EUnetHTA Joint Action 3 WP4

**“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 |

### Major changes from previous version

| Chapter, page no. | Major changes from version 8.0 |
|---|---|
| **Section 3.3** | • Results of first randomised trial published recently. |

### Disclaimer

The content of this “Rolling Collaborative Review” (RCR) represents a consolidated view based on the consensus within the Authoring Team; it cannot be considered to reflect the views of the European Network for Health Technology Assessment (EUnetHTA), EUnetHTA’s participating institutions, the European Commission and/or the Consumers, Health, Agriculture and Food Executive Agency or any other body of the European Union. The European Commission and the Agency do not accept any responsibility for use that may be made of the information it contains.

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| 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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# 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**<br>• 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.<br>**ICD-Codes** (https://www.who.int/classifications/icd/covid19/en)<br>• 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.<br>• 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.<br>• 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.<br>• 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.<br><br>**MeSH-terms**<br>• COVID-19, Coronavirus Disease 2019<br><br>**Target population**<br>(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.<br>• 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.<br>• 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.<br>• 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%.<br>• 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.<br><br>**Rationale**: Since there is no gold standard treatment any comparator is acceptable as well as the above listed interventions. |
| **Outcomes** | Main outcome:<br>• All-cause Mortality (Survival)<br><br>Additional Outcomes:<br>Efficacy:<br>• Length of hospital stay,<br>• Viral burden (2019-nCoV RT-PCR negativity),<br>• Clinical progression (WHO Clinical Progression Scale measured daily over the course of the study),<br>• Rates of hospitalization and of patients entering ICU,<br>• Duration of mechanical ventilation,<br>• Quality of life.<br><br>Safety:<br>• Adverse events (AE),<br>• Severe adverse events (SAE),<br>• Withdrawals due to AEs,<br>• Most frequent AEs,<br>• Most frequent SAEs.<br><br>**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)<br><br>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)<br>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:

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

| | |
|---|---|
| **Population** | People affected by COVID-19, as defined by the authors of the studies. No limits in terms of gender or ethnicity.<br>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<br>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. Appendix 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.

The sources and search methods are described in more detail in Appendix Table 6-2.

| | |
|---|---|
| **Population** | See project Scope |
| **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. |
| **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<br>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. 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, 12]. 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, 13].

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 [14]. 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 [15].

Camostat, its active metabolite GBPA/FOY 251 [12, 16], and nafamostat [16] 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) [17]. 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 [12]. Possibly of relevance, the reversible covalent inhibition by camostat of enteropeptidase (coded by TMPRSS15) showed a long inhibition half-life of 14.3 hours [18].

Camostat, GBPA and nafamostat were shown to inhibit the activation and cellular entry in lung cells of SARS-CoV-2 [11, 12, 19, 20]. 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 [21]. Camostat showed in vitro a synergistic effect in with type type I interferon. https://www.biorxiv.org/content/10.1101/2021.01.05.425331v2

## *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 [22-24].

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*

Very recently, after completing the search, results for 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 here. The 2:1 randomisation assigned 137 patients to camostat 3x200mg for 5 days and 68 to placebo. The recommendation to administer camostat in a fasting state was communicated when the trial was already well underway and was not implemented fully for this trial. The primary outcome was time to discharge or clinical improvement measured as ≥2 points improvement on a 7-point ordinal scale.

The authors report *"Median time to clinical improvement was 5 days (interquartile range [IQR], 3 to 7) in the camostat group and 5 days (IQR, 2 to 10) in the placebo group (P = 0·31). The hazard ratio for 30-day mortality in the camostat compared with the placebo group was 0·82 (95% confidence interval [CI], 0·24 to 2·79; P = 0·75). The frequency of adverse events was similar in the two groups. Median change in viral load from baseline to day 5 in the camostat group was -0·22 log10 copies/mL (p <0·05) and -0·82 log10 in the placebo group (P <0·05)."[25]*

The absence of efficacy may be related to a suboptimal dosing scheme or the administration of the TMPRSS2 inhibitor rather late after the start of the infection. Trials in outpatients are ongoing.

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 [26]. 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 [27]. 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 [28]. 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 [29]. 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) [29].

For the Daewoong pharmaceuticals phase 2a pilot trial in South-Korea a shorter viral shedding period but no statistically significant clinical effect was reported (in the press). For phase 3 a combination treatment with remdesivir is investigated. https://trialsitenews.com/study-combines-korean-pancreatitis-drug-foistar-with-remdesivir-targeting-covid-19/

A brief preprint report from South Korea showed normalisation of CRP in 6 out of 7 patients on camostat compared with 11 out of 18 covid-19 patients treated with Kaletra https://www.medrxiv.org/content/10.1101/2020.12.10.20240689v1.full.pdf.

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 22 trials have been identified including patients in the hospital or ambulatory care setting. Two of the trials concern the preventive use of camostat. End of January 2021, it can be estimated that over 300 ambulatory and hospitalized patients have received camostat in a Covid-19 randomized trial at a dose of 3x200mg daily or 4x200mg daily. Besides some mild gastro-intestinal adverse events no safety issues for camostat were reported by the investigators reporting the recruitment status. After completion of a healthy volunteer study by Ono pharmaceuticals, patient trials have started using camostat at a dose of 4x600mg daily.

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.[30]

In a retrospective analysis of 371 adult patients admitted to the intensive care unit of Al Ain Hospital, Abu Dhabi, United Arabs Emirates, between March 16 and July 19 2020, with COVID-19 pneumonia, camostat 3x200mg was associated with an improved outcome (ao an in hospital mortality reduction from 19 out of 61 in matched controls to 6 out of 61 ICU patients on camostat) using propensity score-based statistical techniques [31].

# 4 SUMMARY

There is a sound scientific rationale to investigate camostat in Covid-19 clinical trials. A first RCT did not show efficacy in hospitalized patients. Additional trials are ongoing that administer camostat early after the start of the infection and at a higher dosing regimen.

### Table 4-1 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 4-2 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 4-3 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, 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 4-4 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 4-5 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 |
| **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 4-6 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, UCSDl) |

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

### Table 4-7 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 |

| | | | |
|---|---|---|---|
| **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 |
| **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] 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, 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.

[12] 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.

[13] 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).

[14] 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).

[15] 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.

[16] 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 Oct 9;3(5):997-1007.

[17] 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

[18] 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 Dec;375(3):510-21.

[19] 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).

[20] 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.

[21] 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.

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

[23] 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.

[24] 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 Feb;128(2):204-12.

[25] 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 Apr 22:100849.

[26] 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/

[27] 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

[28] 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.

[29] 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.

[30] 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 Feb 27;338:109428.

[31] Sakr Y, Bensasi H, Taha A, Bauer M, Ismail K, the UAEJRG. Camostat mesylate therapy in critically ill patients with COVID-19 pneumonia. Intensive Care Med. 2021 Apr 12.

[32] London: EPPI Centre University College London. COVID-19: a living systematic map of the evidence. [updated 04 February 2021]. [cited 9 February 2021]; Available from: http://eppi.ioe.ac.uk/cms/Projects/DepartmentofHealthandSocialCare/Publishedreviews/COVID-19Livingsystematicmapoftheevidence/tabid/3765/Default.aspx

[33] Oslo: Norwegian Institute of Public Health. Live map of COVID-19 evidence. [updated 21 January 2021] [cited 9 February 2021]; Available from: https://www.fhi.no/en/qk/systematic-reviews-hta/map/

# 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 (Appendix Table 6-1). 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]) | 03/05/2021 |

| Database | URL | Search line / Search terms | Date of search |
|---|---|---|---|
| Ovid MEDLINE(R) ALL) | ovidsp.dc2.ovid.com | 1. exp coronavirus/<br>2. ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw.<br>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.<br>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.<br>5. ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (China* or Chinese* or Huanan*)).ti,ab,kw.<br>6. "severe acute respiratory syndrome*".ti,ab,kw.<br>7. or/1-6<br>8. randomized controlled trial.pt.<br>9. controlled clinical trial.pt.<br>10. random*.ab.<br>11. placebo.ab.<br>12. clinical trials as topic.sh.<br>13. random allocation.sh.<br>14. trial.ti.<br>15. or/8-14<br>16. exp animals/ not humans.sh.<br>17. 15 not 16<br>18. 7 and 17<br>19. limit 18 to yr="2019 -Current" | 03/05/2021 |
| OVID EMBASE | ovidsp.dc2.ovid.com | 1. exp Coronavirinae/ or exp Coronavirus/<br>2. exp Coronavirus infection/<br>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.<br>4. or/1-3<br>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/<br>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.<br>7. 5 or 6<br>8. 4 and 7<br>9. limit 8 to yr="2019 -Current" | 03/05/2021 |

### *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.

From September to December 2020, we received records that EPPI Centre has screened after searching weekly in Medline and Embase (until beginning of November 2020), from November onwards Microsoft Academics Graph (MAG). We supplemented these studies with a weekly search in Scopus (Elsevier). Detailed descriptions of the EPPI and NIPHNO searches are given at their websites [32, 33]. The retrieved hits were imported to a reference management tool, Endnote (Clarivate Analytics), for deduplication. We then searched the EndNote database using the generic names and synonyms for the included COVID-19 drugs.

From January onwards, an information specialist at NIPHNO has conducted searches in Medline (Ovid), Embase (Ovid) and Scopus (Elsevier) using the search strategy described in Table 6-2. To screen the references, two reviewers use a binary machine learning (ML) classifier. References that scored above the identified threshold of 30% certainty to be relevant were retained for screening; while those scoring below this threshold score were set aside.

Prior to using the binary ML classifier score to discard low scoring records, we screened 1028 references manually to train the classifier. The classifier is continuously being updated a long with new references being screened. References that have been set aside, can potentially be picked up in a later stage by a new classifier version. For drugs that have less than 5 publications included in the training batch, we combine the classifier with manual text word searches.

As a supplement we used Microsoft Academics Graph (MAG) to identify further relevant research. We used articles previously included in the EUnetHTA rolling collaborative review until last search and ran the Bring up-to-date function in EPPI Reviewer. Bring up-to-date uses the neural networks of MAG to identify publications similar to input articles, added to the MAG database.

**Table 6-2 Search strategy to identify observational studies**

| Database | URL | Search terms / Search modality | Date of search | Hits retrieved |
|---|---|---|---|---|
| Embase 1974 to 2021<br><br>Ovid MEDLINE(R) ALL 1946 to 2021 | | Lines 1 and 2 are copies of Ovid's Expert searches for covid-19 in MEDLINE and Embase<br><br>1 ((((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.) 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) adj2 (CoV or 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. or COVID-19.rx,px,ox,sh. or severe acute respiratory syndrome coronavirus 2.os.) use medall [COVID-19 in MEDLINE]<br><br>2 ((((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.) or (coronavirus disease 2019 or 2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or severe acute respiratory syndrome coronavirus 2 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 or nCoV or covid or coronavirus* or corona virus or pandemi*2)) | From 06/04/2021 until 03/05/2021 | 1032 |

| | | | | |
|---|---|---|---|---|
| | | or ((covid or covid19 or covid-19) and pandemic*2) or (coronavirus* and pneumonia)).mp. or (coronavirus disease 2019 or severe acute respiratory syndrome coronavirus 2).sh,dj.) use oemezd [COVID-19 in Embase]<br><br>3 (COVID-19 serotherapy/ or Immunization, Passive/ or tocilizumab/ or camostat/ or nafamostat/ or AP301 peptide/ or Interleukin 1 Receptor Antagonist Protein/ or alunacedase alfa/ or darunavir/ or favipiravir/ or sarilumab/ or exp Interferons/ or gimsilumab/ or canakinumab/ or baricitinib/ or molnupiravir/ or Aspirin/ or mavrilimumab/ or exp Vitamin D/dt or Vitamin D Deficiency/dt or Ivermectin/) use medall [MeSH-terms for drugs in MEDLINE]<br><br>4 (Hyperimmune globulin/dt or tocilizumab/ or camostat/ or camostat mesilate/ or nafamstat/ or solnatide/ or anakinra/ or darunavir/ or favipiravir/ or sarilumab/ or exp Interferon/ or gimsilumab/ or canakinumab/ or baricitinib/ or acetylsalicylic acid/ or mavrilimumab/ or exp Vitamin D/dt or Vitamin D Deficiency/dt or ivermectin/) use oemezd [Emtree-terms for drugs in Embase]<br><br>5 ((convalescent adj (plasma or sera or serum)) or serotherap* or ((atoxin or hyperimmunoglobulin or hyperimmune globulin or hyperimmune gammaglobulin) adj therap*) or passive immuni?ation or (tocilizumab or atlizumab or (MRA adj monoclonal antibod*) or MSB-11456 or MSB11456 or R-1569 or R1569 or RO-4788533 or RO4788533 or Actemra or Roactemra) or (camostat* or FOY-305 or FOY305 or FOY S 980) or (nafamostat or nafamstat or FUT-175 or FUT175) or (solnatide or AP301 or AP-301 or (TIP adj peptide)) or (anakinra or ((interleukin 1 or IL1 or IL-1) adj2 (antagonist or block* or inhibitor*)) or IL-1Ra or Kineret) or (alunacedase or APN01 or APN-01 or rhACE2 or recombinant human angiotensin converting enzyme 2 or GSK-2586881 or GSK2586881) or (darunavir or prezista or TMC-114 or TMC114 or UIC-94017 or UIC94017) or (favipi?avir or T-705 or T705 or Avigan or Olumiant) or (sarilumab or REGN-88 or REGN88 or SAR-153191 or SAR153191 or Kevzara) or (interferon* or (IFN adj1 (alpha* or beta* or gamma*)) or novaferon or CL-884 or CL884) or (gimsilumab or KIN-1901 or KIN1901 or morab-022 or morab022) or (canakinumab or ACZ-885 or ACZ885 or immunoglobulin G1 or Ilaris) or (baricitinib or LY-3009104 or LY3009104 or INCB-028050 or INCB028050 or INCB-28050 or INCB28050 or Olumiant) or (molnupiravir or MK-4482 or MK4482 or EIDD-2801 or EIDD2801) or (aspirin or acetylsalicylic acid) or (mavrilimumab or immunoglobulin G4 or CAM-3001 or CAM3001) or ((vitamin? D? or D?-vitamin?) adj4 (high-dose* or highdose* or supplement*)) or (ivermect* or MK-933 or MK933)).mp,bt,ot,du,dy,tn,nm. [other terms (title, abstract, author keywords and more) in MEDLINE and Embase]<br><br>6 (20210406 OR 20210407 OR 20210408 OR 20210409 OR 2021041* OR 2021042* OR 2021043* OR 202105*).dt. use medall [time limits in MEDLINE]<br><br>7 (20210406 OR 20210407 OR 20210408 OR 20210409 OR 2021041* OR 2021042* OR 2021043* OR 202105*).dc. use oemezd [time limits in Embase] | | |

| | | | | | |
|---|---|---|---|---|---|
| | | 8 | (1 and (3 or 5) and 6) use medall | | |
| | | 9 | (2 and (4 or 5) and 7) use oemezd | | |

### *6.3 Search strategy to identify ongoing studies*

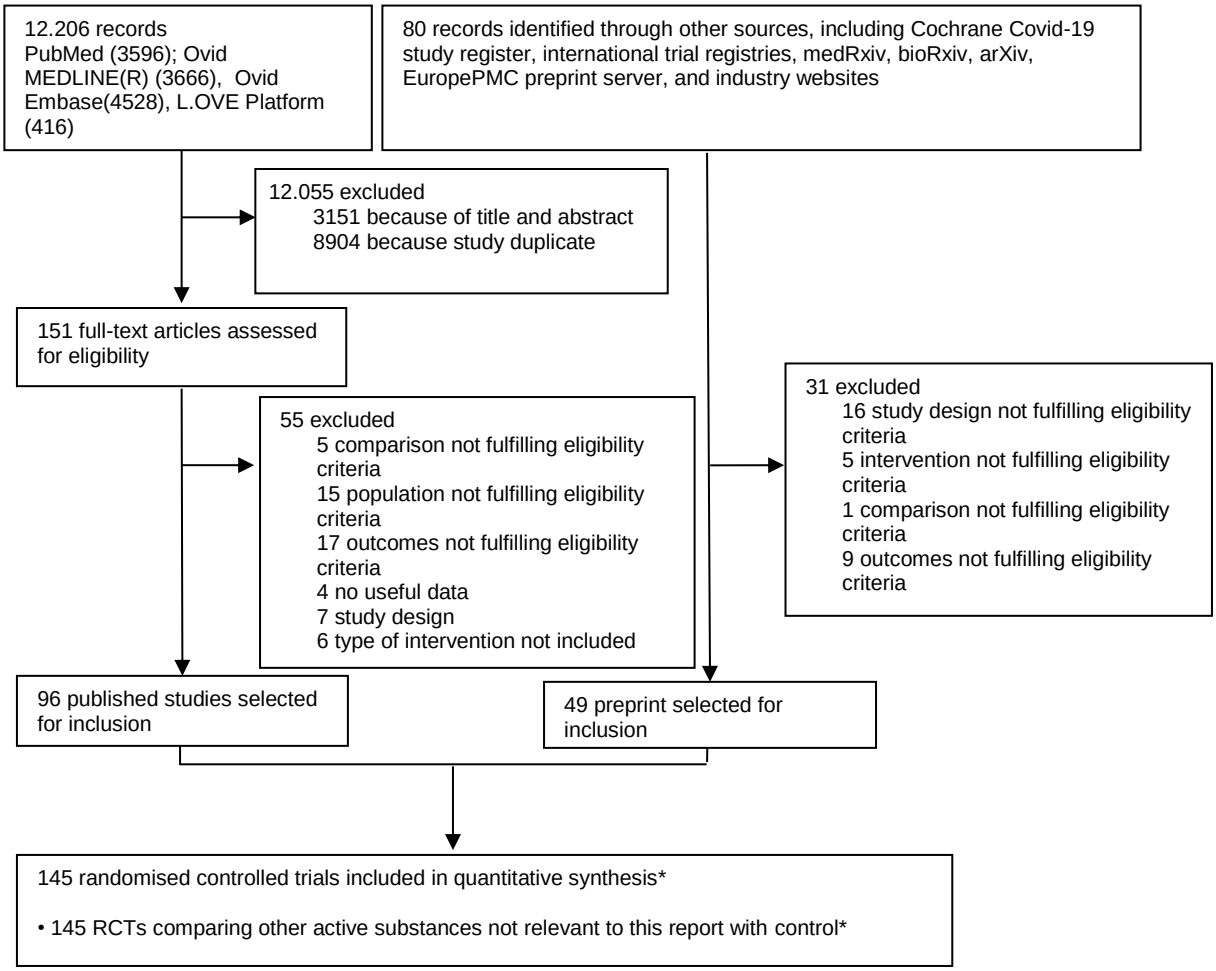
KCE is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and camostat are described in Table 6-3. In addition Google search is performed weekly for recent hits for “camostat”. Local trial registries are checked 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.

**Table 6-3 Search strategy to identify ongoing studies**

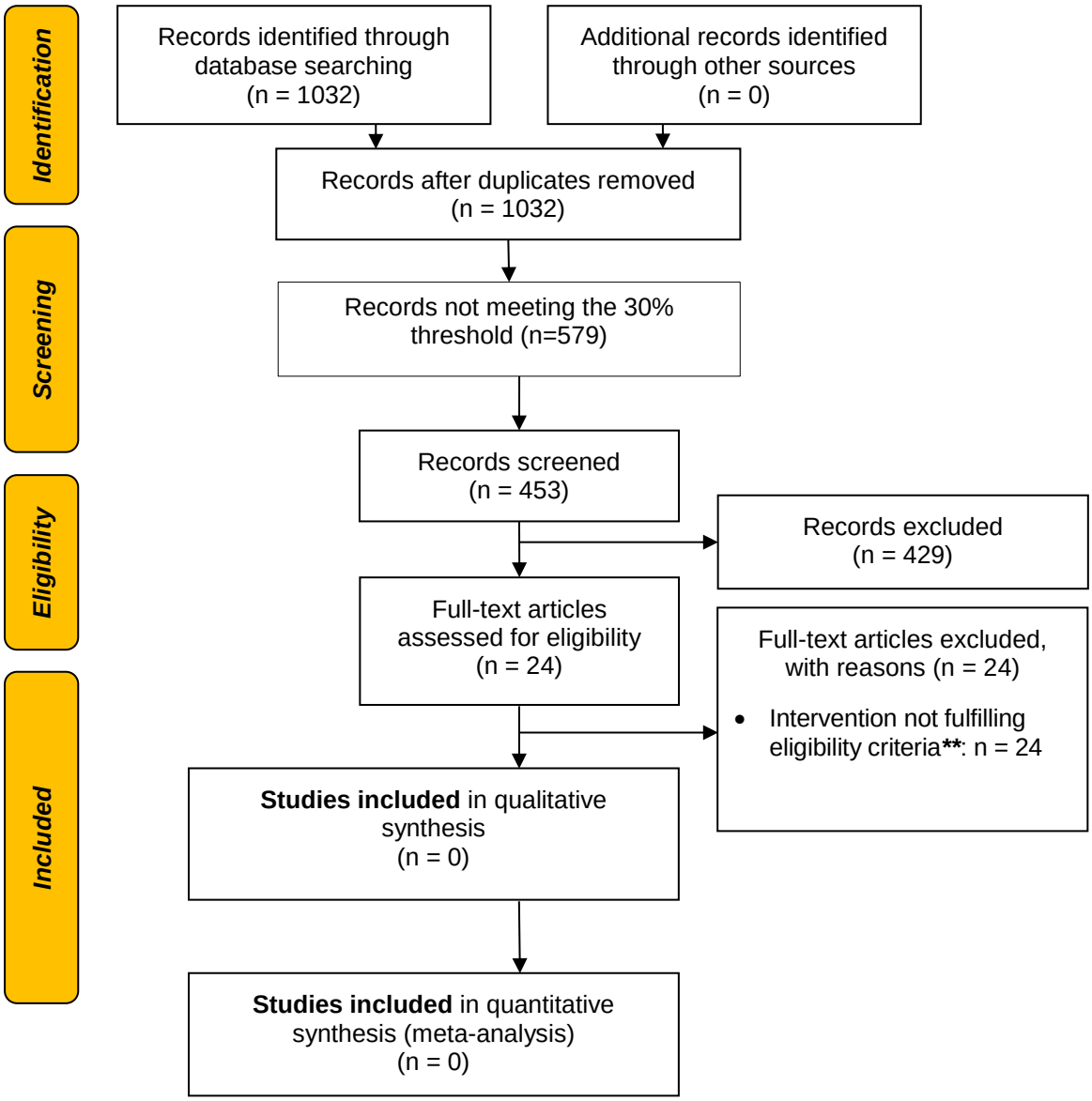
| Database | URL | Search line / search terms | Date of search | Hits retrieved |
|---|---|---|---|---|
| ClinicalTrials.gov | https://clinicaltrials.gov/ | “Basic search mode*”<br>Terms used at Condition or disease:<br>• covid-19<br>Terms used at “other terms”:<br>• camostat | 11/5/2021 | 25 hits<br>0 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)<br>0 new |
| ISRCTN | https://www.isrctn.com/ | Advanced search mode<br>Search terms:<br>1. Camostat | 11/5/2021 | 0 |
| European Clinical Trials Registry | https://www.clinicaltrialsregister.eu/ | Basic search mode<br>Search terms:<br>1. covid-19 and camostat | 11/5/2021 | 6<br>0 new |

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

### *6.4 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