Final Study Report

Study Title: *The potential of oral Camostat in early COVID-19 disease in an ambulatory setting to reduce viral load and disease burden*

EU reference number: *2020-003475-18*

Clinical Investigation identification number (CIV ID): *NA*

Study protocol/CIP code: *COV-AAT*

Investigational device / medicinal product: *Camostat mesilate (Foipan)*

ClinicalTrials.gov identifier: *NCT04625114*

Sponsor: *Ghent University Hospital*

Contact details sponsor: *General Internal Medicine, PI Dr. Marie-Angélique De Scheerder, marie-angelique.descheerder@uzgent.be*

National Coordinator/ Coordinating Investigator: *Dr. Marie-Angélique De Scheerder, marie-angelique.descheerder@uzgent.be*

Funder: *Ono Pharmaceuticals Co. Ltd. (Osaka, Japan) provided the study drug, camostat mesylate. Byteflies (Antwerp, Belgium) provided telemonitoring devices and technological support. No further funding was received.*

Author:
Els Tobback, Sophie Degroote, Sabine Buysse, Liesbeth Delesie, Lucas Van Dooren, Sophie Vanherrewege, Cyril Barbezange, Veronik Hutse, Marta Romano, Isabelle Thomas, Elizaveta Padalko, Steven Callens, Marie-Angélique De Scheerder

Date of report: *2022/10/21*

By signing this final study report, I acknowledge that the information is accurate and complete.

Name and signature Coordinating Investigator: *Dr. Marie-Angélique De Scheerder* .....

Date signature Coordinating Investigator: *2022/10/21*.....

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1. Introduction

Covid-19 discovered at the end of 2019 quickly turned into a global pandemic and caused severe respiratory symptoms in a substantial amount of people with an increased mortality. Due to its high contagiousness, the pandemic caused by the SARS-CoV-2 coronavirus poses a major threat to public health. At the start of this study, no therapeutic intervention had been proven to be efficient in the treatment of this disease and prevention of severe acute respiratory distress.

We propose the use of Camostat, an antiviral drug with potential effects on viral entry of the SARS-CoV-2 virus as shown by in vitro data (Hoffman et al, 2020). Camostat Mesilate is a serine protease inhibitor, licensed for the treatment of chronic pancreatitis in Japan. Camostat inhibits the host cell serine protease TMPRSS2, needed to prime viral protein S for cell entry.

An important point for the use of antiviral drugs in COVID-19 disease is that their effect is to be expected in the early stages of disease. By reducing viral replication early, we hypothesize to prevent progression towards the second phase of infection which is characterised by increase inflammation and cytokine release, mostly responsible for the bad outcome in infected patients (Popov, 2020). Therefore, it seems only logical to provide these antiviral drugs at the early stage of infection, preferentially in an outpatient setting.

We could also hypothesize that in a further stage, these drugs might be of interest to provide prophylaxis to highly exposed, non-immunised individuals eg family members, healthcare workers etc.

The goal of this study is to provide substantial data on the efficacy (in terms of viral clearance), safety and compliance of Camostat. This will allow us to assess the interest of this drug in larger ambulatory trials.

2. Objectives of the study

The aim of the study is to assess whether Camostat, a serine protease inhibitor available in an oral formulation, has the potential to be studied as an antiviral drug in a large scale ambulatory setting to prevent transmission by decreasing viral load, to prevent symptoms after exposure in asymptomatic individuals or to prevent disease progression in the occurrence of early symptomatology.

2.1 Primary objectives

The primary aim is to assess efficacy of the drug in terms of viral load changes at day 5 (D5) compared to baseline in nasopharyngeal swabs. Cycle threshold (CT) values will be used as a surrogate for viral load.

Descriptive objectives are to assess the safety and compliance of the drug in ambulatory setting.

2.2 Secondary objectives

To estimate the clinical outcome of patients based on daily clinical scales.

To estimate the effectiveness of the drug to prevent hospitalization, intensive care hospitalization, oxygenation and death at D14 and D28.

Screening failures substudy: to estimate whether asymptomatic COVID positive individuals with high CT values, not eligible for the drug administration, can transmit the virus and therefore should be isolated and whether they develop antibodies despite their mild infection.

3. Investigational Medicinal Product

IMP: Foipan 100 mg tablets, active substance camostat mesilate 100 mg

Producer and distributor: Ono Pharmaceutical LTD (Japan)

Dosage and administration: Camostat Mesilate (Foipan) 100mg, 3 tablets, 3 times a day (daily dose of 900mg). After inclusion the patient will receive medication for 5 days of treatment (= 45 tablets). The patient will take the medication at home. Oral administration. Fasting state (minimum 60 minutes before the next meal and 2 hours after the previous meal). At D5, the patient will bring the empty bottle and leftover tablets to the consultation visit.

If the treatment is extended to 10 days (if a positive PCR at D5 and/or presence of clinical symptoms), the patient will receive medication at D5 for 5 days of treatment (= 45 tablets). He will take the medication at home and orally in a fasting state (minimum 60 minutes before the next meal and 2 hours after the previous meal). At D10, the patient will bring the empty bottle and leftover tablets to the consultation visit.

Packaging and labeling: Repackaging, labeling, blinding and randomization will be performed by the Pharmacy of Ghent University Hospital.

The Foipan® tablets will be repackaged per 45 tablets (5 consecutive dosing days). Primary packaging, blinding and randomization will be performed in accordance with Circular 596 (of the FAMHP) on the production and distribution activities for experimental medicines. Labelling will be performed compliant to Eudralex volume 4, annex 13.

Storage conditions: The Foipan® tablets must be shipped and stored under the recommended storage conditions (room temperature), locked with restricted access. Temperature excursion will be handled conform local procedures. After repackaging by the pharmacy, the tablets will be stored at the investigators site (internal medicine department) under the same conditions until they are given to the patients. IMP accountability and inventory logs will be kept up-to-date at the investigators site (internal medicine department). Patients are instructed to store the medication under the recommended storage conditions (room temperature). Reconciliation of used/unused IMP will be performed by the unblinded study nurse. At the end of the trial, unused IMP will be discarded conform local procedure by the study nurse.

Placebo: Lactose tablets 500 mg

Producer and distributor: Fagron

Dosage and administration: Placebo tablets are used in the purchased form. There will be no additional preparation. Only repackaging will be conducted at the local pharmacy.

Lactose 500 mg, 3 tablets, 3 times a day (daily dose of 4,5 g).

After inclusion the patient will receive medication for 5 days of treatment (= 45 tablets). The patient will take the medication at home. Oral administration. Fasting state (minimum 60 minutes before the next meal and minimum 2 hours after the previous meal). At D5, the patient will bring the empty bottle and leftover tablets to the consultation visit.

If the treatment is extended to 10 days, the patient will receive medication at D5 for 5 days of treatment (= 45 tablets). He will take the medication at home and orally in a fasting state (minimum 60 minutes before the next meal and minimum 2 hours after the previous meal). At D10, the patient will bring the empty bottle and leftover tablets to the consultation visit.

Packaging and labeling: Repackaging, labeling, blinding and randomization will be performed by the Pharmacy of Ghent University Hospital.

The placebo tablets will be repackaged per 45 tablets (5 consecutive dosing days). Primary packaging, blinding and randomization will be performed in accordance with Circular 596 (of the FAMHP) on the production and distribution activities for experimental medicines. Labelling will be performed compliant to Eudralex volume 4, annex 13.

Storage conditions: The Placebo tablets must be shipped and stored under the recommended storage conditions (room temperature), locked with restricted access. Temperature excursion will be handled conform local procedures .After repackaging by the pharmacy, the tablets will be stored at the investigators site (internal medicine department) under the same conditions until they are given to the patients. IMP/placebo accountability and inventory logs will be kept up-to-date at the investigators site (internal medicine department). Patients are instructed to store the medication under the recommended storage conditions (room temperature). Reconciliation of used/unused study medication will be performed by the unblinded study nurse. At the end of the trial, unused placebo will be discarded conform local procedure by the study nurse.

4. Investigational Medical Device

NA

5. Study Protocol Summary

5.1 Study design

Phase 2 clinical trial

A randomized, placebo controlled, double blinded, prospective trial to assess the efficacy and safety of Camostat, by inhibiting S protein-initiated membrane fusion in the treatment of early phase COVID 19 disease in an ambulatory setting.

5.2 Inclusion criteria

- *Aged ≥18*
- *Willing to participate and fill out a daily symptom diary*
- *Willing to take the parameters such as blood oxygenation and temperature*
- *Willing to attend follow-up visits both by phone as at the clinic*
- *Capable of understanding the commitment in the trial*
- *Signed informed consent*
- *Signs and symptoms suggestive of COVID disease in absence of hospitalization criteria as defined by the flowchart used at the emergency department at Ghent University Hospital (appendix 4), present for maximum 5 days and confirmed by PCR.*

    - *OR documented COVID-19 infection by PCR with CT value below the threshold of 30 in asymptomatic individuals.*
    - *For women of childbearing potential*: they should be willing to use highly effective method of contraception during treatment and until the end of study defined as having a failure rate of less than 1% per year when used consistently and correctly.*
      Such methods include:
        - *combined (estrogen and progestogen containing) hormonal contraception*
        - *associated with inhibition of ovulation: oral, intravaginal or transdermal*
        - *progestogen-only hormonal contraception associated with inhibition of ovulation: oral, injectable or implantable*
        - *intrauterine device (IUD) and intrauterine hormone-releasing system (IUS)*
        - *bilateral tubal occlusion*
        - *vasectomised partner*
        - *sexual abstinence*
    - *For men of reproductive potential**: condom should be used as contraception during treatment and until the end of study when having a partner of childbearing potential*

**a woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.*

***a man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.*

5.3 Exclusion criteria

- *Inability to make a decision to participate*
- *Pregnant or breast feeding*
- *Inability to take oral medication*
- *Inability to provide informed written consent*
- *Known hypersensitivity towards Camostat or other Serine protease inhibitors*
- *Any condition that, in the Investigator's opinion, prevents adequate compliance with study therapy.*
- *Any COVID infection at risk for hospitalisation as described in the flowchart used at the emergency department (appendix 4)*
- *With regard to exclusion of women of child-bearing potential, women who tell us they know they are pregnant are excluded. All women of child-bearing potential who test positive for pregnancy by urine test or serum (if an early pregnancy cannot be excluded) at first visit are excluded.*
- *Severe chronic pancreatitis requiring suction of gastric juice, fasting or abstention from drinking.*
- *Postoperative reflux oesophagitis due to reflux of gastric juice*
- *Postoperative reflux oesophagitis (if improvement of symptoms is not observed).*

5.4 Primary endpoint

The primary aim is to assess efficacy of the drug in terms of viral load changes at D5 compared to baseline in nasopharyngeal swabs. Cycle threshold (CT) values will be used as a surrogate for viral load.

Descriptive objectives are to assess the safety and compliance of the drug in ambulatory setting.

5.5 Secondary endpoints

To estimate the clinical outcome of patients based on daily clinical scales.

To estimate the effectiveness of the drug to prevent hospitalization, intensive care hospitalization, oxygenation and death at D14 and D28.

Screening failures substudy: to estimate whether asymptomatic COVID positive individuals with high CT values, not eligible for the drug administration, can transmit the virus and therefore should be isolated and whether they develop antibodies despite their mild infection.

5.6 Procedures

5.7 Randomisation and blinding

A randomisation plan generator (randomisation.com) is used to allocate in a blind manner. The pharmacist performs a release of the randomisation plan. A transcription of this randomisation list in excel is reviewed and released by a second pharmacist and stored in the pharmacy file.

Printing of all the labels for the blinding is done before repackaging by an operator. Splitting of labels for active and placebo is performed by the same operator and checked and released by pharmacist.

Repackaging is performed with a copy of the transcripted randomisation list in excel and the labels (check of the labels by pharmacist) – repackaging for active and placebo is performed separately. An operator does the repackaging, a pharmacist does the check.

Repackaging records and copy of the transcripted randomisation list is filed in the pharmacy file, with no access for blinded staff.

An unblinded study nurse will allocate the medication to each participant in a chronologic way, so that when treatment is to be prolonged, the participant remains in the same treatment arm.

A sealed envelope will be available from the pharmacy with the transcripted excel sheets for the unblinded study nurse. He/she will sign for acceptance.

This will be a double blinded study. The participant will be blinded. The study nurses and physicians that are in contact with the participants will be blinded. The pharmacy is unblinded and will deliver the randomization lists. At the investigator site (department of internal medicine) 2 study collaborators will be unblinded. There will be also be two back-ups assigned for this function. They will not be in contact with the participants. Only data that is relevant for them shall be shared.

5.8 Monitoring and quality measures

After eligibility assessment participants will be randomized and will receive the study drugs. We will define D1 as the first dose of the medication which can be the morning, midday or evening dose. They will be treated for 5 consecutive days. D0 and D1 can coincide, if the participant starts taking medication on the day of inclusion.

In patients with a positive PCR at D5 (CT value with threshold below 30) and/or presence of clinical symptoms after exclusion of hospitalization criteria, the treatment will be extended up to D10 at the same dosage in both treatment arms for 5 consecutive days: D6→D10).

Follow-up will be as follows:

- *D1→D14: The study participants will be asked to fill in daily questionnaires assessing symptoms (cfr daily self-score). This will be extended to D28 if patients are still symptomatic at D14.*

- *D1→D5 (or D10): They will receive a kit enabling to monitor heart rate (HR), respiratory rate (RR), temperature and oxygen saturation 3 times per day (every 4-8 hours, preferentially at the timing of medication intake on D1 to D5 or D10). The home monitoring can be extended as SOC after termination of the medication, in presence of symptoms and for the period that symptoms persist.*
- *Compliance and tolerance will be assessed during the treatment period, D0→D5 (or D0→D10 if the treatment is prolonged).*
- *During the study D1-D28: If indicated in the opinion of the investigator, a physical exam and biochemistry will be performed through a consultation at the clinic. This can be requested at any time during the study based on clinical symptoms or signs.*
- *Consultation at D0, D5, (D10) and D28 at our COVID consultation facility. This will be done by a study nurse and/or a study physician.*

At D0 (screening and inclusion) a standardized history, clinical exam will be performed, including blood pressure (BP), heart rate (HR), respiratory rate (RR), blood oxygen saturation, temperature. Socio-demographic parameters such as age, gender, treatment, smoking status, BMI, diabetes, race and comorbidities will be assessed. If unavailable, a COVID screening test will be performed to confirm COVID 19 infection. A baseline lab for toxicity will be done at D0 (max 21ml.)

In case of negative screening test and suggestive clinical picture as described above, the test can be completed with additional blood analysis, arterial blood gas and/or lung imaging to assess the probability of COVID-19. The additional tests are standard of care. It is the treating physician who will decide whether these test are valuable. In this case the study physician can decide to rescreen the patient (with PCR) after minimum 24h and within the 5 days of occurrence of symptoms.

The medication will be initiated as soon as possible after inclusion and randomisation. We will define D1 as the first dose of the study medication at whatever point of time during that day. Thus, D0 and D1 can coincide (if the participant starts taking medication on the day of inclusion).

At D1 up to D14 (or until D28 if they still have symptoms at D14), participants will be asked for the presence of symptoms and signs by a questionnaire and to monitor temperature, blood oxygen saturation, heart rate and respiratory rate.

If indicated in the opinion of the investigator, a physical exam and biochemistry will be performed through a consultation at the clinic. This can be requested at any time during the study based on clinical symptoms or signs.

At D5 a scheduled study visit is planned with a clinical exam including BP, RR, HR, temperature, blood oxygen saturation. Nasopharyngeal (or combined nose/throat) swab will be taken for PCR. A toxicity screening will be performed through venous blood draw (max 21ml). At the day of consultation the time point at the hospital will replace the monitoring measurement at home.

At any given time between D1 and D28 an additional blood draw (max. 21 ml) can be asked by the study team to assess severity of infection (peripheral blood count, inflammation, electrolytes, kidney and liver function.) If CRP values are available at baseline or during follow-up, they will be analyzed as part of the study, however they will only be performed as

SOC. If HRCT or a lung X ray are available at baseline or follow-up, they will be analysed as part of the study, however they will only be performed as standard of care.

At D28 an additional blood draw (9 ml) will be done for neutralizing antibodies (NAbs) titer assessment.

At D10 an additional study visit will be planned in individuals that are retested with positive PCR at D5 and when treatment is prolonged after D5 up to D10. This will include a clinical exam including BP, RR, HR, temperature, blood oxygen saturation. At the day of consultation the time point at the hospital will replace the measurement at home. Also, a toxicity screening will be performed through venous blood draw (max 21ml) if any significant abnormalities occurred at D5 (Grade 1-2 adverse events according to CTCAE classification).

At D10 and D28 an additional nasopharyngeal swab or combined nose/throat swab will be performed in individuals that still had a positive PCR result at day 5 and D10 respectively.

Questionnaires will be sent through email and can be filled in online and transferred directly to the eCRF or will be filled in on paper and handed to the study personnel at the time of consultation.

Home monitoring of heart rate, respiratory rate, temperature and oxygen saturation will be done through a kit provided by Byteflies. A manual with usage instructions will be delivered to the patients. The patient will be asked to register these parameters 3 times a day through an online platform. If they are unable to register the parameters themselves, a back-up through email or phone can be proposed. If these parameters are not within normal range as defined by cut-off criteria, the system will ask either to remeasure or to contact the study-team based on the reported values. The study medication will be interrupted in participants that meet hospitalization criteria.

Screening failure substudy: Asymptomatic individuals with positive PCR and high CT values that are not eligible for the clinical trial and drug administration, but who otherwise meet all in- and exclusion criteria, can participate in a substudy, where we want to see whether these individuals, despite their high CT values and therefore low viral load can carry viable virus and therefore can transmit the disease. This implicates whether or not they should be isolated. Furthermore, in individuals with low viral load there is a possibility that they do not develop antibodies against SARS-CoV-2. Therefore we want to 1) culture virus from throat/nose swabs from these individuals at D0 2) measure antibodies at D28.

6. Study analysis

Sample size calculation: The sample size calculation is based on the primary outcome of interest: change in log 10 respiratory (nasopharyngeal (or combined nose/throat) swab RT-PCR) viral load from baseline (D0) day 5 (D5) post-randomization. Given the limited data on the variability of the change in log 10 viral load, we have powered the study based on detecting

a moderate standardized effect size of 0.3 using an analysis of covariance (ANCOVA), adjusting for baseline log 10 viral load. To put into context, one scenario that would produce a 0.3 standardized effect size would be a change of 4 in log 10 viral load in the camostat mesilate group compared to a change of 1 in log 10 viral load in the placebo group assuming a standard deviation of 5.0.

(NOTE: For ANCOVA, the effect size is the standard deviation of the treatment means divided by the pooled standard deviations of the observations.) To be conservative we assume a R-squared of 0 between the log 10 viral RNA at 2-days and baseline log 10 viral RNA. With a power of 90%, and a type I error rate of 5% (2-sided) and a 2:1 randomisation, we would be able to detect the hypothesized 0.3 standardized effect size with 132 total patients - 88 patients versus 44 patients in 2:1 randomization. Increasing this sample size by 15%, 5% for an efficacy and futility look at 50% information (i.e. when half of the patients have been enrolled) and 10% to account for loss to follow up, gives a total of 150 participants (100:50).

When recruitment dropped significantly (no inclusions for more than 2 weeks), we decided to interrupt the inclusion to perform an interim analysis according to the study protocol. The data of 90 participants, being 68.2% of the totally intended inclusion number were analysed. All included participants got a full follow-up until V28.

Statistical analyses: Data were analysed with SPSS 28 IBM Corporation, Armonk NY, USA. The distribution of numerical data was checked for normality. Means and standard deviations (SD) were calculated in case of normal distribution; median and interquartile range (IQR) for data that were not normally distributed. Proportions are presented for categorical data. Differences between both treatment groups were tested using the unpaired Student's t-test or Mann-Whitney U test for numerical data and Chi square test for categorical variables. Differences in Ct between V1 and V5 within each treatment arm were tested using the Wilcoxon or paired Student's t-test.

Change in Ct between day 1 and day 5 was compared using a linear mixed-effects model with random intercepts for participant. Estimates for change in Ct for camostat compared to placebo and corresponding 95% confidence intervals for the linear models were reported.

A Kaplan Meier curve was constructed for time to clinical improvement. Hazard ratios with 95% confidence intervals (CI) were estimated by Cox proportional-hazards model with and without adjustment for potential confounders. Patients were censored at time of last assessment or at end of trial. A two-sided α value of less than 0.05 was considered significant.

7. Independent Ethics Committee and Competent Authority

The study has been approved by the Ethics Committee.

OVERVIEW APPROVED DOCUMENTS		
Initial submission: - *Protocol version 1.2, dd. 13OCT2020* - *ICF version 1.1, dd. 13OCT2020* - *Appendix 1 study schedule version 1.2, dd.13OCT2020* - *Appendix 2 questionnaire daily self-score* - *Appendix 3 socio-demographic parameters version 1.0, dd. 19AUG2020* - *Appendix 4 emergency ward flowchart* - *Appendix 5 byteflies manual version 1.0, dd. 19AUG2020* - *Appendix 6 parameter log version 1.0, dd. 19AUG2020* - *Appendix 7medication log version 1.0, dd. 19AUG2020* - *Appendix 8 cut offs version 1.2, 13OCT2020* - *Appendix 9 DSMB charter version 1.2, dd. 14SEP2020* - *Appendix 10 toxicity lab version 1.0, dd. 13OCT2020*	***Approval date Central EC:*** *21OCT2020* ***Approval date FAMPH:*** *23SEP2020*	*Initial version as approved by the Ethics Committee and the Federal Agency for Medicines and Health Products.*
Amendment 1: - *Protocol version 2.0, dd. 26NOV2020* - *ICF version 2.0, dd. 26NOV2020* - *Appendix 1 study schedule version 2.0, dd.26NOV2020* - *Appendix 9 DSMB charter, dd. 23NOV2020* - *Annex 1: Clinical trial Application Form dd. 09DEC2020* - *Annex 2: Substantial Amendment Notification Form 09DEC2020* - *IMP label version 2.0* - *Recruitment material, affiche A4, A3 dd. NOV2020, tekst social media dd. 26NOV2020* - *Patient card version 2.0, dd. 26NOV2020*	***Approval date Central EC:*** *10DEC2020* ***Approval date FAMPH:*** *29OCT2020*	1. *Change of PI/CI to Prof Steven Callens* 2. *Some changes concerning follow-up and analysis methods:* - *Extra recruitment materials en methods have been added, section* ***Fout! Verwijzingsbron niet gevonden.*** - *Trial conduct in case of hospitalization has been adjusted from patient withdrawal to further study follow-up, section* ***Fout! Verwijzingsbron niet gevonden.*** *and* ***Fout! Verwijzingsbron niet gevonden.*** - *Patient home monitoring period was adjusted from 14 days to the period of intake of study medication (5 or 10 days), section* ***Fout!***

		Verwijzingsbron niet gevonden. - *Protocols for analysis were adjusted based on current practice for PCR and PK/PD, section* ***Fout! Verwijzingsbron niet gevonden.*** - *The gradation of AEs was detailed and references were added* *Clarifications have been added in the section about safety reporting, section* ***Fout! Verwijzingsbron niet gevonden.***
Amendment 2: - *Protocol version 2.1, dd. 02FEB2021* - *ICF version 2.1,, dd. 2FEB2021* - *Annex 1: Clinical trial Application Form dd. 05FEB2021*	***Approval date Central EC:*** *22FEB2021* ***Approval date FAMPH:*** *10FEB2021*	*Clarification was given concerning the discontinuation of treatment and its implication on study follow-up compared to study withdrawal, section* ***Fout! Verwijzingsbron niet gevonden.***
Amendment 3: - *Protocol version 3.0, dd. 04JUN2021* - *ICF version 3.0, dd. 04JUN2021* - *Annex 1: Clinical trial Application Form version 3.0 dd. 04JUN2021* - *Annex 2: Substantial Amendment Notification Form 05JUL2021* - *Recruitment material, flyer dd. 01MAY2021*	***Approval date Central EC:*** *13JUL2021* ***Approval date FAMPH:*** *5JUL2021*	1. *The option to conduct an interim analysis has been added to the protocol, section* ***Fout! Verwijzingsbron niet gevonden..*** 2. *Recruitment strategy has been further explained in section* ***Fout! Verwijzingsbron niet gevonden.*** *to tackle potential pitfalls. The COVID-19 test centre at Ghent University Hospital added the possibility to question patients on their consent to be contacted by the study team, flyers are available in the test centre and when patients that tested positive for COVID-19 are called to inform them about their results, study interest is interrogated.*

		3. *Clarification on the possibility of simultaneity of the time-points D0 and D1, section* ***Fout! Verwijzingsbron niet gevonden.***. 4. *The role of the PI concerning verification of data input of the eCRF has been modified based on clinical practice, section* ***Fout! Verwijzingsbron niet gevonden.***. 5. *The option of serum HCG testing to exclude pregnancy has been added, section* ***Fout! Verwijzingsbron niet gevonden.***. *Premature closure of the substudies is being reported, sections* ***Fout! Verwijzingsbron niet gevonden.***, ***Fout! Verwijzingsbron niet gevonden.*** *and* ***Fout! Verwijzingsbron niet gevonden.***.

8. Results

8.1 Subject enrollment and demographics

Between November 2020 and June 2021, a total of 108 participants were enrolled in the study (first patient first vist: 6NOV2020; last patient last visit: 24JUN2021). Out of these, 12 subjects did not meet the inclusion and exclusion criteria and were excluded from randomization. A total of 96 participants received either camostat mesylate (N=66) or placebo (N=30). Treatment was immediately interrupted in 4 subjects that had to be hospitalized due to clinical deterioration (Table 3). Two other subjects chose to withdraw from the study. Analyses were performed on the data of 90 participants who completed treatment (N=61 camostat mesylate, N=29 placebo, Figure 1).

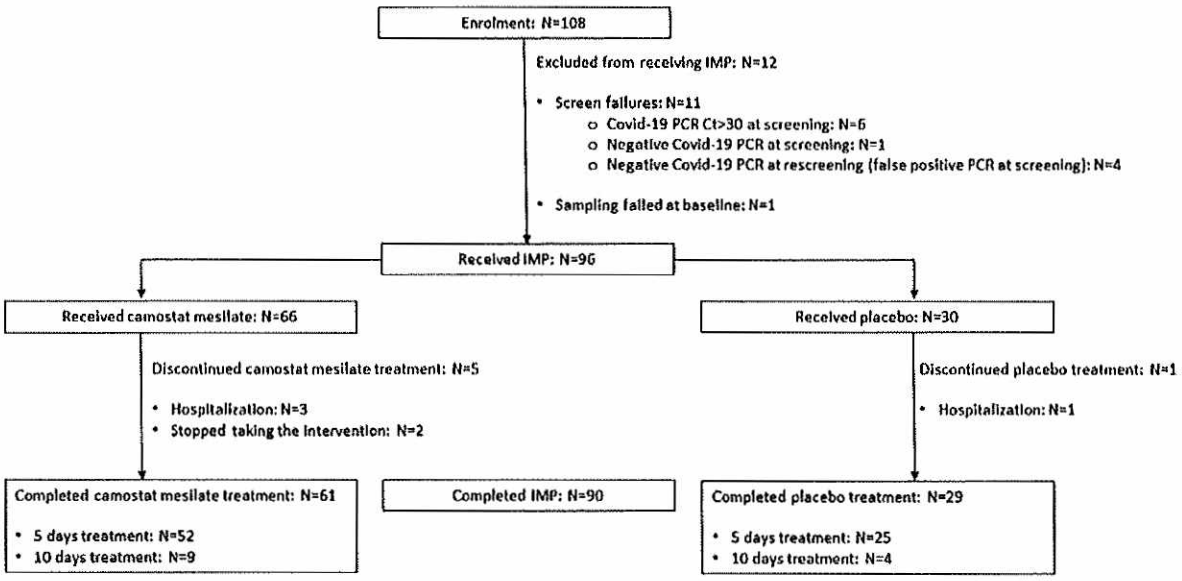

Figure 1. Flow diagram

Most of the participants (N=78, 86.7%) were recruited actively by the study team. In total, 49 participants (54.4%) were female. Median age was 40 (range 19 to 70 years.). Seventy-seven (85.6%) subjects showed symptoms at V1, included coughing (N=68, 79.1%), asthenia (N=64, 74.4%), sneezing (N=62, 72.1%), stuffy nose (N=56, 65.1%) and abnormal sense of smell or taste (N=17, 19.8%). Significant differences in baseline characteristics were not observed between the camostat mesylate and placebo group (p>0.05, Table 1). Covid-19 first vaccination dose was received by 3 patients prior to enrolment and by 3 subjects during the study period. One subject received 2 doses prior to enrolment.

Because of persistent symptoms at V5, IMP treatment was extended up to day 10 for 10 patients (16.4%) who received camostat mesylate and for 4 (13.8%) who received placebo.

The study specific results (see 8.2) did not show evidence that camostat mesylate under the present conditions (300 mg three times daily for 5 or 10 consecutive days, fasted state) is effective as an antiviral drug against SARS-CoV-2. As a result of these interim analyses on 68.2% of the totally intended inclusion number (90 vs 132 participants), it was decided to definitely end the trial (dd. 12JUL2022).

Table 1
Baseline characteristics of participants who completed study treatment.

Characteristics	Total sample N=90	Camostat mesilate N=61	Placebo N=29	p
Median age (IQR), years	40 (24-53)	38 (25-53)	37 (22-51)	0.434
Female gender, N (%)	49 (54.4)	33 (54.1)	16 (55.2)	1.000
Type of recruitment, N (%)		50 (82.0)	28 (96.6)	0.057
Active	78 (86.7)	11 (18.0)	1 (3.4)	
Passive	12 (13.3)			
Symptomatic at baseline, N (%)	77 (85.6)	51 (83.6)	26 (89.7)	0.446
Cough	68 (79.1)	44 (77.2)	24 (82.8)	0.549
Sneeze	62 (72.1)	40 (70.2)	22 (75.9)	0.578
Abnormal sense of smell or taste	17 (19.8)	12 (21.1)	5 (17.2)	0.675
Asthenia	64 (74.4)	44 (77.2)	20 (69.0)	0.408
Stuffy nose	56 (65.1)	35 (61.4)	21 (72.4)	0.311
Mean body mass index ± SD, kg/m²	24.2 ± 3.0	23.8 ± 2.8	25.0 ± 3.9	0.021
Obesity, N (%)	6 (6.7)	2 (3.3)	4 (13.8)	
Smoking behaviour, N (%)	28 (31.1)	19 (31.1)	9 (31.0)	0.991
Smoked in the past	15 (16.7)	10 (16.4)	5 (17.2)	0.920
Smokes currently				
Comorbidities, N (%)	2 (2.2)	1 (1.6)	1 (3.4)	0.586
Diabetes	1 (1.1)	1 (1.6)	0 (0)	0.488
Cancer	6 (6.7)	4 (6.6)	2 (6.9)	0.952
Hypertensia				
Use of medication, N(%)	6 (6.7)	6 (9.8)	0 (0)	0.080
Antihistamins	59 (65.6)	40 (65.6)	19 (65.5)	0.996
Analgesics/antipyretics	7 (7.8)	5 (8.2)	2 (6.9)	0.830
Covid-19 vaccination				
Clinical parameters	77.6 ± 14.1	77.5 ± 15.0	77.9 ± 12.3	0.706
Mean heart rate ± SD, beats per minute	98.1 ± 1.2	98.2 ± 1.1	98.0 ± 1.2	0.901
Mean arterial oxygen saturation ± SD, %	36.5 ± 0.8	36.4 ± 0.9	36.7 ± 0.8	0.538
Mean body temperature ± SD,°C				
Viral load in nasopharyngeal swab (rescreening PCR)	17.8 (15.6-21.2)	17.4 (15.6-21.2)	18.4 (15.3-21.2)	0.988
Median cycle threshold (IQR)				
Blood parameters	1200 (938-1635)	1190 (930-1548)	1200 (962-1750)	0.367
Median lymphocyte count (IQR), /L	2280 (1753-2940)	2240 (1735-2920)	2320 (1768-3010)	0.756
Median neutrophil count (IQR), /µL	29 (13-48)	26 (12-47)	39 (18-69)	0.069
Median C-reactive protein (IQR), mg/L	270 (270-350)	270 (270-385)	270 (270-310)	0.131
Median D-dimers (IQR), ng/mL	1800 (1540-2073)	1780 (1540-1950)	1980 (1565-2150)	0.115
Median lactic acid dehydrogenase (IQR), U/L				

8.2 Study specific results

Primary endpoint

The presence of SARS-CoV-2 E-gene was measured at baseline and at V5. The median CT was 17.8 at baseline and 22.7 at V5, comparable between the camostat and placebo group (Figure 2). Whereas the CT value increased for most patients between both visits, this value decreased within this time frame for 11 participants (7 out of the camostat and 4 out of the placebo group). This subgroup of 11 subjects showed no or only recent symptomatology (0 - 2 days) at enrolment, whereas the median time from symptom-onset to enrolment was 3 days (IQR 1 – 4) for the whole study population. The estimated mean change in CT between day 1 and day 5 between the camostat and placebo group was 1.183 (p=0.511). Potential risk factors for worse Covid-19 disease did not impact on change in CT (aged 60+, p= 0.684; obesity, p=0.087; smoking in the past, p=426; smoking currently, p=795; hypertension, p=0.266; diabetes, p=0.266). Covid-19 vaccination as well had no effect on CT change (p=0.942).

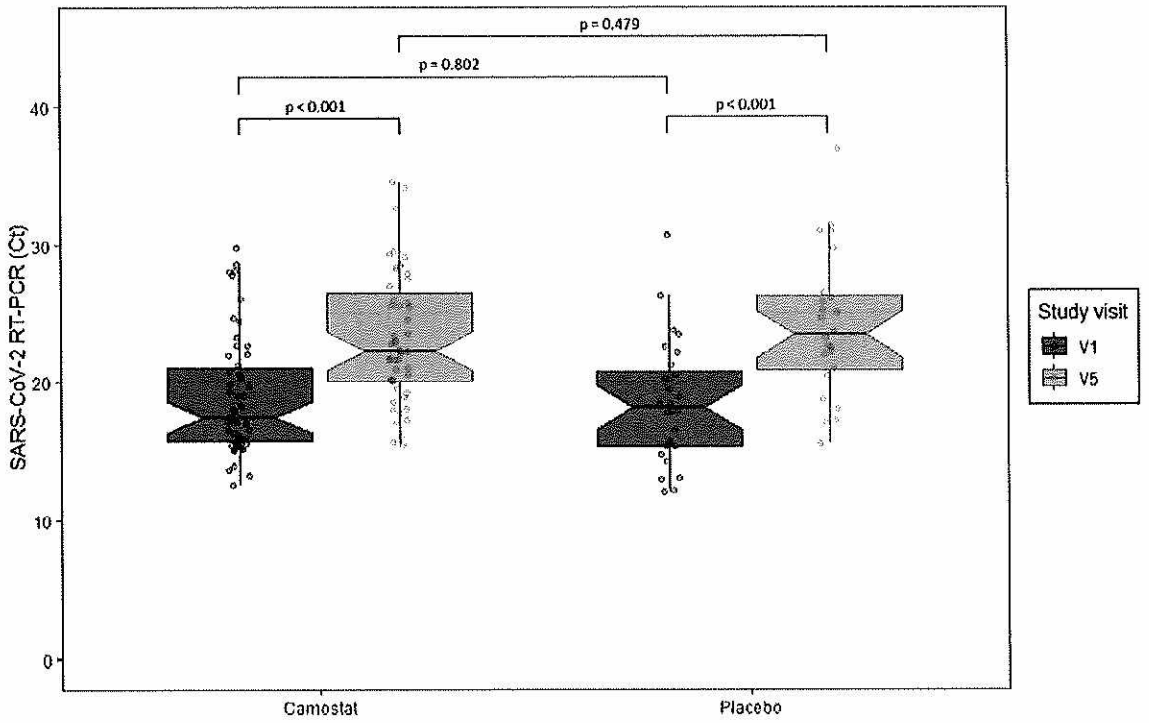

Figure 2. Polymerase chain reaction (PCR) cycle threshold (Ct) values at baseline (V1) and day five visit (V5). Each data point represents the Ct value from one patient in the camostat mesylate versus the placebo group. A lower Ct value corresponds to a higher viral load.

Secondary endpoints

Out of 90 subjects who completed treatment, 4 did not fill out the questionnaire at baseline and consequently, the data of 86 participants were included in the survival analysis. The top 5 self-reported symptoms during the whole study period were coughing, asthenia, sneezing, stuffy nose and abnormal sense of smell or taste. A total of 35 participants (40.7%) experienced a clinical improvement in at least 1 point on the 5-point Likert scale: 22 (38.6%) in the camostat group and 13 (44.8%) in the placebo group. The Kaplan-Meier curve curve for time to clinical improvement is shown in Figure 3. The unadjusted hazard ratio for clinical improvement in the camostat group was 0.965 (95% CI, 0.480 to 1.942, p=0.921 by Cox regression). The hazard ratio adjusted for age was 1.083 (95% CI, 0.534 to 2.195, p=0.826). Other variables did not influence clinical improvement (gender, p=0.641; aged 60+, p=0.483; BMI, p=0.618; obesity, p=0.209; smoking in the past, p=0.227; smoking currently, p=0.354; hypertension, p=0.391; diabetes, p=0.286; Covid-19 vaccine, p=0.405, time from symptom-onset to first visit, p=0.579).

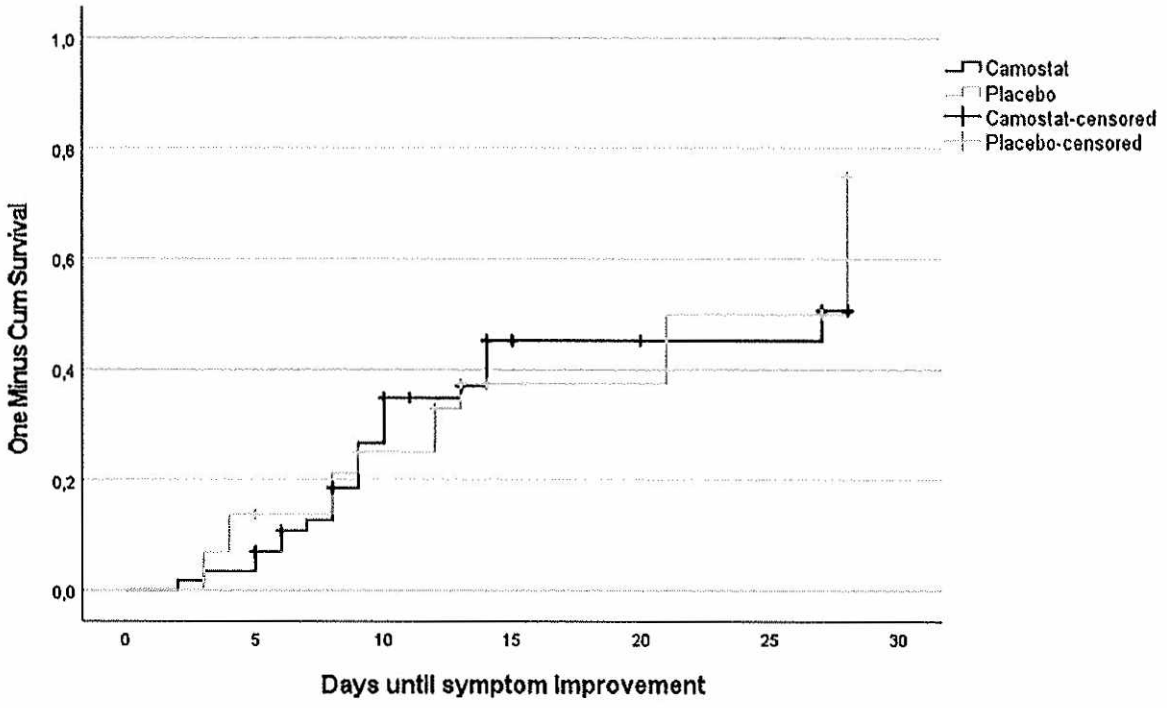

Figure 3. Kaplan-Meier curve for time to clinical improvement

Sampling for NAbs assessment was performed at V28 (median day 28, IQR 28-30). Out of 90 participants, 30 (33.3%) showed a 50% neutralizing antibody titer (NT_{50}) value below 40, comprising of 23 out of 61 (37.7%) in the camostat mesylate and 7/29 (24.1%) in the placebo group. Sixty participants (66.6%) showed a NT_{50} higher than the detection limit (≥40). The percentage distribution was not significantly different between the camostat mesylate and the placebo group (Figure 4, p=0.091). Six out of 7 subjects that received at least one vaccination dose against Covid-19 showed a NT_{50} higher than the detection limit (≥40).

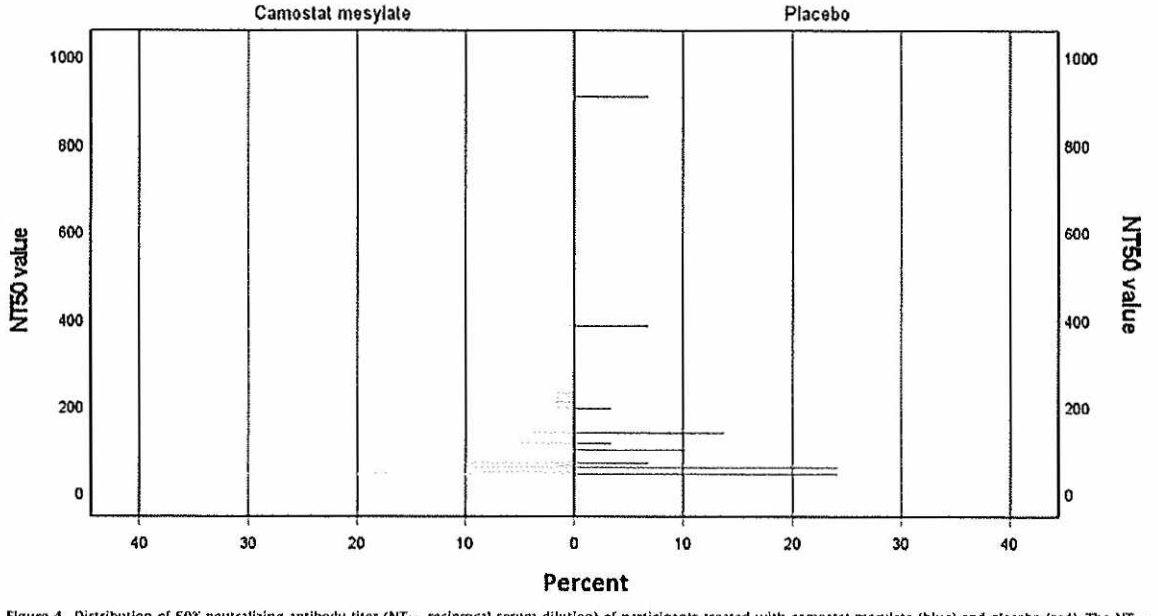

Figure 4. Distribution of 50% neutralizing antibody titer (NT_{50}, reciprocal serum dilution) of participants treated with camostat mesylate (blue) and placebo (red). The NT_{50} value of 40 is the detection limit, and values determined to be less than 40 are treated as 40.

9. Safety

A total of 82 (91.1%) patients, out of 90 participants who completed treatment, experienced adverse events during the trial, 59 (96.7%) in the camostat mesylate group and 23 (79.3%) in the placebo group (Table 2). Four participants were hospitalized following progressive disease, and unrelated to the study medication (Figure 1, 4 SAEs of which 0 SUSARs). SAEs were reported to the EC and Ono Pharmaceuticals Co. Ltd within 24 hours of awareness of the event (Table 3).

Table 2
Adverse events of participants who completed study treatment.

Adverse event, N (%)	Total sample N=90	Camostat mesilate N=61	Placebo N=29
fatigue	23 (25.6)	19 (31.1)	4 (13.8)
change in appetite	11 (12.2)	9 (14.8)	2 (6.9)
diarrhea	11 (12.2)	7 (11.5)	4 (13.8)
nausea	11 (12.2)	9 (14.8)	2 (6.9)
headache	7 (7.8)	5 (8.2)	2 (6.9)
flatulence	4 (4.4)	4 (6.6)	0 (0.0)
dizziness	3 (3.3)	3 (4.9)	0 (0.0)
constipation	2 (2.2)	1 (1.6)	1 (3.4)
dry mouth	2 (2.2)	2 (3.3)	0 (0.0)
palpitations	2 (2.2)	0 (0.0)	2 (6.9)
abdominal pain	1 (1.1)	1 (1.6)	1 (3.4)
amnesia	1 (1.1)	0 (0.0)	1 (3.4)
anaemia	1 (1.1)	1 (1.6)	0 (0.0)
burping	1 (1.1)	1 (1.6)	0 (0.0)
migraine	1 (1.1)	1 (1.6)	0 (0.0)
mouth ulcer	1 (1.1)	0 (0.0)	1 (3.4)
pruritus	1 (1.1)	1 (1.6)	0 (0.0)
reflux	1 (1.1)	1 (1.6)	0 (0.0)
stomach cramps	1 (1.1)	1 (1.6)	0 (0.0)
thirst increase	1 (1.1)	1 (1.6)	0 (0.0)
weight loss	1 (1.1)	1 (1.6)	0 (0.0)
neutropenia	11 (12.2)	9 (14.8)	2 (6.9)
leucopenia	9 (10.0)	7 (11.5)	2 (6.9)
CRP increase	6 (6.7)	4 (6.6)	2 (6.9)
lymphopenia	6 (6.7)	4 (6.6)	2 (6.9)
ALT increase	5 (5.6)	3 (4.9)	2 (6.9)
ferritin increase	5 (5.6)	3 (4.9)	2 (6.9)
fibrin D dimer increase	5 (5.6)	3 (4.9)	2 (6.9)
eosinopenia	3 (3.3)	2 (3.3)	1 (3.4)
APTT increase	2 (2.2)	2 (3.3)	0 (0.0)
AST increase	2 (2.2)	2 (3.3)	0 (0.0)
ferritin decrease	2 (2.2)	2 (3.3)	0 (0.0)
gamma-glutamyltransferase increase	2 (2.2)	1 (1.6)	1 (3.4)
granulocytopenia	2 (2.2)	2 (3.3)	0 (0.0)
hyperkalaemia	2 (2.2)	0 (0.0)	2 (6.9)
INR increase	2 (2.2)	2 (3.3)	0 (0.0)
thrombocytopenia	2 (2.2)	1 (1.6)	1 (3.4)
bicarbonate decrease	1 (1.1)	0 (0.0)	1 (3.4)
calcium decrease	1 (1.1)	1 (1.6)	0 (0.0)
glucose increase	1 (1.1)	1 (1.6)	0 (0.0)
haematocrit increase	1 (1.1)	1 (1.6)	0 (0.0)
haemoglobin increase	1 (1.1)	1 (1.6)	0 (0.0)
hypereosinophilia	1 (1.1)	1 (1.6)	0 (0.0)
liver enzymes increase	1 (1.1)	1 (1.6)	0 (0.0)
lymphocytosis	1 (1.1)	1 (1.6)	0 (0.0)
platelets increase	1 (1.1)	0 (0.0)	1 (3.4)

Table 3. SAE overview

SAE Overview				
Subject ID	Study Arm (if applicable)	SUSAR (Y/N)	SAE Description	Outcome (ongoing, resolved, death, ...)
27	Arm A (Camostat)	N	severe COVID-19 pneumonia	Resolved
32	Arm B (placebo)	N	mild to moderate COVID-19 pneumonia	Resolved
61	Arm A (Camostat)	N	deterioration of COVID-19 disease	Resolved
66	Arm A (Camostat)	N	COVID-19 pneumonia and exhaustion	Resolved

10. Device deficiencies

NA

11. Protocol deviations

Eight minor and 7 major protocol deviations took place.

Minor protocol deviations (n=8)

Concerning trial assessment (n=7)

- *Medication and/or hardcopy daily likert questionnaires were lost by the patient/could not have been collected (n=4). → Registered in the electronic patient chart.*
- *D28 visit was 4 days out of window (n=1). → Reason was registered in the electronic patient chart.*
- *D28 visit was performed for patient who was hospitalized (drop-out), prior to approval of amendment 2 (n=1). → Reported as protocol deviation.*
- *Serum was not collected at D28 visit (n=1). → Reported as protocol deviation.*

Concerning safety (n=1)

- *Treatment elongation was prescribed at D5 visit. However, D5 blood analyses showed rhabdomyolysis (n=1). → The study doctor contacted the patient by phone and advised to stop the study medication immediately. .*

Major protocol deviations (n=7)

Concerning trial assessment (n=4)

- *Subjects did not show up and/or wished to withdraw from the study (drop-outs/withdrawals) (n=3). → Study material was collected, if relevant.*
- *Inability to draw blood during D1 visit (n=1). → Blood draw was tried several times, with assistance of the emergency department personnel, but failed.*

Concerning eligibility (n=3)

- *Rescreening via gene expert revealed COVID-19 negative result (n=3). → Subjects were informed about COVID-19 negative status and medication intake was immediately stopped.*

12. Discussion and overall conclusions

In this randomized, placebo-controlled phase II clinical trial, we assessed the efficacy of orally administered camostat mesylate (300 mg three times daily for 5 or 10 consecutive days) in the treatment of early phase Covid-19 in an ambulatory setting. The change in RT-PCR measured Ct-value targeting the E gene of SARS-CoV-2 was not significantly different in the camostat group compared to the placebo group from baseline to follow-up at day 5. Time to clinical improvement of the 5 most self-reported symptoms did also not differ between both treatment arms.

These findings are consistent with the randomized controlled trial performed by Gunst et al. (2021), who described the lack of positive effects of camostat mesylate treatment on efficacy outcomes including viral load and time to clinical improvement. Nevertheless, Gunst et al. (2021) targeted hospitalized patients, possibly beyond the most active stage of viral replication. In contrast, we focused on Covid-19 patients with a mild to moderate illness in the early stage of illness, as camostat mesylate inhibits viral entry into the cells in vitro (Hoffmann et al., 2020). Additionally, we used a higher treatment dose (300 mg three times daily) than administered in previous efficacy trials (200 mg three times daily; (Gunst et al., 2021, Sakr et al., 2021), to ensure sufficient plasma concentrations of camostat mesylate (Kitagawa et al., 2021). Despite these protocol adaptations, camostat mesylate did not improve clinical outcomes.

It may be hypothesized that SARS-CoV-2 enters the host cells through clathrin-mediated endocytosis, when TMPRSS2-mediated entrance is blocked by camostat mesylate (Jackson et al., 2022). If this is the case, additional inhibition of the cathepsin-mediated entry pathway might lead to a decreased infection rate and improved efficacy. Kreutzberger et al. (2021) indeed found a synergistic block of SARS-CoV-2 infection in different single cell types by the combined use of a TMPRSS2 protease inhibitor (camostat mesylate or nafamostat mesylate) and the lipid kinase inhibitor apilimod (PIKfyve kinase), which interferes with late endosomal viral traffic, or the cathepsin protease inhibitor E-64. The described 5- to 10-fold increase in efficacy of the combined use of these inhibitors in vitro, highlights the potential advantage of using this simultaneous inhibition to reduce the viral load and potentially ameliorate clinical improvement of Covid-19 patients (Kreutzberger et al., 2021).

The inhibitory effect of camostat alone or in combination may also differ between SARS-CoV-2 viral strains. The original Wuhan-Hu-1 and Alpha variants, dominant in Belgium at the time the present study was performed, together with the Delta variant seem to prefer fusion at the cell surface as shown to be primarily inhibited by a TMPRSS2 inhibitor in vitro (Willett et al., 2022). In contrast, the later emerged Omicron variant exhibits E-64 sensitivity in cell lines, indicating a preferred switch from cell surface to endosomal fusion because of genotypic change (Willett et al., 2022) and rendering the use of camostat futile.

Strengths of the present study are the follow-up of participants by means of subjective as well as objective efficacy measures and the similarity of the study population characteristics in both treatment arms (Table 1). A limitation of our study is that the study visits were scheduled within a range of different days. Nevertheless, we did control for this variance in the linear mixed-effects model analysis.

The present trial does not show evidence that camostat mesylate under the present conditions (300 mg three times daily for 5 or 10 consecutive days, fasted state) is effective as an antiviral drug against early phase SARS-CoV-2 disease. However, analysis was performed on the data of 68% of the totally calculated sample size, because the trial was discontinued when recruitment dropped significantly. Additionally, we cannot exclude the possibility that a combined treatment, blocking both the TMPRSS2- and clathrin-mediated viral entrance, might lower disease progression.

13. References

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Appendix 1: Summary of results for lay persons

1. Clinical trial identification

Het vermogen van Camostat om de virale lading en het ziekteverloop te beïnvloeden wanneer het wordt toegediend in vroege COVID-19 infectie in een ambulante setting.

The potential of oral Camostat in early COVID-19 disease in an ambulatory setting to reduce viral load and disease burden

EU reference number: *2020-003475-18*

Study protocol/CIP code: *COV-AAT*

ClinicalTrials.gov identifier: *NCT04625114*

.

2. Name and contact details of the sponsor

Sponsor: *UZ Gent, Ghent University Hospital*

Contact details sponsor: *Algemene Inwendige Ziekten, General Internal Medicine, Dr. M.-A. De Scheerder, marie-angelique.descheerder@uzgent.be*

National Coordinator/ Coordinating Investigator: *Dr. M.-A. De Scheerder, marie-angelique.descheerder@uzgent.be*

Funder: *Ono Pharmaceuticals Co. Ltd. (Osaka, Japan) leverde de studiemedicatie, Byteflies (Antwerpen, België) leverde de pakketten voor thuismonitoring. Geen andere vorm van financiering werd ontvangen.*

Ono Pharmaceuticals Co. Ltd. (Osaka, Japan) provided the study drug, camostat mesylate. Byteflies (Antwerp, Belgium) provided telemonitoring devices and technological support. No further funding was received.

3. General information

Het doel van deze studie was te beoordelen of Camostat kan gebruikt worden in de behandeling van COVID-19 in de thuissetting. We wilden bekijken of Camostat de virale lading kan verminderen en zo het risico op besmetting kan verminderen maar ook in staat is de tijd van ziekte en een ernstig verloop van de ziekte te vermijden en bijgevolg ook het aantal ziekenhuisopnames.

Camostat is een geneesmiddel dat reeds lange tijd wordt gebruikt voor de behandeling van chronische alvleesklierontsteking in Japan en wordt zeer goed verdragen door patiënten. Bovendien is het beschikbaar in tabletvorm en kan het dus gemakkelijk in thuissetting worden ingenomen.

In vitro laboratorium studies hadden de mogelijke werking van Camostat aangetoond op het SARS-CoV-2 virus door het blokkeren van de ingang van het virus in de cellen in de long.

In de huidige studie wilden we kijken of er een verschil was in de hoeveelheid virus nog aanwezig na behandeling met Camostat in vergelijking met placebo. Hiervoor hebben we de hoeveelheid virus gemeten dat aanwezig was in de neus op dag 5 na het opstarten van de behandeling. Zo wilden we onderzoeken of Camostat een effect heeft op de viruslading en bijgevolg een milder ziekteverloop kan geven, sneller herstel en minder kans om anderen te besmetten.

De studie werd uitgevoerd in het UZ Gent tussen november 2020 en juni 2021.

The purpose of this trial was to learn about the role of Camostat in the treatment of COVID-19 in ambulatory setting. We wanted to study whether Camostat has the potential to reduce the viral load and therefore reduce the risk of transmissibility, reduces the disease burden and the time to recovery.

Camostat is a drug that has been used for a very long time in the treatment of pancreatitis in Japan and has a good tolerability profile. It is taken as a tablet and therefore can be easily taken at home.

In vitro laboratory studies had shown the potential effect of Camostat on the entry of the SARS-CoV-2 virus in the lung cells.

In the present study, we wanted to look whether there was a difference in viral load between Camostat and placebo after treating COVID-19 infected individuals during 5 days. Therefore, we measured the amount of virus in the nose at day 5 after treatment start-up. By doing this we wanted to show the effect of Camostat on viral load and by consequence on milder symptoms, time to recovery and transmissibility.

The study was performed at the Ghent University Hospital between November 2020 and June 2021.

4. Population of subjects

Om in aanmerking te komen voor het onderzoek, moesten de deelnemers ≥ 18 jaar oud zijn, COVID-19-symptomen vertonen gedurende maximaal 5 dagen en bevestigd zijn door PCR of een gedocumenteerde COVID-19-infectie hebben door PCR. Zwangere vrouwen of vrouwen die borstvoeding gaven mochten niet deelnemen en vrouwen moesten, indien relevant, tot het einde van het onderzoek anticonceptie gebruiken.

In totaal deden 108 deelnemers mee aan het onderzoek. Hiervan voldeden 12 proefpersonen niet aan de in- en exclusiecriteria en werden uitgesloten van randomisatie naar een behandelarm (camostat of placebo). Er werden analyses uitgevoerd op de gegevens van 90 deelnemers die de behandeling hadden voltooid (61 kregen camostat, 29 placebo).

In totaal waren 49 deelnemers (54,4%) vrouw. De mediane leeftijd was 40 (tussen 19 en 70 jaar).

To be eligible for the study, participants had to be aged ≥ 18, showing COVID-19 symptoms for maximum 5 days and confirmed by PCR or having a documented COVID-19 infection by PCR. Pregnant or breastfeeding women were not allowed to participate and women had to use contraception until the end of the study, if relevant.

A total of 108 participants were enrolled in the study. Out of these, 12 subjects did not meet the inclusion and exclusion criteria and were excluded from randomization to a treatment arm (camostat or placebo). Analyses were performed on the data of 90 participants who completed treatment (61 received camostat, 29 placebo).

In total, 49 participants (54.4%) were female. Median age was 40 (range 19 to 70 years).

5. Investigational medicinal products used

Camostat mesilaat 100 mg of placebo (lactose 500 mg): 3 tabletten, 3 keer per dag, behandeling van 5 opeenvolgende dagen (=45 tabletten). Als op D5 nog steeds symptomen aanwezig waren of de neuswisser positief bleef, werd de behandeling met nog eens 5 dagen verlengd.

Camostat mesilate 100 mg or placebo (lactose 500 mg): 3 tablets, 3 times a day, 5 consecutive days of treatment (=45 tablets). If at D5 symptoms were still present or the nose swab remained positive, treatment was prolonged for an additional 5 days.

6. Description and frequency of adverse reactions

59 (96,7%) van de deelnemers in de camostatgroep en 23 (79,3%) in de placebogroep ondervonden bijwerkingen tijdens het onderzoek. De meest voorkomende bijwerkingen waren vermoeidheid (25,6%), verandering in eetlust (12,2%), diarree (12,2%), misselijkheid (12,2%), neutropenie (afname van het aantal neutrofielen, een type witte bloedcellen; 12,2%) en leukopenie (afname van het aantal leukocyten, een type witte bloedcellen; 10,0%). De andere bijwerkingen waren aanwezig bij 1,1%-7,8% van de deelnemers. Geen van de bijwerkingen was duidelijk gecorreleerd aan het gebruik van de studiemedicatie.

Vier deelnemers werden opgenomen in het ziekenhuis na een progressief verloop van de ziekte, zijnde niet gerelateerd aan de studiemedicatie.

59 (96.7%) of participants in the camostat group and 23 (79.3%) in the placebo group experienced adverse events during the trial. The most common adverse events were fatigue (25.6%), change in appetite (12.2%), diarrhea (12.2%), nausea (12.2%), neutropenia (decrease in the number of neutrophils, a type of white blood cells; 12.2%) and leukopenia (decrease in the number of leukocytes, a type of white blood cells; 10.0%). The other

adverse events were present in 1.1%-7.8% of the participants. None of the adverse events were clearly correlated to use of the study medication.

Four participants were hospitalized following progressive disease and unrelated to the study medication.

7. Overall results and comments on the outcome of the clinical trial

De mediaan CT-waarde, die als maatstaf voor virale lading of hoeveelheid virus wordt gebruikt, werd gemeten bij aanvang van de studie en bij opvolging. Deze was vergelijkbaar tussen de camostat- en placebogroep. De verandering in CT-waarde tussen aanvang en opvolging rond dag 5 was vergelijkbaar voor de camostat- als de placebogroep. Mogelijke risicofactoren (leeftijd, obesitas, roken, hypertensie, diabetes) voor ernstig COVID-19 verloop hadden geen invloed op de verandering in de CT-waarde en bijgevolg ook niet op de hoeveelheid virus.

Symptomen werden dagelijks gemeten door middel van een zelfrapportagevragenlijst. De top 5 zelfgerapporteerde symptomen gedurende de hele studieperiode waren hoesten, moeheid, niezen, verstopte neus en abnormale reuk- of smaakzin. De tijd tot klinische verbetering van deze 5 meest zelfgerapporteerde symptomen verschilde niet tussen de camostat- en de placebogroep. Bovendien hadden mogelijke risicofactoren geen invloed op klinische verbetering.

Neutraliserende antilichamen werden gemeten tijdens de opvolgvisite rond dag 28. De procentuele verdeling van neutraliserende antilichaamtiters, als maat voor de hoeveelheid neutraliserende antilichamen, was niet verschillend tussen de camostat- en placebogroep.

De huidige studie toont geen bewijs aan dat camostat onder de huidige omstandigheden (300 mg driemaal daags gedurende 5 of 10 opeenvolgende dagen, in nuchtere toestand) effectief is als een antiviraal geneesmiddel tegen de vroege fase van de SARS-CoV-2-ziekte. De studie werd uitgevoerd toen de originele Wuhan-Hu-1- en Alpha-varianten dominant waren in België. Deze conclusies moeten met de nodige voorzichtigheid worden geïnterpreteerd met betrekking tot de later verschenen Delta- en Omicron-varianten. Desalniettemin is naar aanleiding van deze resultaten besloten de studie definitief te beëindigen (dd. 12JUL2022).

The median cycle threshold used as a surrogate for viral load was measured at baseline and at follow-up and was comparable between the camostat and placebo group. The change in cycle threshold from baseline to follow-up at day 5 was similar for both the camostat and placebo group. Potential risk factors (age, obesity, smoking, hypertension, diabetes) for worse COVID-19 disease did not impact on change in cycle threshold and consequently on viral load.

Symptoms were daily measured by means of a self-report questionnaire. The top 5 self-reported symptoms during the whole study period were coughing, weakness/tiredness, sneezing, stuffy nose and abnormal sense of smell or taste. Time to clinical improvement of

these 5 most self-reported symptoms did not differ between the camostat and placebo group. Additionally, potential risk factors did not influence clinical improvement.

Neutralizing antibodies were performed at day 28 visit. The percentage distribution of neutralizing antibody titers, as a measurement for the quantity, was not different between the camostat and placebo group.

The present trial does not show evidence that camostat under the present conditions (300 mg three times daily for 5 or 10 consecutive days, fasted state) is effective as an antiviral drug against early phase SARS-CoV-2 disease. The study was performed when the original Wuhan-Hu-1 and Alpha variants were dominant in Belgium. These conclusions should be interpreted with caution concerning the later emerged Delta and Omicron variants. Nevertheless, as a result of these results, it was decided to definitely end the trial (dd. 12JUL2022).