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EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

KCE

"Rolling Collaborative Review" of Covid-19 treatments

CAMOSTAT FOR THE TREATMENT OF COVID-19

Project ID: RCR04

Monitoring Report

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DOCUMENT HISTORY AND CONTRIBUTORS

Version	Date	Description of changes
V 1.0	**14/08/2020**	First version, search includes grey literature and contacts with authors and trial investigators.
V 2.0	**15/09/2020**	Second version
V 3.0	**15/10/2020**	Third version
V 4.0	**16/11/2020**	Fourth version
V 5.0	**15/12/2020**	Fifth version
V 6.0	**15/02/2021**	Sixth version
V 7.0	**15/03/2021**	Seventh version
V 8.0	**20/04/2021**	Eighth version
V 9.0	**17/05/2021**	Ninth version
V 10.0	**15/07/2021**	Tenth version

Major changes from previous version

Chapter, page no.	Major changes from version 9.0
Section 3 and 4	• Results of three RCTs now public, one with scientific publication available

Disclaimer

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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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TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

LIST OF ABBREVIATIONS

AE	Adverse Event
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
ICD	International Classification of Diseases
MD	Mean Difference
MeSH	Medical Subject Headings
NA	Not applicable
NR	Not reported
OR	Odds Ratio
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
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	Camostat (camostat mesylate, FOY-305, ATC B02ABB04) is a synthetic trypsin-like serine protease inhibitor (https://pubchem.ncbi.nlm.nih.gov/compound/camostat) on the market in Japan and South Korea as generic drug in 100mg tablets.
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.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 two main mandatory sources and one optional source of information, as described below:

1. Summary of findings(SoF) table for published RCTs related to effectiveness and safety:

From July on KCE has updated the SoF table monthly based on the literature review and the use of covid-nma.com. (COVID-NMA initiative: find the living review protocol here).

From June 2021, the literature search is used from COVID-NMA initiative according living review protocol [1],[2] and is conducted by authors of this RCR in the following database:

- PubMed

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.

Risk of bias is assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions[3] 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[4].

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

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 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 KCE is searching and extracting the data for the eligible studies. At the drafting stage of each update, the authoring 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 Appendix Table 6-1.

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 [7, 8]. The transmembrane protease, serine 2 (TMPRSS2) [9], has been shown to facilitate viral entry of the coronaviruses SARS-CoV, HCoV-NL63 and MERS-CoV in cells engineered to overexpress TMPRSS2. Viral entry was inhibited by trypsin-like serine protease inhibitors, camostat and nafamostat [10-12]. At a dose of 30mg/kg, camostat caused survival in 60% of the mice in a lethal SARS-CoV BALB/c mouse model [13].

When SARS-CoV-2 emerged, loss- and gain-of-function experiments identified TMPRSS2 as a key mediator of cell infection through virus-cell fusion [14, 15]. 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 (e.g. camostat and nafamostat) might thus have broad therapeutic applicability [7, 16].

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 or TMPRSS13 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 by either blocking furin or TMPRSS2 [17]. Note that these requirements differ from those of viral spreading through cell-cell fusion and involving cathepsin B and L. Unlike ACE2, TMPRSS2 does not appear to exert a cytoprotective role. Inhibiting the function of TMPRSS2 may therefore not exert adverse effects [18].

Camostat, its active metabolite GBPA/FOY 251 [15, 19], and nafamostat [19] directly inhibit TMPRSS2 enzymatic activity. This has been confirmed in a molecular dynamics and Markov model study (https://pubs.rsc.org/en/content/articlehtml/2021/sc/d0sc05064d) [20]. Camostat and GBPA are believed to inhibit TMPRSS2 and TMPRSS13 by first forming a noncovalent precomplex which is then catalysed to form a long-lived covalent complex [15]. Possibly of relevance, the reversible covalent inhibition by camostat of enteropeptidase (coded by TMPRSS15) showed a long inhibition half-life of 14.3 hours [21].

Camostat, GBPA and nafamostat were shown to inhibit the activation and cellular entry in lung cells of SARS-CoV-2 [14, 15, 22, 23]. In a model of SARS-CoV-2 infection of pluripotent stem cell derived human lung alveolar type 2 cells, the addition of camostat successfully blocked downstream activities seen after SARS-CoV-2 infection [24]. Camostat showed in vitro a synergistic effect in with type type I interferon. https://www.biorxiv.org/content/10.1101/2021.01.05.425331v2

Camostat and GBPA have a low potential to act as a perpetrator in pharmacokinetic drug-drug interactions. Only inhibition of OATP2B1 by GBPA warrants further investigation.[25]

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 [26-28].

In South Korea, camostat is on the market since 1989 (e.g. 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 was marketed in India 12 years ago but withdrawn purely for commercial reasons a few years later. 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. (https://www.accessdata.fda.gov/scripts/opdlisting/oopd/). Camostat as active product ingredient (API) is produced in Italy for the Japanese market (www.erregierre.it).

3.3 Level of Evidence

Results of a first randomized clinical trial of camostat in Covid-19 patients were published. This concerns the first RCT (NCT04321096) started in Europe using camostat for covid-19. Both hospitalized patients as well as outpatients were enrolled in this multicentre trial in Denmark and Sweden as separate strata. In absence of outpatient testing services at the start of the pandemic in early April 2020, the in-hospital stratum recruited first and is reported under section 4. The recommendation to administer 3x200mg of camostat in a fasting state was communicated when the trial was already well underway and was not implemented fully for this trial. The frequency of adverse events was similar in the two groups.[29]

In a second 1:1 randomized multicentre trial in hospitalized patients in Japan with mild or moderate disease (NCT04657497) the duration to a negative test result did not differ after 3x600mg camostat daily compared with placebo. (based on a press release by ONO pharmaceuticals, https://www.ono-pharma.com/sites/default/files/en/news/press/enews20210611.pdf)

The AIDS Clinical Trials Group (ACTG) announced June 24, 2021, that camostat will not advance to phase 3 in the ACTIV-2 COVID-19 outpatient treatment study.(https://www.eurekalert.org/pub_releases/2021-06/actg-aac062421.php). ACTIV-2 includes both phase 2 and phase 3 evaluations of multiple investigational agents for treating early COVID-19 in a single trial. Camostat, provided by Sagent Pharmaceuticals (a Nichi-Iko Group Company), was dosed as 4x200 mg daily for seven days. The camostat arm of ACTIV-2 completed phase 2 enrollment with 224 participants on April 26, 2021. When the Therapeutic and Prevention Data and Safety Monitoring Board (DSMB) met on June 14, 2021 to review the data and determine whether camostat would advance to phase 3, they determined that while there were no safety concerns, the phase 2 data failed to meet the criteria for graduation (which is based on demonstrating early changes in viral shedding or improvement in symptoms).

4 SUMMARY

There is a sound scientific rationale to investigate TMPRSS2 inhibitors such as camostat in COVID-19 clinical trials. The first results however do not show efficacy in covid-19 in two hospitalized patient RCTs and in an outpatient RCT. Additional trials are ongoing and a pooled analysis of outpatient trials is being planned.

Table 4-1 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of camostat

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with placebo	Risk with camostat				
Time to clinical improvement	5 days (IQR, 2 to 10)	5 days (IQR, 3 to 7)	HR for clinical improvement in the camostat group was 1·14 (95% CI, 0·84 to 1·55)	205 (mITT)	moderate	logrank test, *P* = 0·37
Death within 30 days	58 per 1000	59 per 1000	HR 0·70 (95% CI, 0·17 to 2·15)	205 (mITT)	moderate	

Source: based on publication by Gunst et al, 2021[29] Risk of bias assessments from covid-nma.com; outcome data, descriptions and layout by KCE.
Abbreviations: RR=relative risk; IQR=interquartile range from 25th to 75th percentile; HR=hazard ratio; SAEs=serious adverse events.
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	Gunst et al, 2021 NCT04321096; EudraCT 2020-001200-42
Study design, study phase	2:1 randomized, placebo-controlled
Centres (single centre or multicentre), country, setting	Multicentre, Denmark and Sweden, in hospital setting (the trial also includes an outpatient stratum, not reported here)
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	mITT: 215: 137 (camostat) and 68 (placebo); median age 62y; 60% male, severity : mild: n=69 / moderate: n=120/ severe: n=16 critical: n=0
Inclusion criteria	Symptomatic Covid-19 infection defined as PCR-positive for SARS-CoV-2 in respiratory tract samples and hospital admission for ≤ 48 h.
Exclusion criteria	Patients unable to understand or sign the informed consent form (*e.g.* those requiring invasive mechanical ventilation at study entry). Baseline values of serum total bilirubin ≥ 3 upper limit of normal range and estimated glomerular filtration rate (eGFR) ≤ 30 mL/min, pregnancy or breastfeeding
Intervention (generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	Camostat (Foipan) 3x200mg daily for 5 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)	Placebo
Primary Outcome(s)	Time to clinical improvement, defined as live hospital discharge or an improvement of at least 2 points from baseline on the 7-point ordinal scale, which ever came first.
Patient-relevant secondary outcome(s)	30-day mortality
Follow-up (days, months)	30 days
Sponsor/ lead institution	Aarhus University, Denmark

Table 4-3 Ongoing trials of single agent camostat

Trial Identifier/registry ID(s)/contact	NCT04321096; EudraCT 2020-001200-42	NCT04353284	NCT04374019	NCT04455815; EudraCT 2020-002110-41
Study design, study phase	1:1 (ambulatory) and 2:1 (hospitalized) randomized, placebo-controlled	1:1 randomized, placebo-controlled	randomized multiple arm adaptive pick the winner design (amended)	1:1 randomized open label
Recruitment status	Active, not recruiting, over 250 patients recruited January 24, 2021. Analysis completed for the in hospital stratum.	Recruiting, 70 patients recruited April 13, 2021.	Recruiting, 6 outpatients recruited October 29, 2020.	Recruiting, 22 patients recruited January 28, 2021.
Number of Patients, Disease severity*	ambulatory (2x200) and hospitalized (120+60 patients), mild and severe	2x57, mild	60 patients per arm	2x195 patients
Setting (hospital, ambulatory,..)	Ambulatory and hospital	Ambulatory	Ambulatory and hospital (not ventilated)	Ambulatory
Intervention (generic drug name and dosage)	Camostat (Foipan) 3x200mg daily for 5 days	Camostat 4x200mg daily for 7 days	Camostat (camostat Sagent) 3x200mg for 14 days	Camostat (Foipan) 4x200mg for 14 days
Comparator (standard care or generic drug name and dosage)	placebo	placebo	ivermectin	standard of care
Primary Outcome(s)	Ambulatory: no fever 48h plus symptom improvement; 7 point clinical scale for hospitalized patients	Viral load (analysis in batch, including saliva test) and symptoms	2 point deterioration on 7 point clinical scale	Hospitalization requiring supplemental oxygen, time frame days 1-28
Sponsor/ lead institution, country (also country of recruitment if different)	Aarhus University, Denmark (Contact: Ole Schmeltz Søgaard)	Yale University, US (Contact: Joseph Vinetz)	Kentucky University, US (Contact: Suzanne Arnold)	CRUK/Edinburgh University, UK (Contact: Ken Dhaliwal)

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

Table 4-4 Ongoing trials of single agent camostat, continued

Trial Identifier/registry ID(s)/contact	NCT04470544	NCT04435015	www.irct.ir/trial/46573 IRCT20200317046797N1	NCT04608266 EudraCT 2020-003366-39 (CAMOVID)
Study design, study phase	1:1 randomised placebo controlled	1:1 randomised placebo controlled	1:1 randomised open label	1:1 randomized placebo controlled
Recruitment status	Recruiting, 75 patients recruited April 13, 2020	planned	recruitment complete	Recruiting, 60 patients recruited April 14, 2021.
Number of Patients, Disease severity*	2x138 patients	2x100 patients	2x20 patients	2x298 patients
Setting (hospital, ambulatory,..)	hospital	hospital	hospital	ambulatory
Intervention (generic drug name and dosage)	4x200mg camostat (Foipan Ono) daily for ? days	3x200mg camostat (Foipan) daily until discharge	3x200mg daily for 3 days	3x200mg camostat (Foipan) daily for 14 days
Comparator (standard care or generic drug name and dosage)	placebo	placebo	standard of care	placebo
Primary Outcome(s)	Alive and free from respiratory failure at day 28	D-dimer	Pneumonia severity	Hospitalisation
Sponsor/ lead institution, country (also country of recruitment if different)	Mayo Clinic Arizona, US (Contact: Alan Bryce)	Yale University, US (Contact: Arya Mani)	Tabriz hospital, Iran (Contact: Sepide Zununi)	Paris public hospitals, France (Contact: David Boutboul)

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

Table 4-5 Ongoing trials of single agent camostat, continued

Trial Identifier/registry ID(s)/contact	NCT04625114	NCT04524663; NCT04662073; NCT04662086	NCT04530617	NCT04521296
Study design, study phase	1:1 randomized placebo controlled	1:1 placebo controlled RCT (adaptive design, sharing controls)	1:1:1:1 randomized placebo controlled	1:1 randomized placebo controlled
Recruitment status	Recruiting, 96 patients recruited April 13, 2021	Recruiting, 21 patients recruited January 26, 2021	recruiting	recruitment complete
Number of Patients, Disease severity*	2x75 patients, mild symptoms or no symptoms with high viral load	2x60 patients	4x90 patients	2x45 patients in phase2a, 300 patients in phase 2b, mild to moderate
Setting (hospital, ambulatory,..)	ambulatory	ambulatory	ambulatory	
Intervention (generic drug name and dosage)	camostat (Foipan Ono) 3x300mg for 5 to 10 days	Camostat (Foipan Ono) 4x200mg 10days	camostat (Foistar Daewoong) 3x200mg for 14 days	Camostat (Foistar Daewoong, DWJ1248) 3x200mg 14days
Comparator (standard care or generic drug name and dosage)	placebo	placebo	Artemisia Annua thea, placebo thea, placebo tablets	placebo
Primary Outcome(s)	Viral load change from D0 to D5.	Viral shedding, up to day 28	Hospitalisation and oxygen use at day 14	Time to negative RNA
Sponsor/ lead institution, country (also country of recruitment if different)	Ghent University, Belgium (Contact: Marie-Angélique De Scheerder)	Stanford University, US (Contact: Julie Parsonnet)	National institute Zubiran, Mexico (Contact: Jose Gotes Palazuelos)	Daewoong Pharmaceutical, South Korea

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

Table 4-6 Ongoing trials of single agent camostat, continued

Trial Identifier/registry ID(s)/contact	JPRN-jRCTs031200113	NCT04355052	NCT04338906; EudraCT 2020-004695-18	NCT04583592 (CAMELOT)
Study design, study phase	1:1 randomized placebo controlled	2:1 randomized open label (amended)	2:2:1:1 randomized placebo controlled (amended)	2:1 randomized placebo controlled
Recruitment status	recruiting	Recruiting, 23 patients recruited January 24, 2021	Recruiting, 9 patients recruited January 29, 2021	Recruitment complete
Number of Patients, Disease severity*	2x300 patients, preventive use	160+80 patients	332+332+166+166 patients	200+100 patients
Setting (hospital, ambulatory,..)	ambulatory	Hospital	early treatment ambulatory/hospital	ambulatory
Intervention (generic drug name and dosage)	Camostat 5mg in 100ml for mouth rinsing 4x per day for 56 days	camostat 3x200mg for 10 days	camostat (Foipan Ono) 3x200mg for 7 days	camostat (camostat Sagent) 4x200mg for 14 days
Comparator (standard care or generic drug name and dosage)	placebo	standard of care	(convalescent plasma;) standard of care; placebo	placebo
Primary Outcome(s)	Positive antibody or PCR test	NEWS and PCR	Progression to clinical status >= 4b WHO	Hospitalisation or death before D28
Sponsor/ lead institution, country (also country of recruitment if different)	Tokai University Tokyo Hospital (Contact: Nishizaki Yasuriro)	Sheba Medical center, Israel (Contact: Itsik Levi)	Duesseldorf University, Germany (Contact: Thorsten Feldt)	Sagent Pharmaceuticals

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

Table 4-7 Ongoing trials of single agent camostat, continued

Trial Identifier/registry ID(s)/contact	NCT04730206; EudraCT 2020-005911-27	NCT04652765	NCT04657497	NCT04721535
Study design, study phase	1:1 randomized placebo controlled	1:1:1 randomized open label	1:1 randomized placebo controlled	1:1 randomized placebo controlled
Recruitment status	Not yet recruiting	Recruiting, so safety issues	Recruiting	Not yet recruiting
Number of Patients, Disease severity*	2x653 patients, symptomatic 50+ years of age	3x20 patients, symptomatic 60+ years of age	2x55 patients, mild (no oxygen)	2x506 subjects, exposed to SARS-COV-2
Setting (hospital, ambulatory,..)	ambulatory	ambulatory	hospital	ambulatory
Intervention (generic drug name and dosage)	camostat 4x200mg for 7 days	camostat 4x600mg for 7 days;	Camostat 4x600mg for up to 14 days	Camostat (DWJ248, Daewoong) 3x200mg for up to 14 days

Trial Identifier/registry ID(s)/contact	NCT04730206; EudraCT 2020-005911-27	NCT04652765	NCT04657497	NCT04721535
Study design, study phase	1:1 randomized placebo controlled	1:1:1 randomized open label	1:1 randomized placebo controlled	1:1 randomized placebo controlled
Recruitment status	Not yet recruiting	Recruiting, so safety issues	Recruiting	Not yet recruiting
Comparator (standard care or generic drug name and dosage)	placebo	Standard of care; camostat 4x600mg for 7 days plus bicalutamide 1x150mg for 7 days	placebo	placebo
Primary Outcome(s)	Hospitalisation >24h or death before D30	Hospitalisation before D28	Time to SARS-CoV-2 negative test	Subjects with RT-PCR positive test
Sponsor/ lead institution, country (also country of recruitment if different)	Leuven University, Belgium (Contact: Ann Van den Bruel)	Johns Hopkins, Baltimore, US (Contact: Catherine Marshall)	Ono Pharmaceutical	Daewoong Pharamaceutical

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

Table 4-8 Ongoing trials of single agent camostat, continued

Trial Identifier/registry ID(s)/contact	NCT04518410 (ACTIV-2)
Study design, study phase	1:1 randomized placebo controlled adaptive platform trial
Recruitment status	Recruiting
Number of Patients, Disease severity*	2000 patients, symptomatic and at higher risk of progression to severe disease
Setting (hospital, ambulatory,..)	ambulatory
Intervention (generic drug name and dosage)	camostat (Sagent) 4x200mg for 7 days
Comparator (standard care or generic drug name and dosage)	Intravenous bamlanivimab, BRII-196/BRII-198 or AZD7442 Inhaled SNG001 Intramuscular AZD7442 Subcutaneous C135-LS + C144-LS
Primary Outcome(s)	Duration of symptoms
Sponsor/ lead institution, country (also country of recruitment if different)	National Institute of Allergy and Infectious Diseases (NIAID) (Contact: David Smith, UCSDI)

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

Table 4-9 Ongoing trials of combination therapies camostat

Trial Identifier/registry ID(s)/contact	jRCTs031200196	NCT04713176	EudraCT 2020-002233-15
Study design, study phase	1:1 randomized open label	1:1 randomized open label	randomized placebo controlled
Recruitment status	recruiting	recruiting	recruiting
Number of Patients, Disease severity*	2x50 patients, mild	2x560 patients, severe	40 patients, mild
Setting (hospital, ambulatory,..)	hospital	hospital	ambulatory
Intervention (generic drug name and dosage)	Camostat + favipiravir + inhaled ciclesonide for 10 days	Camostat (DWJ1248, Daewoong) 3x200mg up to 14 days + remdesivir iv up to 5 days	Camostat 4x600mg + niclosamide 2g for 7 days
Comparator (standard care or generic drug name and dosage)	Standard of care	Placebo + remdesivir iv up to 5 days	placebo
Primary Outcome(s)	Length of hospital stay	Mortality or ECMO up to 29 days	Viral load
Sponsor/ lead institution, country (also country of recruitment if different)	Narita University Hospital, Japan (contact: Tsushima Kenji)	Daewoong Pharmaceutical	Charité research organisation, Berlin, Germany (contact Robert Schultz-Heienbrok)

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

5 REFERENCES

1. COVID-NMA. The COVID-NMA initiative ; A living mapping and living systematic review of Covid-19 trials 2021 [04-06-2021]. Available from: https://covid-nma.com/.

2. Boutron I., haimani A., Devane D., Meerpohl J. J., Rada G., Hróbjartsson A. et al. Interventions for the prevention and treatment of COVID-19: a living mapping of research and living network meta-analysis Cochrane Database of Systematic Reviews 2020;11.

3. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019): Cochrane; 2019. Available from: http://www.training.cochrane.org/handbook.

4. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.

5. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177-88.

6. Balshem H, Helfand M, Schunemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-6.

7. Laporte M, Naesens L. Airway proteases: an emerging drug target for influenza and other respiratory virus infections. Curr Opin Virol. 2017;24:16-24.

8. Shen LW, Mao HJ, Wu YL, Tanaka Y, Zhang W. TMPRSS2: A potential target for treatment of influenza virus and coronavirus infections. Biochimie. 2017;142:1-10.

9. Thunders M, Delahunt B. Gene of the month: TMPRSS2 (transmembrane serine protease 2). J Clin Pathol. 2020.

10. Kawase M, Shirato K, van der Hoek L, Taguchi F, Matsuyama S. Simultaneous treatment of human bronchial epithelial cells with serine and cysteine protease inhibitors prevents severe acute respiratory syndrome coronavirus entry. J Virol. 2012;86(12):6537-45.

11. Shirato K, Kawase M, Matsuyama S. Middle East respiratory syndrome coronavirus infection mediated by the transmembrane serine protease TMPRSS2. J Virol. 2013;87(23):12552-61.

12. Yamamoto M, Matsuyama S, Li X, Takeda M, Kawaguchi Y, Inoue JI, et al. Identification of Nafamostat as a Potent Inhibitor of Middle East Respiratory Syndrome Coronavirus S Protein-Mediated Membrane Fusion Using the Split-Protein-Based Cell-Cell Fusion Assay. Antimicrob Agents Chemother. 2016;60(11):6532-9.

13. Zhou Y, Vedantham P, Lu K, Agudelo J, Carrion R, Jr., Nunneley JW, et al. Protease inhibitors targeting coronavirus and filovirus entry. Antiviral Res. 2015;116:76-84.

14. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020;181(2):271-80 e8.

15. Hoffmann M, Hofmann-Winkler H, Smith JC, Kruger N, Sorensen LK, Sogaard OS, et al. Camostat mesylate inhibits SARS-CoV-2 activation by TMPRSS2-related proteases and its metabolite GBPA exerts antiviral activity. bioRxiv. 2020.

16. Cannalire R, Stefanelli I, Cerchia C, Beccari AR, Pelliccia S, Summa V. SARS-CoV-2 Entry Inhibitors: Small Molecules and Peptides Targeting Virus or Host Cells. Int J Mol Sci. 2020;21(16).

17. Bestle D, Heindl MR, Limburg H, Van Lam van T, Pilgram O, Moulton H, et al. TMPRSS2 and furin are both essential for proteolytic activation of SARS-CoV-2 in human airway cells. Life Sci Alliance. 2020;3(9).

18. Baughn LB, Sharma N, Elhaik E, Sekulic A, Bryce AH, Fonseca R. Targeting TMPRSS2 in SARS-CoV-2 Infection. Mayo Clin Proc. 2020;95(9):1989-99.

19. Shrimp JH, Kales SC, Sanderson PE, Simeonov A, Shen M, Hall MD. An Enzymatic TMPRSS2 Assay for Assessment of Clinical Candidates and Discovery of Inhibitors as Potential Treatment of COVID-19. ACS Pharmacol Transl Sci. 2020;3(5):997-1007.

20. Hempel T, Raich L, Olsson S, Azouz NP, Klingler AM, Rothenberg M, et al. Molecular mechanism of SARS-CoV-2 cell entry inhibition via TMPRSS2 by Camostat and Nafamostat mesylate (preprint 21.07.2020) 2020 [Available from: https://www.biorxiv.org/content/10.1101/2020.07.21.214098v1.full.pdf.

21. Sun W, Zhang X, Cummings MD, Albarazanji K, Wu J, Wang M, et al. Targeting Enteropeptidase with Reversible Covalent Inhibitors To Achieve Metabolic Benefits. J Pharmacol Exp Ther. 2020;375(3):510-21.

22. Hoffmann M, Schroeder S, Kleine-Weber H, Muller MA, Drosten C, Pohlmann S. Nafamostat Mesylate Blocks Activation of SARS-CoV-2: New Treatment Option for COVID-19. Antimicrob Agents Chemother. 2020;64(6).

23. Ko M, Jeon S, Ryu WS, Kim S. Comparative analysis of antiviral efficacy of FDA-approved drugs against SARS-CoV-2 in human lung cells. J Med Virol. 2020.

24. Huang J, Hume AJ, Abo KM, Werder RB, Villacorta-Martin C, Alysandratos KD, et al. SARS-CoV-2 Infection of Pluripotent Stem Cell-Derived Human Lung Alveolar Type 2 Cells Elicits a Rapid Epithelial-Intrinsic Inflammatory Response. Cell Stem Cell. 2020.

25. Weiss J, Bajraktari-Sylejmani G, Haefeli WE. Low risk of the TMPRSS2 inhibitor camostat mesylate and its metabolite GBPA to act as perpetrators of drug-drug interactions. Chem Biol Interact. 2021;338:109428.

26. Uno Y. Camostat mesilate therapy for COVID-19. Intern Emerg Med. 2020.

27. Sato T, Uchino J, Matsuno S. A Dose-Finding Study of FOY-305 in Postoperative Reflux Esophagitis – A Double-Blind Comparative Study. . J Clin Ther Med. 1992;8:1877–91.

28. Breining P, Frolund AL, Hojen JF, Gunst JD, Staerke NB, Saedder E, et al. Camostat mesylate against SARS-CoV-2 and COVID-19-Rationale, dosing and safety. Basic Clin Pharmacol Toxicol. 2021;128(2):204-12.

29. Gunst JD, Staerke NB, Pahus MH, Kristensen LH, Bodilsen J, Lohse N, et al. Efficacy of the TMPRSS2 inhibitor camostat mesilate in patients hospitalized with Covid-19-a double-blind randomized controlled trial. EClinicalMedicine. 2021:100849.

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]. 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

KCE is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and camostat are described in Table 6-1Table 6-1 Search strategy to identify ongoing studies. In addition Google search is performed weekly for recent hits for "camostat". Local trial registries are checked or investigators of identified trials are contacted to check the trial status, planned and ongoing studies are discussed during video conferences with investigators. Non-randomized trials are excluded.

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": • camostat	11/5/2021	25 hits 0 new
ICTRP	https://apps.who.int/trialsearch/	Terms: camostat	11/5/2021	Site not accessible. Previously 12/3/2021: 32 hits for 29 trials (22 plus 2 phase 1 studies, 1 retracted and 4 older trials) 0 new
ISRCTN	https://www.isrctn.com/	Advanced search mode Search terms: 1. Camostat	11/5/2021	0
European Clinical Trials Registry	https://www.clinicaltrialsregister.eu/	Basic search mode Search terms: 1. covid-19 and camostat	11/5/2021	6 0 new

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