EUnetHTA Joint Action 3 WP4

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

# ANAKINRA FOR THE TREATMENT OF COVID-19

**Project ID: RCR07**
Monitoring Report

**Version 2.0, September 2020**

Template version August 2020

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# DOCUMENT HISTORY AND CONTRIBUTORS

| Version | Date | Description of changes |
|---|---|---|
| **V 1.0** | **14/08/2020** | First version |
| **V 1.1** | **September 2020** | Literature searches, Literature screening, Data extraction |
| **V 1.2** | **09/09/2020** | Data extraction and analysis complete |
| **V 1.3** | **10/09/2020** | Check of data extraction and analysis |
| **V 2.0** | **15/09/2020** | Second version |

### Major changes from previous version

| Chapter, page no. | Major changes from version 1.0 |
|---|---|
| | • No major changes (only the collaborators and secondary outcomes of ongoing studies in clinical trials registers were deleted; these data can be found in the Version 1.0, August 2020) |

### Disclaimer

The content of this "Rolling Collaborative Review" (RCR) represents a consolidated view based on the consensus within the Authoring Team; it cannot be considered to reflect the views of the European Network for Health Technology Assessment (EUnetHTA), EUnetHTA's participating institutions, the European Commission and/or the Consumers, Health, Agriculture and Food Executive Agency or any other body of the European Union. The European Commission and the Agency do not accept any responsibility for use that may be made of the information it contains.

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| 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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# LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| ARR | Absolute Risk Reduction |
| ATC | Anatomical Therapeutic Chemical [Classification System] |
| ATMP | Advanced therapy medicinal product |
| CI | Confidence Interval |
| DOI | Declaration of interest |
| EUnetHTA | European Network of Health Technology Assessment |
| GRADE | Grading of Recommendations, Assessment, Development and Evaluation |
| HR | Hazard Ratio |
| HRQOL | Health-related Quality of Life |
| ICD | International Classification of Diseases |
| ITT | Intention-to-treat |
| MD | Mean Difference |
| MeSH | Medical Subject Headings |
| NA | Not applicable |
| NR | Not reported |
| OR | Odds Ratio |
| PP | Per Protocol |
| RCT | Randomized Controlled Trial |
| RCR | Rolling Collaborative Review |
| REA | Relative Effectiveness Assessment |
| RR | Relative Risk |
| SAE | Serious Adverse Event |
| SD | Standard Deviation |
| SMD | Standardized Mean Difference |
| SmPC | Summary of product characteristics |
| SOP | Standard Operating Procedure |
| WP4 | Work Package 4 |

# 1 OBJECTIVE

The aim of this EUnetHTA Rolling Collaborative Review is

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

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

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

# 2 METHODS

This Rolling Collaborative Review is prepared according to the project plan ("Rolling Collaborative Review (RCR) on Covid-19 treatments: Project description and planning", published on the EUnetHTA website) and will be updated monthly. Monthly updates are published on the EUnetHTA Covid-19 Website (https://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**<br>• 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.<br>**ICD-Codes** (https://www.who.int/classifications/icd/covid19/en)<br>• 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.<br>• 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.<br>• 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.<br>• 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.<br><br>**MeSH-terms**<br>• COVID-19, Coronavirus Disease 2019<br><br>**Target population**<br>(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.<br>• 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.<br>• 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.<br>• 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%.<br>• Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction. |
| **Intervention** | Anakinra (Kineret®): immunosuppressive medicine, a copy of a natural human protein - 'human interleukin 1 receptor antagonist' (r-metHuIL-1ra, produced in Escherichia coli cells by recombinant DNA technology); it neutralises the biologic activity of interleukin-1α (IL-1α) and interleukin-1β (IL-1β) by competitively inhibiting their binding to interleukin-1 type I receptor (IL-1RI). Interleukin-1 (IL-1) is a pivotal pro-inflammatory cytokine mediating many cellular responses including those important in synovial inflammation. |
| **Comparison** | Any active treatment, placebo, or standard of care.<br><br>**Rationale**: Since there is no gold standard treatment any comparator is acceptable as well as the above listed interventions. |
| **Outcomes** | <u>Main outcome:</u><br>• All-cause Mortality (Survival)<br><br><u>Additional Outcomes:</u><br>Efficacy:<br>• Length of hospital stay,<br>• Viral burden (2019-nCoV RT-PCR negativity),<br>• Clinical progression (WHO Clinical Progression Scale measured daily over the course of the study),<br>• Rates of hospitalization and of patients entering ICU,<br>• Duration of mechanical ventilation,<br>• Quality of life.<br><br>Safety:<br>• Adverse events (AE),<br>• Severe adverse events (SAE),<br>• Withdrawals due to AEs,<br>• Most frequent AEs,<br>• Most frequent SAEs.<br><br>**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)<br><br>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)<br>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.<br>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<br>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** | Anakinra (Kineret®): immunosuppressive medicine, a copy of a natural human protein - 'human interleukin 1 receptor antagonist' (r-metHuIL-1ra, produced in Escherichia coli cells by recombinant DNA technology); it neutralises the biologic activity of interleukin-1α (IL-1α) and interleukin-1β (IL-1β) by competitively inhibiting their binding to interleukin-1 type I receptor (IL-1RI). Interleukin-1 (IL-1) is a pivotal pro-inflammatory cytokine mediating many cellular responses including those important in synovial inflammation. |
| **Comparison** | Any active treatment, placebo, or standard of care. |
| **Outcomes** | See project Scope |
| **Study design** | Prospective non-randomised controlled trials, prospective case series, registries<br>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*

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

## *3.2 Regulatory Status*

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

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

## *3.3 Level of Evidence*

As of September 09, 2020, no publications related to RCTs evaluating anakinra treatment in COVID-19 patients were found.

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

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

**Several ongoing RCTs and one interventional nRCT are registered in EudraCT and ClinicalTrials.gov registers, including 40 to 342 COVID-19 patients per study. Four RCTs evaluate anakinra alone, as well as one interventional nRCT; two RCTs evaluate anakinra alone and in combination with ruxolitinib, and one RCT evaluates anakinra alone and in combination with siltuximab or tocilizumab. Details can be found in Table 4-2,**

Table 4-3 and Table 4-4.Table 4-2**Fehler! Verweisquelle konnte nicht gefunden werden.** No completed, withdrawn, suspended or terminated interventional studies were found in ClinicalTrials.gov and EUdraCT registers.

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

# 4 SUMMARY

## *4.1 Effectiveness and Safety evidence from RCTs*

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

## *4.2 Safety evidence from observational studies*

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

## *4.3 Ongoing studies*

Several RCTs and one interventional nRCT related to anakinra alone or in combination therapy are currently ongoing.

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

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

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

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

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

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

*by arms

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

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

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

| Active substance | Anakinra | Anakinra | Anakinra |
|---|---|---|---|
| | saturation normalization; Stay in ICU and hospitalization | | |
| **Results/Publication** | Not applicable (ongoing trial) | Not applicable (ongoing trial) | Not applicable (ongoing trial) |

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

| Active substance | Anakinra | Anakinra |
|---|---|---|
| **Sponsor** | Swedish Orphan Biovitrum | Hellenic Institute for the Study of Sepsis |
| **Trial Identifier** | NCT04324021<br>EudraCT 2020-001167-93 | NCT04339712, EudraCT 2020-001039-29<br>(ESCAPE) |
| **Phase & Intention** | Phase 2/3, to assess the efficacy and safety of emapalumab or anakinra, versus standard of care (SoC) | Phase 2, to assess personalized immunotherapy in patients with SARS-CoV-2 (COVID-19) associated with organ dysfunction and with laboratory findings of macrophage activation syndrome or immune dysregulation |
| **Study design** | RCT, open label, parallel group assignment | nRCT interventional study |
| **Status of trial** | Recruiting | Recruiting |
| **Duration/End of Study** | April 2020 - September 2020 | April 2020 - April 2022 |
| **Study details** | | |
| **Number of Patients** | 54 | 40 |
| **Disease severity** | Patients With SARS-CoV-2 Infection | Life-threatening organ dysfunction by SARS-CoV-2 |
| **Setting** | Hopsital | Hospital |
| **Location/Centres** | Italy | Greece |
| **Intervention drug name and dosage** | Anakinra i.v infusion four times daily for 15 days. 400 mg/day in total, divided into 4 doses given every 6 hours + Standard of care<br><br>Emapalumab i.v infusion every 3rd day for a total 5 infusions. Day 1: 6mg/kg. Days 4, 7, 10 and 13: 3 mg/kg + Standard of care | Anakinra 200mg three times daily (every eight hours) for 7 days<br><br>Tocilizumab 8mg/kg body weight once up to a maximum of 800mg |
| **Comparator (drug name and dosage)** | Standard of care | No comparator |
| **Duration of observation/ Follow-up** | Up to weeks 10 | Up to day 90 |

| | | |
|---|---|---|
| **Active substance** | **Anakinra** | **Anakinra** |
| **Primary Outcomes** | Primary: Treatment success [Time Frame: Up to Day 15] | Primary: Change of baseline total sequential organ failure assessment (SOFA) score; Improvement of lung involvement measurements; Increase of pO2/FiO2 ratio |
| **Results/Publication** | Not applicable (ongoing trial) | Not applicable (ongoing trial) |

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

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

| **Active substance** | **Anakinra alone** (and **Anakinra + Siltuximab** and **Anakinra + Tocilizumab**) | **Anakinra alone** (and **Anakinra plus Ruxolitinib** | **Anakinra alone** (and **Anakinra plus Ruxolitinib**) |
|---|---|---|---|
| | Siltuximab alone (via single IV infusion at a dose of 11 mg/kg)<br><br>Tocilizumab alone (via single IV infusion at a dose of 8 mg/kg with a maximum infusion of 800 mg/injection)<br><br>Anakinra + Siltuximab<br><br>Anakinra + Tocilizumab | | |
| **Comparator (drug name and dosage)** | Usual care | See above | See above |
| **Duration of observation/ Follow-up** | Up to 28 days and 10-20 weeks | Up to 28 days and 12 months | Up to 28 days |
| **Primary Outcomes** | Primary: Time to Clinical Improvement [Time Frame: at day 15] | Primary: Ventilation free days at D28 (VFD28) (an increase of 5 days VFD28 is expected) | Primary: Biological criteria: validation if at least 3 parameters are met including CRP and/or Ferritin<br>1) CRP: decrease > 50% 2) Ferritinemia: decrease > 1/3 3) Serum creatinine: decrease > 1/3 4) AST/ALT: decrease > 50% 5) Eosinophils > 50 /mm3 6) Lymphocytes > 1000 /mm3 |
| **Results/Publication** | Not applicable (ongoing trial) | Not applicable (ongoing trial) | Not applicable (ongoing trial) |

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