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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Major changes from previous version

Chapter, page no.	Major changes from version 1.0
Chapter 4, Tables 4-1, 4-2 and 4-3	• Secondary outcomes removed

Disclaimer

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Rolling Collaborative Review team

Author(s)	Norwegian Institute of Public Health (NIPHNO), Division for Health Services, Norway
Co-Author(s)	Department of Epidemiology Lazio Regional Health Service (DEPLazio), Italy

Further contributors

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

Conflict of interest

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

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Contact the EUnetHTA Secretariat EUnetHTA@zinl.nl with inquiries about this assessment.

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
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
ICD	International Classification of Diseases
IL	Interleukin
MeSH	Medical Subject Headings
NMA	Network Meta-Analysis
NR	Not reported
RCT	Randomized Controlled Trial
RCR	Rolling Collaborative Review
RR	Relative Risk
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome - Corona Virus - 2
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.

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.

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/
- https://www.ncbi.nlm.nih.gov/research/coronavirus/docsum?filters=topics.General%20Info

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	Prospective non-randomised controlled trials, prospective case series, registries Exclusion criteria: retrospective case series, case studies

One researcher carries out title and abstract screening and assesses the full texts of all potentially eligible studies. One researcher extracts the data and assesses the risk of bias using Robins-I (https://training.cochrane.org/handbook/current/chapter-25).

Results are presented in tabular form for all included studies.

3. Table(s) on ongoing trials:

The following clinical trial registries are searched on a monthly basis:

- ClinicalTrials.gov: https://clinicaltrials.gov/
- ISRCTN: https://www.isrctn.com/
- European Clinical Trials Registry: https://www.clinicaltrialsregister.eu/

Inclusion criteria: Randomised controlled trials, Controlled trials

One researcher is searching and extracting the data for the eligible studies.

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 Pharmaceuticalsand 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. KEVZARA® 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 or observational studies with more than 50 patients 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.

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 [14].

4.2 Safety evidence from observational studies

No evidence from observational studies with more than 50 patients (treated with Sarilumab (Kevzara®) for COVID-19) are currently available for this compound.

Sources:https://www.ncbi.nlm.nih.gov/research/coronavirus/docsum?filters=topics.General%20Info [15] and https://www.fhi.no/en/qk/systematic-reviews-hta/map/ [16].

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 4-1, Table 4-2 and 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 Ongoing trials of single agent Sarilumab

Active substance	Sarilumab	Sarilumab	Sarilumab	Sarilumab	Sarilumab
Sponsor/Collaborator	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)	Sanofi/ Regeneron Pharmaceuticals
Trial Identifier	NCT04357808 EudraCT 2020-001634-36 (SARCOVID)	NCT04315298 EudraCT 2020-001162-12	NCT04359901	NCT04357860 EudraCT 2020-001531-27 (SARICOR)	NCT04327388
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.	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, open-label, comparative trial (sarilumab plus standard of care vs. standard of care in	RCT, Randomized, Double-Blind, Placebo-Controlled Study, quadruple masking (participant, care provider, investigator, outcomes	RCT, Randomised (open-labelled) controlled trial, parallel assignment	RCT, Randomised (open-labelled) controlled trial, parallel assignment	RCT, Randomised controlled trial, quadruple masked participant, care provider, investigator,

Active substance	Sarilumab	Sarilumab	Sarilumab	Sarilumab	Sarilumab
	a 2:1 ratio), parallel assignment	assessor), parallel assignment			outcomes assessor), parallel assignment
Status trial	Recruiting	Active, not recruiting,	Recruiting	Not yet recruiting	Active, not recruiting
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	Estimated Primary Completion Date: July 2020 Estimated Study Completion Date: August 2020
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)	n = 409 (18 years and older)
Location/Centres	Spain	USA	USA	Spain	Argentina, Brazil, Canada, Chile, France, Germany, Israel, Italy, Japan, Russian Federation, Spain
Intervention	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]	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.

Active substance	Sarilumab	Sarilumab	Sarilumab	Sarilumab	Sarilumab
Controls	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.	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	Not indicated	Not indicated	Not indicated	Not indicated	Approximately 60 days from screening to follow-up on day 60 ±7 days.
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 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)	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 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	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: -High flow nasal oxygenation (HFNO) -Non-invasive mechanical ventilation type BiPAP -Non-invasive mechanical ventilation type CPAP -Invasive mechanical ventilation	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	Sarilumab	Sarilumab	Sarilumab	Sarilumab
	Duration of hospitalisation (days) [Time Frame: 30 days from enrolment] Number of deaths [Time Frame: 30 days from enrolment]	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			
Results/Publication	Not provided	Not provided	Not provided	Not provided	Not provided

Sources: https://clinicaltrials.gov/ and https://www.clinicaltrialsregister.eu/ and https://www.isrctn.com/

Table 4-2 Ongoing trials of single agent Sarilumab continued

Active substance	Sarilumab	Sarilumab	Sarilumab	Sarilumab
Sponsor/Collaborator	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	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-	Phase III study to evaluate the efficacy and safety of sarilumab in the early treament of hospitalized patients with mild-moderate neumonia and	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

Active substance	Sarilumab	Sarilumab	Sarilumab	Sarilumab
	with severe SARS-CoV-2 pneumonia.	pneumonia in Hospitalized Patients	COVID19 infection versus standard of care	
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 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
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)
Location/Centres	Denmark	Spain	Spain	Italy
Intervention	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
Controls	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 oxygen therapy [Time Frame: days from enrolment up 28 days]	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

Active substance	Sarilumab	Sarilumab	Sarilumab	Sarilumab
				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 4-3 Ongoing trials of single agent Sarilumab continued

Active substance	Sarilumab	Sarilumab	Sarilumab	Sarilumab
Sponsor/Collaborator	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 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	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

Active substance	Sarilumab	Sarilumab	Sarilumab	Sarilumab
	treatment of moderate-to-severe COVID-19 pneumonia			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 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
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
Location/Centres	Denmark	Italy	France	Australia, Belgium, Canada, Croatia, Germany, Hungary, Ireland, Netherlands, New Zealand, Portugal, Romania, Spain, UK, USA
Intervention	Sarilumab 200 mg	Various immunomodulating compounds (arms). Among these Sarilumab administered 150 mg (in addition to hydroxicloroquine)	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.
Controls	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;	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
			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 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

Sources: https://clinicaltrials.gov/ and https://www.clinicaltrialsregister.eu/ and https://www.isrctn.com/

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