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"Rolling Collaborative Review" of Covid-19 treatments

ANAKINRA FOR THE TREATMENT OF COVID-19

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Monitoring Report

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V2.0	**15/09/2020**	Second version
V3.0	**15/10/2020**	Third version
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V6.0	**20/01/2021**	Sixth version
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V8.0	**15/03/2021**	Eighth version
V9.0	**20/04/2021**	Ninth version
V10.0	**17/05/2021**	Tenth version
V 11.0	**15/06/2021**	Eleventh version
V 12.0	**15/07/2021**	Twelfth version
V 12.1	**August 2021**	Literature searches, Literature screening, Clinical Trials Registries search, Data extraction
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Chapter, page no.	Major changes from version 12.0
Chapter 3 and 4	New regulatory data added New outcome (Viral negative conversion D7) in SoF table provided (covid-nma source) Summary of effectiveness and safety revised

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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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/covid-19-treatment/) and on the EUnetHTA Rolling Collaborative Review Sharepoint page each 15th of the month.

2.1 Scope

Table 2-1 Scope of the RCR

Description	Project Scope
Population	**Disease** • SARS-CoV-2 is a novel coronavirus causing a respiratory illness termed Covid-19. The full spectrum of Covid-19 ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multi-organ failure, and death. **ICD-Codes** (https://www.who.int/classifications/icd/covid19/en) • An emergency ICD-10 code of 'U07.1 COVID-19, virus identified' is assigned to a disease diagnosis of COVID-19 confirmed by laboratory testing. • An emergency ICD-10 code of 'U07.2 COVID-19, virus not identified' is assigned to a clinical or epidemiological diagnosis of COVID-19 where laboratory confirmation is inconclusive or not available. • Both U07.1 and U07.2 may be used for mortality coding as cause of death. See the International guidelines for certification and classification (coding) of COVID-19 as cause of death following the link below. • In ICD-11, the code for the confirmed diagnosis of COVID-19 is RA01.0 and the code for the clinical diagnosis (suspected or probable) of COVID-19 is RA01.1. **MeSH-terms** • COVID-19, Coronavirus Disease 2019 **Target population** (https://www.covid19treatmentguidelines.nih.gov/overview/management-of-covid-19/) • Asymptomatic or pre-symptomatic Infection: Individuals who test positive for SARS-CoV-2 by virologic testing using a molecular diagnostic (e.g., polymerase chain reaction) or antigen test, but have no symptoms.

	• Mild Illness: Individuals who have any of the various signs and symptoms of COVID 19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnoea, or abnormal chest imaging. • Moderate Illness: Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO2) ≥94% on room air at sea level. • Severe Illness: Individuals who have respiratory frequency >30 breaths per minute, SpO2 <94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mmHg, or lung infiltrates >50%. • Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.
Intervention	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. **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.pdf) 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) - not mandatory from June 2021

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:

From June 2021, AIHTA has updated the SoF table monthly with the use of covid-nma.com (COVID-NMA initiative: find the living review protocol here).

In addition, from June 2021, the literature search is used from COVID-NMA initiative according living review protocol [1-3] or is conducted by authors of this RCR in the following databases:

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

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

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

- medRxiv Health Sciences
- bioRxiv Biology

In addition to the sources and strategies described above, registers of ongoing studies are screened. Key conferences and conference proceedings are considered.

Data extraction, Risk of bias assessment, data synthesis:

The search results are screened, full texts of studies are assessed and study characteristics and outcome data are extracted according to pre-defined criteria.

Risk of bias is assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [4] or reused from one living SR/MA source [2]. Each study was presented with the Cochrane Risk of bias 2 (RoB 2) tool for RCTs [5].

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 [6]. For rating the certainty of the evidence, the GRADE approach is being used [7].

From June 2021, if new RCTs are published, certainty of evidence have been reused from already published living systematic reviews/meta-analysis (SRs/MA) source from the international COVID-NMA initiative.

- Sources: https://covid-nma.com/for SoF

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

From June 2021, only RCTs are used for assessment of safety.

3. Table(s) on ongoing trials:

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

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

Inclusion criteria: Randomised controlled trials, Controlled trials

One researcher of AIHTA is searching and extracting the data for the eligible studies. 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 6-1.

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 [8]. 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 [8, 9]. 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) [9].

On July 19, 2021 EMA has started evaluating an application to extend the use of anakinra (Kineret) to include treatment of coronavirus disease 2019 (COVID-19) in adult patients with pneumonia who are at risk of developing severe respiratory failure [10].

3.3 Level of Evidence

Currently, three publications (two as preprint) related to an RCTs of anakinra treatment in hospitalised COVID-19 patients were found. Summary of effectiveness and safety could be found in Table 4-1.

The CORIMUNO-19 Collaborative group published results from a multicentre, open-label, Bayesian randomised clinical trial (**CORIMUNO-ANA-1, NCT04341584**), nested within the CORIMUNO-19 cohort in France, with mild-to-moderate COVID-19 pneumonia, **severe** acute respiratory syndrome coronavirus 2 infection confirmed by real-time RT-PCR, requiring at least 3 L/min of oxygen by mask or nasal cannula but without ventilation assistance, a score of 5 on the WHO Clinical Progression Scale (WHO-CPS), and a C-reactive protein serum concentration of more than 25 mg/L not requiring admission to the intensive care unit at admission to hospital [11]. Eligible patients were randomly assigned (1:1), stratified by centre and blocked with varying block sizes (randomly of size two or four), to either usual care plus anakinra (200 mg twice a day on days 1–3, 100 mg twice on day 4, 100 mg once on day 5) or usual care alone. Usual care was provided at the discretion of the site clinicians. The two co-primary outcomes were the proportion of patients who had died or needed non-invasive or mechanical ventilation by day 4 (i.e., a score of >5 on the WHO-CPS) and survival without need for mechanical or non-invasive ventilation (including high-flow oxygen) at day 14. Details can be found in Table 4-2.

The study was **stopped early,** following the recommendation of the data and safety monitoring board, after the recruitment of 116 patients: 59 were assigned to the anakinra group and 57 were assigned to the usual care group. Two patients in the usual care group withdrew consent and were not analysed. In the analysable population, the median age was 66 years (IQR 59 to 76) and 80 (70%) participants were men. In the anakinra group, 21 (36%) of 59 patients had a WHO-CPS score of more than 5 at day 4 versus 21 (38%) of 55 in the usual care group (median posterior absolute risk difference –2·5%, 90% credible interval [CrI] –17.1 to 12.0), with a posterior probability of ARD of less than 0 (i.e., anakinra better than usual care) of 61.2%. At day 14, 28 (47%; 95% CI 33 to 59) patients in the anakinra group and 28 (51%; 95% CI 36 to 62) in the usual care group needed ventilation or died, with a posterior probability of any efficacy of anakinra (hazard ratio being less than 1) of 54.5% (median posterior HR 0.97; 90% CrI 0.62 to 1.52). At day 90, 16 (27%) patients in the anakinra group and 15 (27%) in the usual care group had died. Serious adverse events occurred in 27 (46%) patients in the anakinra group and 21 (38%) in the usual care group (p=0.45).

Kyriazopoulou et al. 2021 [12] **NCT04680949, EUdraCT 2020-005828-11**) published as preprint results from the **SAVE-MORE** multicenter trial, 594 hospitalised patients with **moderate and severe COVID-19** pneumonia and plasma suPAR 6 ng/ml or more and receiving standard-of-care were 1:2 randomized to subcutaneous treatment with placebo or 100 mg anakinra once daily for 10 days. The primary endpoint was the overall clinical status of the 11-point World Health Organization ordinal Clinical Progression Scale (WHO-CPS) at day 28. The changes of the WHO-CPS and of the sequential organ failure assessment (SOFA) score were the main secondary endpoints. Baseline characteristics and co-administered treatments were similar between the two arms. Majority of patients (81.6%) has severe COVID-19. Details can be found in Table 4-2.

1060 patients were screened and 606 were randomized. 12 patients withdrew consent and requested removal of all data, leaving a final ITT analysis cohort of 594 patients; 189 patients were allocated to the SoC and placebo arm, and 405 patients were allocated to the SoC and anakinra arm. Only one patient was lost to follow-up. Patients with severe disease by the WHO definition were also receiving intravenous 6 mg daily dexamethasone for 10 days. Remdesivir treatment was left at the discretion of the attending physicians. Anakinra-treated patients were distributed to lower strata of WHO-CPS by day 28 (adjusted odds ratio-OR 0.36; 95%CI 0.26-0.50; p<0.001); anakinra protected from severe disease or death (6 or more points of WHO-CPS) (OR: 0.46; p=0.010). The median absolute decrease of WHO-CPS in the placebo and anakinra groups from baseline was 3 and 4 points respectively at day 28 (OR 0.40; p<0.001; 2 and 3 points at day 14 (OR 0.63; p=0.003); the absolute decrease of SOFA score was 0 and 1 points (OR 0.63; p=0.004). 28-day mortality decreased (hazard ratio: 0.45; p=0.045). Hospital stay was shorter for 1 day and the time until ICU discharge was 4 days shorter. The incidence of serious TEAEs through day 28 was lower in patients in the anakinra and SoC group (16.5%) compared to the placebo and SoC group (21.2%). The non-serious TEAEs were similar in both treatment groups.

Derde et al. 2021 published final results as preprint [13] from **REMAP-CAP RCT** (**NCT02735707**): Adult participants with (severe and) **critical COVID-19** were randomized to receive tocilizumab, sarilumab, anakinra (intravenously as 300mg loading dose, followed by 100mg every 6 hours for 14 days or until either free from invasive mechanical ventilation for more than 24 hours, or discharge from ICU), or standard care (control). In addition, a small group (n=21) of participants were randomized to interferon-β1a. The primary outcome was an ordinal scale combining in-hospital mortality (assigned -1) and days free of organ support to day 21. Among survivors, respiratory and cardiovascular organ support-free days were calculated up to day 21, such that a higher number represents faster recovery. Secondary outcomes were 90-day Survival (time to event); Freedom from progression to intubation, ECMO, or death; Respiratory support-free days; Cardiovascular support-free days; Time to ICU discharge; Time to hospital discharge; WHO scale at day 14; Progression to invasive mechanical ventilation, ECMO or death, restricted to those not intubated at baseline; Secondary analysis of major thrombotic events or death; Secondary analysis of major thrombotic events; Secondary analysis of major bleeding events. The trial used a Bayesian statistical model with pre-defined triggers for superiority, equivalence or futility. Baseline characteristics for critically ill participants were balanced across intervention groups. All but four participants were receiving respiratory support at the time of randomization, including high flow nasal oxygen (536/2235, 24%), non-invasive (958/2235; 42.9%) and invasive (735/2235; 32.9%) mechanical ventilation. Only five non-critically ill participants were randomized, two to anakinra and three to control. Statistical triggers for equivalence between tocilizumab and sarilumab; and for inferiority of anakinra to the other active interventions were met at a planned adaptive analysis. Of the 2274 critically ill participants enrolled, 972 were assigned to tocilizumab, 485 to sarilumab, 378 to anakinra and 418 to control.
Median organ support-free days were 7 (interquartile range [IQR] –1, 16), 9 (IQR –1, 17), 0 (IQR –1, 15) and 0 (IQR –1, 15) for tocilizumab, sarilumab, anakinra and control, respectively. Median adjusted odds ratios were 1.46 (95%CrI 1.13, 1.87), 1.50 (95%CrI 1.13, 2.00), and 0.99 (95%CrI 0.74, 1.35) for tocilizumab, sarilumab and anakinra, yielding 99.8%, 99.8% and 46.6% posterior probabilities of superiority, respectively, compared to control. Median adjusted odds ratios for hospital survival were 1.42 (95%CrI 1.05,1.93), 1.51 (95%CrI 1.06, 2.20) and 0.97 (95%CrI 0.66, 1.40) for tocilizumab, sarilumab and anakinra respectively, compared to control, yielding 98.8%, 98.8% and 43.6% posterior probabilities of superiority, respectively, compared to control. Tocilizumab and sarilumab were both effective across all secondary outcomes, including 90-day survival, and both led to more rapid ICU and hospital discharge. There was no evidence of any effect of anakinra in any of the secondary outcome analyses. Subgroup results for anakinra showed no beneficial effect. The rates of serious adverse events were similar between all interventions (adjusted OR for anakinra 1.20, 95%CrI 0.51 to 2.77; rate of any SAEs: 0.027% in anakinra group; 0.072% in control; 0.025% in tocilizumab and 0.017% in

sarilumab group). In patients with critical COVID-19, tocilizumab and sarilumab are similarly effective at improving survival and reducing duration of organ support. Anakinra is not effective in this population (anakinra is inferior to tocilizumab and sarilumab and no more effective than control-standard care).
From June 2021, only RCTs are used for assessment of safety. Previous evidence from prospective observational studies, can be found in EUnetHTA JA3 version, May 2021.

Several ongoing RCTs and one interventional nRCT are registered in EudraCT, ISRCTN and ClinicalTrials.gov registers, including 30 to 600 COVID-19 patients per study. Eight RCTs evaluate anakinra alone (2 now completed), as well as one interventional nRCT (completed); one RCT evaluates 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 4-3,

Table 4-4, Table 4-5 and Table 4-6. One RCT is the RECOVERY (Randomised Evaluation of COVid-19 thERapY) trial, led by the University of Oxford, in which anakinra is investigated as a third option in the second randomisation for children >1 year old with hyperinflammatory syndrome associated with COVID-19 in children (PIMS-TS) [14].

One RCT was found in ClinicalTrials.gov and EUdraCT registers – ANACONDA (NCT04364009) – which was terminated due to efficiency and safety reasons after enrolment of 71 hospitalized COVID-19 patients in France. The intermediate review of data from this clinical trial showed early excess mortality in the group of patients treated with anakinra combined with standard optimized care, compared to the group of patients treated with standard optimized care alone. A deleterious effect of anakinra (Kineret®) cannot be ruled out, as the information available at this stage does not explain this difference between the two treatment arms. In this context, the CHRU de Tours, sponsor of this clinical trial, suspended inclusions in the ANACONDA-COVID-19 trial.
On October 29, 2020, the French National Agency for Medicines and Health Products Safety (ANSM) announced that inclusions in clinical trials evaluating anakinra (Kineret®) in the treatment of COVID-19 are suspended due to safety information regarding the ANACONDA-COVID-19 clinical trial.

In December 2020, ANSM lifted the suspension of trials with anakinra because after further analysis in France and the EU, the risk was not confirmed.

Two others terminated RCTs were found: NCT04366232 (JAKINCOV), due to an investigator decision in France, on anakinra alone and in combination with ruxolitinib, and NCT04324021/EudraCT 2020-001167-93 (in Italy and US) due to recruitment issues.

The US COVID-19 Treatment Guidelines Panel stated that there are insufficient data to recommend either for or against anakinra therapy in patients with COVID-19 disease [15].

4 SUMMARY

4.1 Effectiveness and Safety evidence from RCTs

Anakinra vs standard care/placebo in hospitalised moderate to critical COVID-19 patients

Low certainty evidence from two published RCTs (CORIMUNO-19, SAVE-MORE) in hospitalised patients with moderate to severe COVID-19 showed that anakinra, compared to standard care/placebo, may reduce all-cause mortality at day 28 (RR 0.69, 95% CI 0.34 to 1.39; 32 fewer per 1.000, 95% CI from 68 fewer to 40 more). Low certainty evidence from two published RCTs in hospitalised patients with severe and critical COVID-19 (CORIMUNO-19, REMAP-CAP) showed that anakinra, compared to standard care/placebo, may not reduce all-cause mortality at day 60 (RR 1.16, 95% CI 0.98 to 1.37; 56 more per 1.000, 95% CI from 7 fewer to 129 more).

In hospitalised patients with moderate to severe COVID-19 showed that anakinra probably increases clinical improvement at day 28 (RR 1.06, 95% CI 1.00 to 1.12; 40 more per 1.000, 95% CI from 0 fewer to 97 more, moderate certainty of evidence, 2 RCTs: CORIMUNO-19, SAVE-MORE).

Anakinra, compared to standard care/placebo, may reduce WHO progression score (level 7 or above) at day 28 (RR 0.67, 95% CI 0.36 to 1.22; 55 fewer per 1.000, 95% CI from 107 fewer to 37 more, low certainty of evidence, 2 RCTs: CORIMUNO-19, SAVE-MORE). The evidence is very uncertain about the effect of anakinra on viral negative conversion at day 7 (RR 0.93, 95% CI 0.63 to 1.37; 12 fewer per 1000, 95% CI from 61 fewer to 61 more, very low certainty of evidence ,1 RCT: SAVE-MORE).

Anakinra probably does not increase the number of patients with any adverse events (RR 0.99, 95% CI 0.88 to 1.11; 8 fewer per 1.000, 95% CI from 92 fewer to 85 more, moderate certainty of evidence, 2 RCTs: CORIMUNO-19, SAVE-MORE).The evidence is very uncertain about the effect of anakinra on the number of patients with serious adverse events (RR 0.97, 95% CI 0.61 to 1.52; 7 fewer per 1.000, 95% CI from 96 fewer to 128 more, very low certainty of evidence, 2 RCTs: CORIMUNO-19, SAVE-MORE) (Table 4-1).

Anakinra vs tocilizumab and sarilumab in hospitalised critical COVID-19 patients

Evidence from one RCT in critical COVID-19 patients (REMAP-CAP), related to primary outcome and all secondary outcomes, showed that anakinra is inferior compared to tocilizumab and sarilumab in this group of patients. The rates of serious adverse events were similar between all interventions.

4.2 Safety evidence from observational studies

From June 2021, only RCTs are used for assessment of safety. Previous evidence from prospective observational studies can be found in EUnetHTA JA3 10.0 version, May 2021.

4.3 Ongoing studies

Several RCTs related to anakinra alone or in combination therapy are currently ongoing. One RCT–ANACONDA (NCT04364009) – was terminated due to efficiency and safety reasons after enrolment of 71 hospitalized COVID-19 patients. On October 29, 2020, the French National Agency for Medicines and Health Products Safety (ANSM) announced that inclusions in clinical trials evaluating anakinra (Kineret®) in the treatment of COVID-19 in France are suspended due to safety information regarding the ANACONDA-COVID-19 clinical trial. In December, ANSM lifted the suspension of trials with anakinra because after further analysis in France and the EU, the risk was not confirmed. Two further RCTs were terminated: NCT04366232 (JAKINCOV), due to an investigator decision in France, on anakinra alone and in combination with ruxolitinib, and NCT04324021/EudraCT 2020-001167-93 (in Italy and US) due to recruitment issues.

4.4 Scientific conclusion about status of evidence generation

Anakinra vs standard care/placebo in hospitalised moderate to critical COVID-19 patients

Low certainty evidence from two published RCTs in hospitalised moderate to severe COVID-19 patients showed that anakinra, compared to standard care/placebo, may reduce all-cause mortality at day 28. Low certainty evidence from two published RCTs in hospitalised patients with severe to critical COVID-19 showed that anakinra, compared to standard care/placebo, may not reduce all-cause mortality at day 60.

In hospitalised moderate to severe COVID-19 patients anakinra probably increases clinical improvement at day 28 and probably does not increase the number of patients with any adverse events (moderate certainty of evidence). Anakinra, compared to standard care/placebo, may reduce WHO progression score (level 7 or above) at day 28 (low certainty of evidence). The evidence is very uncertain about the effect of anakinra on the viral negative conversion and the number of patients with serious adverse events (very low certainty of evidence).

Anakinra vs tocilizumab and sarilumab in hospitalised critical COVID-19 patients

Evidence from one RCT in critical COVID-19 patients (REMAP-CAP) showed that anakinra is inferior compared to tocilizumab and sarilumab in this group of patients. The rates of serious adverse events were similar between all interventions.

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

On July 19, 2021 EMA has started evaluating an application to extend the use of anakinra to include treatment of COVID-19 in adult patients with pneumonia who are at risk of developing severe respiratory failure.

Table 4-1 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of anakinra in hospitalised COVID-19 patients

Patient or population: COVID-19 patients (moderate to critical, 3 RCTs, last update 30/07/2021)
Setting: Worldwide Hospitalised patients
Intervention: Anakinra **Comparison**: Standard care/Placebo

Outcome	Anticipated absolute effects (95% CI) [a]		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with Standard treatment/Placebo	Risk with Anakinra				
All-cause mortality at 28 days	104 per 1000	71 per 1000	**RR: 0.69** (0.34 - 1.39)	722 (2 RCTs) [b, c]	⨁⨁◯◯ LOW [d]	**Absolute effect (95% CI) 32 fewer per 1000** (from 68 fewer to 40 more)
All-cause mortality D60	349 per 1000	405 per 1000	**RR: 1.16** (0.98 - 1.37)	912 (2 RCTs) [e]	⨁⨁◯◯ LOW [f]	**Absolute effect (95% CI) 56 more per 1000** (from 7 fewer to 129 more)
Clinical improvement D28	809 per 1000	857 per 1000	**RR: 1.06** (1.00 - 1.12)	722 (2 RCTs) [b, c]	⨁⨁⨁◯ MODERATE [g]	**Absolute effect (95% CI) 49 more per 1000** (from 0 fewer to 97 more)
WHO progression score (level 7 or above) D28	167 per 1000	112 per 1000	**RR: 0.67** (0.36 - 1.22)	722 (2 RCTs) [b, c]	⨁⨁◯◯ LOW [h]	**55 fewer per 1000** (from 107 fewer to 37 more)
Number of patients with any adverse event	769 per 1000	761 per 1000	**RR: 0.99** (0.88 - 1.11)	722 (2 RCTs) [b, c]	⨁⨁⨁◯ MODERATE [i]	**Absolute effect (95% CI) 8 fewer per 1000** (from 92 fewer to 85 more)
Number of patients with serious adverse events	247 per 1000	240 per 1000	**RR: 0.97** (0.61 - 1.52)	722 (2 RCTs) [b, c]	⨁◯◯◯ VERY LOW [i]	**Absolute effect (95% CI) 7 fewer per 1000** (from 96 fewer to 128 more)
Viral negative conversion D7	165 per 1000	153 per 1000	**RR: 0.93** (0.63 – 1.37)	606 (1 RCT) [c]	⨁◯◯◯ VERY LOW [k]	**Absolute effect (95% CI) 12 fewer per 1000** (from 61 fewer to 61 more)

Source: [16], last update 30/07/2021 **Abbreviations**: CI=Confidence interval; RR=Risk ratio; **Explanations**: a The risk in the intervention group is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI); b [11] c [12]; d Imprecision: Very serious due to very wide confidence interval consistent with the possibility for benefit and the possibility for harm; e [11] [13] ; f Imprecision: Very serious due to wide confidence interval consistent with the possibility for no effect and the possibility for harm and low number of participants; g Risk of bias: Serious Risk of bias downgraded by 1 level: some concerns regarding adequate randomization and outcome measurement; h Inconsistency: Serious Inconsistency downgraded by 1 level: I²=60%; Imprecision: Serious due to wide confidence interval consistent with the possibility for benefit and the possibility for no effect; i Risk of bias: Serious Risk of bias downgraded by 1 level: Imprecision: Serious due to wide confidence interval consistent with the possibility for no effect and the possibility for harm; j Risk of bias: Serious Risk of bias downgraded by 1 level: some concerns regarding adequate randomization, outcome measurement, and selection of the reported result Inconsistency: Serious Inconsistency downgraded by 1 level: I²=62% Imprecision: Serious due to wide confidence interval consistent with the possibility for benefit and the possibility for harm; k Risk of bias: Indirectness: Serious despite a multicentre design this is a single study from a single country, therefore results in this population might not be generalizable to other settings. Imprecision: Very serious due to wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of participants.

GRADE Working Group grades of evidence: High certainty: We are very confident that the true effect lies close to that of the estimate of the effect; **Moderate certainty**: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; **Low certainty**: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect; **Very low certainty**: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Table 4-2 Study characteristics of included RCTs

Author, year, reference number/Study name/Study ID	CORIMUNO-19 Collaborative [11] group / CORIMUNO-ANA-1, NCT04341584**	Kyriazopoulou E, medRxiv, 2021 [12]/ SAVE-MORE NCT04680949; EudraCT 2020-005828-11
Study design, study phase	RCT	RCT
Centres (single centre or multicentre), country, setting	Multicentre, France, inpatient	Multicenter / Greece, Italy, inpatient
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	116 patients: 59 were assigned to the anakinra group, and 57 were assigned to the usual care group; 66 years (IQR 59 to 76) and 80 (70%) participants were men; Severe	606 participants randomized (anakinra group n=412 / placebo group n=194); Mean age: 61.8; 344 males Severity: Mild: n=0 / Moderate: n=109/ Severe: n=485 Critical: n=0
Inclusion criteria	Adults with mild-to-moderate COVID-19 pneumonia, severe acute respiratory syndrome coronavirus 2 infection confirmed by real-time RT-PCR, requiring at least 3 L/min of oxygen by mask or nasal cannula but without ventilation assistance, a score of 5 on the WHO Clinical Progression Scale (WHO-CPS), and a C-reactive protein serum concentration of more than 25 mg/L not requiring admission to the intensive care unit at admission to hospital	Adults of either gender; molecular diagnosis of infection by SARS-CoV-2; involvement of the lower respiratory tract as confirmed by chest computed tomography or X-ray; in need for hospitalization; plasma suPAR 6 ng/ml or more
Exclusion criteria	Known hypersensitivity to anakinra or any of its excipients, pregnancy, current documented bacterial infection, an absolute neutrophil count of $1{\cdot}0 \times 10^9$ per L or less, a platelet concentration of less than 50 G/L, serum aspartate aminotransferase or serum alanine aminotransferase of more than five-times the upper limit of normal, or severe renal insufficiency defined by an estimated glomerular filtration rate of less than 30 mL/min	Ratio or partial oxygen pressure to fraction of inspired oxygen less than 150; need of non-invasive ventilation (CPAP or BPAP) or mechanical ventilation; neutropenia; stage IV malignancy; end-stage renal disease; severe hepatic failure; immunodeficiencies; chronic intake of corticosteroids and biological anti-cytokine drugs
Intervention (generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	Usual care plus anakinra (200 mg twice a day on days 1–3, 100 mg twice on day 4, 100 mg once on day 5), n=59	Anakinra 100 mg subcutaneously once daily for 7-10 days
Comparator(s) (standard care or generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	Usual care alone, n=57	Placebo
Primary Outcome(s)	Proportion of patients who had died or needed non-invasive or mechanical ventilation by day 4 (ie, a score of >5 on the WHO-CPS) and survival without need for mechanical or non-invasive ventilation (including high-flow oxygen) at day 14	Overall comparison of the distribution of frequencies of the scores from the 11-point WHO Clinical Progression ordinal Scale (CPS) between the two arms of treatment at Day 28
Patient-relevant secondary outcome(s)	Clinical status assessed with the WHO-CPS at days 4, 7, and 14; overall survival at days 14, 28, and 90; time to discharge from hospital; time to oxygen supply independency;	Changes of WHO-CPS by days 14 and 28 from the baseline (before start of the study drug); the change of SOFA score by day 7 from baseline; the time until hospital discharge; the time of stay in the intensive care unit (ICU)

Author, year, reference number/Study name/StudyID	CORIMUNO-19 Collaborative [11] group / CORIMUNO-ANA-1, NCT04341584**	KyriazopoulouE, medRxiv, 2021 [12]/ SAVE-MORE NCT04680949; EudraCT 2020-005828-11
	time to negative viral excretion (not assessed due to paucity of data); biological factors (eg, C-reactive protein concentration) and adverse events.	for patients eventually admitted to the ICU; and the comparison of biomarkers
Follow-up (days, months)	Up to 90 days	28 days
Sponsor/ lead institution	The Ministry of Health, Programme Hospitalier de Recherche Clinique, Foundation for Medical Research, and AP-HP Foundation	Mixed (Hellenic Institute for the Study of Sepsis and Swedish Orphan Biovitrum AB (Sobi))

**Stopped early

Author, year, reference number/Study name/Study ID	Derde et al. 2021[13] / REMAP-CAP (NCT02735707)
Study design, study phase	RCT, phase 3
Centres (single centre or multicentre), country, setting	Multicentre (133 sites across 9 countries)
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	2274 critically ill participants; Mean age 60.3 (SD 12.5); Male sex 1550 (69.4%); Critical COVID-19
Inclusion criteria	Participants aged > 18 years, within 24 hours of receiving respiratory or cardiovascular organ support in an ICU with suspected or microbiologically confirmed COVID-19 (critically ill)
Exclusion criteria	Presumption that death was imminent with lack of commitment to full support, and prior participation in REMAP-CAP within 90 days. Additional exclusion criteria, specific for the Immune Modulation Therapy domain, are listed in the Supplementary appendix (https://www.medrxiv.org/content/10.1101/2021.06.18.21259133v2.supplementary-material)
Intervention (generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	Tocilizumab (dose of 8mg/kg of actual body weight (up to a maximum of 800mg), as an intravenous infusion over one hour; this dose could be repeated 12-24 hours later at the discretion of the treating clinician if clinical improvement was judged insufficient. Sarilumab, 400mg, as a single intravenous infusion. Anakinra intravenously as 300mg loading dose, followed by 100mg every 6 hours for 14 days or until either free from invasive mechanical ventilation for more than 24 hours, or discharge from ICU. 2274 critically ill participants had been randomized in the Immune Modulation Therapy domain (972 tocilizumab, 485 sarilumab, 378 anakinra, 21 interferon-β1a and 418 control); All but four participants were receiving respiratory support at the time of randomization, including high flow nasal oxygen (536/2235, 24%), non-invasive (958/2235; 42.9%) and invasive (735/2235; 32.9%) mechanical ventilation; Mean age 60.3 (12.5); Male sex 1550 (69.4); Critical COVID-19
Comparator(s) (standard care or generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	Standard of care
Primary Outcome(s)	An ordinal scale combining in-hospital mortality (assigned -1) and days free of organ support to day 21. Among survivors, respiratory and cardiovascular organ support-free days were calculated up to day 21, such that a higher number represents faster recovery.
Patient-relevant secondary outcome(s)	90-day Survival (time to event); Freedom from progression to intubation, ECMO, or death; Respiratory support-free days; Cardiovascular support-free days; Time to ICU discharge; Time to hospital discharge; WHO scale at day 14; Progression to invasive mechanical ventilation, ECMO or death, restricted to those not intubated at baseline; Secondary analysis of major thrombotic events or death; Secondary analysis of major thrombotic events; Secondary analysis of major bleeding events.
Follow-up (days, months)	21 days up to 90 days
Sponsor/ lead institution	The Platform for European Preparedness Against (Re-) emerging Epidemics (PREPARE) consortium by the European Union, FP7-HEALTH-2013-INNOVATION-1, the Rapid European COVID-19 Emergency Research response (RECOVER) consortium by the European Union's Horizon 2020 research and innovation program, the Australian National Health and Medical Research Council, the Health Research Council of New Zealand, and the Canadian Institute of Health Research Strategy for Patient-Oriented Research Innovative Clinical Trials Program Grant, the UK National Institute for Health Research (NIHR) and the NIHR Imperial Biomedical Research Centre, the Health Research Board of Ireland (CTN 2014-012), the UPMC Learning While Doing Program, the Translational Breast Cancer Research Consortium, the Global Coalition for Adaptive Research, the French Ministry of Health (PHRC-20-0147), the Minderoo Foundation, the Wellcome Trust Innovations Project (215522), and the Netherlands Organization for Health Research and Development ZonMw (nr 10150062010003). Roche Products Ltd, Sanofi (Aventis Pharma Ltd), Swedish Orphan Biovitrum AB (Sobi™) and Faron Pharmaceuticals supported the trial through provision of drugs in some countries.

Table 4-3 Ongoing trials of single agent anakinra

Trial Identifier/registry ID(s)/contact	NCT04443881, EudraCT 2020-001825-29 (ANA-COVID-GEAS)	NCT04412291, EudraCT 2020-001748-24 (ImmCoVA) Study	NCT04364009, EudraCT 2020-001734-36 (ANACONDA)	NCT04324021 EudraCT 2020-001167-93
Study design, study phase	RCT, phase 2/3	RCT, phase 2	RCT, phase 3	RCT, phase 2/3
Recruitment status	**Completed**	Recruiting	**Terminated (Efficiency and safety reasons)**	**Terminated (recruitment issues)**
Number of Patients, Disease severity*	180, Severe	120, Severe	240, COVID19, Mixed	54, Mixed
Setting (hospital, ambulatory,..)	Hospital	Hospital	Hospital	Hospital
Intervention (generic 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)	Anakinra i.v infusion four times daily for 15 days. 400 mg/day in total, divided into 4 doses given every 6 hours + Standard of care Emapalumab i.v infusion every 3rd day for a total 5 infusions. Day 1: 6mg/kg. Days 4, 7, 10 and 13: 3 mg/kg + Standard of care
Comparator (standard care or generic drug name and dosage)	Standard of care	Tocilizumab: 8mg/kg for a single infusion iv up to max 800 mg + Standard of care Standard of care alone	Optimized Standard of Care (oSOC)	Standard of care
Primary Outcome(s)	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	Time to recovery [Time Frame: Day 1 through Day 29]	Treatment success [Time Frame: After 14 days of treatment]	Treatment success [Time Frame: Up to Day 15],
Sponsor/ lead institution, country (also country of recruitment if different)	Fundacion Miguel Servet, Spain	Karolinska University Hospital, Sweden	University Hospital, Tours, France	Swedish Orphan Biovitrum, Italy

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

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

Trial Identifier/registry ID(s)/contact	NCT04339712, EudraCT 2020-001039-29 (ESCAPE)	NCT04603742 (SOBI)	NCT04362111	NCT04341584 (CORIMUNO-ANA)
Study design, study phase	nRCT interventional study, phase 2	RCT, phase 2	RCT, phase 3	RCT, phase 2
Recruitment status	**Completed**	Not yet recruiting	Recruiting	**Completed**
Number of Patients, Disease severity*	40, Critical	100, Severe	30, Severe	240, Mixed (severe and critical)
Setting (hospital, ambulatory,..)	Hospital	Hospital	Hospital	Hospital
Intervention (generic drug name and dosage)	Anakinra 200mg three times daily (every eight hours) for 7 days Tocilizumab 8mg/kg body weight once up to a maximum of 800mg	Anakinra 100 mg IV 4 times a day for 7 days	Anakinra 100 mg subcutaneously every 6-12 hours for a period of 10 days	Anakinra two IV infusions / day 200mg (total 400 mg) at day 1 (D1), D2 and D3, two IV infusions / day 100mg (total 200 mg) at day 4 (D4), and one IV infusion 100mg (total 100 mg) at day 5 (D5)
Comparator (standard care or generic drug name and dosage)	No comparator	Normal saline IV	Normal saline placebo subcutaneously every 6-12 hours for period of 10 days	Standard of care
Primary Outcome(s)	Change of baseline total sequential organ failure assessment (SOFA) score; Improvement of lung involvement measurements; Increase of pO2/FiO2 ratio	Number of subjects alive without having required mechanical ventilation [Time Frame: 28 days post randomization]	Percentage of patients discharged from the hospital alive and without the need for mechanical ventilation [Time Frame: Variable up to Day 28]	Survival without needs of ventilator utilization at day 14 [Time Frame: 14 days]; WHO progression scale ≤ 5 [Time Frame: 4 days]; Cumulative incidence of successful tracheal extubation; Decrease of at least one point in WHO progression scale score [Time Frame: 4 days]
Sponsor/ lead institution, country (also country of recruitment if different)	Hellenic Institute for the Study of Sepsis, Greece	Weill Medical College of Cornell University, US	University of Alabama at Birmingham, US	Assistance Publique - Hôpitaux de Paris, France

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

Table 4-5 Ongoing trials of single agent anakinra (continued)

Trial Identifier/registry ID(s)/contact	ISRCTN67000769; NCT02735707; EudraCT2015-002340-14 (REMAP-CAP)	NCT04643678	NCT04680949, EudraCT2020-00528-11, (SAVE-MORE)	NCT04381936 RECOVERY EudraCT 2020-001113-21 ISRCTN50189673
Study design, study phase	RCT, phase 4	RCT, phase 2/3	RCT, phase 3	RCT, phase 2/3
Recruitment status	Recruiting	Recruiting	Recruiting	Recruiting
Number of Patients, Disease severity*	7100, Severe	80, Critical	600, Moderate and Severe	20000, Mixed
Setting (hospital, ambulatory...)	Hospital	Hospital	Hospital	Hospitalised
Intervention (generic drug name and dosage)	Anakinra (loading dose 300mg, followed by maintenance doses of 100mg administered every 6 hours) (as COVID-19 immune modulation – pandemic) (As one intervention among other drugs in pandemic - antivirals, immune modulation, immunoglobulin therapy, anticoagulation, simvastatin, vitamin C therapy, corticosteroids, antibiotic domain, macrolide domain...)	Anakinra 100 mg SC injection every 12 hours for 3 days, then 100 mg once daily from day 4 to day 7 plus Standard of Care	Anakinra 100 mg once daily for 10 days + Standard of care	Lopinavir-Ritonavir, Hydroxychloroquine, Corticosteroids, Azithromycin, IV Immunoglobulin (children >44 weeks gestational age with PIMS-TS only), Convalescent plasma, Synthetic neutralizing antibodies (REGN-COV2) single dose of REGN10933 + REGN10987 8 g, Tocilizumab, Aspirin, Colchicine, Baricitinib 4 mg, Anakinra (children with PIMS-TS only)
Comparator (standard care or generic drug name and dosage)	No immune modulation for COVID-19	Standard care alone	Placebo + Standard of care	Standard care
Primary Outcome(s)	All-cause mortality; Days alive and outside of ICU	Treatment Success at day 14 [Time Frame: Day 14]	Comparison of the distribution of frequencies of each score of a 5-scale patient state evaluated from the 11-point WHO Clinical Progression ordinal Scale (CPS) between the two arms of treatment [Time Frame: 28 days]	All-cause mortality [Within 28 days after randomisation]
Sponsor/ lead institution, country (also country of recruitment if different)	Hospital/treatment centre, Australia, Belgium, Canada, Croatia, Germany, Hungary, Ireland, Netherlands, New Zealand, Portugal, Romania, Spain, United Kingdom	Hamad Medical Corporation, Qatar	Hellenic Institute for the Study of Sepsis, Greece	University of Oxford United Kingdom

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19; PIMS-TS=hyperinflammatory syndrome associated with COVID-19 in children

Table 4-6 Ongoing trials of singe agent anakinra (continued) and combination therapies

Trial Identifier/registry ID(s)/contact	NCT04330638, EudraCT 2020-001500-41 (COV-AID)	EudraCT 2020-001754-21, NCT04424056 (INFLAMMACOV)	EudraCT 2020-001963-10, NCT04366232 (JAKINCOV)
Study design, study phase	RCT, phase 3	RCT, phase 3	RCT, phase 3
Recruitment status	Active, not recruiting	Ongoing	**Terminated (Investigator decision)**
Number of Patients, Disease severity*	342, Critical	150, Severe (stage 2b and 3)	54, Mixed (severe and Critical)
Setting (hospital, ambulatory...)	Hospital	Hospital	Hospital
Intervention (generic drug name and dosage)	Anakinra alone (as a daily subcutaneous injection of 100 mg for 28 days or until hospital discharge, whichever is first) Siltuximab alone (via single IV infusion at a dose of 11 mg/kg) Tocilizumab alone (via single IV infusion at a dose of 8 mg/kg with a maximum infusion of 800 mg/injection) Anakinra + Siltuximab Anakinra + Tocilizumab	Anakinra alone Tocilizumab alone or in combination with Ruxolitinib	Anakinra with or without Ruxolitinib
Comparator (standard care or generic drug name and dosage)	Usual care	Standard of care	Standard of care
Primary Outcome(s)	Time to Clinical Improvement [Time Frame: at day 15]	Ventilation free days at D28 (VFD28) (an increase of 5 days VFD28 is expected)	Biological criteria: validation if at least 3 parameters are met including CRP and/or Ferritin 1) CRP: decrease > 50% 2) Ferritinemia: decrease > 1/3 3) Serum creatinine: decrease > 1/3 4) AST/ALT: decrease > 50% 5) Eosinophils > 50 /mm3 6) Lymphocytes > 1000 /mm3
Sponsor/ lead institution, country (also country of recruitment if different)	University Hospital, Ghent / Belgium Health Care Knowledge Centre, Belgium	Assistance Publique Hôpitaux de Marseille, France	Centre Hospitalier Intercommunal de Toulon La Seyne-sur-mer, France

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

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6 APPENDIX

6.1 Search strategy to identify randomised controlled trials

From June 2021, literature search strategy and results from COVID-NMA initiative were used, according living review protocol [1, 3]. 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 were included. Early-phase clinical trials, single-arm trials, non-randomized studies or modelling studies of interventions for COVID-19 were excluded, as well as studies about prognosis, systematic reviews and meta-analyses and diagnostic test accuracy studies. Details can be found in COVID-NMA Protocol [2].

6.2 Search strategy to identify ongoing studies

AIHTA is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and anakinra are described in Appendix Table 6-1.

Table 6-1 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": • Anakinra • IL-1RA	10/08/2021	29 0 new
ISRCTN	https://www.isrctn.com/	Basic search mode Search terms: 1. covid-19 and Anakinra 2. covid-19 and Kineret 3. covid-19 and Kinaret 4. covid-19 and IL-1RA 5. covid-19 and rIL-1ra 6. SARS-CoV-2 and Anakinra 7. SARS-CoV-2 and Kineret 8. SARS-CoV-2 and Kinaret 9. SARS-CoV-2 and IL-1RA 10. SARS-CoV-2 and rIL-1ra	10/08/2021	3 0 new
European Clinical Trials Registry	https://www.clinicaltrialsregister.eu/	Basic search mode Search terms: 1. covid-19 and Anakinra 2. covid-19 and Kineret 3. covid-19 and Kinaret 4. covid-19 and IL-1RA 5. covid-19 and rIL-1ra 6. SARS-CoV-2 and Anakinra 7. SARS-CoV-2 and Kineret 8. SARS-CoV-2 and Kinaret 9. SARS-CoV-2 and IL-1RA 10. SARS-CoV-2 and rIL-1ra	10/08/2021	16 0 new

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