EUnetHTA Joint Action 3 WP4

“Rolling Collaborative Review” of Covid-19 treatments

CANAKINUMAB FOR THE TREATMENT OF COVID-19

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Monitoring Report

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DOCUMENT HISTORY AND CONTRIBUTORS

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V 1.1	**[11/09/2020]**	Literature searches, Literature screening, Data extraction
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V 2.0	**15/09/2020**	Second version

Major changes from previous version

Chapter, page no.	Major changes from version 1.0
	One additional observational study (Sheng et al.,2020), and one additional planned RCT (NCT04510493), no other major changes.

Disclaimer

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Rolling Collaborative Review team

Author(s)	State Medicines Control Agency of Lithuania (SMCA), Lithuania
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.

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LIST OF ABBREVIATIONS

ATC	Anatomical Therapeutic Chemical [Classification System]
DOI	Declaration of interest
EUnetHTA	European Network of Health Technology Assessment
RCT	Randomized Controlled Trial
RCR	Rolling Collaborative Review
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** • 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	Treatment with canakinumab - a human monoclonal anti-human interleukin-1 beta (IL-1 beta) antibody of the IgG1/κ isotype. Canakinumab binds with high affinity specifically to human IL-1 beta and neutralises the biological activity of human IL-1 beta by blocking its interaction with IL-1 receptors, thereby preventing IL-1 beta-induced gene activation and the production of inflammatory mediators.
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	Treatment with canakinumab - a human monoclonal anti-human interleukin-1 beta (IL-1 beta) antibody of the IgG1/κ isotype. Canakinumab binds with high affinity specifically to human IL-1 beta and neutralises the biological activity of human IL-1 beta by blocking its interaction with IL-1 receptors, thereby preventing IL-1 beta-induced gene activation and the production of inflammatory mediators.
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

Canakinumab is a human monoclonal anti-human interleukin-1 beta (IL-1 beta) antibody of the IgG1/κ isotype manufactured by Novartis Pharma AG. Canakinumab binds with high affinity specifically to human IL-1 beta and neutralises the biological activity of human IL-1 beta by blocking its interaction with IL-1 receptors, thereby preventing IL-1 beta-induced gene activation and the production of inflammatory mediators [4].

3.2 Regulatory Status

Canakinumab – ATC-code L04AC08. Has orphan designation for familial mediterranean fever; cryopyrin-associated periodic syndromes; juvenile rheumatoid arthritis; inflammation; peroxisomal disorders; familial autosomal dominant periodic fever [4, 5].
Canakinumab has EMA approved indications for:

- Periodic fever syndromes;
- Cryopyrin-associated periodic syndromes;
- Cryopyrin-associated periodic syndromes
- Tumour necrosis factor receptor associated periodic syndrome (TRAPS);
- Hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD);
- Familial Mediterranean fever (FMF)
- Still's disease;
- Gouty arthritis

3.3 Level of Evidence

There are two ongoing studies (Phase II and Phase III) of canakinumab. The results haven't been published yet [6, 7].

4 SUMMARY

4.1 Effectiveness and Safety evidence from RCTs

There are no published RCTs related to effectiveness and safety of canakinumab for Covid-19. Two studies of canakinumab are still ongoing: one Phase III study, estimated study completion date on December 2020 and one Phase II study, estimated completion date on December 2020 [6, 7].

4.2 Safety evidence from observational studies

There are no published safety results from observational studies of canakinumab for Covid-19 treatment.

4.3 Ongoing studies

Three studies of canakinumab are ongoing: For the Phase III studies, the estimated study completion dates are in December 2020 and September 2023. The estimated completion date of the Phase II study is in December 2020. Also, one observational study (NCT04348448) of canakinumab is planned, but not yet recruiting. The study is configured as a retrospective and prospective observational study. The study will be multi-center and will involve all COVID-19 pneumonia patients treated with canakinumab administered subcutaneously. Estimated study completion date is in September 2020 [6-8].

Currently, there are no published results from observational studies related to effectiveness and safety of canakinumab for Covid-19. One observational study (NCT04348448) of canakinumab is planned, but not yet recruiting. The study is configured as a retrospective and **prospective observational** study. The study will be multi-center and will involve all COVID-19 pneumonia patients treated with canakinumab administered subcutaneously. Estimated study completion date is on September 2020 [7].

4.4 Scientific conclusion about status of evidence generation

There are three ongoing RCTs, the results not published yet. So far no conclusions can be drawn.

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

Author, year	Calvin C Sheng et al., 2020 [9]
Country	USA
Sponsor	An investigator-initiated study conducted by the Cleveland clinic supported by Novartis.
Intervention/Product (drug name)	Canakinumab
Dosage	IV canakinumab 600 mg x 1 dose and IV canakinumab 300 mg x 1 dose
Comparator	Placebo
Study design	Phase II, double-blinded, randomized single center study
Setting	Hospital setting
Number of pts	Is planned to enroll 45 patients, now available data from 20 patients
Inclusion criteria	• Hospitalized due to Covid-19 infection with positive Covid-19 test within 5 days of enrollment • Documented SARS-CoV2 acute myocardial injury: Defined as upper respiratory tract specimen positive for Covid-19 AND troponin greater than 99% upper reference range without signs or symptoms of acute myocardial ischemia • NT-proBNP or BNP greater than upper reference limit • Receiving current standard therapy • C-reactive protein (CRP) > 50 mg/L
Age of patients (yrs)	67.0 (median)
Disease severity	Severe pneumonia, defined as tachypnea, severe respiratory distress, or SpO2 </= 93% on room air, because initial myocardial injury
Follow-up (months)	5 month follow up period.
Loss to follow-up, n (%)	Not provided
RoB	--
Overall AEs, n (%)	Not provided
Serious AE (SAE), n (%)	Not provided
Most frequent AEs n (%)	Not provided
Most frequent SAEs, n (%)	Not provided
AEs of special interest, n (%)	Not provided
Death as SAE, n (%)	Not provided
Withdrawals due AEs, n (%)	Not provided

Table 4-2 Ongoing trials of single agent Canakinumab

Active substance	Canakinumab	Canakinumab	Canakinumab
Sponsor	Novartis Pharmaceuticals	The Cleveland Clinic in collaboration with Novartis	University Hospital, Basel, Switzerland in collaboration with Novartis and Swiss National Science Foundation
Trial Identifier	NCT04362813	NCT04365153	NCT04510493
Phase & Intention	Phase III. To assess the efficacy and safety of **canakinumab** in patients with COVID-19-induced pneumonia and CRS.	Phase II. To demonstrate as a proof of concept that early treatment with **canakinumab** prevents progressive heart and respiratory failure in patients with COVID-19 infection. These results will lead to and inform a Phase III randomized placebo-controlled trial.	Phase III. The purpose of this study is to evaluate whether **canakinumab** has beneficial effects on patients with Type 2 diabetes mellitus and coronavirus disease 19 (COVID19).
Study design	**RCT**, multicenter, randomized, double-blind, placebo-controlled study	**RCT**, single center, quadruple-blinded, randomized, placebo-controlled study	**RCT**, parallel assignment, double-blinded, placebo-controlled study
Status trial	Recruiting, started April 30, 2020	Recruiting, started April 24, 2020	Not yet recruiting
Duration/End of Study	Estimated Primary Completion Date: August 28, 2020 Estimated Study Completion Date: December 4, 2020	Estimated Primary Completion Date: December 31, 2020; Estimated Study Completion Date: December 31, 2020	Estimated Primary Completion Date: September 2023 Estimated Study Completion Date: September 2023
Study details			
Number of Patients	Estimated Enrollment n=450 (12 Years and older)	n=45 (Adult, Older Adult; 18 Years and older)	n= 116 (Adult, Older Adult; 18 Years and older)
Location/Centres	France, Germany, Hungary, Italy, Russian Federation, Spain, United Kingdom, United States	US	Switzerland
Intervention	Canakinumab 450 mg for body weight 40-<60 kg, 600 mg for 60-80 kg or 750 mg for >80 kg in 250 mL of 5% dextrose infused IV over 2 hours. Single dose on Day 1.	Arm 1: Canakinumab Injection 600mg Subjects will be given one-time intravenous infusion of 600 mg of canakinumab (8 mg/kg for patients </= 40 kg) in 250 mL of 5% dextrose infused IV over 2 hours; Arm 2: Canakinumab Injection 300mg Subjects will be given one-time intravenous infusion of 300 mg of canakinumab (4 mg/kg for patients </= 40 kg) in 250 mL of 5% dextrose infused IV over 2 hours	Arm 1:Treatment with Canakinumab i.v. body weight adjusted dose in 250 ml 5% dextrose solution i.v. over 2 hours. Arm 2: Placebo treatment: Aqua ad injectabilia in 250 ml 5% dextrose solution i.v. over 2 hours
Controls	Placebo. 250 mL of 5% dextrose infused IV over 2 hours. Single dose on Day 1.	Placebo. 250 mL of 5% dextrose infused IV over 2 hours.	Placebo. Aqua ad injectabilia in 250 ml 5% dextrose solution i.v. over 2 hours

			Other Name: Aqua ad injectabilia in 250 ml 5% dextrose solution
Duration of observation/ Follow-up	Study period from initial dose on Day 1 to Day 29 or hospital discharge. Follow-up to Day 127.	The follow-up period is 5 months for each patient enrolled	From randomization up to 4 weeks
Primary Outcomes	Primary outcome: Number of patients with clinical response [Time Frame: Day 3 to Day 29]; Secondary outcomes: COVID-19-related death rate during the 4-week period after study treatment [Time Frame: 4 weeks]; Ratio to baseline in the CRP [Time Frame: Baseline, Day 29]; Ratio to baseline in the serum ferritin [Time Frame: Baseline, Day 29]; Ratio to baseline in the D-dimer [Time Frame: Baseline, Day 29]; Number of participants with AE, SAE, clinically significant changes in laboratory measures, and vital signs [Time Frame: 127 days]	Primary outcome: Time to clinical improvement up to day 14, defined as the time in days from randomization to either an improvement of two points on a seven-category ordinal scale or discharge from the hospital, whichever occurs first. [Time Frame: Up to day 14]; Secondary outcomes: Mortality at day 28 [Time Frame: Up to day 28]	Primary outcome: Unmatched win ratio after treatment with canakinumab compared to Placebo (composite endpoint) [Time Frame: within 4 weeks after treatment with canakinumab or placebo] Treatment and placebo will be compared on the basis of the unmatched win-ratio approach of Pocock. When comparing two patients, the winner will be determined by the first component in which the two patients differ (4 weeks after randomization): a. longer survival time b. longer ventilation-free time c. longer ICU-free time d. shorter hospitalization time Secondary outcomes: Time to clinical improvement [Time Frame: From randomization up to 4 weeks]; Time to clinical improvement [Time Frame: From randomization up to 4 weeks]; Admission to ICU [Time Frame: 4 weeks]; Secondary worsening of disease [Time Frame: 4 weeks]; Prolonged hospital stay [Time Frame: >3 weeks]; Change in ratio to baseline in the glycated hemoglobin [Time Frame: Baseline, Day 29 and Day 90]
Results/Publication	Not provided.	Not provided.	Not provided

Abbreviations: [CRS]=[cytokine release syndrome]; [CRP]=[C-reactive protein]; [AE]=[adverse event]; [SAE]=[serious adverse events]; [IV]=[intravenous]; [US]=[United States]; [ICU]=[intensive care unit].

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