation (HFNO) -Non-invasive mechanical ventilation type BiPAP -Non-invasive mechanical ventilation type CPAP -Invasive mechanical ventilation
Results/Publication	Not provided	Not provided	Not provided	Not provided

Table 4-3 Ongoing trials of single agent Sarilumab, continued

Active substance	Sarilumab	Sarilumab	Sarilumab	Sarilumab
Sponsor	Marius Henriksen, Frederiksberg University Hospital/ Lars Erik Kristensen	Cristina Avendaño Sola	Consorci Parc de Salut Mar (PSMAR)	ISTITUTO NAZIONALE PER LE MALATTIE INFETTIVE "LAZZARO SPALLANZANI"
Trial Identifier	NCT04322773 EudraCT 2020-001275-32	EudraCT 2020-002037-15	EudraCT 2020-001290-74 (SARICOVID)	EudraCT 2020-001390-76 (ESCAPE)
Phase & Intention	Phase II study to compare compare the effect of either one of three IL-6 inhibitor administrations (tocilizumab 400 mg, tocilizumab 2 x 162 mg and sarilumab 1 x 200 mg) relative to the standard of care in patients with severe SARS-CoV-2 pneumonia.	Phase II study to evaluate the efficacy and safety of Standard of care + Sarilumab versus Standard of Care for the Early Treatment of COVID-19-pneumonia in Hospitalized Patients	Phase III study to evaluate the efficacy and safety of sarilumab in the early treament of hospitalized patients with mild-moderate neumonia and COVID19 infection versus standard of care	Phase III study comparing clinical efficacy and safety of intravenous sarilumab plus standard of care compared to standard of care, in the treatment of patients with severe COVID-19 pneumonia
Study design	RCT, randomised (open-labelled), sequencial assignment	RCT, randomized, open-label study, parallel groups	RCT, randomized, open-label study, not parallel groups	RCT, randomized, (open-labeled) trial, not parallel groups
Status of trial	Recruiting	Ongoing	Ongoing	Ongoing
Duration/End of Study	Estimated Primary Completion Date: June 1, 2021 Estimated Study Completion Date: June 1, 2021 14 months	Date of first record: 2020-05-26 11 months	Date of first record: 2020-04-13) 4 months	Date of first record 2020-06-24 90 days
Study details				
Number of Patients	n = 200 (18 years and older)	n = 200 (18 years and older)	n = 216 (18 years and older)	n = 171 (18 years and older)
Disease severity				
Setting				
Location/Centres	Denmark	Spain	Spain	Italy
Intervention drug name and dosage	One of the 3 arms: Single dose treatment with 1 x 200 mg sarilumab subcutaneously and standard medical care	Standard care + sarilumab (200 mg)	Sarilumab (200 mg)	Sarilumab (200 mg) + standard of care
Comparator (drug name and dosage)	Standard care	Standard care	Standard of care (including azithromycin, hydroxychloroquine)	Standard of care
Duration of observation/ Follow-up	Not indicated	Not indicated	Not indicated	Not indicated
Primary Outcomes	Time to independence from supplementary	Proportion of patients progressing to	Time to clinical improvement, defined as the time	Time to clinical improvement, defined as the

Active substance	Sarilumab	Sarilumab	Sarilumab	Sarilumab
	oxygen therapy [Time Frame: days from enrolment up 28 days]	severe respiratory failure (Brescia-COVID Scale ≥2), ICU admission, or death (From baseline up to Day-15)	from randomization to a two-point improvement (from randomization status) on an ordinal scale of seven categories or hospital discharge, whichever occurs first.	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); 6. hospitalized, requiring ECMO, invasive mechanical ventilation, or both; 7. death.
Results/Publication	Not provided	Not provided	Not provided	Not provided

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

Active substance	Sarilumab	Sarilumab	Sarilumab	Sarilumab
Sponsor	Department of Infectious Diseases, Hvidovre Hospital	SOCIETA' ITALIANA MALATTIE INFETTIVE E TROPICALI	Assistance Publique - Hôpitaux de Paris	MJM Bonten, UMC Utrecht/ Australian and New Zealand Intensive Care Research Centre Medical Research Institute of New Zealand Unity Health Berry Consultants Global Coalition for Adaptive Research

Active substance	Sarilumab	Sarilumab	Sarilumab	Sarilumab
				University of Pittsburgh Medical Center
Trial Identifier	EudraCT 2020-001367-88	EudraCT 2020-001854-23 (AMMURAVID)	NCT04324073 (CORIMUNO-SARI) EudraCT 2020-001246-18	NCT02735707 EudraCT 2015-002340-14 (REMAP-CAP)
Phase & Intention	Phase III study to evaluate efficacy and safety of five treatment options (one of them sarilumab) in combination with standard of care (SOC) for the treatment of moderate-to-severe COVID-19 pneumonia	Phase II and III study	Phase III and III study to determine the therapeutic effect and tolerance of Sarilumab in patients with moderate, severe pneumonia or critical pneumonia associated with Coronavirus disease 2019 (COVID-19).	Phase IV study to evaluate the effect of a range of interventions to improve outcome of patients admitted to intensive care with community-acquired pneumonia, including s a sub-platform of REMAP-CAP that evaluates treatments specific to COVID-19.
Study design	RCT, randomised double-blinded, parallel group	RCT, randomised (open labelled), parallel groups	RCT, randomised (Bayesian open-label) trial, parallel assignment	RCT, randomised (open-labelled), factorial assignment
Status of trial	Ongoing	Ongoing	Active, not recruiting	Recruiting
Duration/End of Study	Date of first record 2020-04-01 1 year and 2 months	Date of first record: 2020-06-26 4 months	Estimated Primary Completion Date: March 27, 2021	Estimated Primary Completion Date: December 2021 Estimated Study Completion Date: December 2023
Study details				
Number of Patients	n = 1500 (≥18 years of age)	n = 1400 (≥18 years of age)	Estimated Primary Completion Date: March 27, 2021	n = 7100 (18 years and older) with community-acquired pneumonia, influenza, COVID-19
Disease severity				
Setting				
Location/Centres	Denmark	Italy	France	Australia, Belgium, Canada, Croatia, Germany, Hungary, Ireland, Netherlands, New Zealand, Portugal, Romania, Spain, UK, USA
Intervention drug name and dosage	Sarilumab 200 mg	Various immunomodulating compounds (arms). Among these Sarilumab administered 150	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

Active substance	Sarilumab	Sarilumab	Sarilumab	Sarilumab
		mg (in addition to hydroxicloroquine)		through peripheral or central line over a one-hour period.
Comparator (drug name and dosage)	Placebo	No information	Standard of care	No interventions
Duration of observation/ Follow-up	Not indicated	Not indicated	Not indicated	Not indicated
Primary Outcomes	All-cause mortality or need of invasive mechanical ventilation up to 28 days.	Proportion of patients with PaO2/FiO2 <200 mmHg at day 10 in each intervention arm as compared to the control arm	Survival without needs of ventilator utilization at day 14. [Time Frame: 14 days] WHO progression scale <=5 at day 4 [Time Frame: 4 days] (WHO progression scale: Uninfected; non viral RNA detected: 0 Asymptomatic; viral RNA detected: 1 Symptomatic; Independent: 2 Symptomatic; Assistance needed: 3 Hospitalized; No oxygen therapy: 4 Hospitalized; oxygen by mask or nasal prongs: 5 Hospitalized; oxygen by NIV or High flow: 6 Intubation and Mechanical ventilation, pO2/FIO2>=150 OR SpO2/FIO2>=200: 7 Mechanical ventilation, (pO2/FIO2<150 OR SpO2/FIO2<200) OR vasopressors (norepinephrine >0.3 microg/kg/min): 8 Mechanical ventilation, pO2/FIO2<150 AND vasopressors (norepinephrine >0.3 microg/kg/min), OR Dialysis OR	All-cause mortality [Time Frame: Day 90] Days alive and not receiving organ support in ICU [Time Frame: Day 21]

Active substance	Sarilumab	Sarilumab	Sarilumab	Sarilumab
			ECMO: 9 Dead: 10) Cumulative incidence of successful tracheal extubation (defined as duration extubation > 48h) at day 14 [Time Frame: 14 days] WHO progression scale at day 4 [Time Frame: 4 days]	
Results/Publication	Not provided		Not provided	No results published on Sarilumab for COVID-19

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

Active substance	Sarilumab
Sponsor	Sanofi/ Regeneron Pharmaceuticals
Trial Identifier	NCT04327388
Phase & Intention	Phase III to evaluate the clinical efficacy of sarilumab relative to the control arm in adult patients hospitalized with severe or critical COVID-19
Study design	RCT, Randomised controlled trial, quadruple masked participant, care provider, investigator, outcomes assessor), parallel assignment
Status of trial	Active, not recruiting
Duration/End of Study	Estimated Primary Completion Date: July 2020 Estimated Study Completion Date: August 2020
Study details	
Number of Patients	n = 409 (18 years and older)
Disease severity	
Setting	
Location/Centres	Argentina, Brazil, Canada, Chile, France, Germany, Israel, Italy, Japan, Russian Federation, Spain
Intervention drug name and dosage	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 (drug name and dosage)	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.
Duration of observation/ Follow-up	Approximately 60 days from screening to follow-up on day 60 ±7 days.
Primary Outcomes	Time to improvement of 2 points in clinical status assessment from baseline using the 7-point ordinal scale [Time Frame: Baseline to Day 29] The ordinal scale is an assessment of the clinical status. Score ranges 1-7. Lower score is worse.

Active substance	**Sarilumab**
Results/Publication	Not provided

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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])	06/11/2020

Database	URL	Search line / Search terms	Date of search
Ovid MEDLINE(R) ALL)	ovidsp.dc2.ovid.com	1. exp coronavirus/ 2. ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw. 3. (coronavirus* or coronovirus* or coronavirinae* or Coronavirus* or Coronovirus* or Wuhan* or Hubei* or Huanan or "2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCoV or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese*).ti,ab,kw. 4. (((respiratory* adj2 (symptom* or disease* or illness* or condition*)) or "seafood market*" or "food market*") adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw. 5. ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (China* or Chinese* or Huanan*)).ti,ab,kw. 6. "severe acute respiratory syndrome*".ti,ab,kw. 7. or/1-6 8. randomized controlled trial.pt. 9. controlled clinical trial.pt. 10. random*.ab. 11. placebo.ab. 12. clinical trials as topic.sh. 13. random allocation.sh. 14. trial.ti. 15. or/8-14 16. exp animals/ not humans.sh. 17. 15 not 16 18. 7 and 17 19. limit 18 to yr="2019 -Current"	06/11/2020
OVID EMBASE	ovidsp.dc2.ovid.com	1. exp Coronavirinae/ or exp Coronavirus/ 2. exp Coronavirus infection/ 3. ((("Corona virinae" or "corona virus" or Coronavirinae or coronavirus or COVID or nCoV) adj4 ("19" or "2019" or novel or new)) or (("Corona virinae" or "corona virus" or Coronavirinae or coronavirus or COVID or nCoV) and (wuhan or china or chinese)) or "Corona virinae19" or "Corona virinae2019" or "corona virus19" or "corona virus2019" or Coronavirinae19 or Coronavirinae2019 or coronavirus19 or coronavirus2019 or COVID19 or COVID2019 or nCOV19 or nCOV2019 or "SARS Corona virus 2" or "SARS Coronavirus 2" or "SARS-COV-2" or "Severe Acute Respiratory Syndrome Corona virus 2" or "Severe Acute Respiratory Syndrome Coronavirus 2").ti,ab,kw. 4. or/1-3 5. Clinical-Trial/ or Randomized-Controlled-Trial/ or Randomization/ or Single-Blind-Procedure/ or Double-Blind-Procedure/ or Crossover-Procedure/ or Prospective-Study/ or Placebo/ 6. (((clinical or control or controlled) adj (study or trial)) or ((single or double or triple) adj (blind$3 or mask$3)) or (random$ adj (assign$ or allocat$ or group or grouped or patients or study or trial or distribut$)) or (crossover adj (design or study or trial)) or placebo or placebos).ti,ab. 7. 5 or 6 8. 4 and 7 9. limit 8 to yr="2019 -Current"	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
OVID Medline	Imported from EPPI Centre	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 ((20191* 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	27/09/2020 until 25/10/2020
OVID EMBASE		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. 6 ((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.	27/09/2020 until 25/10/2020

		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	
Scopus		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 > 20200920[date changes from week to week] AND ORIG-LOAD-DATE < 20200928 [date changes from week to week] AND NOT INDEX(medline)	27/09/2020 until 25/10/2020

6.3 Search strategy to identify ongoing studies

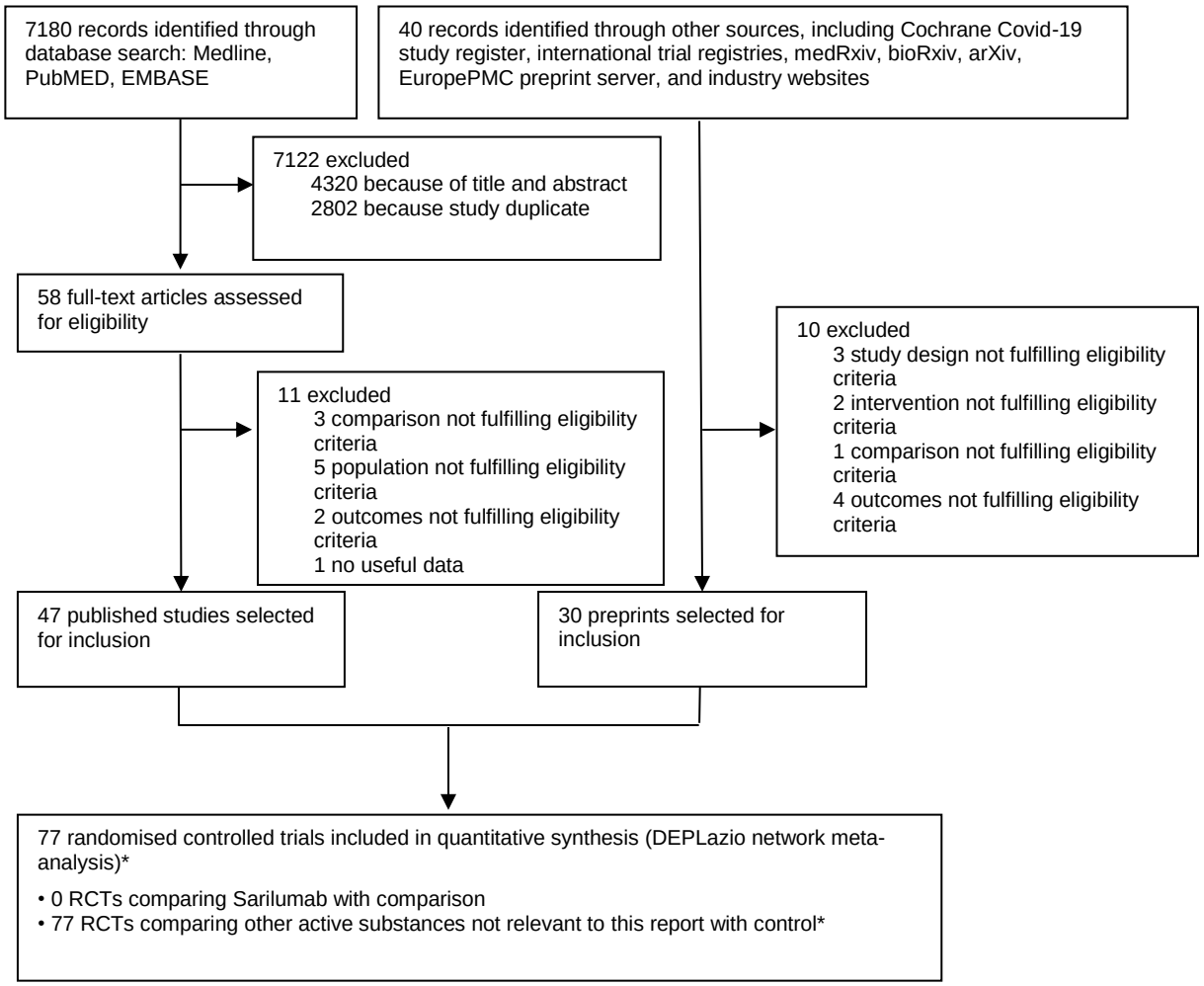
NIPHNo is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and Sarilumab are described in Appendix Table 6-3.

Table 6-3 Search strategy to identify ongoing studies

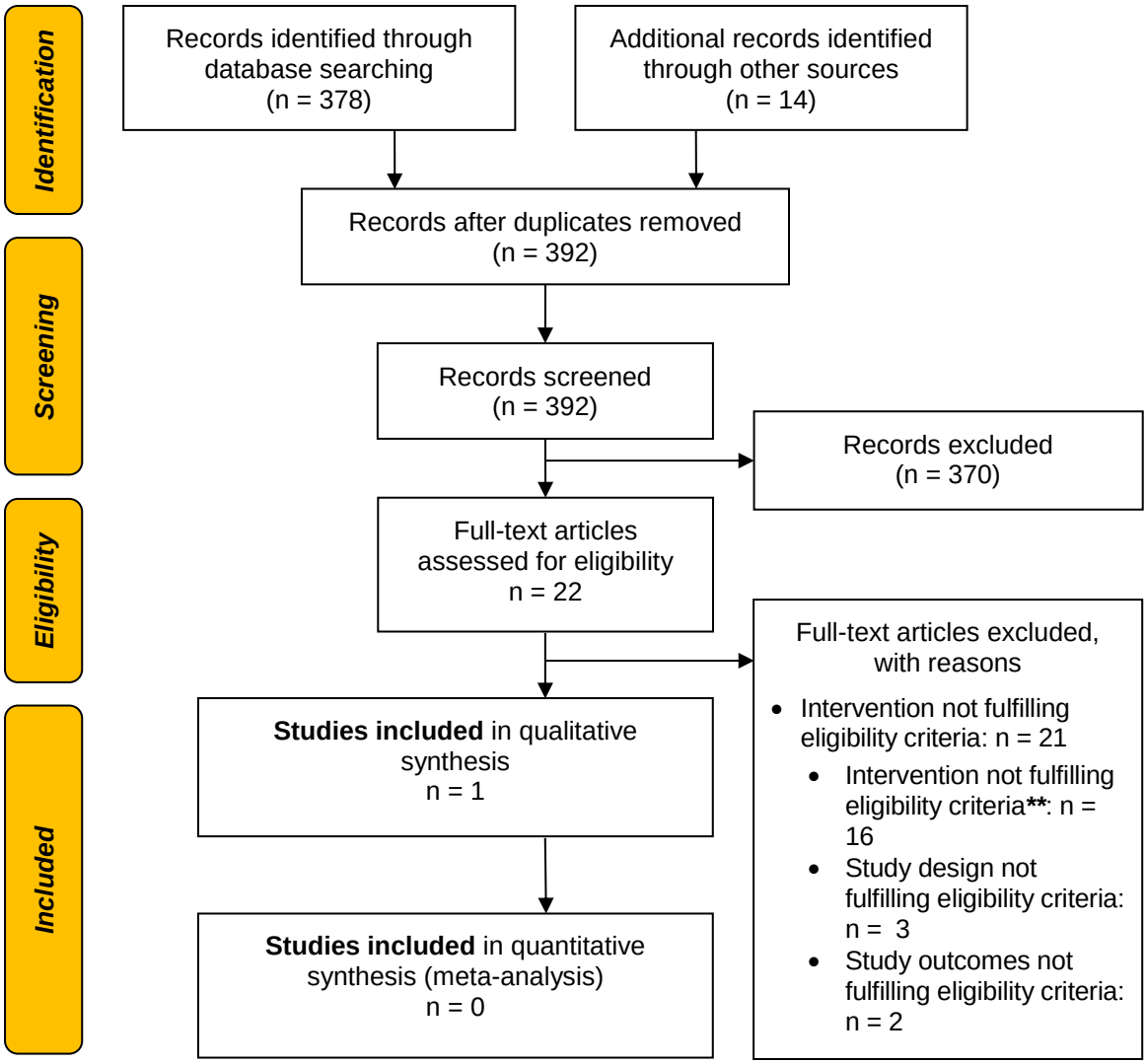
Database	URL	Search line / search terms	Date of search	Hits retrieved
ClinicalTrials.gov	https://clinicaltrials.gov/	"Basic search mode*" Terms used at Condition or disease: • covid-19 Terms used at "other terms": • Sarilumab	05/11/2020	16 0 new
ISRCTN	https://www.isrctn.com/	Basic search mode Search terms: • Sarilumab in category "text search" • COVID-19 in category "condition"	05/11/2020	3 0 new
European Clinical Trials Registry	https://www.clinicaltrialsregister.eu/	Basic search mode Search terms: • COVID-19 AND sarilumab	05/11/2020	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".

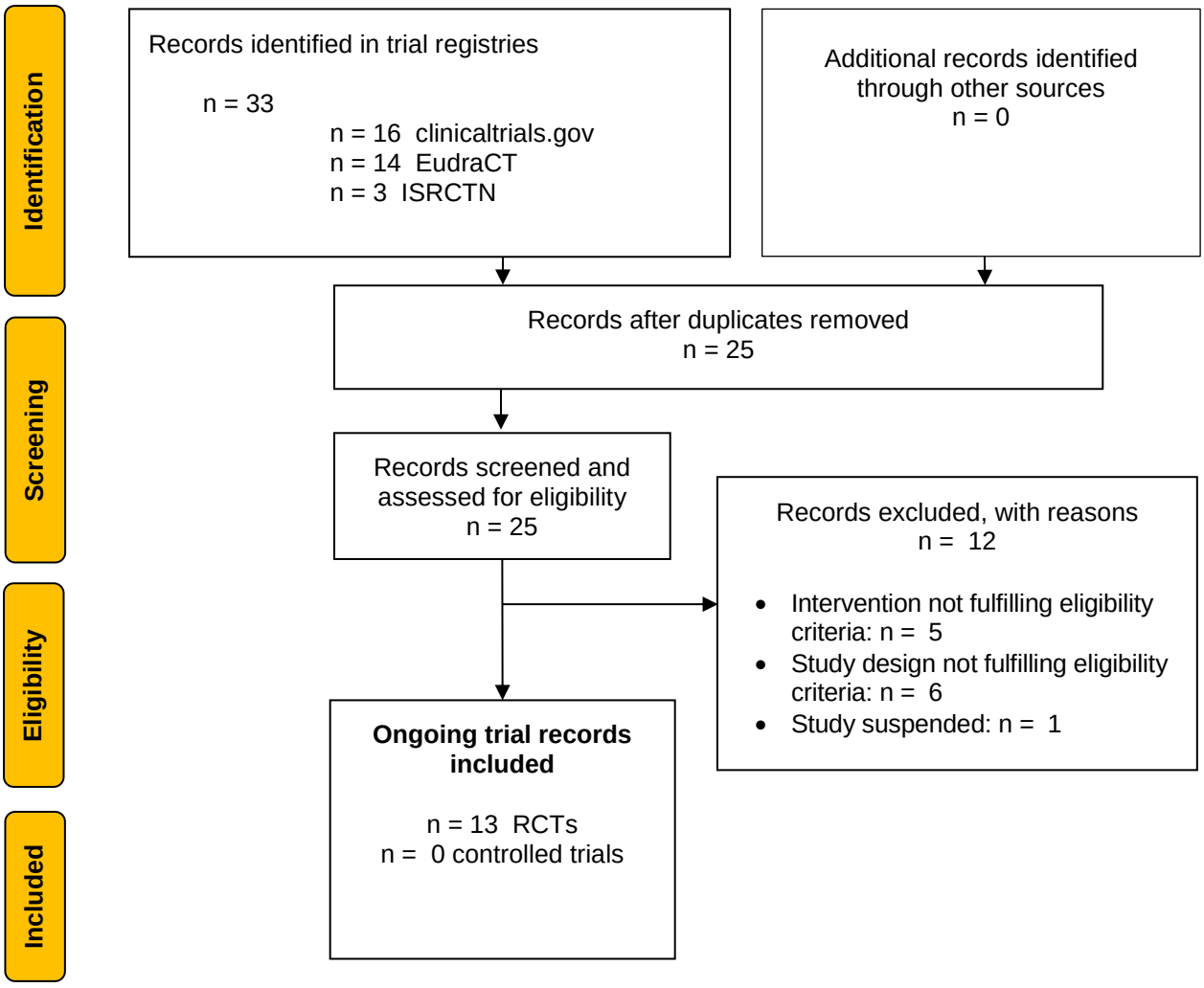
6.4 Flow diagrams



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. N=13
RCT = randomised controlled trial;