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 4.0, November 2020

Template version October 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
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

Major changes from previous version

Chapter, page no.	Major changes from version 3.0
Tables with trials, p. 12 ff	• More trials, planned and ongoing, have been added; trial contact, design and recruitment status were added or updated

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.

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).

Copyright

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]. 26 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
RCR	Rolling Collaborative Review
REA	Relative Effectiveness Assessment
RR	Relative Risk
SAE	Serious Adverse Event
SD	Standard Deviation
SMD	Standardized Mean Difference
SmPC	Summary of product characteristics
SOP	Standard Operating Procedure
WP4	Work Package 4

1 OBJECTIVE

The aim of this EUnetHTA Rolling Collaborative Review is

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

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

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

2 METHODS

This Rolling Collaborative Review is prepared according to the project plan ("Rolling Collaborative Review (RCR) on Covid-19 treatments: Project description and planning", published on the EUnetHTA website) and will be updated monthly. Monthly updates are published on the EUnetHTA Covid-19 Website (https://eunethta.eu/services/covid-19/) and on the EUnetHTA Rolling Collaborative Review Sharepoint page each 15th of the month.

2.1 Scope

Table 2-1 Scope of the RCR

Description	Project Scope
Population	**Disease** • 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 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. Table 6-1 describes in detail the sources searched, the search terms used and the dates at which the searches are executed.

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. The process of study selection is depicted as a flow diagram in Appendix Figure 6-1.

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/

Search methods are described in more detail in Table 6-2.

Population	See project Scope
Intervention	Camostat
Comparison	Any active treatment, placebo, or standard of care.
Outcomes	See project Scope
Study design	Inclusion criteria: Prospective non-randomised controlled trials, prospective case series (i.e. comparative or single-arm prospective studies), registries Exclusion criteria: retrospective studies, case studies/ case reports, observational studies that do not report safety data

Two researchers from NIPHNO carry out title and abstract screening and assess the full texts of all potentially eligible studies. The study selection process is depicted in a flow diagram (Appendix Figure 6-2). One researcher of KCE 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 of KCE is searching and extracting the data for the eligible studies. The process of study selection is depicted in a flow diagram (Appendix Figure 6-3). 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 6-3.

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 [4, 5]. The transmembrane protease, serine 2 (TMPRSS2) [6], 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 [7-9]. At a dose of 30mg/kg, camostat caused survival in 60% of the mice in a lethal SARS-CoV BALB/c mouse model [10].

When SARS-CoV-2 emerged, loss- and gain-of-function experiments identified TMPRSS2 as a key mediator of cell infection through virus-cell fusion [11]. 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 [4, 12].

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 to some extent also 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 [13]. 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 [14].

Camostat, its active metabolite GBPA/FOY 251 [11, 15], and nafamostat [15] directly inhibit TMPRSS2 enzymatic activity. This has been confirmed in a molecular dynamics and Markov model study (paper in preprint) [16]. Camostat and GBPA are believed to inhibit TMPRSS2 by first forming a noncovalent precomplex which is then catalysed to form a long-lived covalent complex [11]. Possibly of relevance, the reversible covalent inhibition by camostat of enteropeptidase (coded by TMPRSS15) showed a long inhibition half-life of 14.3 hours.
(preprint: https://jpet.aspetjournals.org/content/jpet/early/2020/10/08/jpet.120.000219.full.pdf)

Camostat, GBPA and nafamostat were shown to inhibit the activation and cellular entry in lung cells of SARS-CoV-2 [11, 17-19]. 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 [20].

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 [21, 22].

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

Until now, no scientific publication on randomized clinical trials of camostat in Covid-19 patients could be identified.

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 [23]. Up to August 1, 2020, 35 to 60 Covid-19 patients have been treated with the centrally procured camostat as part of an individual medical treatment. There was no obligation for the treating physicians to collect data in a registry (personal communication on 7/8/2020 with Dr. Bärbel Witte, German Federal Ministry of Health).

In a preprint, a case series of 6 severe covid-19 patients in Germany treated with 3x200mg camostat for 5 days was compared to 5 patients treated with HCQ. Inflammation markers improved under camostat which was not the case after HCQ [24]. Meanwhile 25 severe covid-19 patients were treated with camostat at the University Hospital Goettingen (personal communication on 2/11/2020 with Dr. Martin Winkler).

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 [25]. Analysis of administrative data on camostat use level was not conclusive (personal communication on 9/7/2020 with Dr. Jaehun Jung, corresponding author).

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 [26]. 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 on 28/5/2020 and follow-up communications with Dr. Ji-Young Rhee, corresponding author) [26].

An invitation-only mini-symposium on TMPRSS2 inhibitors took place on October 29, 2020, hosted by Oxford University with preclinical experts and most of the investigators of the planned and ongoing trials. A total of 18 trials have been identified with 11 of these already recruiting patients. Eleven trials include ambulatory patients. In early November 2020, it can be estimated that over 100 ambulatory and hospitalized patients have received camostat in a Covid-19 randomized trial at a dose of 3x200mg daily or 4x200mg daily. Two trials are expected to complete enrolment in early 2021 (Aarhus and Yale). No safety issues for camostat were reported by the investigators at the mini-symposium.

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	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)
Trial Identifier	NCT04321096; EudraCT 2020-001200-42	NCT04353284	NCT04374019	NCT04455815; EudraCT 2020-002110-41
Phase & Intention	Phase 2	Phase 2	Phase 2	Phase 2
Study design	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
Status of trial	Recruiting, recruitment October 29, 2020: 35 ambulatory and 101 hospitalized patients.	Recruiting, completion expected early 2021.	Recruiting, 6 outpatients recruited October 29, 2020.	Recruitment started.
Duration/End of Study				
Study details				
Number of Patients	ambulatory (2x200) and hospitalized (120+60 patients).	2x57 patients	60 patients per arm	2x195 patients
Disease severity	Mild and severe	Mild		
Setting	Ambulatory and hospital	Ambulatory	Ambulatory and hospital (not ventilated)	Ambulatory
Location/Centres	Multicentre in Denmark	Multicentre in US		
Intervention 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 (drug name and dosage)	placebo	placebo	ivermectin	standard of care
Duration of observation/ Follow-up				
Primary Outcomes	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

.

Table 4-2 Ongoing trials of single agent camostat (continued)

Active substance	**Camostat**			
Sponsor	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)
Trial Identifier	NCT04470544	NCT04435015	www.irct.ir/trial/46573 IRCT20200317046797N1	NCT04608266 EudraCT 2020-003366-39
Phase & Intention	Phase 2	Phase 2	Phase 2	Phase 2
Study design	1:1 randomised placebo controlled	1:1 randomised placebo controlled	1:1 randomised open label	1:1 randomized placebo controlled
Status of trial	Recruiting, 11 patients recruited october 29, 2020	planned	In register	Planned to start recruitment mid November 2020
Duration/End of Study				
Study details				
Number of Patients	2x138 patients	2x100 patients	2x20 patients	2x298 patients
Disease severity				
Setting	hospital	hospital	hospital	ambulatory
Location/Centres				
Intervention 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 (drug name and dosage)	placebo	placebo	standard of care	placebo
Duration of observation/ Follow-up				
Primary Outcomes	Alive and free from respiratory failure at day 28	D-dimer	Pneumonia severity	Hospitalisation

Table 4-3 Ongoing trials of single agent camostat (continued)

Active substance	**Camostat**				
Sponsor	Charité, Berlin, Germany (Contact: Robert Schultz-Heienbrok)	Stanford University, US (Contact: Julie Parsonnet)	National institute Zubiran, Mexico (Contact: Jose Gotes Palazuelos)	Daewoong Pharmaceutical, South Korea	Tokai University Tokyo Hospital (Contact: Nishizaki Yasuriro)

Active substance	**Camostat**				
Trial Identifier	EudraCT 2020-002233-15	NCT04524663	NCT04530617	NCT04521296	JPRN-jRCTs031200113
Phase & Intention	Phase 2	Phase 2	Phase 2	Phase 2	Phase 2
Study design	1:1:1 randomised placebo controlled dose escalation and combination	1:1 placebo controlled RCT (adaptive design, sharing controls)	1:1:1:1 randomized placebo controlled	1:1 randomized placebo controlled	1:1 randomized placebo controlled
Status of trial	recruiting	planned	recruiting	planned	recruiting
Duration/End of Study					
Study details					
Number of Patients	3x8 patients followed by 3x8 patients leading to best option in 20 patients (vs 20 placebo)	2x60 patients	4x90 patients	2x45 patients	2x300 patients
Disease severity				Mild to moderate	Prevention
Setting	ambulatory/hospital	ambulatory	ambulatory		ambulatory
Location/Centres					
Intervention drug name and dosage	Camostat (Camostat Sawai) dose escalation; **camostat + niclosamide**	Camostat (Foipan Ono) 4x200mg 10days	camostat (Foistar Daewoong) 3x200mg for 14 days	Camostat (Foistar Daewoong 3x200mg 14days	Camostat 5mg in 100ml for mouth rinsing 4x per day for 56 days
Comparator (drug name and dosage)	Niclosamide, placebo	placebo	Artemisia Annua thea, placebo thea, placebo tablets	placebo	placebo
Duration of observation/ Follow-up					
Primary Outcomes	Tolerability and safety	Viral shedding, up to day 28	Hospitalisation and oxygen use at day 14	Time to negative RNA	Positive antibody or PCR test

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

Active substance	**Camostat**				
Sponsor	Sheba Medical center, Israel (Contact: Itsik Levi)	Duesseldorf University, Germany (Contact: Thorsten Feldt)	Sagent Pharmaceuticals	Ghent University, Belgium (Contact: Marie-Angélique De Scheerder)	Leuven University, Belgium (Contact: Ann Van den Bruel)

Active substance	**Camostat**				
Trial Identifier	NCT04355052	NCT04338906; EudraCT 2020-004695-18	NCT04583592	NCT04625114	
Phase & Intention	Phase 2	Phase 2	Phase 2	Phase 2	Phase 3
Study design	2:1 randomized open label RCT (amended)	2:2:1:1 randomized placebo controlled (amended)	2:1 randomized placebo controlled	1:1 randomized placebo controlled	1:1 randomized placebo controlled
Status of trial	Recruiting, 17 patients recruited November 1, 2020	Recruitment planned to start in November 2020	Recruitment started.	Recruitment started, 5 patients recruited November 10, 2020	planned
Duration/End of Study					
Study details					
Number of Patients	160+80 patients	332+332+166+166 patients	200+100 patients	2x75 patients	2x650 patients
Disease severity					
Setting	hospital	early treatment ambulatory/hospital	ambulatory	ambulatory, mild symptoms or no symptoms with high viral load	ambulatory, symptomatic 50+ years of age
Location/Centres					
Intervention drug name and dosage	camostat 3x200mg for 10 days	camostat (Foipan Ono) 3x200mg for 7 days	camostat (camostat Sagent) 4x200mg for 14 days	camostat (Foipan Ono) 3x300mg for 5 to 10 days	camostat 4x200mg for 7 days
Comparator (drug name and dosage)	standard of care	convalescent plasma; standard of care; placebo	placebo	placebo	placebo
Duration of observation/ Follow-up					
Primary Outcomes	NEWS and PCR	Progression to clinical status >= 4b WHO	Hospitalisation or death before D28	Viral load change from D0 to D5.	Hospitalisation >24h or death before D30

5 REFERENCES

[1] 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.

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

[3] 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 Apr;64(4):401-6.

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

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

[6] Thunders M, Delahunt B. Gene of the month: TMPRSS2 (transmembrane serine protease 2). J Clin Pathol. 2020 Sep 1.

[7] 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 Jun;86(12):6537-45.

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

[9] 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 Nov;60(11):6532-9.

[10] 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 Apr;116:76-84.

[11] 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 Aug 5.

[12] 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 Aug 9;21(16).

[13] 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 Sep;3(9).

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

[15] 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. bioRxiv. 2020 Jun 23.

[16] 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 [cited 7/9/2020]; Available from: https://www.biorxiv.org/content/10.1101/2020.07.21.214098v1.full.pdf

[17] 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 Apr 16;181(2):271-80 e8.

[18] 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 May 21;64(6).

[19] 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 Aug 7.

[20] 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 Sep 18.

[21] Uno Y. Camostat mesilate therapy for COVID-19. Intern Emerg Med. 2020 Apr 29.

[22] 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.

[23] ABDA. 13/20 Informationen der Institutionen und Behörden: BMG: Zentrale Beschaffung von Arzneimitteln zur Therapie schwerwiegender Verläufe COVID-19 infizierter Patienten und Verteilung an Apotheken durch die Bundeswehr (24.03.2020). 2020 [cited 7/9/2020]; Available from: 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/

[24] Hofmann-Winkler H, Moerer O, Alt-Epping S, Bräuer A, Büttner B, Müller M, et al. Camostat Mesylate but Not Hydroxychloroquine May Reduce Severity of Organ Failure in COVID-19 Sepsis: A Case-Control Study (6/15/2020) 2020 [cited 7/9/2020]; Available from: https://ssrn.com/abstract=3631278

[25] Ji W, Huh K, Kang M, Hong J, Bae GH, Lee R, et al. Effect of Underlying Comorbidities on the Infection and Severity of COVID-19 in Korea: a Nationwide Case-Control Study. J Korean Med Sci. 2020 Jun 29;35(25):e237.

[26] Jang S, Rhee JY. Three cases of treatment with Nafamostat in elderly patients with COVID-19 pneumonia who need oxygen therapy. Int J Infect Dis. 2020 May 26.

6 APPENDIX

6.1 Search strategy to identify randomised controlled trials

DEPLazio, the Department of Epidemiology of the Regional Health Service Lazio in Rome, Italy is responsible for setting up the search strategy to identify randomised controlled trials (RCTs). DEPLazio performed a search in Medline, PubMed, and Embase, which has been updated weekly from March 2020 (Table 6-2). DEPLazio searched medRxiv.org (https://www.medrxiv.org/), bioRxiv.org (https://www.bioRxiv.org/), and arXiv.org (https://www.arXiv.org/) for preprints of preliminary reports of randomised trials. The Cochrane Covid-19 Study Register (https://covid-19.cochrane.org/), ClinicalTrials.gov (www.clinicaltrials.gov) and World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en/) were search in addition. Other sources included journal alerts, contact with researchers, websites such as Imperial College, London School of Hygiene and Tropical Medicine, and Eurosurveillance. We applied no restriction on language of publication.

We included 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. We excluded studies comparing two dosages of the same pharmacological agent. We did not exclude studies on individuals with a comorbid disorder.

Four authors independently screened the references retrieved by the search, selected the studies, and extracted the data, using a predefined data-extraction sheet. The same reviewers discussed any uncertainty regarding study eligibility and data extraction until consensus was reached; conflicts of opinion were resolved with other members of the review team. Two authors independently assessed the risk of bias of the included studies with the Cochrane tool. Three authors used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, to evaluate the strength of evidence.

The methods described above are part of a living review of pharmacological agents for the treatment of Covid-19 conducted by the Department of Epidemiology of the Regional Health Service Lazio, Italy, to inform national regulatory agencies and clinicians, available at https://www.deplazio.net/farmacicovid. The review is registered on Prospero (CRD42020176914).

Table 6-1 Search strategy to identify randomised controlled studies

Database	URL	Search line / Search terms	Date of search
Pubmed	pubmed.ncbi.nlm.nih.gov	1. (((((((("Coronavirus"[Mesh]) OR (coronavirus*[Title/Abstract] OR coronovirus*[Title/Abstract] OR coronavirinae*[Title/Abstract] OR Coronavirus*[Title/Abstract] OR Coronovirus*[Title/Abstract] OR Wuhan*[Title/Abstract] OR Hubei*[Title/Abstract] OR Huanan[Title/Abstract] OR "2019-nCoV"[Title/Abstract] OR 2019nCoV[Title/Abstract] OR nCoV2019[Title/Abstract] OR "nCoV-2019"[Title/Abstract] OR "COVID-19"[Title/Abstract] OR COVID19[Title/Abstract] OR "CORVID-19"[Title/Abstract] OR CORVID19[Title/Abstract] OR "WN-CoV"[Title/Abstract] OR WNCoV[Title/Abstract] OR "HCoV-19"[Title/Abstract] OR HCoV19[Title/Abstract] OR CoV[Title/Abstract] OR "2019 novel*"[Title/Abstract] OR Ncov[Title/Abstract] OR "n-cov"[Title/Abstract] OR "SARS-CoV-2"[Title/Abstract] OR "SARSCoV-2"[Title/Abstract] OR "SARSCoV2"[Title/Abstract] OR "SARS-CoV2"[Title/Abstract] OR SARSCov19[Title/Abstract] OR "SARS-Cov19"[Title/Abstract] OR "SARSCov-19"[Title/Abstract] OR "SARS-Cov-19"[Title/Abstract] OR Ncovor[Title/Abstract] OR Ncorona*[Title/Abstract] OR Ncorono*[Title/Abstract] OR NcovWuhan*[Title/Abstract] OR NcovHubei*[Title/Abstract] OR NcovChina*[Title/Abstract] OR NcovChinese*[Title/Abstract])) OR ((((respiratory*[Title/Abstract] AND (symptom*[Title/Abstract] OR disease*[Title/Abstract] OR illness*[Title/Abstract] OR condition*))[Title/Abstract] OR "seafood market*"[Title/Abstract] OR "food market*")[Title/Abstract] AND (Wuhan*[Title/Abstract] OR Hubei*[Title/Abstract] OR China*[Title/Abstract] OR Chinese*[Title/Abstract] OR Huanan*))[Title/Abstract])) OR ("severe acute respiratory syndrome*")) OR ((corona*[Title/Abstract] OR corono*)[Title/Abstract] AND (virus*[Title/Abstract] OR viral*[Title/Abstract] OR virinae*)[Title/Abstract])) AND (((((((randomized controlled trial [pt]) OR (controlled clinical trial [pt])) OR (randomized [tiab])) OR (placebo [tiab])) OR (clinical trials as topic [mesh: noexp])) OR (randomly [tiab])) OR (trial [ti]))) NOT (animals [mh] NOT humans [mh]) AND (2019/10/01:2020[dp])	06/11/2020

Database	URL	Search line / Search terms	Date of search
Ovid MEDLINE(R) ALL)	ovidsp.dc2.ovid.com	1. exp coronavirus/ 2. ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw. 3. (coronavirus* or coronovirus* or coronavirinae* or Coronavirus* or Coronovirus* or Wuhan* or Hubei* or Huanan or "2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCoV or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese*).ti,ab,kw. 4. (((respiratory* adj2 (symptom* or disease* or illness* or condition*)) or "seafood market*" or "food market*") adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw. 5. ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (China* or Chinese* or Huanan*)).ti,ab,kw. 6. "severe acute respiratory syndrome*".ti,ab,kw. 7. or/1-6 8. randomized controlled trial.pt. 9. controlled clinical trial.pt. 10. random*.ab. 11. placebo.ab. 12. clinical trials as topic.sh. 13. random allocation.sh. 14. trial.ti. 15. or/8-14 16. exp animals/ not humans.sh. 17. 15 not 16 18. 7 and 17 19. limit 18 to yr="2019 -Current"	06/11/2020
OVID EMBASE	ovidsp.dc2.ovid.com	1. exp Coronavirinae/ or exp Coronavirus/ 2. exp Coronavirus infection/ 3. ((("Corona virinae" or "corona virus" or Coronavirinae or coronavirus or COVID or nCoV) adj4 ("19" or "2019" or novel or new)) or (("Corona virinae" or "corona virus" or Coronavirinae or coronavirus or COVID or nCoV) and (wuhan or china or chinese)) or "Corona virinae19" or "Corona virinae2019" or "corona virus19" or "corona virus2019" or Coronavirinae19 or Coronavirinae2019 or coronavirus19 or coronavirus2019 or COVID19 or COVID2019 or nCOV19 or nCOV2019 or "SARS Corona virus 2" or "SARS Coronavirus 2" or "SARS-COV-2" or "Severe Acute Respiratory Syndrome Corona virus 2" or "Severe Acute Respiratory Syndrome Coronavirus 2").ti,ab,kw. 4. or/1-3 5. Clinical-Trial/ or Randomized-Controlled-Trial/ or Randomization/ or Single-Blind-Procedure/ or Double-Blind-Procedure/ or Crossover-Procedure/ or Prospective-Study/ or Placebo/ 6. (((clinical or control or controlled) adj (study or trial)) or ((single or double or triple) adj (blind$3 or mask$3)) or (random$ adj (assign$ or allocat$ or group or grouped or patients or study or trial or distribut$)) or (crossover adj (design or study or trial)) or placebo or placebos).ti,ab. 7. 5 or 6 8. 4 and 7 9. limit 8 to yr="2019 -Current"	06/11/2020

6.2 Search strategy to identify observational studies

As of October 2020, NIPHNO is responsible for setting up the search strategy to identify observational studies. We receive studies that EPPI Centre has screened after searching weekly in Medline and Embase. We supplement these studies with a weekly search in Scopus. The retrieved hits were imported into an Endnote database and combined with generic names of the 15 included COVID-19 drugs.

Table 6-2 Search strategy to identify observational studies

Database	URL	Search terms / Search modality	Date of search
OVID Medline	Imported from EPPI Centre	1 exp Coronavirus/ 2 exp Coronavirus Infections/ 3 (coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*).mp. 4 (or/1-3) and ((20191* or 202*).dp. or 20190101:20301231.(ep).) 5 4 not (SARS or SARS-CoV or MERS or MERS-CoV or Middle East respiratory syndrome or camel* or dromedar* or equine or coronary or coronal or covidence* or covidien or influenza virus or HIV or bovine or calves or TGEV or feline or porcine or BCoV or PED or PEDV or PDCoV or FIPV or FCoV or SADS-CoV or canine or CCov or zoonotic or avian influenza or H1N1 or H5N1 or H5N6 or IBV or murine corona*).mp. 6 ((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp. 7 (2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV on nCoV or covid or coronavirus* or corona virus or Pandemi*2)) or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp. 8 COVID-19.rx,px,ox. or severe acute respiratory syndrome coronavirus 2.os. 9 ("32240632" or "32236488" or "32268021" or "32267941" or "32169616" or "32267649" or "32267499" or "32267344" or "32248853" or "32246156" or "32243118" or "32240583" or "32237674" or "32234725" or "32173381" or "32227595" or "32185863" or "32221979" or "32213260" or "32205350" or "32202721" or "32197097" or "32196032" or "32188729" or "32176889" or "32088947" or "32277065" or "32273472" or "32273444" or "32145185" or "31917786" or "32267384" or "32265186" or "32253187" or "32265567" or "32231286" or "32105468" or "32179788" or "32152361" or "32152148" or "32140676" or "32053580" or "32029604" or "32127714" or "32047315" or "32020111" or "32267950" or "32249952" or "32172715").ui. 10 or/6-9 11 5 or 10	27/09/2020 until 25/10/2020
OVID EMBASE		1 exp Coronavirus Infections/ 2 exp coronavirinae/ 3 (coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*).mp. 4 or/1-3 5 4 not (SARS or SARS-CoV or MERS or MERS-CoV or Middle East respiratory syndrome or camel* or dromedar* or equine or coronary or coronal or covidence* or covidien or influenza virus or HIV or bovine or calves or TGEV or feline or porcine or BCoV or PED or PEDV or PDCoV or FIPV or FCoV or SADS-CoV or canine or CCov or zoonotic or avian influenza or H1N1 or H5N1 or H5N6 or IBV or murine corona*).mp. 6 ((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp. 7 (2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV on nCoV or covid or coronavirus* or corona virus or Pandemi*2)) or ((covid	27/09/2020 until 25/10/2020

		or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp. 8 6 or 7 9 5 or 8	
Scopus		TITLE-ABS-KEY(((pneumonia OR covid* OR coronavirus* OR "corona virus*" OR ncov* OR 2019-ncov OR sars*) AND Wuhan) OR 2019-ncov OR ncov19 OR ncov-19 OR "2019-novel CoV" OR sars-cov2 OR sars-cov-2 OR sarscov2 OR sarscov-2 OR sars-coronavirus2 OR sars-coronavirus-2 OR "SARS-like coronavirus*" OR coronavirus-19 OR covid19 OR covid-19 OR "covid 2019" OR ((novel OR new OR nouveau) W/1 (CoV OR nCoV OR covid OR coronavirus* OR "corona virus*" OR pandemi*)) OR ((covid OR covid19 OR covid-19) AND pandemic*) OR ((coronavirus* OR "corona virus*") AND pneumonia)) AND ORIG-LOAD-DATE > 20200920[date changes from week to week] AND ORIG-LOAD-DATE < 20200928 [date changes from week to week] AND NOT INDEX(medline)	27/09/2020 until 25/10/2020

6.3 Search strategy to identify ongoing studies

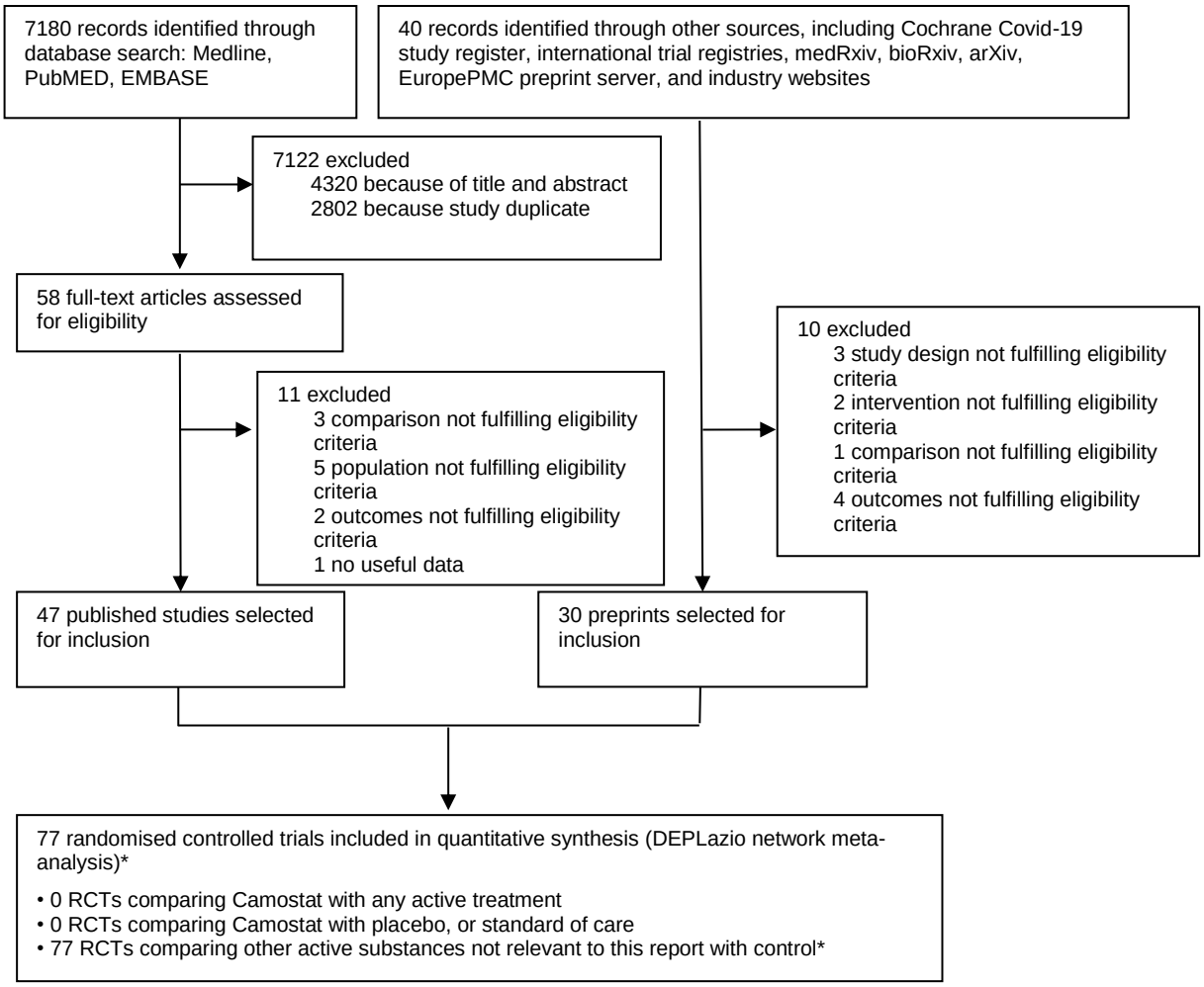
KCE is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and camostat are described in Table 6-3. In addition Google search is performed weekly for recent hits for “camostat”. Local trial registries are checked 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. A trial listed on the local trials registry in Iran and a trial planned Leuven were thus identified.

Table 6-3 Search strategy to identify ongoing studies

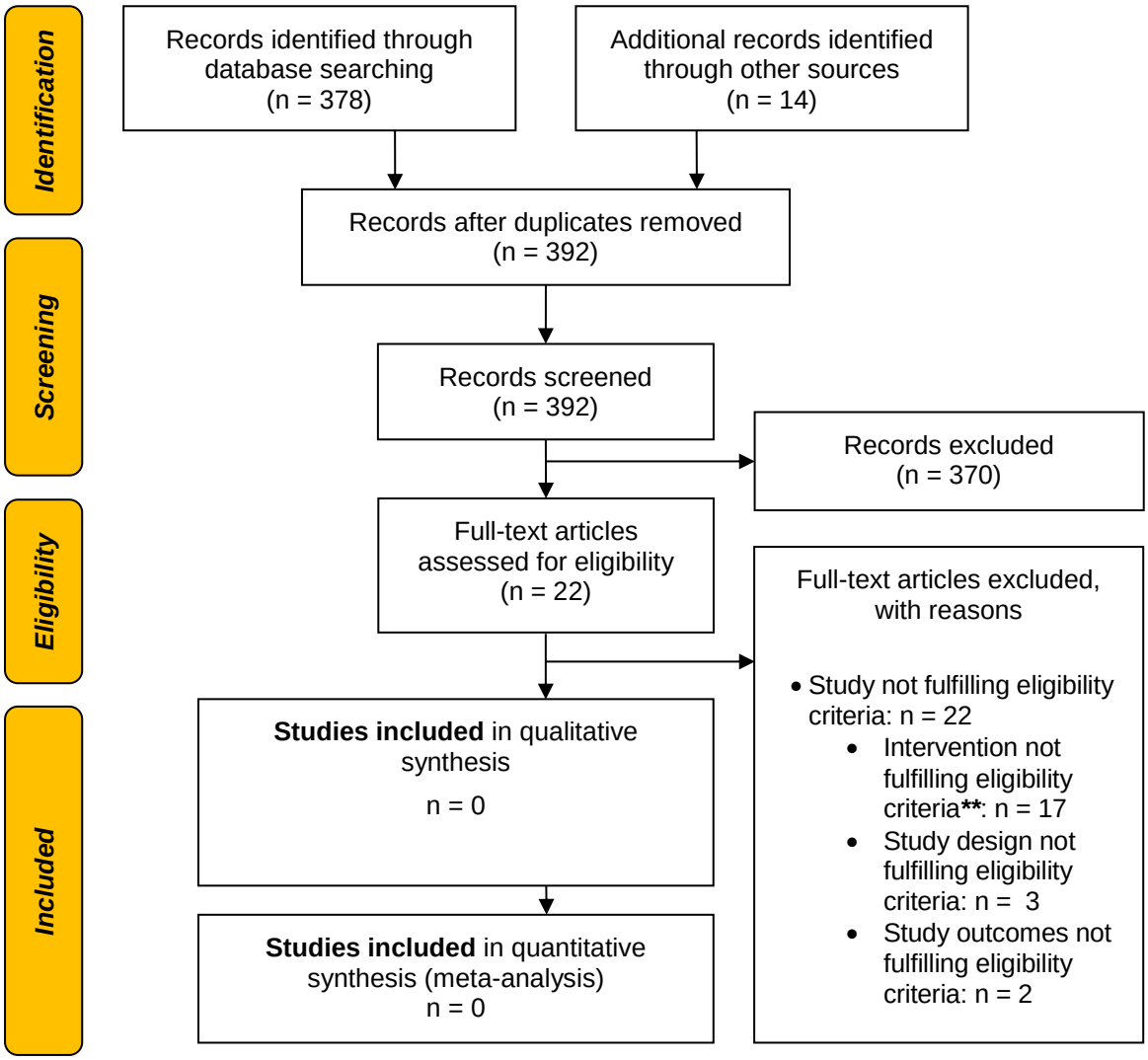
Database	URL	Search line / search terms	Date of search	Hits retrieved
ClinicalTrials.gov	https://clinicaltrials.gov/	“Basic search mode*” Terms used at Condition or disease: • covid-19 Terms used at “other terms”: • camostat	16/11/2020	14 2 new
ICTRP	https://apps.who.int/trialsearch/	Terms: Covid-19 and camostat	16/11/2020	14 0 new
ISRCTN	https://www.isrctn.com/	Advanced search mode Search terms: 1. Condition: Covid-19 AND Interventions: Camostat	16/11/2020	0 0 new
European Clinical Trials Registry	https://www.clinicaltrialsregister.eu/	Basic search mode Search terms: 1. covid-19 and camostat	16/11/2020	4 1 new

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

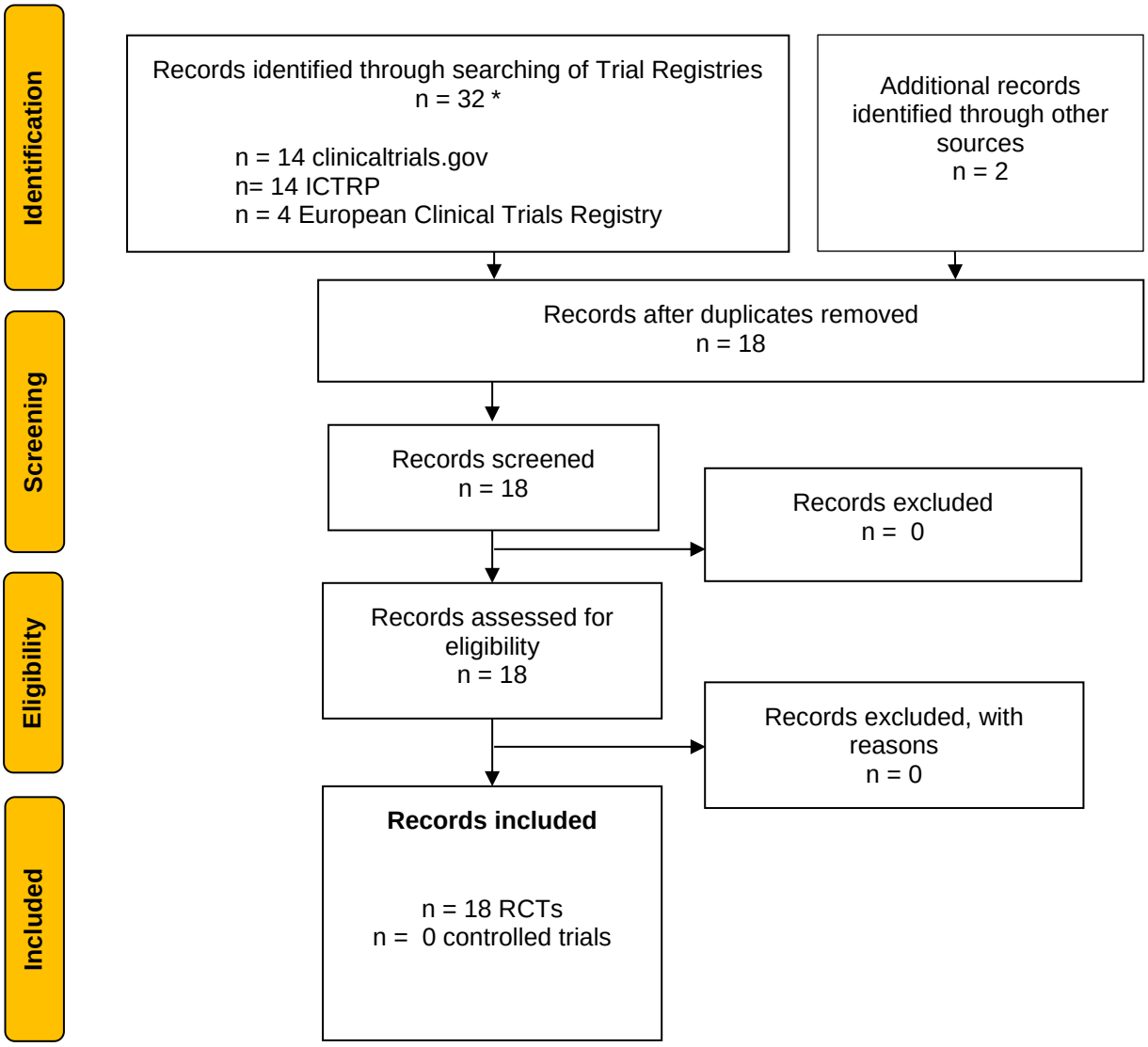
6.1 Flow diagrams



Appendix Figure 6-1. Flow diagram depicting the selection process of RCTs
RCT = randomised controlled trial; * The selection process was part of an external project, see https://www.deplazio.net/farmacicovid and Prospero ID CRD42020176914.



Appendix Figure 6-2. Flow diagram depicting the selection process of observational studies
** studies evaluating active substances relevant to other EUNETHTA rolling collaborative reviews



Appendix Figure 6-3. Flow diagram depicting the selection process of ongoing studies
** 3 added in this update; RCT = randomised controlled trial*