EUnetHTA Joint Action 3 WP4

"Rolling Collaborative Review" of Covid-19 treatments

CAMOSTAT FOR THE TREATMENT OF COVID-19

Project ID: RCR04
Monitoring Report

Version 1.0, August 2020

Template version July 2020

This Rolling Collaborative Review Living Document is part of the project / joint action '724130 / EUnetHTA JA3' which has received funding from the European Union's Health Programme (2014-2020)

DOCUMENT HISTORY AND CONTRIBUTORS

Version	Date	Description of changes
V1.0	**14/08/2020**	First version
V0.2	**10/08/2020**	Data extraction and analysis complete
V0.3	**11/08/2020**	Check of data extraction and analysis
V1.0	**14/08/2020**	First version

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Rolling Collaborative Review team

Author(s)	Belgian Health Care Knowledge Centre (KCE), Belgium
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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How to cite this assessment

Please cite this assessment as follows:

EUnetHTA Rolling Collaborative Review (RCR04). Authoring Team. Camostat for the treatment of Covid-19. Diemen (The Netherlands): EUnetHTA; 2020. [date of citation]. 14 pages. Report No.: RCR04. Available from: https //www.eunethta.eu

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

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

AE	Adverse Event
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
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, aiming at critical appraisal of the clinical evidence based on the Submission Dossier submitted by the 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	Camostat
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	Main outcome: • All-cause Mortality (Survival) Additional Outcomes: 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)

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. Table 1 - Summary of findings (SoF) 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 table1 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 (Higgins et al., 2019).

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 (DerSimonian 1986).Network meta-analysis (NMA) is performed for the primary outcome. For rating the certainty of the evidence, the GRADE approach is being used.

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

2. Table 2 - 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	Camostat
Comparison	Any active treatment, placebo, or standard of care.
Outcomes	See project Scope
Study design	Observational studies (comparative or single-arm prospective studies and 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 3 - 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

To enter into airway epithelial cells, coronaviruses rely on host cell proteases for activation of the viral protein involved in membrane fusion. [1, 2] The transmembrane protease, serine 2 (TMPRSS2) has been shown to facilitate viral entry of the coronaviruses SARS-CoV, HCoV-NL63, MERS-CoV in cells engineered to overexpress TMPRSS2. Viral entry was inhibited by trypsin-like serine protease inhibitors, camostat and nafamostat.[3-5] When SARS-CoV-2 emerged loss- and gain-of-function experiments identified TMPRSS2 as a key mediator of cell infection through virus-cell fusion.[6] In addition to coronaviruses, TMPRSS2 and the structurally similar serine protease, human airway trypsin-like protease, have been linked to influenza virus activation. Active site inhibitors of these airway proteases might thus have broad therapeutic applicability.[1] and Cannalieri et al (https://www.mdpi.com/1422-0067/21/16/5707)

The SARS-CoV-2 virus enters cells via its spike protein first binding to the cell-surface enzyme ACE2. Then the spike protein is cleaved by furin at the S1/S2 site followed by cleavage by TMPRSS2 at the S2′ site. This triggers a conformation change that ‘primes’ the spike protein for fusion of the viral and cellular membranes, releasing the virus genome into the host cell. This process can be inhibited either by blocking furin or TMPRSS2.[7] Note that these requirements differ from those of viral spreading through cell-cell fusion.

Camostat, its active metabolite GBPA/FOY 251 (Shrimp et al https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7315994/ and third paper Hoffmann et al https://www.biorxiv.org/content/10.1101/2020.08.05.237651v1), and nafamostat (Shrimp) directly inhibit TMPRSS2 enzymatic activity. This has been confirmed in a molecular dynamics and Markov modeling study (Hempel Noe https://www.biorxiv.org/content/10.1101/2020.07.21.214098v1.full.pdf). All three molecules were also shown to inhibit the activation and cellular entry of SARS-CoV-2[6, 8] (third paper Hoffman et al)

3.2 Regulatory Status

Camostat mesilate (FOY-305, https://pubchem.ncbi.nlm.nih.gov/compound/Camostat, Foipan® tablets of 100mg, ATC B02ABB04) is a synthetic trypsin-like serine protease inhibitor developed at ONO pharmaceuticals, Japan. Camostat has been licensed and marketed in Japan since 1985 for the treatment of acute symptoms of chronic pancreatitis at a daily dose of 3x200mg. A second indication approved in 1994 is postoperative reflux esophagitis at 3x100mg daily. The substance patent expired in January 1996. Safety up to 3x300mg daily has been demonstrated in a postoperative reflux study.[9, 10]

In South Korea camostat is on the market since 1989 (eg Foistar®, Daewoong pharma). Currently, multiple companies market camostat as a generic drug in Japan and South Korea. Camostat has a known and acceptable safety profile. Camostat is not approved for any use by EMA or FDA. Orphan drug designation was received in May 2011 from the FDA for the treatment of chronic pancreatitis in May 2011 .
(https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=338211)
Camostat as active product ingredient (API) is produced in Italy for the Japanese market (www.erregierre.it)

3.3 Level of Evidence available

There are no RCT results published yet.

Foipan (camostat) is one of the drugs for which the German Federal Ministry of Health initiated centralized procurement in April 2020 for the treatment of infected and seriously ill COVID-19 patients in Germany. https://www.abda.de/fuer-apotheker/arzneimittelkommission/amk-nachrichten/detail/13-20-informationen-der-institutionen-und-behoerden-bmg-zentrale-beschaffung-von-arzneimitteln-zur-therapie-schwerwiegender-verlaeufe-covid-19-infizierter-patienten-und-verteilung-an-apotheken-durch-die-bundeswehr/ Up to August 1, 2020, 35 to 60 Covid-19 patients have been treated with the

centrally procured medicinal product Foipan (Camostat) as part of an individual medical treatment. There was no obligation for the treating physicians to collect data in a registry.(personal communication Dr. Bärbel Witte, German Federal Ministry of Health)

Very low rates of chronic pancreatitis were seen as comorbidity in covid-19 patients in South-Korea, findings in line with a possible protective effect of camostat.[11] Analysis of administrative data on camostat use level was not conclusive.(personal communication corresponding author)

Until now no scientific publication on clinical trials of camostat in Covid-19 patients could be identified.
In South Korea three COVID-19 pneumonia patients over 65 years requiring oxygen and progressing despite treatment with HCQ and lopinavir/ritonavir; improved and could be discharged after intravenous administration of 200 mg daily of nafamostat for 4 to 13 days followed by oral camostat 3x200mg daily for 4 days.[12] Hospitalisation duration was shorter and viral shedding was 1 week shorter compared with HCQ after camostat 3x200mg given to mild and severe covid-19 patients.(unpublished data, personal communication corresponding author Dr Ji-Young Rhee)[12]

4 SUMMARY

There is a sound scientific rationale to investigate camostat in covid-19 clinical trials. Such trials are currently ongoing.

Table 4-1 Ongoing trials of single agent Camostat

Active substance	**Camostat**			
Sponsor/Collaborator	Aarhus University, Denmark	Yale University, US	Kentucky University, US	CRUK/Edinburgh University,UK
Trial Identifier	NCT04321096	NCT04353284	NCT04374019	NCT04455815
Phase & Intention	Phase 2	Phase 2	Phase 2	Phase 2
Study design	1:1 randomized, placebo-controlled RCT	1:1 randomized, placebo-controlled RCT	1:1:1:1 randomized, open label RCT	1:1 randomized open label RCT
Status of trial	recruiting	planned	recruiting	starting
Duration/End of Study				
Study details				
Number of Patients	ambulatory (2x200) and hospitalized (2x90 patients),	2x57 patients	4x60 patients	2x195 patients
Disease severity	Mild and severe	Mild	High risk	
Setting	Ambulatory and hospital	Ambulatory		Ambulatory
Location/Centres	Multicentre in Denmark	Multicentre in US		
Intervention drug name and dosage	**Camostat 3x200mg daily for 5 days**	Camostat 3x200mg daily for 7 days	Camostat 3x200mg for 14 days	Camostat 4x200mg for 14 days
Comparator (drug name and dosage)	**placebo**	placebo	HCQ; HCQ+azithromycin; HCQ+ivermectin	Standard of care
Duration of observation/ Follow-up				
Endpoints Primary Outcomes Secondary Outcomes	Ambulatory: no fever 48h plus symptom improvement; 7 point clinical scale for hospitalized patients	Viral load and symptoms	7 pint clinical scale	Hospitalization requiring oxygen
Results/Publication				

Active substance	**Camostat**			
Sponsor/Collaborator	Mayo clinic, US	Yale University, US	Tabriz hospital, Iran	Paris hospitals, France
Trial Identifier	NCT04470544	NCT04435015	www.irct.ir/trial/46573	
Phase & Intention	Phase 2	Phase 2	Phase 2	Phase 2
Study design	1:1 randomised placebo controlled RCT	1:1 randomised placebo controlled RCT	1:1 randomised open label RCT	1:1 randomized placebo controlled
Status of trial	recruiting	planned	In register	planned
Duration/End of Study				
Study details				
Number of Patients	2x132 patients	2x100 patients	2x20 patients	2x500 patients
Disease severity				
Setting	hospital	hospital	hospital	ambulatory

Active substance	**Camostat**			
Location/Centres				
Intervention drug name and dosage	**4x200mg daily**	3x200mg daily	3x200mg daily for 3 days	3x200mg daily for 14 days
Comparator (drug name and dosage)	**placebo**	placebo	Standard of care	placebo
Duration of observation/ Follow-up				
Endpoints Primary Outcomes Secondary Outcomes	Alive and free from respiratory failure at day 28	D-dimer	Pneumonia severity	hospitalisation
Results/Publication				

Table 4-2 Ongoing trials of combination therapies Camostat

Active substance	**Camostat**			
Sponsor/Collaborator	Duesseldorf University, Germany	Sheba Medical center, Israel		
Trial Identifier	NCT04338906	NCT04355052		
Phase & Intention	Phase 2	Phase 2		
Study design	1:1 randomized placebo controlled RCT	2:2:1 randomized open label RCT		
Status of trial	planned	recruiting		
Duration/End of Study				
Study details				
Number of Patients	2x167 patients	100 + 100 + 50 patients		
Disease severity				
Setting	hospital	hospital		
Location/Centres				
Intervention drug name and dosage	**HCQ + camostat 3x200mg for 7 days**	HCQ+camostat 3x200mg for 10 days		
Comparator (drug name and dosage)	**HCQ + placebo**	HCQ + azythro: Standard of care		
Duration of observation/ Follow-up				
Endpoints Primary Outcomes Secondary Outcomes	Duration of hospitalisation	NEWS and PCR		
Results/Publication				

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