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

Acronym / Protocol code	COV-AAT
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Phase	Phase 2
EudraCT n°	2020-003475-18
Sponsor	Ghent University Hospital
Financial/Material Support:	Ono Pharmaceutical LTD
	Byteflies
Coordinating Investigator:	Steven Callens

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

Protocol Coordinating Investigator signature page

I certify that I will conduct the study in compliance with the protocol, any amendments, GCP and the declaration of Helsinki, and all applicable regulatory requirements.

Investigator:

Name:

Function:

Institution:

Date: **Signature:**

Protocol Amendment History:

Version	Date	Description of amendment
1.2	13OCT2020	Initial version as approved by the Ethics Committee and the Federal Agency for Medicines and Health Products.
2.0	26NOV2020	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 7.2 - Trial conduct in case of hospitalization has been adjusted from patient withdrawal to further study follow-up, section 8.1.4 and 8.2.4 - Patient home monitoring period was adjusted from 14 days to the period of intake of study medication (5 or 10 days), section 9.2.1 - Protocols for analysis were adjusted based on current practice for PCR and PK/PD, section 10.3 - The gradation of AEs was detailed and references were added 3. Clarifications have been added in the section about safety reporting, section 13
2.1	02FEB2021	Clarification was given concerning the discontinuation of treatment and its implication on study follow-up compared to study withdrawal, section 7.1.2
3.0	04JUN2021	1. The option to conduct an interim analysis has been added to the protocol, section 11.4. 2. Recruitment strategy has been further explained in section 7.2 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 9.2.1. 4. The role of the PI concerning verification of data input of the eCRF has been modified based on clinical practice, section 12.1.1. 5. The option of serum HCG testing to exclude pregnancy has been added, section 6.2. 6. Premature closure of the substudies is being reported, sections 9.2.2, 9.2.3 and 9.2.4.

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LIST OF ABBREVIATIONS

AE	=	Adverse Event
CI	=	Coordinating Investigator
CT	=	Clinical Trial Unit
CT	=	Cycle Threshold
DSMB	=	Data Safety Monitoring Board
DSUR	=	Development Safety Update Report
EC	=	Ethics Committee
eCRF	=	electronic Case Report Form
EDC	=	Electronic Data Capture
EPD	=	Electronic Patient Dossier
FAMHP	=	Federal Agency for Medicines and Health Products
FPI	=	First Patient In
GCP	=	Good Clinical Practice
GDPR	=	General Data Protection Regulation
GMP	=	Good Manufacturing Practice
HIRUZ	=	Health, Innovation and Research Institute UZ Ghent
HR	=	Heart Rate
IB	=	Investigator's Brochure
ICF	=	Informed Consent Form
ICH	=	International Council for Harmonisation
IMP	=	Investigational Medicinal Product
IMPD	=	Investigational Medicinal Product Dossier
LN	=	Liquid Nitrogen
LVLS	=	Last Visit, Last Subject
PD	=	Pharmacodynamics
PI	=	Principal Investigator
PK	=	Pharmacokinetics
POC	=	Point of care
RR	=	Respiratory rate
SAE	=	Seriouse Adverse Event

SmPC	=	Summary of Product Characteristics
SOC	=	Standard of care
SOP	=	Standard Operating Procedure
SUSAR	=	Suspected Unexpected Serious Adverse Reaction
TERENA	=	Trans-European Research and Education Networking Association
TLS	=	Transport Layer Security

1. Protocol Summary

1.1. Protocol specifics

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

Protocolcode: COV-AAT

EudraCT number: 2020-003475-18

Sponsor: Ghent University Hospital

1.2. Study Type and Study Phase

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.

The trial is adaptive and can be adjusted if new data on PK/PD, safety or efficacy becomes available. Adjustments will only be implemented after written approval from the Ethics Committee and Competent Authority (if applicable).

1.3. Aim of the study (including primary endpoints)

We are conducting a pilot trial where we will study safety, efficacy and compliance in a cohort of ambulatory patients in the Ghent region with confirmed COVID-19 infection, in both an early stage of disease, defined as less than 5 days of symptoms and who at presentation do not meet any criteria for hospitalisation as well as asymptomatic individuals with a PCR CT value below 30.

The primary endpoint is to assess the efficacy of the drug in terms of change from day 0 to day 5 in respiratory (oropharyngeal swab RT-PCR) log10 viral load.

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 (PEP) in asymptomatic individuals or to prevent disease progression in the occurrence of early symptomatology.

1.3.1. Number of subjects

We aim to include 150 participants. Symptomatic individuals will be included either directly through the emergency room at Ghent University Hospital or after referral from regional hospitals and general practitioners (general practitioners outposts) to the emergency room or the COVID consultation area at Ghent University Hospital. Asymptomatic individuals with positive PCR can be included through the COVID test centre at the Ghent University Hospital and at the COVID consultation. Inclusions will be done exclusively at Ghent University Hospital. The follow-up will be done through a monitoring tool provided by Byteflies, by phone and/or email and at the COVID consultation area that has been installed on the Ghent University Hospital Campus.

1.3.2. Target group

Patients will be selected either based on the presence of symptoms suggestive of COVID-19 disease based on clinical symptoms and signs or any asymptomatic individual that presents with a positive screening test with CT value below the threshold of 30. Inclusion will be based on a positive COVID screening by RT-PCR, gene expert, IgM antibody screening or any other comparable test confirming COVID infection and eligibility will be checked based on the flowchart used at the emergency department (appendix 4). Patients that need to be hospitalised or have a high risk of hospitalization, based on these criteria, will not be included.

In case of negative screening test and suggestive clinical picture, the test can be completed with additional blood analysis, arterial blood gas and/or lung imaging to assess the probability of COVID-19. These additional tests are a decision of the treating physician and will only be performed if necessary for the patient's standard of care. In this case the study physician can decide to rescreen the patient after minimum 24h and within the 5 days of occurrence of symptoms (with PCR).

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).

1.4. Inclusion and exclusion criteria

Inclusion

- 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.

Exclusion

- 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).

1.5. Study Interventions

1.5.1. IMPs and dosage

Standard of care (SOC) + Camostat mesilate (Foipan) 100mg 3 tablets 3 times a day for 5 consecutive days (D1→D5);

versus

SOC + placebo 500 mg 3 tablets 3 times a day for five consecutive days (D1→D5).

Randomisation 2:1 Camostat versus placebo.

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 (flowchart emergency department appendix 4, the treatment will be extended up to D10 at the same dosage in both treatment arms for 5 consecutive days: D6→D10).

1.5.2. Schematic overview of the data collection & interventions

1.5.2.1 Core study

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 (flowchart emergency department appendix 4), 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 at D1 to D5 or D10). This can be extended after completion of the medication as SOC 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 on 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 SOC. 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. CRP can be assessed by point of care test or routine lab when clinically relevant as part of SOC. A toxicity screening will be performed through a 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 and/or follow-up they will be analyzed as part of the study, however this will only be performed as SOC. If HRCT or a lung X ray are available at baseline or follow-up, they will be analyzed as part of the study, however they will only be performed as SOC.

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 a venous blood draw (max 21ml) if any significant abnormalities occurred at D5 (Grade 1-2 adverse events as defined by CTCAE[1].

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.

[1] https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf

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 (appendix 8), the system will ask either to remeasure or to contact the study-team based on the reported values.

Participants that meet hospitalization criteria will not be considered drop-outs/withdrawals. These patients will no longer take any study medication but their outcomes will still be monitored for the duration of the study period. This means:

- Study medication will be interrupted completely (and will not be reinitiated).
- As long as the patient is submitted to the hospital (and maximum until D28):
    - No study-specific interventions (from the core study nor the substudies) will be performed.
    - Patient's standard of care COVID-19 data will be collected. If the patient is hospitalized in Ghent University Hospital, the study team will consult the EPD. If the patient is hospitalized in another hospital, the study team will contact the treating physician or GP.
- After the patient has been released from the hospital:
    - In case the patient has been discharged before D28, only some of the study-specific interventions will be carried out:
        - If the patient has been discharged before D14: the study participants will be asked to fill in daily questionnaires assessing symptoms (cfr daily self-score) until D14. This will be extended to D28 if patients are still symptomatic at D14.
        - If the patient has been discharged on or after D14 and if symptoms are still present at the time of discharge: the study participants will be asked to fill in daily questionnaires assessing symptoms (cfr daily self-score) until D28.
        - The study visit on D28 will be performed as stipulated in the study protocol, except for the medication log check and the check on compliance and tolerance of the study medication, as this will no longer be applicable.
        - Except for the PK/PD substudy, all substudies will be carried out as indicated in the protocol (only those for which the patient agreed on participating).
    - In case the patient has been discharged after D28, no further study-specific interventions (from the core study nor the substudies) will be performed.

1.5.2.2 PK/PD substudy

Participants will be asked to participate in a PK/PD substudy. We aim to include 50 patients samples in the Camostat treatment arm, therefore sampling approx. half of the participants in both arms. When we have 50 participants in the camostat arm, inclusions will be stopped. Drop-outs however will be

replaced. If the participant agrees, PK/PD samples will be taken during the treatment phase between D1 and D5. 4 additional blood samples will be taken between two intakes of the study medication: at 30', 60', 2-4h, and 4-8h (on the same day, between D1 and D5). The samples will be deblinded during the study by an unblinded person. After unblinding, only the samples from patients in the Camostat group will be sent for analysis. Samples that are not used for PK/PD analysis, will be stored in the prospective Biobank for future studies. 2x3ml of blood will be taken per sampling point =24ml.

Update dd. 04JUN2021: This study was prematurely closed after a test phase due to logistic reasons.

1.5.2.3 Odor substudy: Odor sampling SARS-CoV-2 patients

All participants will be asked to participate in a substudy analysing odor samples from COVID 19 infected individuals. The goal of this study is to take odor samples at the arm pit and between the legs, in order to train dogs to identify COVID-19 infected individuals. In this way, dogs can be trained to identify COVID 19 infected individuals in groups and avoid transmissions. If participants consent, at D5 a cotton pad will be put in the arm pits and between the legs to capture the odors for approx 60 minutes. The samples will be sent to the dog training centre (K9 Training Centrum, Brugsesteenweg 105 8450 Bredene, responsible: Johan Weckhuyzen (CEO)) where they will be used to train dogs to identify COVID-19 infected individuals. These samples will be used one time and will be destroyed after usage at the training centre.

Update dd. 04JUN2021: This study ended at the end of May 2021 after having recruited a sufficient amount of participants and in the absence of budget to prolong the inclusions.

1.5.2.4 COVIM2.0 substudy: Immunological and virological assessment

Deep characterization of patients' inflammatory profile offers a unique opportunity for comprehensive understanding of the pathophysiological mechanisms behind SARS-CoV2. All participants will be therefore asked for additional blood sampling at D0 and D28 (8X9ml). The lipidomics analysis will be performed at the laboratory of Dr. Jesmond Dalli. In addition, we will study immunological functions on the level of both adaptive and innate immunity by performing extensive immunophenotyping, cytokine analysis and RNA sequencing analysis. Biomarker analysis will be performed on protein and on RNA single cell level. Infectivity of different cell types including macrophages will performed. These analyses will be performed at the HCRC laboratory, the laboratory of Prof. Rafick-Pierre Sékaly and the VIB-UGent Center for Inflammation Research. To gain a deeper understanding of pathways potentially leading to severe disease courses, and also to chart where in the body there is tissue damage (apart from the lungs), we aim to analyze patient plasma samples with several other analytics technologies as well. Bacterial extracellular vesicles, due to microbial translocation after hyperinflammation, will be quantified from plasma in the laboratory of Experimental Cancer Research of Ghent University. Furthermore, normal cell turnover in tissues results in the release of some of their nucleic acid content into the blood. This can then be found as circulating free RNA and DNA (cfRNA and cfDNA). These analyses will be performed at the laboratory of Prof. Jo Vandesompele (Biogazelle). Virological evaluations will be based on nasopharyngeal (or nose-throat) swab samples, used to diagnose and quantify SARS-CoV2. In addition a swab will be taken to culture the SARS-CoV2 virus at D0. This will be repeated at D5, D10 and D28 if PCR is positive on these timepoints (an extra swab will be taken). On a selection of nasopharyngeal swab samples from patients whole genome sequencing of the SARS-CoV2 virus will be performed to study the viral diversity and trace patterns of spread across multiple epidemiological scales. In addition, a viral metagenomics analysis using Nanopore sequencing will be used to reveal the presence of other viruses besides SARS-CoV2 (lab of Hans Nauwynck).

Update dd. 04JUN2021: This substudy was not initiated due to the lack of availability of lab technicians.

1.5.2.5 Screening failures 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 SARSCOV2. Therefore we want to 1) culture virus from throat/nose swabs from these individuals at D0 2) measure antibodies at D28.

1.5.2.6 Flowchart

Cfr appendix 1.

1.6. Study duration

1.6.1. For an individual subject

The duration of the study will be 28 days of follow-up after inclusion, i.e. maximum 29 days in total for the patient.

1.6.2. For the whole study

We expect the whole study to take 2 years starting in November 2020. This is a rough estimation as we cannot predict when, how hard and how long the second and/or third wave of the COVID19 epidemic will hit us.

2. Rationale and background

2.1. Rationale

Covid-19 is a new emerging disease causing severe respiratory symptoms in a substantial amount of people with an increased mortality especially in elderly and in men with cardio-vascular comorbidities (hypertension, obesity and diabetes) (Kunyu Yang et a., Clinical characteristics, outcomes, and risk factors for mortality in patients with cancer and COVID-19 in Hubei, China: a multicentre, retrospective, cohort study, The Lancet Oncology, 2020). Due to its high contagiousness, the pandemic caused by this novel SARS-CoV-2 coronavirus poses a major threat to public health.

So far, no therapeutic intervention has 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. Besides Camostat, another drug in its class shows promising results. Nafamostat however is only available in iv formulation but phase I studies are being planned to see whether an oral formulation can be proposed as an alternative to Camostat, potentially reaching higher drug levels in serum and tissues.

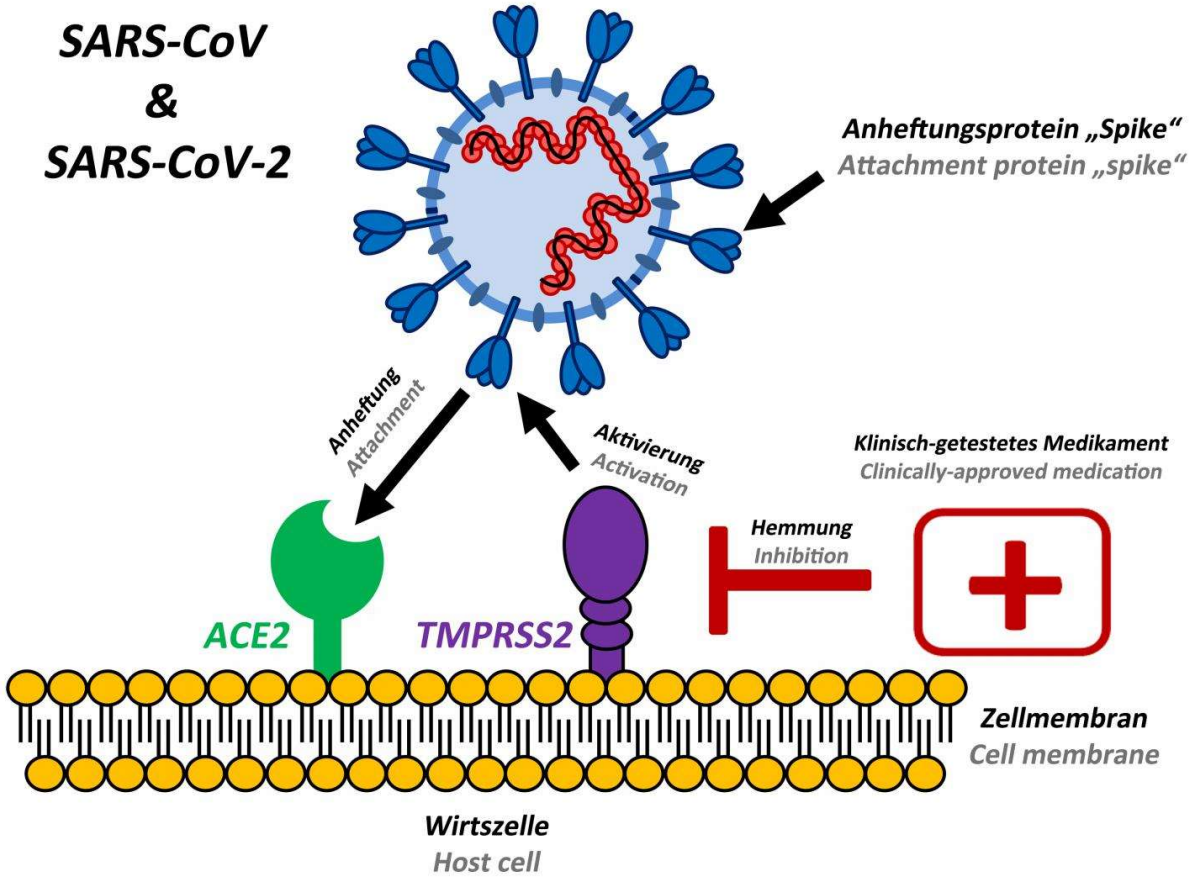


Figure 1: Viral entry of SARS-CoV-2 Illustrator: Hoffman Marcus

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 that we can 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 (Dimitar Popov. "Treatment of Covid-19 Infection. A Rationale for Current and Future Pharmacological Approach". EC Pulmonology and Respiratory Medicine 9.4 (2020): 38-58.). Therefore, it seems only logical to provide these antiviral drugs at the early stage of infection, preferentially in an outpatient setting.

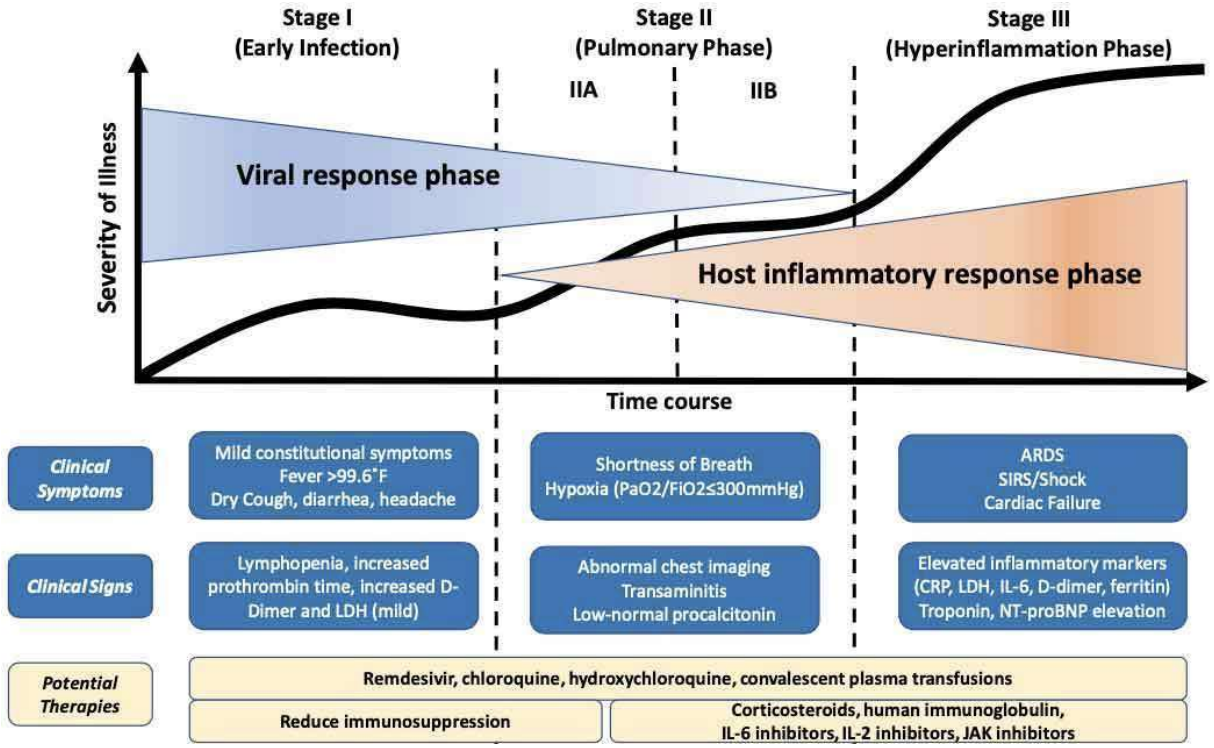


Figure 2: Disease stages

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, compliance and pharmacokinetics of Camostat (and possibly other drugs of the same class). This will allow us to assess the interest of this drug in larger ambulatory trials.

In a first phase, participants will be enrolled at the University Hospital in Ghent after presentation at the emergency room and can be referred to us by the general practitioners in the region around Ghent and other regional hospitals. They will be randomised (2:1) SOC + Camostat versus SOC + placebo. The trial will be placebo controlled, double blinded and adaptive based on our data or the data on efficacy and safety from other trials currently assessing these drugs (Ono pharmaceutical LTD, SPIKE-1 trial Oxford, CamoCO-19 Denmark, Yale University).

The primary endpoint will be to assess the efficacy of the drug in terms of viral clearance based on nasopharyngeal (or combined nose/throat) PCR, the safety and compliance of the drug in ambulatory setting. Furthermore, we want to assess whether the administration of antiviral drugs has an effect on

the presence of neutralising antibodies at D28. The secondary outcome will be to assess the efficacy of the antiviral drug in terms of clinical outcome, in terms of hospitalised participants at D14, the disappearance of symptoms and the clinical status will be assessed by collecting symptoms and using the daily clinical score. The emergence of viral resistance in response to therapy can be assessed in case of prolonged viral shedding.

2.2. Background

In April 2020 Hoffman et al. Published a paper showing how Camostat (orally) and Nafamostat (iv) have an effect on the entry of SARS-CoV-2 in the host cells (https://doi.org/10.1016/j.cell.2020.02.052, https://aac.asm.org/content/aac/64/6/e00754-20.full.pdf). 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. It has the advantage to be a safe drug, which is licensed at 600mg daily dosing for the treatment of chronic pancreatitis in Japan. Due to its use in ambulatory care in Japan without major side effects, it is a good candidate in the setting of early COVID treatment and prevention. Therefore this drug was selected as a strong candidate for this pilot study and if we can confirm its efficacy and safety and the chosen dose, whether we can apply it in a large setting.

Rationale for dose selection:

The approved dose for Foipan is 100mg three times daily for postoperative reflux oesofagitis and 200mg three times daily for symptomatic treatment of chronic pancreatitis. Much higher doses have been used in some smaller studies without any severe adverse effects up to 7,2g daily for severe oral carcinomas (Ohkoshi et al, J. Maxillofac Surgery 1984; 12:148-52).

Camostat is a drug which is not detectable in blood or plasma after oral administration. PK data of its active metabolite 4-(4-guanidinobenzoyloxy)phenylacetic acid (GBPA) are scarce and only available in healthy volunteers (ONO pharmaceutical LTD, not published).

Although this dose is not used in clinical practice, this dosing regimen has been studied by Sato et al, 1992 in a phase II trial in 62 patients with postoperative reflux esophagitis during 8 weeks of treatment. Three adverse reactions (edema, feeling of nasal congestion, and urticaria) occurred in 2 of 62 patients. No clinically meaningful events were reported. More recently ONO pharmaceuticals conducted a phase I trial with dosing schedules up to 2400mg/day and only report one adverse event (hyperuricemia) (unpublished data).

The proposed regimen for this trial is based on simulations using population PK parameters from a Phase I healthy volunteer study (ONO Pharmaceuticals; dose 600 mg 4 times daily) and the recently reported in vitro EC50 of antiviral activity of GBPA against the SARS Cov2.

From these simulations, it can be derived that time above the EC50 equals 5.3 h per day if a dose of 300 mg is administered three times daily in fasted condition. Results are presented in the Figure and Table below.

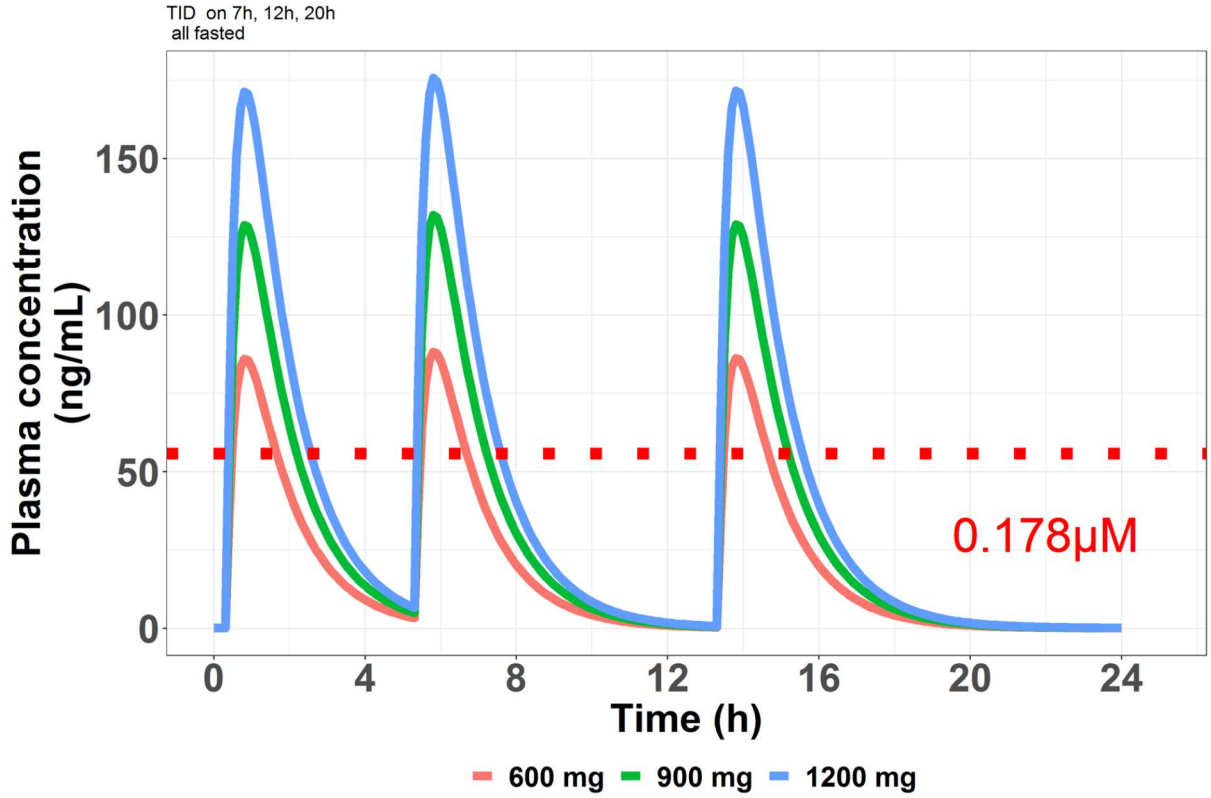


Figure 3: Simulated concentration-time profile using popPK parameters from a pilot Population PK model in healthy volunteers (ONO pharmaceuticals). The red dashed line represents the EC50 of the active metabolite of camostate mesilate (GBPA).

Dose	Time above EC50 (h)	Cave (ng/mL)
200 mgTID (600 mg/day)	3.60	20.6
300 mgTID (900 mg/day)	5.30	30.9
400 mgTID (1200 mg/day)	6.60	41.1

Table 3. Time above the EC50 and average concentration per day of the active metabolite of camostate mesilate (GBPA)

Studies in rat and dog revealed [14C]camostat in the lung to be 1- to 3.8-fold that in the plasma. If accumulation occurs in humans, this would result in an even higher time above EC50 using a 300 mg 3 times daily dosing regimen.

Data are currently lacking on the magnitude of accumulation in human lung tissue and the required tissue concentration for optimal efficacy, however we believe the above rationale provides enough support to select a 3 x 300mg dosing regimen in this phase II clinical trial.

A daily dose of 900mg is the highest dose for which enough safety data is available to be used in a phase II clinical trial. For compliance reasons, we preferred a 3 daily dosing regimen over a 4 daily dosing regimen. From their data in healthy volunteers, ONO pharmaceuticals also reported that food intake has a large impact on drug disposition and a fasting state should be recommended in future clinical trials. Therefore, patients in our study will be taking their medication in a fasting state.

We are aware that ONO pharmaceutical LTD and other research groups (Oxford University, Aarhus University, University of Vienna, Yale University) are launching a phase I/ II and III trial to assess safety and efficacy at lower and higher dosing regimens (up to 2400mg daily). Moreover, more data from in vitro and animal experiments are expected to be published in the coming months. If these data become available during the trial, this could be used to optimize the study dosing regimen in terms of efficacy, tolerability and patient compliance. Adjustments will only be implemented after written approval from the Ethics Committee and Competent Authority (if applicable).

Rationale for duration of treatment:

This is based on current guidelines for the treatment of lower respiratory tract infections with antiviral and antibacterial drugs. For influenza the treatment with oseltamivir (Tamiflu) is 5 days. For mild to moderate bacterial pneumonia recommendations are 5 days of antibiotics or even less (DOI:10.1056/NEJMoA1912400).

If the PCR remains positive and above a CT value of <30, we will continue the treatment for an additional 5 days as we assess that these individuals are still infectious and therefore will benefit from prolonged treatment. Also in patients with persisting symptoms we will extend the treatment.

Rationale for an outpatient trial in COVID-19:

The rationale for enrolling patients in early phase of disease and with mild to moderate symptoms not requiring hospitalisation is to assess whether these antivirals can have an effect on symptom reduction, viral shedding and risk of disease progression. Our data can support a larger trial assessing the effect on clinical outcome but could also support their usage in PEP after exposure or to reduce transmission in co-housing (eg households or care facilities) due to their effect on viral shedding. Moreover, this drug has an interesting safety profile and therefore the potential benefits of Camostat on COVID-19 are likely to counter the low risk of significant adverse effects.

2.3. Risk/Benefit Assessment

A study-specific risk assessment plan (separate document) will be available to address, in detail, the most relevant potential risks and to specify the mitigation of those risks. Risks will be scaled into low, medium and high risks.

2.4. Limitations

The Belgian government has successfully reduced the incidence of COVID-19 to a low level transmission, with an R0 that has been estimated below 1 for several weeks now. However, the 7 day average number of diagnosis has remained stable and even increased at the end of June. We expect that due to the changing behavioral pattern of the population at risk of infection and the low level of immunity in the community, a second, albeit smaller, wave can occur. However, conversely to the first wave, more paucisymptomatic or asymptomatic people will be tested, thus increasing the number of eligible subject for this trial significantly.

The numbers of participants we can include in this pilot trials will likely be underpowered to show an effect on clinical outcome and hospitalisation. Therefore, these results should be interpreted with caution as the risk exists that a valid drug candidate might be rejected based on these results when not put in the right perspective.

3. Objectives

3.1. Primary Objectives

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 (PEP) in asymptomatic individuals or to prevent disease progression in the occurrence of early symptomatology. In this pilot we will assess efficacy of the drug in terms of viral load changes at D5 compared to baseline in nasopharyngeal (or nose/throat) swabs. Cycle threshold 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.

3.2. 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.

Objectives substudies:

- PK/PD substudy: quantify PK/PD parameters of camostat metabolite and interpatient variability in covid-19 infected patients.
- Odor substudy: to estimate whether dogs can be trained to successfully detect covid 19 positive individuals based on odor.
- COVIM2.0 substudy: understanding of the pathophysiological mechanisms behind SARS-CoV2.

- 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.

4. End Points and Time Points

4.1. Primary End Points and Time Points

The primary endpoint is to assess the efficacy of the drug in terms of change from day 0 to day 5 in respiratory (oropharyngeal swab RT-PCR) log10 viral load.

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

4.2. Secondary End Points and Time Points

- Days to clinical improvement from study enrolment, defined as no fever for at least 48 hrs AND improvement in other symptoms (e.g. cough, expectoration, myalgia, fatigue, or head ache) using a standardised symptom assessment scale modified from the FLU-PRO tool by DR. Vinetz, Yale University. Symptoms will be assessed daily from D1-D14 and up to D28 if patients are still symptomatic at D14 and compared to baseline using questionnaires and monitoring of temperature 4x daily, oxygen saturation, respiratory rate and heart rate.
- Clinical status as assessed by the 7-point ordinal scale at day 0, 3, 5, 10 and 28 (Not hospitalized, no limitations on activities; Not hospitalized, limitation on activities; Hospitalized, not requiring supplemental oxygen; Hospitalized, requiring supplemental oxygen; Hospitalized, on noninvasive ventilation or high flow oxygen devices; Hospitalized, on invasive mechanical ventilation or ECMO; Death)
- The effectiveness of the selected drug to prevent death at D14 and D28
- The effectiveness of the selected drug to prevent hospitalization and oxygenation at D14 and D28
- The effectiveness of the selected drug to prevent intensive care hospitalization at D14 and D28
- If available, the effect of the selected drug on pulmonary infiltrates by RX or HRCT will be assessed at D5 or D10 compared to baseline. The CO-RADS classification will be used to assess the findings.
- If available, the effect of the selected drug on inflammatory parameters at D5 and D10 compared to baseline.
- The efficacy of the drug in terms of change from day 0 to day 10 in respiratory (oropharyngeal swab RT-PCR) log10 viral load in patients with positive PCR at D5.
- The efficacy of the drug in terms of change from day 0 to day 28 in respiratory (oropharyngeal swab RT-PCR) log10 viral load in patients with positive PCR at D10.
- The probability of finding viable virus after virus culture from swabs in COVID 19 infected individuals at D0 (and at D5, D10 and D28 if PCR remains positive).

- The emergence of resistance for each of the selected drug regimens in case of prolonged viral shedding at D10 and D28 in individuals with positive PCR at these timepoints.
- The presence of neutralising antibodies at D28.
- Number of participant-reported secondary infection of housemates (and/or close contacts) at D28.

Endpoints and timepoints of the substudies:

- PK/PD substudy: PK (volume of distribution, clearance, Cmax, Tmax) and PD (Emax and EC50) parameters of camostat metabolite and predictors for interpatient variability. 4 additional blood samples. Between two drug administrations between D1 and D5: at 30', 60', 2-4h, and 4-8h (on the same day). Efficacy parameters are collected on timepoints as described above from which Emax and EC50 and viral load decline parameters will be estimated.
- Odor substudy: to correctly distinct COVID 19 positive from negative individuals. 3 odor samples at 1 sampling timepoint at D5.
- COVIM2.0 substudy: to study the inflammatory patterns and virological characteristics of SARSCOV2. 1 additional blood sample (8x9ml) at D0 and D28. 1 additional swab at D0 and D5, D10 and D28 if PCR remains positive at these timepoints).
- Screening failures substudy: to see whether asymptomatic individuals with positive PCR but high CT values (>30) are carrying viable virus and whether these individuals produce neutralising antibodies and therefore have immunity against SARSCOV2. 1 additional swab at D0. 1 blood sampling at D28.

5. Study design

5.1. Description of study design

Randomised, double blinded, placebo controlled

Prospective

The trial is adaptive and can be adjusted if new data on PK/PD, safety or efficacy becomes available. Adjustments will only be implemented after written approval from the Ethics Committee and Competent Authority (if applicable).

Phase 2 clinical trial

Monocentric in collaboration with regional hospitals and general practices (GPs) in the region of Ghent for referral of potential candidates.

The trial is a pilot trial in order to provide information on Camostat, dosing, safety and efficacy, to support the roll-out of a possible multicentre trial with clinical outcomes.

Medication will be provided orally in an ambulatory setting.

Camostat or placebo will be taken for 5 consecutive days (D1→D5) at a daily dose of 900mg (300mg TID) for the Camostat arm.

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 (flowchart emergency department appendix 4), the treatment will be extended up to D10 at the same dosage in both treatment arms for 5 consecutive days: D6→D10).

5.2. End of Study Definition

5.2.1. For an individual subject

The subject has completed the study if he or she has completed all phases of the study, including the last visit or the last scheduled procedures, as described in this protocol (see section "9. Study Specific Procedures").

5.2.2. For the whole study

Overall, the end of the study is reached when the last study procedure for the last subject has occurred: last subject, last visit (LSLV).

As soon as the whole study has ended (cfr the definition above), the Coordinating Investigator shall notify the HIRUZ Clinical Trial Unit, so that the Competent Authority and the Ethics Committee can be informed in a timely manner according to the regulatory requirements (within 90 days after end of the study, or if the study had to be terminated early, this period must be reduced to 15 days and the reasons should be clearly explained).

The final study report will be submitted no later than 1 year after the end of the study.

5.3. Estimated duration of the study

5.3.1. For an individual subject

The study will take maximum 29 days from initiation to completion (and minimum 28 days).

5.3.2. For the whole study

We expect the whole study to take 2 years starting in November 2020. This is a rough estimation as we cannot predict when, how hard and how long the second and/or third wave of the COVID19 epidemic will hit us.

6. Inclusion and Exclusion Criteria

6.1. 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 of our institution (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.

6.2. 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 emergency department flowchart (cfr 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 test (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 or gastric juice
- Postoperative reflux oesophagitis (if improvement of symptoms is not observed).

6.3. Screen failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information will be kept to ensure transparent reporting of screen failure subjects.
Individuals who do not meet the criteria for participation in this study (screen failure) can be rescreened after minimum 24h and within the 5 days of onset of symptoms.

7. Target Population

7.1. Subjects

7.1.1. Number of subjects and planned recruitment rate

We aim to include 150 participants in this study. Drop-outs will not be replaced.

The patients will be randomised 2:1 into two study arms:

- SOC + camostat 300mg 3x/d during 5 consecutive days
- SOC + placebo 3x/d during 5 consecutive days

It is expected that overall an accrual rate of 10 subjects per month is realistic in the whole study.

7.1.2. Withdrawal and replacement of subjects

Subjects are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue the treatment in a subject from the study for the following reasons:

- Pregnancy
- If any clinical or biochemical adverse event (AE) (grade 3-4 according to the CTCAE classification), or other medical condition or situation occurs such that continued treatment in the study would not be in the best interest of the subject
- Disease progression which requires discontinuation of the study intervention (including hospitalization as described in section 8.1.4 and 8.2.4).
- If the subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further treatment (not including the need for hospitalization as defined in the flowchart (appendix 4), cfr. infra section 8.1.4 and 8.2.4).

In case of study noncompliance or if the investigator decides for whatever reason that study participation of the subject is no longer advisable, the investigator can decide to withdraw the subject from the study at any time during the study.

In all cases, the reason why subjects are being discontinued their treatment or withdrawn from the trial must be recorded in detail in the eCRF and in the subject's medical records.

A subject will be considered lost to follow-up if he or she fails to return for 1 scheduled visit and is unable to be contacted by the study site staff.
The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site will attempt to contact the subject and reschedule the missed visit within 48 hours and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record or study file.
- Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

7.2. Method of recruitment

Participants will be recruited at the emergency department of Ghent University Hospital or the COVID consultation and test center at Ghent University Hospital after referral by the GPs in the region around Ghent and regional hospitals. Asymptomatic individuals with positive PCR can be referred directly to the COVID consultation or can be picked up after positive testing at the test center.

A poster was designed by the Ghent University Hospital communication service and will be distributed to the above mentioned places of recruitment to inform care givers and potential participants of the study. The poster will also be used on social media and will be spread by snowball sampling via friends, colleagues, acquaintances, etc. of the study team.

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 and flyers are available in the test centre. When patients that tested positive for COVID-19 are called to inform them about their results, study interest is being interrogated.

7.3. Screening

Patients will be selected either based on the presence of symptoms suggestive of COVID-19 disease based on clinical symptoms and signs or any asymptomatic individual that has a positive screening test with CT value below the threshold of 30. Inclusion will be based on a positive COVID screening by RT-PCR, gene expert, IgM antibody screening or any other comparable test confirming COVID infection.

Eligibility will be checked based on the flowchart used at the emergency room (appendix 4).

In case of negative screening test and suggestive clinical picture, the test can be completed with additional blood analysis, arterial blood gas and/or lung imaging to assess the probability of COVID-19. This is SOC and will be decided by the treating physician. In this case the study physician can decide to rescreen the patient (with PCR) after minimum 24h and within the 5 days of onset of symptoms.

8. Investigational Medicinal Product (IMP)

8.1. Camostat Mesilate

8.1.1. Composition and active substance of the IMP

Foipan 100 mg tablets, active substance camostat mesilate 100 mg

8.1.2. Producer and Distributor of the IMP

Ono Pharmaceutical LTD (Japan)

8.1.3. Preparation + Dosage + administration of the IMP

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, 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.

The Foipan® (Camostat 100 mg) tablets will be used outside the conditions of the Summary of Product Characteristics:

- The Foipan® (Camostat mesilate 100 mg) tablets are used in a phase II clinical trial to assess the efficacy and safety of oral serine protease inhibitors that inhibit S protein-initiated membrane fusion in the treatment of early phase COVID 19 disease in an ambulatory setting. This indication is not mentioned in the SmPC.

- The maximum dose mentioned in the SmPC is 600 mg of camostat mesilate daily in three divided doses. In this clinical trial a dose of 900 mg of camostat mesilate daily in three divided doses will be administered. The Foipan® tablets will be packaged conform Circular 596 (of the FAMHP) on the production and distribution activities for experimental medicines.

8.1.4. Permitted dose adjustments and interruption of treatment

Participants should take this medication 3 times a day during 5 consecutive days with a maximum of 4 hours delay. If the patient forgets to take his medication within the 4 hours window, he will skip that dose and report it in the medication log. The time between two intakes should be at least 4 hours. So if one intake is delayed (with maximum 4 hours), the next intake should be adjusted, taken into account a minimum of 4 hours between each intake. A medication log will be available and should be filled in by the participants.

If any clinical or biochemical adverse event (AE) (grade 3-4 according to CTCAE classification), or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject, treatment will be interrupted.

The study medication will be interrupted in participants that meet hospitalization criteria, as defined in the flowchart used at the emergency department of Ghent University Hospital. Participants that meet hospitalization criteria will not be considered drop-outs/withdrawals. These patients will no longer take any study medication but their outcomes will still be monitored for the duration of the study period. This means:

- Study medication will be interrupted completely (and will not be reinitiated).
- As long as the patient is submitted to the hospital (and maximum until D28):
    - No study-specific interventions (from the core study nor the substudies) will be performed.
    - Patient's standard of care COVID-19 data will be collected. If the patient is hospitalized in Ghent University Hospital, the study team will consult the EPD. If the patient is hospitalized in another hospital, the study team will contact the treating physician or GP.
- After the patient has been released from the hospital:
    - In case the patient has been discharged before D28, only some of the study-specific interventions will be carried out:
        - If the patient has been discharged before D14: the study participants will be asked to fill in daily questionnaires assessing symptoms (cfr daily self-score) until D14. This will be extended to D28 if patients are still symptomatic at D14.
        - If the patient has been discharged on or after D14 and if symptoms are still present at the time of discharge: the study participants will be asked to fill in daily questionnaires assessing symptoms (cfr daily self-score) until D28.
        - The study visit on D28 will be performed as stipulated in the study protocol, except for the medication log check and the check on compliance and tolerance of the study medication, as this will no longer be applicable.

- Except for the PK/PD substudy, all substudies will be carried out as indicated in the protocol (only those for which the patient agreed on participating).

- In case the patient has been discharged after D28, no further study-specific interventions (from the core study nor the substudies) will be performed.

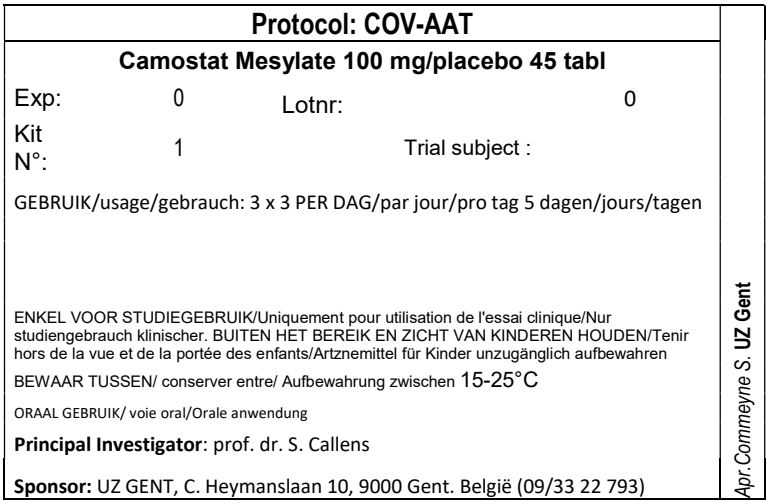
8.1.5. Duration of treatment

Five consecutive days (D1→D5). 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 (flowchart emergency department appendix 4), the treatment will be extended up to D10 at the same dosage in both treatment arms for 5 consecutive days (D6→D10).

8.1.6. Packaging and Labeling of the IMP

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.



8.1.7. Storage conditions of the IMP

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.

8.1.8. Known side effects of the medication

Hypersensitivity reactions including rash (0.4%), pruritus (0.2%), nausea (0.3%), abdominal discomfort (0.2%), abdominal fullness (0.2%).

Increase in liver tests are reported (AST/ALT) (0,3%), diarrhea (0,2%) and nausea (0,1%).

Besides hypersensitivity reactions, the SmPC also refers to potential complications such as thrombocytopenia, hyperkaliemia and increased liver enzymes (incidence not reported).

8.2. Placebo

8.2.1. Composition of the placebo

Lactose tablets 500 mg

8.2.2. Producer and Distributor of the placebo

Fagron

8.2.3. Preparation + Dosage + administration of the placebo

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.

8.2.4. Permitted dose adjustments and interruption of treatment

Participants should take this medication 3 times a day during 5 consecutive days with a maximum of 4 hours delay. If the patient forgets to take his medication within the 4 hours window, he will skip that dose and report it in the medication log. The time between two intakes should be at least 4 hours. So if one intake is delayed (with maximum 4 hours), the next intake should be adjusted, taken into account a minimum of 4 hours between each intake. A medication log will be available and should be filled in by the participants.

If any clinical or biochemical adverse event (AE) (grade 3-4 according to CTCAE classification), or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject, treatment will be interrupted.

The study medication will be interrupted in participants that meet hospitalization criteria, as defined in the flowchart used at the emergency department of Ghent University Hospital.

Participants that meet hospitalization criteria will not be considered drop-outs/withdrawals. These patients will no longer take any study medication but their outcomes will still be monitored for the duration of the study period. This means:

- Study medication will be interrupted completely (and will not be reinitiated).
- As long as the patient is submitted to the hospital (and maximum until D28):
    - No study-specific interventions (from the core study nor the substudies) will be performed.
    - Patient's standard of care COVID-19 data will be collected. If the patient is hospitalized in Ghent University Hospital, the study team will consult the EPD. If the patient is hospitalized in another hospital, the study team will contact the treating physician or GP.
- After the patient has been released from the hospital:
    - In case the patient has been discharged before D28, only some of the study-specific interventions will be carried out:
        - If the patient has been discharged before D14: the study participants will be asked to fill in daily questionnaires assessing symptoms (cfr daily self-score) until D14. This will be extended to D28 if patients are still symptomatic at D14.
        - If the patient has been discharged on or after D14 and if symptoms are still present at the time of discharge: the study participants will be asked to fill in daily questionnaires assessing symptoms (cfr daily self-score) until D28.
        - The study visit on D28 will be performed as stipulated in the study protocol, except for the medication log check and the check on compliance and tolerance of the study medication, as this will no longer be applicable.
        - Except for the PK/PD substudy, all substudies will be carried out as indicated in the protocol (only those for which the patient agreed on participating).
    - In case the patient has been discharged after D28, no further study-specific interventions (from the core study nor the substudies) will be performed.

8.2.5. Duration of treatment

5 consecutive days (D1→D5).

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 (flowchart emergency department appendix 4), the treatment will be extended up to D10 at the same dosage in both treatment arms for 5 consecutive days (D6→D10).

8.2.6. Packaging and Labeling of the placebo

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.

Protocol: COV-AAT	
Camostat Mesylate 100 mg/placebo 45 tabl	
Exp: 0 Lotnr: 0	
Kit N°: 1 Trial subject :	
GEBRUIK/usage/gebrauch: 3 x 3 PER DAG/par jour/pro tag 5 dagen/jours/tagen	
ENKEL VOOR STUDIEGEBRUIK/Uniquement pour utilisation de l'essai clinique/Nur studiengebrauch klinischer. BUITEN HET BEREIK EN ZICHT VAN KINDEREN HOUDEN/Tenir hors de la vue et de la portée des enfants/Artznemittel für Kinder unzugänglich aufbewahren	
BEWAAR TUSSEN/ conserver entre/ Aufbewahrung zwischen 15-25°C	
ORAAL GEBRUIK/ voie oral/Orale anwendung	
Principal Investigator: prof. dr. S. Callens	
Sponsor: UZ GENT, C. Heymanslaan 10, 9000 Gent. België (09/33 22 793)	*Apr.Commeyne S.* **UZ Gent**

8.2.7. Storage conditions of the placebo

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.

8.2.8. Known side effects of the medication

Lactose tablets can cause gastro-intestinal symptoms such as diarrhea when administered to people with lactose intolerance, although this most likely occurs when administered in higher dosing (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4586575/pdf/nutrients-07-05830.pdf).

8.3. Concomitant / Rescue Medication

There are no restrictions regarding concomitant medication.
In case of hospitalization or unfavorable clinical evolution, participants will not be excluded from other protocols or SOC treatments for COVID.
The study site will not supply rescue medication.

9. Study Specific Procedures

9.1. Randomisation/blinding

9.1.1. Randomisation

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

Repackaging is performed with a copy of the transcripted randomisation list in excel and the labels (check of the labels by QC) – repackaging for active and placebo is performed separately. An operator does the repackaging, a pharmacist QC 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 excelsheets for the unblinded studynurse. He/she will sign for acceptance.

9.1.2. Blinding

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. They will conduct the following procedures:

- Deliver medication based on the randomization list both at D0 and at D5 in case of prolonged treatment.
- Accountability of the tablets and destruction of the remaining tablets.
- In case of AEs they will communicate the AEs in the Camostat group to ONO
- In case for medical or safety reasons there is a need for urgent deblinding, they will break the code and pass this information to the treating physician of the participants. In this case, the physician treating the participant is preferentially not the same one as the study physician.
- Deblind the PK/PD samples for analysis during the trial. Shipment of the PK/PD samples.

To minimize the risk for unblinding the other (blinded) study personnel we will take the following measurements:

- Two co-workers will be delegated as unblinded personnel at the clinic, in order to set up a back-up system. Another two collaborators will be assigned as back-up for the two co-workers.

- Unblinded personnel and their study activities will be clearly documented on the delegation log.
- Unblinded personnel at the clinic have no contact with study participants in any way.
- All communication between unblinded and blinded personnel concerning allocation of treatment will be traceable.

9.1.3. Deblinding procedures

Deblinding of the participants will take place after completion of the study (LPLV). The blinded study nurses and physicians will also stay blinded until that moment.

The study code should only be broken for valid medical or safety reasons e.g. in the case of a severe adverse event where it is necessary for the investigator or treating health care professional to know which treatment the subject is receiving before he or she can be treated. If possible, other study team members should remain blinded.

The code breaks for the study are held at the department of internal medicine.

The CI/PI documents the breaking of the code and the reasons for doing so on the CRF/study documents, in the site file and medical notes. It will also be documented at the end of the study in any final study report and/or statistical report.

The study team will notify the Sponsor in writing as soon as possible following the code break detailing the necessity of the code break.

As the investigator is responsible for the medical care of the individual study subject (Declaration of Helsinki 3§ and ICH 4.3) the coding system in blinded studies should include a mechanism that permits rapid un-blinding (ICH GCP 5.13.4). The investigator cannot be required to discuss unblinding if he or she feels that emergent unblinding is necessary.

PK/PD samples will be deblinded during the study. An unblinded collaborator of the study will deblind the samples and arrange for the shipment of samples from the Camostat arm and storage of the samples in the placebo arm.

9.2. Study specific interventions

9.2.1. Core trial

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 (flowchart emergency department appendix 4), 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 SOC. 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 SOC.

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 (appendix 8), 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 as defined by the flow chart used at the emergency department of Ghent University Hospital (appendix 4).

9.2.2. PK/PD substudy

Participants will be asked to participate in a PK/PD substudy. We aim to include 50 patients samples in the Camostat treatment arm, therefore sampling approx. half of the participants in both arms. When we have 50 participants in the camostat arm, inclusions will be stopped. Drop-outs however will be replaced. If the participant agrees, PK/PD samples will be taken during the treatment phase between D1 and D5. 4 additional blood samples will be taken between two intakes of the study medication: at 30', 60', 2-4h, and 4-8h (on the same day, between D1 and D5). The samples will be deblinded during the study by an unblinded person. After unblinding, only the samples from patients in the Camostat group will be sent for analysis. Samples that are not used for PK/PD analysis, will be stored in the prospective Biobank for future studies. 2x3ml of blood will be taken per sampling point =24ml.

Update dd. 04JUN2021: This study was prematurely closed after a test phase due to logistic reasons.

9.2.3. Odor substudy: Odor sampling SARS-CoV-2 patients

Participants will be asked to participate in a substudy analysing odor samples from COVID 19 infected individuals. The goal of this study is to take odor samples at the arm pit and between the legs, in order to train dogs to identify COVID-19 infected individuals. In this way, dogs can be trained to identify COVID 19 infected individuals in groups and avoid transmissions. If participants consent, at D5 a cotton pad will be put in the arm pits and between the legs to capture the odors for approx 60 minutes. The samples will be send to the dog training centre (K9 Training Centrum, Brugsesteenweg 105 8450 Bredene, responsible: Johan Weckhuyzen (CEO)) where they will be used to train dogs to identify

COVID-19 infected individuals. These samples will be used one time and will be destroyed after usage at the training centre.

Update dd. 04JUN2021: This study ended at the end of May 2021 after having recruited a sufficient amount of participants and in the absence of budget to prolong the inclusions.

9.2.4. COVIM2.0 substudy: Immunological and virological assessment

Deep characterization of patients' inflammatory profile offers a unique opportunity for comprehensive understanding of the pathophysiological mechanisms behind SARS-CoV2. All participants will be therefore asked for additional blood sampling at D0 and D28 (8X9ml). The lipidomics analysis will be performed at the laboratory of Dr. Jesmond Dalli, In addition, we will study immunological functions on the level of both adaptive and innate immunity by performing extensive immunophenotyping, cytokine analysis and RNA sequencing analysis. Biomarker analysis will be performed on protein and on RNA single cell level. Infectivity of different cell types including macrophages will performed. These analyses will be performed at the HCRC laboratory, the laboratory of Prof. Rafick-Pierre Sékaly and the VIB-UGent Center for Inflammation Research. To gain a deeper understanding of pathways potentially leading to severe disease courses, and alsoto chart where in the body there is tissue damage (apart from the lungs), we aim to analyze patient plasma samples with several other analytics technologies as well. Bacterial extracellular vesicles, due to microbial translocation after hyperinflammation, will be quantified from plasma in the laboratory of Experimental Cancer Research of Ghent University. Furthermore, normal cell turnover in tissues results in the release of some of their nucleic acid content into the blood. This can then be found as circulating free RNA and DNA (cfRNA and cfDNA). These analyses will be performed at the laboratory of Prof. Jo Vandesompele (Biogazelle). Virological evaluations will be based on nasopharyngeal swab samples, used to diagnose and quantify SARS-CoV2. In addition a swab will be taken to culture the SARS-CoV2 virus at D0. This will be repeated at D5, D10 and D28 if PCR is positive on these timepoints (an extra swab will be taken). On a selection of nasopharyngeal swab samples from patients whole genome sequencing of the SARS-CoV2 virus will be performed to study the viral diversity and trace patterns of spread across multiple epidemiological scales. In addition, a viral metagenomics analysis using Nanopore sequencing will be used to reveal the presence of other viruses besides SARS-CoV2 (lab of Hans Nauwynck).

Update dd. 04JUN2021: This substudy was not initiated due to the lack of availability of lab technicians.

9.2.5. Screening failures 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 SARSCOV2. Therefore we want to 1) culture virus from throat/nose swabs from these individuals at D0 2) measure antibodies at D28.

9.3. Overview of collected data

- Clinical exam including blood pressure, respiratory rate, heart rate, temperature and blood oxygen saturation: D0-D5-(D10)-D28. D10 additional visit will be planned if PCR is positive at D5 and treatment is prolonged.

- At D0: Socio-demographic parameters such as age, gender, treatment, smoking status, BMI, diabetes, race and comorbidities will be assessed.
- Symptoms, signs, compliance and tolerance will be assessed by questionnaire daily D0→D14 and up to D28 in patients that still have symptoms at D14.
- A monitoring kit will be provided for self-assessment of temperature, HR, RR and saturation (D0→D5 (or D10)).
- Clinical 7 points score: D0-D5-(D10)-D28
- Toxicity lab at D0-D5 (and D10 if necessary cfr. protocol)
- Optional: lung imaging (RX or HRCT): D0, D5 or D10 when clinically relevant and based upon availability.
- Optional : (POC) CRP: D0-D5 or D10
- Nasopharyngeal (or combine nose/throat) swab: D0-D5-(D10-D28 when positive at D5 or D10 respectively)
- Neutralising Abs: D28
- Substudies:
    - PK/PD sampling between D1 and D5: 4 additional blood samples on the same day (2x3ml per timepoint =24ml)
    - Odor sampling: D5: 3 cotton pads
    - COVIM2.0:
      Peripheral blood draw:
      o Day 0: 8 EDTA tubes (9mL)
      o Day 28: 8 EDTA tubes (9mL)
      Swabs for SARS-CoV2 culture and infectivity
      o Day 0, day 5, day 10 and day 28: one additional swab (with viral transport medium) to culture virus in BSL3 lab if PCR is positive at these timepoints (an extra swab will be taken for the COVIM2.0 substudy).
    - Screening failures: additional swab for viral culture D0 and blood sample for neutralizing Abs D28

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 and safety (peripheral blood count, inflammation, electrolytes, kidney and liver function.)

9.4. Schematic overview of the data collection & interventions

Appendix 1

9.5. Restrictions for subjects during the study

There are no extra restrictions for the subjects (apart from the restrictions from the government for COVID-19 positive patients).

10. Sampling

10.1. Types and number of samples

- Nasopharyngeal (or combined nose/throat) swab for COVID PCR: D0-D5 and D10-D28 if positive at D5 or D10 respectively
- Toxicity lab D0, D5 (and at D10 if necessary cfr. protocol) (max 21ml).
- Additional blood analysis can be performed at any given time during the study to assess the severity of infection, for follow-up or in case of the safety issues. This includes peripheral blood count, CRP, liver, renal function and electrolytes (max 21 ml).
- Additional: capillary blood for POC CRP or regular blood draw for CRP (max 6ml): D0-D5-D10
- Blood test for neutralizing Abs titer at D28 (max 9ml).
- Substudies
    - PK/PD: 4 additional blood draws (6ml 4x=24ml) between D1-D5 between 2 intakes of the medication (on the same day, at 30', 60', 2-4h, and 4-8h).
    - Odor sampling: 3 cotton (gauze) pads at D5
    - COVIM2.0:
        - Peripheral blood draw:
          o Day 0: 8 EDTA tubes (9mL)
          o Day 28: 8 EDTA tubes (9mL),
        - Swabs for SARS-CoV2 culture and infectivity
          o Day 0, day 5, day 10 and day 28: one additional swab (with viral transport medium) to culture virus in BSL3 lab if PCR is positive at these timepoints (an extra swab will be taken for the COVIM2.0 substudy)
    - Screening failure: 1 swab for viral culture at D0 and 1 blood sample (9ml) at D28 for neutralizing antibodies

10.2. Timepoints of sampling

D0-D5-(D10)-D28

PK/PD substudy: between D1-D5, 4 timepoints between 2 drug administrations (30', 60', 2-4h, 4-8h)

10.3. Sample Handling & Analysis

Nasopharyngeal (or combine nose/throat) swab: PCR

Gene expert Cepheid

The Xpert Xpress SARS-CoV-2 test is an automated in vitro diagnostic test for qualitative detection of nucleic acid from SARS-CoV-2. The Xpert Xpress SARS-CoV-2 test is performed on GeneXpert Instrument Systems. The GeneXpert Instrument Systems automate and integrate sample preparation, nucleic acid extraction and amplification, and detection of the target sequences in simple or complex samples using real-time PCR assays. The systems consist of an instrument, computer, and preloaded

software for running tests and viewing the results. The systems require the use of single use disposable cartridges that hold the RT-PCR reagents and host the RT-PCR process. Because the cartridges are self-contained, cross-contamination between samples is minimized. For a full description of the systems, see the GeneXpert Dx System Operator Manual or the GeneXpert Infinity System Operator Manual. The Xpert Xpress SARS-CoV-2 test includes reagents for the detection of RNA from SARS-CoV-2 in nasopharyngeal, oropharyngeal, nasal, or mid-turbinate swab and/or nasal wash/aspirate specimens. A Sample Processing Control (SPC) and a Probe Check Control (PCC) are also included in the cartridge utilized by the GeneXpert instrument. The SPC is present to control for adequate processing of the sample and to monitor for the presence of potential inhibitor(s) in the RT-PCR reaction. The SPC also ensures that the RT-PCR reaction conditions (temperature and time) are appropriate for the amplification reaction and that the RT-PCR reagents are functional. The PCC verifies reagent rehydration, PCR tube filling, and confirms that all reaction components are present in the cartridge including monitoring for probe integrity and dye stability. The nasopharyngeal, oropharyngeal, nasal, or mid-turbinate swab specimen and/or nasal wash/aspirate specimen is collected and placed into a viral transport tube containing 3 mL transport medium or 3 mL of saline. The specimen is briefly mixed by rapidly inverting the collection tube 5 times. Using the supplied transfer pipette, the sample is transferred to the sample chamber of the Xpert Xpress SARS-CoV-2 cartridge. The GeneXpert cartridge is loaded onto the GeneXpert Instrument System platform, which performs hands-off, automated sample processing, and real-time RT-PCR for detection of viral RNA.

Because of current limitation to perform these tests in house due to the high demand in the COVID epidemic, we looked for alternatives:

- In house PCR based on the protocol of Corman et al. Eurosurveillance 2020 can be used:
  - Real-time reverse transcription PCR, Extraction with Easymag from Biomérieux, amplification on CFX96 from Bio-Rad.
  - Target = Egene
  - Internal control (this is added to the sample before extraction; amplification of this signal is a sign of good extraction and succeeded PCR) Diagenode RNA extraction and inhibition Real-Time PCR
  - Startvolume = 200µL/sample.
- Besides PCR, we will perform Antigen testing on the NFS samples. RNA extracted from NFS samples will be shipped to Sciensano and both Antigen testing and 3 PCRS (E-gen, CDC N1 and N2 test and RdRP Pasteur assay) will be performed at Sciensano. This way we will have ample comparative data. Antigen ELISA SARS COV 2: test kitEQ 2606-9601 is used from Euroimmun. The test kit contains microplate strips each with 8 reagent wells coated with a monoclonal anti-SARS-CoV-2 antibody. Throat swabs and controls should be lysed before pipetting them into the reagent wells in the first incubation step. In the second incubation step, biotinylated anti-SARS-CoV-2 antibody is added to the sample which is then detected by streptavidin-bound horseradish peroxidase. The colour intensity is proportional to the SARS-CoV-2 antigen concentration in the sample.

Neutralising AB test:

A standard 3 or 5ml collection tube is enough to get about 1 to 2ml of serum, that would be more than sufficient and allow to repeat analysis if needed.
After clotting it should be centrifuged (1,000–2,000 x g for 10 minutes ideally in a refrigerated centrifuge, but room temperature is also fine), transferred to a new tube and stored at -80°C before it is shipped. Serum samples should be stored at the clinical trial site at – 80°C and shipped to Sciensano on dry ice. There they will be stored at -80°C and analyzed when enough samples for a common seroneutralisation run are available. After analyses have been performed, all residual material will be destroyed by Sciensano.

Microneutralisation Assay:
Vero-E6 cells are seeded in 96 well plate at 2.10^4 cells/well. The day after, 100 TCID50 of virus (strain BetaCoV/Belgium/S1871/2020) are incubated with serial 2-fold dilutions of sera, starting from 1:10, in 100 µl of DMEM for 1 hour at 37°C. Mixes are then added to cells and incubated for 4-5 days at 37°C. Cytopathic effect (CPE) reading is performed by direct observation under the microscope and after cell coloration with crystal violet. Microneutralisation titers are expressed as the serum dilution for which 50% neutralisation is observed.

PK/PD substudy analyses:

Blood (2x 3ml) is sampled on ice and collected in citrate tubes at 4 timepoints between 2 drug administrations at the Ghent University Hospital (between D1 and D5, on the same day: at 30', 60', 2-4h, and 4-8h).

The inhibitor diisopropylflurophosphat (DFP) (Sigma-Aldrich (Merck) cat. No. D0879-1G), dissolved in 2-propanol at 1 M (184 mg/ml)10 ul of this solution added to 1 ml blood, ie. 30 ul in 1 citrate-tube that contains 3 ml blood. The solution will be added to the tube prior to use. These tubes are then transferred to the COVID consultation and kept on ice. After blood is drawn (via venous puncture or from a venous catheter that will remain in place for the 4 consecutive PK blood samples), blood will be aspirated using a syringe and the blood is transferred at the COVID consultation to the tubes containing the inhibitor and transferred immediately after on ice to the MRB2 lab. The blood sample is centrifuged at 1000-2000 g for 10-20 min at 4°C at Ghent University Hospital as soon as possible after the sampling. The plasma is stored within one hour at -80°C at HCRC lab until shipment for bio-analysis at the Aarhus University Hospital, Denmark (prof. Mads Fuglsang and team).

PK/PD data analysis will be performed at the Heymans Institute of Pharmacology, Ghent university (Prof. dr. P. De Paepe and dr De Cock) and the Leiden Academic Centre of Drug Research, Leiden, The Netherlands (prof Coen van Hasselt and team).
After analysis, all PK/PD residual material will be destroyed by the Aarhus University.
Samples that are not shipped for PK/PD analysis, will be stored in the prospective Biobank HCRC for future studies.

Odor sampling substudy:
Sampling at hospital.

Odor measurement is performed by means of a sterile cotton pad or gauze worn, rubbed or kept in the axilla and groin for approx. 60 min.

- Sterile cotton pads or gauze are put by the patient under the armpit for 60' to capture the odor.
- After this time, the cotton pad is transferred by the patient into a sterile plastic bag.
- The caretaker then transfers the bag into an extra sterile plastic bag and stores the sample in the freezer (-20°C or -80°C).
- For long term storage, it is best to store the sample as cold as possible (-80°C or on dry ice).

Transport of samples.

- A trained person transfers the samples in a closed container on dry ice to the dog training center (K9 Training Centrum, Brugsesteenweg 105 8450 Bredene, responsible: Johan Weckhuyzen (CEO))
- Ideally, the sample is kept in the cold chain until it reaches the training center.
- The container is marked with address of origin, address of final destination.

- The box cannot be opened during transportation.
- The box is marked with the proper logo's for these types of samples.

Sampling at odor assessment location.

- The samples are opened by a trained person in a well-ventilated room. One skilled person is handling the samples, using gloves, plastic arm cover, labcoat and mouth mask.
- The cotton pads are presented to the dogs behind a wall so that there is no direct contact between nose of the dog and the cotton pad. There is a distance of min 15cm between cotton pad/gauze and the dogs nose.
- The odor containers are aluminum containers with a cone-like outlet. After odor assessment, the aluminum containers are sterilized using ethanol 70%.
- The cotton pads are destroyed after usage at the site (K9 Training Centrum)

COVIM2.0 substudy

Immunological assays that will be performed include lipidomics, immunophenotyping, single cell RNA seq, serologic testing and cytokine analysis. Novel mediators of the so-called immune resolution pathways have been recently identified, collectively described as "pro-resolution" factors that include lipoxins, resolvins, protectins and maresins. So far, their presence and their impact on adaptive immune responses controlling viral replication has rarely been studied, especially not in the context of the emerging SARS-CoV2 epidemic. Therefore, deep characterization of patients' inflammatory profile offers a unique opportunity for comprehensive understanding of the pathophysiological mechanisms behind SARS-CoV2.

- The lipidomics analysis will be performed at the laboratory of Dr. Jesmond Dalli (London, U.K.). Plasma (1ml) will be extracted from fresh blood samples and stored at -80°C until shipment.
- In addition, we will study immunological functions on the level of both adaptive and innate immunity by performing extensive immunophenotyping, cytokine analysis and RNA sequencing analysis. Biomarker analysis will be performed on protein and on RNA single cell level. Infectivity of different cell types including macrophages will performed.
  These analyses will be performed at the HCRC laboratory, the laboratory of Prof. Rafick-Pierre Sékaly (Cleveland, U.S.) and the VIB-UGent Center for Inflammation Research.
  PBMCS and plasma will be extracted from blood and stored at HCRC Biobank (PBMCs in liquid nitrogen, plasma at-80°C). 2ml of plasma and 10 million PBMCs will be shipped to the lab of Sekaly. The rest of the PBMCs and plasma will be stored at HCRC until they are being used.
- To gain a deeper understanding of pathways potentially leading to severe disease courses, and also to chart where in the body there is tissue damage (apart from the lungs), we aim to analyze patient plasma samples with several other analytics technologies as well.
  * Bacterial extracellular vesicles, due to microbial translocation after hyperinflammation, will be quantified from plasma in the laboratory of Experimental Cancer Research of Ghent University.
  * Furthermore, normal cell turnover in tissues results in the release of some of their nucleic acid content into the blood. This can then be found as circulating free RNA and DNA (cfRNA and cfDNA). These analyses will be performed at the laboratory of Prof. Jo Vandesompele

(Biogazelle nv). Plasma will be extracted from fresh blood and stored at -80°C. 1ml of plasma will be shipped for analysis.

After analysis, all COVIM2.0 residual material of samples that were shipped, will be destroyed by the party that did the analysis. The samples that are stored in the HCRC Biobank and that are not used for studies described in COVIM2.0 will remain there for 25 years and can be used for future studies.
Virological evaluations will be based on nasopharyngeal swab samples, used to diagnose and quantify SARS-CoV2. **In addition** a swab will be taken to culture the SARS-CoV2 virus at D0. This will be repeated at D5, D10 and D28 if PCR is positive at these timepoints (an extra swab will be taken). On a selection of nasopharyngeal swab samples from patients whole genome sequencing of the SARS-CoV2 virus will be performed to study the viral diversity and trace patterns of spread across multiple epidemiological scales. In addition, viral metagenomics analysis using Nanopore sequencing will be used to reveal the presence of other viruses besides SARS-CoV2. These analyses will be performed at the HCRC laboratory, the Laboratory of Microbiology of Ghent University Hospital and the Laboratory of Virology of the Department of Veterinary Medicine of Ghent University. These analysis will be done on RNA extracted from the swab in the core study.

Viral culture will be performed in collaboration with the Xavier Saelens lab (VIB). Viral swabs will be transferred immediately after sampling and put into culture in the lab.

Screening failure substudy

Blood analysis at D28 will be sent to Sciensano for antibody analysis cfr core study. An additional swab at D0 will be taken for viral culture cfr COVIM2.0 study.

Additional blood analyses

Monitoring of safety and severity of the infection : SOC laboratory analysis as described above

POC CRP: Afinion CRP (immediate analysis on blood spot) or CRP through the routine lab: SOC laboratory analysis as described above

10.4. Sample Storage and/or shipping

Nasopharyngeal (or combined nose/throat) swabs: Storage at the microbiology department (Ghent University Hospital). RNA extraction. PCR. Because of limitations to perform these analysis in house, samples will be shipped to Sciensano for Antigen detection and 3 PCRS as described above.

If available, samples will be stored for resistance analysis (-80°C). After analysis, samples will be kept at the biobank at Ghent University Hospital for future research. POC CRP: immediate analysis after capillary blood extraction through the Afinion platform. Sample is destroyed immediately after analysis.

Nabs: 2ml of serum stored at -80° at HCRC Biobank. Batch shipment to Sciensano. After analysis, residual material will be destroyed by Sciensano.

Samples for PK/PD will be stored after centrifugation at -80°C until analysis at the Biobank HCRC. They will be shipped to Aarhus University for analysis. After analysis, residual material will be destroyed by Aarhus University. Samples that are not shipped for PK/PD analysis, will be stored in the prospective Biobank HCRC for future studies.

COVIM2.0 samples: isolated PBMCs from blood and plasma will be stored at the Biobank at Ghent University Hospital. Plasma will be stored at -20°/-80°C and PBMCs will be transferred to Liquid nitrogen. 1ml plasma will be transferred to the lab of Jo Vandesompele (Biogazelle) for cell free RNA sequencing. 1ml of plasma will be shipped to the lab of Desmond Dalli for lipidomics study. 2ml plasma and 10 MIO PBMCs will be shipped to the lab of Raffick Sekaly. Selected samples of RNA extracted from the nasopharygeal swab will be shipped to the lab of Hans Nauwynck for whole genome sequencing (WGS) and metagenomics sequencing. After analysis, all COVIM2.0 residual material that was shipped, will be destroyed by the party that did the analysis. The samples that are stored in the HCRC Biobank and that are not used for studies described in COVIM2.0 will remain there for 25 years and can be used for future studies.

The cotton pads for odor analysis are transferred to a sterile bag and stored in the freezer at Ghent University Hospital (-20-80°) until transfer to the dog training centre (K9 Training Centrum, Brugsesteenweg 105 8450 Bredene, responsible: Johan Weckhuyzen (CEO)). Samples for odor analysis will be destroyed after the analysis at the K9 training centre.

Swabs from screening failure substudy: viral culture cfr COVIM2.0. Blood from screening failure substudy: Antibody analysis will be done by Sciensano, cfr core study.

SOC blood analysis and toxicity labs will be performed by the routine lab and will be destroyed according to SOC.

10.5. Future use of stored samples

Samples that remain in Ghent will be stored for 25 years at Ghent University Hospital Biobank.

Samples for neutralizing antibody detection and PK/PD samples will be destroyed after analysis in external laboratories we collaborate with (Sciensano; Aarhus University, Denmark). Plasma that will not be sent to these labs, will be stored at the UZ Ghent Biobank for 25 years, to be used in future clinical research.

Nose/throat swabs will be stored in the UZ Ghent Biobank for 25 years, to be used in future clinical research.

Samples for odor analysis will be destroyed after the analysis at the dog training centre.

Samples for COVIM2.0 analysis that are sent to external collaborators will be destroyed after analysis. All COVIM2.0 residual material that was shipped, will be destroyed by the party that did the analysis. The samples that are stored in the HCRC Biobank and that are not used for studies described in COVIM will remain there for 25 years and can be used for future studies.

Samples from the screening failure substudy (blood/swab): cfr neutralizing antibody detection Sciensano, viral culture COVIM2.0.

11. Statistical Considerations

11.1. Sample size calculation

This is a pilot trial where we want to assess the value of Camostat as a potential candidate for a larger trial in the ambulatory setting where the primary objective would be to prevent hospitalisation and to improve outcome in COVID infection if initiated in an early stage.

This pilot will assess the efficacy of Camostat in terms of viral clearance, confirm its safety and look at the pharmacokinetic profile. Neutralising Abs will be assessed after 28 Days. The trial is adaptive and can be adjusted if new data on PK/PD, safety or efficacy becomes available.

All tests performed will be tests of superiority.

For the primary endpoint, we will test the hypothesis that camostat mesylate results in a significantly greater change from baseline (D0) to day 5 in respiratory (Nasopharyngeal (or combined nose/throat) swab RT-PCR) log 10 viral load compared to placebo.

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).

POPULATIONS FOR ANALYSES

Intention-to-Treat Analysis Dataset: Participants will be analyzed based on their treatment assignment.

Per Protocol Analyses Dataset: All participants completing the study who complied with the protocol.

Safety Analysis Dataset: all study participants.

11.2. Type of statistical methods

GENERAL APPROACH

All primary analyses will be performed as intent-to-treat analyses with a type I error rate of 5% (two-sided). Parametric distributional assumptions will be checked. If assumptions fail, other distributions will be considered prior to transformations and non-parametric methods. SAS (version 9.4) or the latest version of R (currently 3.6.3) will be used to analyze the data.

ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary analysis will be according to intent-to-treat and conducted using ANCOVA, adjusting for baseline log 10 viral load (or conversion from Ct value assuming 1 log 10 = 3.3 Ct units). We will use the t-statistic for the treatment effect to determine whether the treatment is statistically different from the placebo at the overall 10% level of significance, controlling for baseline log 10 viral load. Because of the interim analysis (see below), a p-value of 0.06 (2-sided), corresponding to an efficacy boundary value of 1.875 at the last look, will be used for the level of significance for the primary outcome at the final analysis. In sensitivity analyses, we will adjust for age and time since onset of symptoms. We will also conduct a per-protocol analysis as a secondary analysis. We will assess the missing mechanism and the impact of missing data. Sensitivity analyses under either missing at random or missing not at random will be considered, as appropriate.

ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary outcomes of interest include change of COVID-19 symptom score from baseline (day 0), as measured at D1→D14 and D28. Linear mixed models will be used to describe trajectories of change in the symptom score. The models will include fixed effects for treatment, time and the interaction of treatment and time. An unstructured covariance pattern will allow for correlation between repeated observations. Differences in means at each timepoint will be estimated along with 90% confidence intervals. All statistical tests will be conducted at 5% level of significance (two-sided) with no adjustment for multiple testing.

Monitoring tool + questionnaires for symptoms and signs.

Time to complete absence of symptoms the components of the symptom assessment scale (e.g. nose, throat, cough); and hospitalization. Time to complete absence of symptoms will be analyzed using the Cox model and event-free rates determined by Kaplan-Meier. Individuals will be administratively censored at 28 days. Those who die will be censored at time of death. We will conduct sensitivity analyses using death as a semi-competing risk. Twenty-eight day hospitalization rates will be compared using an exact binomial distribution. We will also consider additional biomarkers (using similar methods as described for the primary and secondary outcomes) and the individual components of the symptoms (using similar methods as described above).

SAFETY ANALYSES

Safety will be reported by treatment arm using descriptive statistics (means and standard deviations or frequencies and counts) and assessed by comparing the adverse events in the treatment group using Type I error of 5% (2-sided); no control for multiplicity will be done for safety outcomes. We will consider Wilcoxon rank sum tests or two-sample t-tests for continuous outcomes and the exact binomial distribution for proportions.

BASELINE DESCRIPTIVE STATISTICS

Baseline characteristics (including demographic, lab, and clinical variables) will be presented by treatment group (camostat mesylate and placebo). Means and standard deviations will presented for continuous variables and frequencies and proportions will be presented for categorical variables. No inferential statistics will be presented.

MISSING DATA

Regarding missing data, we will try to limit the amount of missing data by setting up alarm systems to remind participants to adhere to these data collections. Regarding the parameters, the system of Byteflies can send a message through email or phone, to remind people to submit their data if this has not been done within the desired timeframe. For the questionnaire through the REDCap system, a daily email will be sent to the participants. We consider therefore that we can monitor and follow this up in a strict manner.

The study nurse will pay attention that on the specific day of PK/PD-sampling, all parameters and questionnaires are submitted during the patient's stay at the clinic.

We realise that missing data in an ambulatory care trial is a potential problem and we will also evaluate this and see whether a daily monitoring system is feasible in routine clinical care, whether patients are motivated enough to do this so that we can adjust this for future trails or a broader roll-out.

Concerning data analysis, we should primarily investigate the patterns of missing data in order to decide which technique(s) could be used to handle the missing data. In case of less than 5% missingness, this is ignorable and a complete-case analysis could be performed. Other options are single imputation, model-based methods for repeated measures (mixed models, generalised estimation equations) or multiple imputation.

11.3. Statistical analysis team

Dr. Wim Trypsteen, HCRC, wim.trypsteen@ugent.be

11.4. Interim analysis

An interim analysis will be performed if recruitment drops significantly (no inclusions for more than 2 weeks) or there is an important decrease in patients that have a positive screening test for COVID, and after at least 2/3 of the intended total amount of participants have been recruited. An interim analysis will be conducted to see whether significance is reached and whether it seems useful to continue the trial based on efficacity or futility in 3 endpoints: viral outcomes, symptom control and safety.

This interim analysis will be performed by an unblinded statistical team who will not perform any blinded tasks and/or have contact with participants. In case blinded study personnel becomes unblinded in order to perform the interim analysis, they will stay unblinded from that moment on and they cannot perform any more study related procedures which require being blinded. The interim analysis will be carried out as described above, in section 11.2.

12. Data handling

12.1. Method of data collection

Subjects that are included in the study, will be assigned a unique study number upon their registration in REDCap. On all documents submitted to the coordinating centre, sponsor or CI, patients will only be identified by their study number. The subject identification list will be safeguarded by the site. The name and any other directly identifying details will not be included in the study database.

12.1.1. Case Report Form

An electronic data capture (EDC) system, i.e. REDCap, will be used for data collection. Data reported on each eCRF should be consistent with the source data. If information is not known, this must be clearly indicated on the eCRF. All missing and ambiguous data will be clarified.

Only the data required by the protocol are captured in the eCRF. The eCRFs and the database will be developed, based on the protocol. The final eCRF design will be approved by the Coordinating Investigator.

All data entries and corrections will only be performed by study site staff, authorized by the investigator. Data will be checked by trained personnel (monitor, data manager) and any errors or inconsistencies will be clarified.

Before signing off the eCRF, the investigator must verify with the data manager that all data entries in the eCRF are accurate and correct.

REDCap is provided and maintained by Vanderbilt University; a license for use was granted to the Health, Innovation and Research Institute (HIRUZ). REDCap is a web-based system.

The study site staff is responsible for data entry in REDCap.

12.1.2. Data directly collected in the CRF (no source available)

Source documentation will be available for all information captured in the eCRF, except for the daily questionnaires which can be filled in directly through a link sent by email and transferred to the eCRF.

12.2. Data storage

The data is accessed through a web browser directly on the secure REDCap server. The server is hosted within the Ghent University Hospital campus and meets hospital level security and back-up requirements.

Privacy and data integrity between the user's browser and the server is provided by mandatory use of Transport Layer Security (TLS), and a server certificate issued by TERENA (Trans-European Research and Education Networking Association). All study sites will have access to REDCap. Site access is controlled with IP restriction.

12.3. Archiving of data

The investigator and sponsor specific essential documents will be retained for at least 25 years. At that moment, it will be judged whether it is necessary to retain them for a longer period, according to applicable regulatory or other requirement(s).

12.4. Access to data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit study-related monitoring, audits and inspections.

Login in REDCap is password controlled. Each user will receive a personal login name and password and will have a specific role which has predefined restrictions on what is allowed in REDCap. Furthermore, users will only be able to see data of subjects of their own site. Any activity in the software is traced and transparent via the audit trail and log files.

13. Safety

13.1. Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Unexpected Adverse Event	An adverse event, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).
Adverse Reaction (AR)	An untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject. The phrase "response to an investigational medicinal product" means that a causal relationship between a study medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the study medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity

	• consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the subject or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the study treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product • we expect that the adverse events described in the SmPC of the IMP are relevant for our dosing schedule, despite the fact that we use a slightly higher dose than what is used in the SmPC. However, a study that used the same dosing schedule as we propose currently, did not report adverse events different from those described in the SmPC (Sato et al, 1992). Recently, ONO pharmaceuticals conducted a study where they tested dosing up to 2400mg daily. They did not report any AE except for one person presenting with grade 1 hyperuricemia (unpublished data).

<u>Attribution definitions</u>

An adverse event is considered associated with the use of the drug if the attribution is possible, probable or definitive.

Not related

An adverse event which is not related to the use of the drug.

Unlikely

An adverse event for which an alternative explanation is more likely - e.g. concomitant drug(s), concomitant disease(s), and/or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event which might be due to the use of the drug. An alternative explanation - e.g. concomitant drug(s), concomitant disease(s), - is inconclusive. The relationship in time is reasonable; therefore the causal relationship cannot be excluded.

Probable

An adverse event which might be due to the use of the drug. The relationship in time is suggestive (e.g. confirmed by dechallenge). An alternative explanation is less likely - e.g. concomitant drug(s), concomitant disease(s).

Definitely

An adverse event which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation - e.g. concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g. it is confirmed by dechallenge and rechallenge).

13.2. Reporting requirements

13.2.1. AE reporting

AEs will be recorded from the first drug administration until the end of the study for the patient, as defined in section 5.2. The Institution and the Investigator shall record adverse events (serious and non-serious) on the Case Report Form from the time the subject has taken at least one dose of study treatment (D1) through the last visit of this subject (D28).

Special attention will be given to those subjects who have discontinued the study treatment for an AE, or who experienced a severe or a serious AE. All AEs should be recorded in the patient's file and in the CRF.

13.2.2. SAE reporting

SAEs occurring within a period of 30 days following the last intake of study medication will be reported as below.

All serious adverse events (initial and follow up information) and pregnancies occurring during this study must be reported by the study team within 24 hours after becoming aware of the SAE to:

- HIRUZ CTU of the Ghent University Hospital, who will report the SAE to the central ethics committee
- The company that provides the IMP (as stipulated in the agreement with Ono Pharmaceutical LTD)

This reporting is done by using the appropriate SAE form(s). For the contact details, see below.

13.2.3. SUSAR reporting

In case the Coordinating Investigator, in consultation with HIRUZ CTU, decides the SAE is a SUSAR (Suspected Unexpected Serious Adverse Reaction), HIRUZ CTU will report the SUSAR to the Central EC and the FAMHP within the timelines as defined in national legislation.

For fatal and life-threatening SUSARs the sponsor should report at least the minimum information as soon as possible and in any case no later than 7 calendar days after being made aware of the case.
In case of a non life-threatening SUSAR the reporting process must be completed within 15 calendar days.

13.2.4. Other reporting requirements

- report to Ono pregnancy occurring from the start of Clinical Study drug treatment to the completion of the final tests (other than the determination of outcome) within twenty-four (24) hours of becoming aware of the pregnancy by email. As for the pregnancy, the Investigator shall follow up the pregnancy until delivery or the end of pregnancy;

- provide Non-serious Adverse Events (NSAEs) to Ono by completing and signing a designated CIOMS II Line listing form** in English. Such Line listing shall be sent via email to [pmsmailbox@ono.co.jp] at the completion of the Clinical Study. NSAE means any Adverse Event that does not meet any of the "Serious" criteria described above.

** See p.35 of final report of CIOMS Working Group II:

https://cioms.ch/wp-content/uploads/2018/09/cioms-international-reporting-periodic-drug-safety-update-summaries.pdf

- cooperate with Ono and its affiliates in the case Ono or its affiliates needs the follow-up investigation on the concerned case. The Investigator shall respond to the queries made by Ono or its affiliates promptly after receiving them and forward the information to Ono by e-mail. Follow up may also be requested by Ono or its affiliates if an SAE information is considered to be incomplete or if Ono or its affiliates determines that additional follow up information is required. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information shall be reported; and

- cooperate with Ono and its affiliates to enable Ono and its affiliates to comply with their obligations in relation to the reporting of adverse effects under applicable laws, regulations and/or acts.

13.3. List of contact details for safety reporting

HIRUZ CTU :	e-mail:	hiruz.ctu@uzgent.be
	Tel:	+3293320500
Coordinating Investigator:	email:	steven.callens@uzgent.be
	Tel:	+3293320171

Marketing Authorisation Holder: Name: Ono Pharmaceutical Co., Ltd. (Osaka, Japan)

e-mail: pmsmailbox@ono.co.jp

Since the subjects are not under 24-hour supervision of the investigator or his/her staff (out-patients, volunteers), they (or their designee, if appropriate) must be provided with a "study card" indicating the name of the investigational product, the study number, the investigator's name and a 24-hour emergency contact number.

13.4. Flowchart Reporting

Type of Adverse Event	*Action to be taken*
AE	List all AEs per subject in the patient's file and add this information to the CRF. → study team informs company that provides the IMP (of all NSAEs, only for patients in the Camostat arm)
SAE	Notify to HIRUZ CTU within 24 hours after becoming aware of the SAE + add the SAE to a list that will be reported yearly (see section 13.7) → HIRUZ CTU will submit to the central EC → study team informs company that provides the IMP (only for patients in the Camostat arm)
SAR	Notify to HIRUZ CTU within 24 hours after becoming aware of the SAR → HIRUZ CTU will submit to the central EC → study team informs company that provides the IMP (only for patients in the Camostat arm)
SUSAR	Notify to HIRUZ CTU within 24 hours after becoming aware of the SUSAR → HIRUZ CTU will submit to the central EC. → HIRUZ CTU will submit to the FAMHP → study team informs company that provides the IMP (only for patients in the Camostat arm)
Pregnancy	→ study team informs company that provides the IMP (only for patients in the Camostat arm)

13.5. Events, excluded from reporting

Not applicable.

13.6. Data Safety Monitoring Board (DSMB)

We will make use of the 'DSMB COVID-19 trials Dept. Internal Medicine' at Ghent University Hospital. Although the medication is current practice in Japan and no significant adverse effects have been reported in a clinical trial with the dosing that will be used, this dose is not registered (SmPC) and furthermore the drug itself is not licensed in Europe. This way we are providing an additional safety evaluation of the Camostat dosing. The DSMB charter can be found as appendix 9.

13.7. Development Safety Update Report

The Coordinating Investigator will provide DSURs once a year throughout the clinical study, or on request, to the Competent Authority (FAMHP in Belgium), Ethics Committee and Sponsor. This DSUR will include all SAEs (who were not categorized as SARs and were not immediately reported to the EC).

The report will be submitted within 60 days after one year after the start of the study (FPI), and will subsequently be submitted each year until the study is declared ended.

HIRUZ CTU can provide a template that can be used to complete this DSUR.

14. Monitoring/Auditing/Inspection

14.1. Monitoring

14.1.1. General

Monitoring of the study will be performed in compliance with GCP E6(R2) and the applicable regulatory requirements. The study team will be trained in an initiation visit by the monitor. A detailed description of the monitoring tasks can be found in the latest version of the (study-specific) 'Monitoring plan'.

14.1.2. Monitoring team

Monitoring services will be provided by HIRUZ CTU. All relevant contact details (e.g. primary contact person), can be found in the 'Monitoring plan'.

14.1.3. Scope

Monitoring services will consist of the following (non-exhaustive list):

- review of informed consents and the followed process
- check on recruitment status
- checking for protocol deviations/violations
- checking GCP compatibility
- check on safety reporting compliance
- IMP handling and storage

- review of study data
- …

14.2. Inspection

This study can be inspected at any time by regulatory agencies during or after completion of the study. Therefore access to all study records, including source documents, must be accessible to the inspection representatives. Subject privacy must be respected at all times, in accordance to GDPR, GCP and all other applicable local regulations.

The investigator/study team should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

14.3. Protocol Deviation policy

Sponsor and all investigators agree to take any reasonable actions to correct protocol deviations/violations noted during monitoring/inspection, in consultation with the monitoring team. All deviations must be documented on a protocol deviation log by the study team that is kept available at any time for monitoring/inspection purposes. Under emergency circumstances, deviations from the protocol to protect the rights, safety or well-being of human subjects may proceed without prior approval of the sponsor and the EC.

14.4. Serious breach to GCP and/or the protocol

Critical issues that significantly affect patient safety, data integrity and/or study conduct should be clearly documented and will be communicated with the Coordinating Investigator, HIRUZ CTU and possibly both the applicable Ethics Committee(s) and Competent authority. (Please contact HIRUZ CTU asap in case of a serious breach: hiruz.ctu@uzgent.be and/or +3293320500).

Early termination of the study (in a specific center or overall) may be necessary in case of major non-compliance.

15. Ethical and legal aspects

15.1. Good Clinical Practice

The study will be conducted cfr the latest version of the ICH E6 (R2) GCP guidelines, creating a standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of

clinical studies that provides assurance that the data and reported results are accurate and that the rights, integrity and confidentiality of study subjects are protected.

15.2. Informed Consent

Eligible subjects may only be included in the study after providing written (witnessed, if needed) Ethics Committee-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative(s) of the subject.
Informed consent must be obtained before conducting any study-specific procedures (as described in this protocol).

Prior to entry in the study, the investigator must explain to potential subjects or their legal representatives the study and the implication of participation. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. Participating subjects will be told that their records may be accessed by competent authorities and by authorized persons without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) and/or regulations. By signing the Informed Consent Form (ICF), the subjects or legally acceptable representatives are authorizing such access.

After this explanation and before entry to the study, written, dated and signed informed consent should be obtained from the subject or legally acceptable representative. The ICF should be provided in a language sufficiently understood by the subject. Subjects must be given the opportunity to ask questions.

The subject or legally acceptable representative will be given sufficient time to read the ICF and to ask additional questions. After this explanation and before entry to the study, consent should be appropriately recorded by means of either the subject's or his/her legal representative's dated signature or the signature of an independent witness who certifies the subject's consent in writing. After having obtained the consent, a copy of the ICF must be given to the subject.

In case the subject or legally acceptable representative is unable to read, an impartial witness must attest the informed consent.

The following information should be added to the electronic patient dossier (EPD):

- which version of the ICF was obtained
- who signed the ICF
- if sufficient time has been given to consider participation into the study
- which investigator obtained ICF with the date of signature
- if a copy was provided to the patient
- start and end of participation in the study

15.3. Approval of the study protocol

15.3.1. General

The protocol has been reviewed and approved by the Ethics Committee of the Ghent University (Hospital), designated as the central Ethics Committee, and the Federal Agency for Medicine and Health Products (FAMHP). This study cannot start before both approvals have been obtained.

15.3.2. Protocol amendments

Any significant change or addition to the protocol can only be made in a written protocol amendment that must be approved by the Central Ethics Committee (and the FAMHP if applicable).

Only amendments that are intended to eliminate an apparent immediate safety threat to patients may be implemented immediately.

Notwithstanding the need for approval of formal protocol amendments, the investigators are expected to take any immediate action, required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. These actions should always be notified to the sponsor.

15.4. Confidentiality and Data Protection

All study data will be handled in accordance with the law on General Data Protection Regulation (GDPR) and institutional rules [Belgian law dated on 30 July 2018 and 22 Aug. 2002].

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations.
Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor and site personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.
The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, Ethics Committee review and regulatory inspection. This consent also addresses the transfer of the data to other entities, if applicable.

Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.
Stored samples will be pseudonymized throughout the sample storage and analysis process and will not be labeled with personal identifiers.

15.5. Liability and Insurance

The sponsor has taken a no fault insurance for this study, in accordance with the relevant legislation (article 29, Belgian Law of May 7, 2004).

Sponsor: Ghent University Hospital
Insurance Details: Allianz Global Corporate & Specialty, Uitbreidingstraat 86, 2600 Berchem, tel: +32 33 04 16 00
Polis number: BEL000862

15.6. End of Study Notification

If all subjects have completed the study, a notification of the end of the study should be submitted to the (Central) Ethics Committee and FAMHP. This notification should be made within 90 days of the end of the clinical study. In case of early termination (definition in CT-1, 4.2), this is reduced to 15 days.

16. Publication policy

Because of the global interest in finding antiviral drugs that can be used in the treatment of COVID-19, available data will be made public as soon as possible.

We hope to have the publication data available as soon as possible but will be limited by the number of patients that are currently presenting with COVID-19.

This study will be registered at ClinicalTrials.gov, and results information from this study will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

17. Reference List

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18. Appendices

18.1. Appendix 1: Study Schedule

18.2. Appendix 2: Questionnaire Daily self score

18.3. Appendix 3: Socio-demographic parameters

18.4. Appendix 4: Emergency ward flow chart

18.5. Appendix 5: Byteflies manual

18.6. Appendix 6: Parameter log

18.7. Appendix 7: Medication log

18.8. Appendix 8: Proposed cut-offs for abnormal values

18.9. Appendix 9: DSMB charter

18.10. Appendix 10: Toxicity lab