"CAMOVID: A multicenter randomized trial to evaluate the efficacy and safety of camostat mesylate for the treatment of SARS-CoV-2 infection – COVID-19 in ambulatory adult patients"

INTERVENTIONAL RESEARCH PROTOCOL INVOLVING HUMAN PARTICIPANTS CONCERNING A MEDICINAL PRODUCT FOR HUMAN USE
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SIGNATURE page for a research PROTOCOL

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Title: CAMOVID: A multicenter randomized trial to evaluate the efficacy and safety of camostat mesylate for the treatment of SARS-CoV-2 infection – COVID-19 in ambulatory adult patients

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The study will be carried out in accordance with the protocol, with current good practices and with statutory and regulatory requirements.

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1 SUMMARY

Full title	CAMOVID: A multicenter randomized trial to evaluate the efficacy and safety of camostat mesylate for the treatment of SARS-CoV-2 infection – COVID-19 in ambulatory adult patients
Acronym/reference	CAMOVID
Coordinating investigator	Dr David BOUTBOUL
Scientific Director	Pr Lara ZAFRANI
Sponsor	Assistance Publique – Hôpitaux de Paris
Scientific justification	Since December 2019, a novel coronavirus called SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) has caused an international outbreak of respiratory illness described as COVID-19. On the 22nd March 2020, 2920142 confirmed cases of COVID-19 including 12784 deaths were reported by The World Health Organization (1). On the 31 March 2020, there were 52827 severe cases in France, including 3532 deaths. The spectrum of symptomatic infection ranges from mild to critical. If most infections are not severe, 15% of infected patients will require hospitalization and 5% will require intensive care unit admission (2). The diagnosis of SARS-CoV-2 infection relies on clinical symptoms and microbiological testing. To test for SARS-CoV-2 infection, testing centers use a reverse-transcription polymerase chain reaction (RTPCR) on nasal swab in patients with productive cough. A number of investigational agents are being explored for antiviral treatment of COVID-19. However, to date, there are no controlled data supporting the use of any specific treatment (anti-viral drugs or immunomodulatory drugs), and their efficacy for COVID-19 is unknown (3). SARS-CoV-2 infects human cells through the binding of its spike (S) protein to the membranous aminopeptidase called ACE2 (Angiotensin Converting Enzyme 2). Among other tissues, ACE2 expression has mainly been found on pneumocytes, enterocytes, renal tubular cells and podocytes. Cellular entry of SARS-CoV-2 requires S protein priming by cellular serine protease TMPRSS2, which entails S protein cleavage and allows fusion of viral and cellular membranes (4). In a murine model of SARS-CoV pneumonia, Iwata-Yoshikawa et al. showed that TMPRSS2-KO mice had weakened inflammatory cytokine responses and reduced lung injury than control mice (5). Hoffmann et al. found that a TMPRSS2 inhibitor, the camostat mesylate, blocked viral entry and reduce infection of human primary pneumocytes and lung cell lines by SARS-CoV-2. They also showed that the sera from convalescent SARS patients cross-neutralized SARS-2-S-driven entry (4). Another study performed by Bojkova et al (5) showed that camostat mesylate reduced cytopathogenic effect due to SARS-CoV-2 in human colonic cell lines. Camostat mesylate is a serine protease inhibitor that is commonly used in Japan (at a dose of 600 mg/day) and has been successfully and safely used to treat pancreatitis-associated pain (6) and post-operative reflux oesophagitis (7). Side effects that have been reported are rare at these doses (nausea, diarrhea,

	hypersensitivity in 0.1 to 0.5% of the cases, cytopenias in less than 0.1% and hyperkaliemia and abnormal hepatic function in less than 0.05%). We hypothesize that camostat mesylate, initiated early in SARS-CoV2 infection, can reduce viral infection and viral cytopathogenic effect by blocking SARS-CoV2 entry into cells, and therefore prevent deterioration toward severe forms of COVID19.
Main objective and primary endpoint	Objective: Evaluate the efficacy of camostat mesylate in the treatment of SARS-CoV-2 infection in high-risk adult patients with confirmed COVID-19 not requiring initial hospitalization, , in terms of hospitalization needs, up to day 21 after randomization Primary endpoint: Proportion of patients hospitalized for COVID-19 deterioration or who died without hospitalization between day 1 and day 21. As an indicative basis, criteria for hospitalization will be the presence of any of the following: respiratory rate > 24 /min at rest, Sp02 < 95% on room air, blood pressure < 100 mmHg, lethargy or unconsciousness, brutal overall deterioration or lethargy in the elderly [HCSP] and any all other reasons requiring hospitalization left at the discretion of the physician
Secondary objectives and endpoints	Secondary objectives : In adult patients diagnosed with laboratory confirmed COVID-19 not requiring initial hospitalization, to evaluate the impact of camostat mesylate compared to placebo on: - Safety up to day 21 - Efficacy in terms of need for hospitalization for COVID-19 management, by independent blinded committee review - Overall clinical improvement at day 21 - Clinical efficacy in terms of intensive care needs, up to day 21 - Clinical efficacy in terms of time to hospitalization, up to day 21 - Clinical efficacy on respiratory functions, up to day 21 - Overall survival at day 21 and 90 after randomization - Patient-reported outcome on initial symptoms, up to day 21 - Virological, serological and immunological efficacy, up to day 90, including surrogacy assessment of candidate markers up to day 90 - Renal complications, up to day 21 - Liver complications, up to day 21 - COVID-19 transmission within the same household Secondary endpoints : - Adverse events (AEs) : number of AEs, number of serious AEs (SAEs), investigational medication discontinuation (for any reason), up to 21 days - Independent endpoint adjudication committee-reviewed proportion of patients hospitalized between day 1 and day 21, for COVID-19 deterioration. The independent EAC will review patients'files, blinded to the randomized group, and determine whether hospitalization criteria were related to COVID-19 or not. - WHO COVID-19 clinical improvement ordinal scale [3], at day

7, 14 and 21

OMS Progression scale	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalized : mild disease	Hospitalized; No oxygen therapy	3
	Hospitalized; oxygen by mask or nasal prongs	4
Hospitalized : severe disease	Hospitalized; oxygen by NIV or High flow	5
	Intubation and Mechanical ventilation	6
	Mechanical ventilation + additional organ support – pressors, RRT, ECMO	7
Dead	Dead	8

- Admission to an ICU within 21 days from inclusion
- Number of days alive without hospitalization, up to 21 days

- Initiation of invasive mechanical ventilation for COVID19-severe within 21 days from inclusion
- Initiation of oxygen-therapy for COVID19 within 21 days from inclusion
- Overall survival up to day 90
- Number of days alive without symptoms, up to day 21
- SARS-CoV-2 virological assessment at day 1, day 7, day 14 and day 21 (nasal swab and droplet quantification of SARS-CoV2 RNAemia)
- SARS-CoV-2 serological assessment at day 1, day 7, day 14, day 21
- Plasma IL-6, IL-1b, TNFa, IL-8 levels at day 1, 7, 14
- Peripheral blood lymphocyte phenotyping and telomere length measurement at day 1, day 7, day 14
- Acute kidney failure defined as at least serum creatinine increase of 0.3mg/dl or 1.5-1.9 times baseline and/or oliguria < 0.5ml/kg/h (KDIGO2012 scale), within 21 days
- Serum electrolytes and estimated Glomerular Filtration Rate at day 7, 14 and 21
- Liver transaminases, gamma-GT, alkaline phosphatase at day 7, 14 and 21
- Percentage of COVID-19 affected individuals sharing the same household at day 1, 7 and 14

Design of the study	Multicenter single-blinded placebo-controlled two-arm parallel 1:1 randomized phase III trial
Population of study participants	Ambulatory adult high-risk patients with laboratory confirmed COVID-19 not requiring initial hospitalization
Inclusion criteria	1) Patients ≥ 18 years old 2) Patients with an increased risk of severe COVID-19 belonging to one or more of the following groups : * Age ≥ 50 years * Body Mass Index ≥ 30 kg/m² * Diabetes * Hypertension * Chronic renal failure (eGFR <60 mL/min) * Chronic heart disease *Asthma/Chronic Obstructive Pumonary Disease/Cystic fibrosis * Chronic liver disease * Chronic neurological disease * Solid organ transplant * Bone marrow transplant * Sickle cell anemia/ Major thalassemias * Active *or* currently treated *or* <1 year diagnosed cancer * Active *or* currently treated *or* <1 year diagnosed malignant blood disease * Immunosuppressive treatment observed for more than 1 month 3) Laboratory confirmed SARS-CoV2 infection with mild COVID-19, fulfilling all the following criteria: - Positive SARS-CoV-2 RT-PCR nasal or saliva swab samples or positive SARS-CoV-2 antigen test performed within 96h of inclusion visit AND - Clinical symptoms and signs consistent with SARS-CoV2 infection including but not limited to, fever, upper respiratory tract infection signs, digestive signs, muscle pain, anosmia, dysgueusia…(1) 4) Informed consent to participate to the trial 5) Patients must be able and willing to comply with study visits and procedures
Exclusion criteria	1) Initial need for hospitalization for COVID-19 management : defined as any of the following severity criteria : respiratory rate > 24 /min at rest, Sp02 < 95% on room air, blood pressure < 100 mmHg, lethargy or unconsciousness, brutal overall deterioration or lethargy in the elderly (recommendations HCSP) all other reasons requiring immediate hospitalization left at the discretion of the physician 2) Pregnancy and breastfeeding 3) Participation to another interventional drug trial 4) Subject protected by law under guardianship or curatorship 5) Absence of health insurance 6) Known hypersensitivity to camostat mesylate 7) Known person sharing the same household already included in the study 8) Participation to another COVID-19 ambulatory interventional study

	9) Patients having completed a full SARS-CoV2 vaccine immunization procedure less than 4 weeks prior to COVID-19 diagnosis (last vaccine injection performed less than 4 weeks prior to COVID-19 diagnosis).
Investigational medicinal product(s)	Camostat mesylate, oral administration 600mg/day (2 x 100mg every 8 hours) for 14 days (day 1 to day 14)
Comparator treatment	Placebo tablets, following the same schedule as investigational drug
Interventions added for the study	Oral medication (camostat mesylate or placebo).
Expected benefits for the participants and for society	The trial will evaluate a candidate therapeutic strategy in the context of SARS-CoV-2 pandemics. Specifically, the proposed treatment targets ambulatory high-risk patients newly diagnosed with confirmed COVID-19, and not requiring initial hospitalization. The strategy aims to improve short-term outcomes in ambulatory patients and prevent clinical evolution to more severe forms, requiring hospitalization. It will therefore participate in reducing hospitalization needs (quantitative and qualitative and relieving the healthcare system) and may reduce contagiosity. Moreover, it can be a useful therapeutic option for ambulatory patients, with early diagnoses, in the management of the epidemics in the upcoming months and lockdown removal.
Risks and burdens added by the study	Additional risks are those of camostat mesylate. Known side effects are : digestive (nausea, vomiting diarrhea) and hypersensitivity < 0.5%, cytopenias <0.1%, liver abnormal function and hyperkaliemia in <0.05% Risk level of the study : D
Practical implementation	Patients will be screened from the consults of participating primary care general practitioners (GPs), 4 emergency departments (Saint Louis hospital, Bichat hospital, Mondor hospital and Argenteuil hospital), 2 hospital outpatientCOVID-19 screening center (Bichat hospital, Mondor hospital), outpatient consult of internal medicine at Saint Louis hospital and of the Sickle Cell Disease and inherited RBC genetic disorders, coordinating referral center. at Henri Mondor hospital . At the initial consult, patients will be screened for eligibility, with the standard of care sampling for SARS-CoV2 RT-PCR (nasal or saliva) or antigen test. Upon positive laboratory confirmation of COVID19, after information, eligible patients who consent to participate to the trial will be randomly assigned to one of the following treatments: - Arm A: camostat mesylate 600mg (2x100mg/8h) (n=298) - Arm B: Placebo (2 tablets/8h) (n=298) Patients will be blinded to the treatment arm. After the inclusion visit, follow-up visits will be performed at 7, 14, 21 and 90 days. Follow-up visits will include a medical interview (either in person or teleconsultation) and paramedical assessment by registered nurses with vital signs measurement and biological sampling. All included patients will benefit from standard of care ambulatory monitoring for COVID-19.

	Biological monitoring (blood sampling for serum electrolytes, creatinine and liver enzymes) and virological monitoring (RT-PCR on nasal swab) on day 7, 14, 21 will be performed locally, following standard practice in primary care. Data will be collected via a web-based standardized electronic case report form. In case of hospitalization, the hospital report will be used as source for data collection by the GP. Randomization will be performed centrally via a web-based system, to ensure allocation concealment, with the use of pre-specified randomization lists based on permutation blocks.
Number of participants included	N=596 planned From the current knowledge on SARS-CoV2 infection in adults , we expect roughly 20% of newly diagnosed high-risk patients being hospitalized within 21 days (8). The design initially included a planned interim analysis after one third of observations had been completed. A maximum total sample size of 536 evaluable patients (268 per treatment group) would allow 90% power to detect an absolute difference of 10% in the probability of hospitalization at day 21 between groups (e.g. reduction from 20% to 10%), using a z-test, with one-sided 2.5%-significance level for efficacy, using Lan & DeMets risk-spending functions (O'Brien & Fleming boundaries approximation), for efficacy and futility stopping rules. Overall, 596 patients (298 in each group) would be included to anticipate a potential 10% drop-out rate, given the ambulatory follow-up. However, due to the status of the pandemics as of fall 2021 and global use of vaccines, the scientific comittee decided to stop recruitment to eventually discontinue the trial early. The planned interim sample size has not been reached. Eventually, only a single final analysis will be performed at the 2.5% one-sided significance level, for the primary endpoints. Other endpoints will be analysed as planned.
Number of centres	Recruiting centers: 1. Emergency department of Saint Louis Hospital, Paris 2. COVID-19 screening center at Bichat hospital 3. Emergency department of Argenteuil hospital 4. Centre de Santé Richerand, 75010 Paris 5. Emergency department of H. Mondor hospital, Créteil 6. Outpatient consult of the infectious disease deparment – COVID screening center of Henri Mondor hospital, Créteil 7. Outpatient consult of the Sickle Cell Disease and inherited Red Blood Cell genetic disorders, coordinating referral center at H.Mondor hospital, Créteil 8. Post-emergency – Internal medicine department of H. Mondor hospital, Créteil 9. Department of Infectious and Tropical Diseases / Public Health Unit, Groupe Hospitalier Sud Ile de France (GHSIF), Melun 10. Emergency department of Lariboisière hospital, Paris Non-recruiting centers (follow-up visits):

	- Internal medicine department of Argenteuil hospital - Office of Dr K. Amazzough, 75011 Paris - Office of Dr J Marzouk, 75017 Paris
Duration of the study	- *inclusion period : 12 months* - *participation period (treatment + follow-up): 90 days* - *total duration : 15 months*
Number of enrolments expected per site and per month	5 patients/month/recruiting center (on average given the total required sample size and the planned inclusion period)
Statistical analysis	Descriptive analyses will use either frequencies and percentages for categorical variables, or median and interquartile range for quantitative variables. Number of missing values will be reported. The primary endpoint (probability of hospitalization within 21 days) will be compared between groups using a two-sided z-test. Secondary endpoints will be compared across groups using Fisher's exact test when comparing probabilities between groups and Wilcoxon's rank sum test when comparing quantitative endpoints. All analyses will be performed under the intention-to-treat principle. A 5% two-sided significance-level will be used for comparisons of secondary endpoints.
Funding sources	PHRC COVID-19-20-0095
Study will have a Data Safety Monitoring Board	Yes

2 GLOSSARY

ACE2: Angiotensin Converting Enzyme 2
AGEPS: Agence générale des équipements et produits de santé
AE: adverse event
ANSM: Agence nationale de sécurité du medicament et des produits de santé
APHP: Assistance Publique Hôpitaux de Paris
ALT: Alanine aminotransferase
ANC: Absolute neutrophil count
AST: Aspartate aminotransferase
BMI: Body mass index
BUN: Blood urea nitrogen
CNIL : Commission nationale informatique et libertés
COPD: chronic obstructive pulmonary disease
CPK: Creatinine phosphokinase
CPP: comité de protection des personnes
CRA: Clinical Research Associates
CRB : Centre de Ressources Biologiques
CRP: C Reactive protein
CRPV : Centre Régional de Pharmacovigilance
CTCAE : Common Terminology Criteria for Adverse Events
DRCI: Délégation à la Recherche Clinique et à l'Innovation
DSMB : Data safety monitoring board
DSUR: Development Safety Update Report
ECMO: extra corporeal membrane oxygenation
eCRF: electronic case report form
EMA: European Medicine Agency
ER: emergency room
Gamma-GT: gamma glutamyl transpeptidase
GCP: Good Clinical Practices
GP: general practitioner
HCSP: Haut Conseil à la Santé Publique
ICU : intensive care unit
ITT: intent to treat
IEAC : independent endpoint adjudication comittee
NIV : non invasive ventilation
PHRC: programme hospitalier de recherche clinique
PI : principal investigator
RTPCR: reverse-transcription polymerase chain reaction
SpO2: Peripheral oxygen saturation by pulse oxymeter
RRT: renal replacement therapy
SAE: serious adverse event
SBIM: Service de Biostatistique et Information Médicale
TMPRSS2: cellular serine protease
WHO: World health organization

3 SCIENTIFIC JUSTIFICATION FOR THE STUDY

3.1 Hypothesis for the study

We hypothesize that camostat mesylate, initiated in early SARS-CoV2 infection, can reduce viral infection, viral cytopathogenic effect and viral spreading, by blocking SARS-CoV2 entry into cells, and therefore prevent deterioration toward severe forms of COVID-19 in high-risk patients.

3.2 Description of knowledge relating to the condition in question

Since December 2019, a novel coronavirus called SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) has caused an international outbreak of respiratory illness described as COVID-19. On the 22nd March 2020, 2920142 confirmed cases of COVID-19 including 12784 deaths were reported by The World Health Organization(1). On the 31 March 2020, there were 52827 severe cases in France, including 3532 deaths. The spectrum of symptomatic infection ranges from mild to critical. If most infections are not severe, some individuals are at increased risk of developing severe COVID-19, with a 20% risk of hospitalization (8,9). These high-risk patients have been defined in recent publications (10,11).The diagnosis of SARS-CoV-2 infection relies on clinical symptoms and microbiological testing. To test for SARS-CoV-2 infection, testing centers use a reverse-transcription polymerase chain reaction (RTPCR) on nasal swab in patients. A number of investigational agents are being explored for antiviral treatment of COVID-19. However, to date, there are no controlled data supporting the use of any specific treatment (anti-viral drugs or immunomodulatory drugs), and their efficacy in ambulatory patients with COVID-19 is unknown(3).

3.3 Summary of relevant pre-clinical experiments and clinical trials

Several lines of evidence indicate that camostat could be a good candidate in the treatment of SARS-CoV-2 infection.

SARS-CoV-2 infects human cells through the binding of its spike (S) protein to the membranous aminopeptidase called ACE2 (Angiotensin Converting Enzyme 2). Among other tissues, ACE2 expression has mainly been found on pneumocytes, enterocytes, renal tubular cells and podocytes. Cellular entry of SARS-CoV-2 requires S protein priming by cellular serine protease TMPRSS2, which entails S protein cleavage and allows fusion of viral and cellular membranes (4). In a murine model of SARS-CoV pneumonia, Iwata-Yoshikawa et al. showed that TMPRSS2-KO mice had weakened inflammatory cytokine responses and reduced lung injury than control mice (12). A study by Zhou et al demonstrated that a TMPRSS2 inhibitor, the camostat mesylate reduced mortality in a murine model of SARS-CoV infection, when administered orally at a dosage of 8 mg/kg (13). Hoffmann et al. recently found that camostat mesylate, blocked entry of SARS-CoV-2 into human lung cells. These data were obtained in vitro on primary lung cells and lung cancer cell lines using viral pseudotypes integrating the Spike sequence but also using whole Sars-CoV2 and showed decreased cellular infection. They also showed that the sera from convalescent SARS patients cross-neutralized SARS-2-S-driven entry (4). A paper by Bojkova et al showed that camostat reduced the cytopathogenic effect of SarsCoV2 on cancer cell lines and that this effect was superior in SARS-CoV-2 than in SARS-CoV infection (5). These data argue for a potential strong effect of camostat on evolution of COVID-19 infection.

Moreover, two recent publications gave additional weight on a possible activity of camostat on COVID-19 course :

- A study by Hoffman et al (14) showed that camostat mesylate also inhibits other serine proteases involved in the cleavage of the S protein and that this activity is achievable at usual dosage (200 mg t.i.d) of camostat.

- A first clinical trial published in the Lancet Infectious Disease (15) indicated that camostat may have a beneficial effect on COVID-19 course in hospitalized patients with severe forms of infection.

Finally, camostat may display an immunoregulatory role by decreasing IL-6 and TNFa production in virally-infected respiratory cells (16). This latter role is of particular importance due to the fact that severe forms of the disease are related to a cytokine storm syndrome with major roles of IL-6 and TNFa (17).

Camostat mesylate is a serine protease inhibitor that is commonly used in Japan (at a dose of 600 mg/day) and has been successfully and safely used to treat pancreatitis-associated pain (6) and post-operative reflux oesophagitis (7) .Side effects that have been reported are rare at these doses (nausea, diarrhea, hypersensitivity in 0.1 to 0.5% of the cases, ~~abnormal~~ cytopenias in less than 0.1% and hyperkaliemia and abnormal hepatic function in less than 0.05%). No Market Authorization application has been addressed to the FDA or EMA.

3.4 Description of the population to be studied and justification for the choice of participants

This study will be the first to evaluate the efficacy and safety of camostat mesylate in the treatment of ambulatory COVID-19 patients. This innovating repurposing of camostat mesylate aims to specifically block SARS-CoV2 cell entry, an early event in the infectious process and to prevent evolution towards severe forms of COVID19. Moreover, the proposed therapeutic strategy targets an ambulatory population and evaluates a primary care intervention, upstream and at the front line of COVID-19 medical management, rather than hospital-based treatments.

Nine studies testing camostat mesylate are ongoing worldwide but their design differ from the one proposed here, either by the aimed population (outpatients), the placebo-controlled nature of the study or the chosen primary endpoints (reduction of hospitalization rate).

Moreover, due to the resurgence of COVID-19 cases in France (1000 new cases/day, Ministry of Health - Direction Générale de la Santé data on July 28th, 2020) with a high incidence in the Ile de France region, we will be able to include the required number of patients on a short period, thus justifying the feasibility of this study. The number of new cases diagnosed in each screening center has been detailed below (approximately 130 inclusions/week, section 5.2.2).

Due to the current characteristics of the epidemics (8), we chose to aim our study at high-risk populations in order to fully reach the chosen primary endpoint. High risk patients have been defined in several reports (9–11) and are listed as follows :

* Age ≥ 50 years
* Body Mass Index ≥ 30kg/m²
* Diabetes
* Hypertension
* Chronic renal failure (eGFR<60 mL/min)
* Chronic heart disease
*Asthma/Chronic Obstructive Pumonary Disease/Cystic fibrosis
* Chronic liver disease
* Chronic neurological disease
* Solid organ transplant
* Bone marrow transplant
* Sickle cell anemia/ Major thalassemias
* Active *or* currently treated *or* <1 year diagnosed cancer
* Active *or* currently treated *or* <1 year malignant blood disease
* Immunosuppressive treatment observed for more than 1 month

3.5 Identification and description of the investigational medication or medications

Camostat mesylate is a serine protease inhibitor that is commonly used in Japan (at a dose of 600 mg/day) and has been successfully and safely used to treat pancreatitis-associated pain (6) and post-operative reflux oesophagitis (7).
See Section 7 for further information about the administration of the product.

3.6 Description and justification of the dosage, route of administration, administration schedule and treatment duration

Camostat mesylate by oral administration on empty stomach (i.e, 90 minutes before or after having a meal), 600mg/day (200mg every 8 hours) for 14 days (day 1 to day 14). Has been shown effective and safe in previous studies, and strengthened by pharmalogical data. Moreover, oral camostat given at the dose of 8 mg/kg/day was shown to be associated with decreased mortality in a SARS-CoV murine model (13). A recent publication also showed that antiviral activity may be achievable at usual doses of camostat (14). The necessity of administration on empty stomach is justified by recent pharmalogic data obtained from Ono on healthy volunteers (enclosed to this protocol after authorization from Ono).
See Section 7 for further information about the administration of the product.

3.7 Summary of the known and foreseeable benefits and risks for the research participants

The trial will evaluate a candidate therapeutic strategy in the context of SARS-CoV-2 pandemics. Specifically, the proposed treatment targets high-risk ambulatory patients newly diagnosed with confirmed COVID-19, not requiring initial hospitalization. The strategy aims to improve short-term outcomes in ambulatory patients and prevent clinical evolution to more severe forms, requiring hospitalization. It will therefore participate in reducing hospitalization needs (quantitative and qualitative and relieving the healthcare system). Moreover, it can be a useful therapeutic option for ambulatory patients, with early diagnoses, in the management of the epidemics in the upcoming months and lockdown removal, as it may also reduce interindividual transmission by reducing viral replication in the host. As the single blinded design of the study precludes to the inclusion of multiple members of the same household, one additional secondary endpoint will be the percentage of COVID-19 affected relatives measured at day 7 and day 14 and compared to day 0, in the population of patients living with at least one person in their household.

Additional risks are those of camostat mesylate. Known side effects are: nausea, diarrhea, hypersensitivity in 0.1 to 0.5% of the cases, abnormal cytopenias in less than 0.1% hyperuricemia (reported in a mild and asymptomatic form in healthy volunteers in a recent study from Ono, enclosed to this protocol) and hyperkaliemia and abnormal hepatic function in less than 0.05%

4 OBJECTIVES

4.1 Primary objective

Evaluate the efficacy of camostat mesylate in the treatment of SARS-CoV-2 infection in high-risk adult patients with confirmed COVID-19 not requiring initial hospitalization, in terms of hospitalization needs, up to day 21 after randomization.

4.2 Secondary objectives

In adult patients diagnosed with laboratory confirmed COVID-19 not requiring initial hospitalization, to evaluate the impact of camostat mesylate compared to placebo on:

- Safety up to day 21 after randomization

- Efficacy in terms of need for hospitalization for COVID-19 management, by independent blinded committee review

- Overall clinical improvement at day 21 after randomization

- Clinical efficacy in terms of intensive care needs, up to day 21 after randomization

- Clinical efficacy in terms of time to hospitalization, up to day 21 after randomization

- Clinical efficacy on respiratory functions, up to day 21 after randomization

- Overall survival at day 21 and 90 after randomization

- Patient-reported outcome on initial symptoms, up to day 21 after randomization

- Virological, serological, immunological efficacy, up to day 90 after randomization, including surrogacy assessment of candidate markers up to day 90

- Renal complications, up to day 21 after randomization

- Liver complications, up to day 21 after randomization

- COVID-19 transmission within the same household (in patients with a least 1 person in the same household)

5 STUDY DESIGN

5.1 *Study endpoints*

5.1.1 Primary endpoint

Proportion of patients hospitalized between day 1 and day 21 for COVID-19 deterioration, or who died without hospitalization between day 1 and day 21.

Investigators will collect information about patients' hospitalization at day 21 visit, and, in case of hospitalization, use the hospitalization report as data source.

As an indicative basis, criteria for hospitalization will be the presence of any of the following: respiratory rate > 24 /min at rest, Sp02 < 95% on room air, blood pressure < 100 mmHg, lethargy or unconsciousness, brutal overall deterioration or lethargy in the elderly [as per the Haut Conseil à la Santé Publique's (HCSP) recommendations, (9)] and any all other reasons requiring hospitalization left at the discretion of the physician

5.1.2 Secondary endpoints

- Adverse events (AEs): number of AEs, number of serious AEs (SAEs), investigational medication discontinuation (for any reason), up to 21 days

- Independent endpoint adjudication committee-reviewed proportion of patients hospitalized between day 1 and day 21, for COVID-19 deterioration.
The independent EAC will review patients'files, blinded to the randomized group, and determine whether hospitalization was related to COVID-19 or not.

- WHO COVID-19 clinical improvement ordinal scale (3), at day 7, 14 and 21

OMS Progression scale	**Descriptor**	**Score**
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalized : mild disease	Hospitalized; No oxygen therapy	3
	Hospitalized; oxygen by mask or nasal prongs	4
Hospitalized : severe disease	Hospitalized; oxygen by NIV or High flow	5
	Intubation and Mechanical ventilation	6
	Mechanical ventilation + additional organ support – pressors, RRT, ECMO	7
Death	Dead	8

- Admission to an ICU within 21 days from inclusion

- Number of days alive without hospitalization, up to 21 days

- Initiation of invasive mechanical ventilation for COVID19- severe within 21 days from inclusion

- Initiation of oxygen-therapy for COVID19 within 21 days from inclusion

- Overall survival up to day 90

- Number of days alive without symptoms, up to day 21

- SARS-CoV-2 virological assessment at day 7, day 14 and day 21 (nasal swab and droplet quantification of SARS-CoV2 RNAemia, a new candidate surrogate marker as defined in (18))

- SARS-CoV-2 serological assessment at day 7, day 14, day 21 and day 90

- IL-6, IL-1b, TNFa, IL-8 levels at day 1, 7, 14 (17)

Blood sample will be collected at day 1, 7, 14, 21 and 90 for biobanking and evaluation of potential candidate surrogate markers, in the future.

- Peripheral blood lymphocyte phenotyping and telomere length measurement at day 1, day 7 and day 14

- Acute kidney failure defined as at least serum creatinine increase of 0.3mg/dl or 1.5-1.9 times baseline and/or oliguria < 0.5ml/kg/h (KDIGO2012 scale), within 21 days

- Serum electrolytes, uricemia and estimated Glomerular Filtration Rate at day 7, 14 and 21

- Liver transminases, gamma-GT and alkaline phosphatase levels at day 7, 14 and 21

5.2 *Description of research methodology*

5.2.1 Design of the study

Phase III trial

Multicenter single-blinded placebo-controlled two-arm parallel superiority 1:1 randomized trial..

5.2.2 Number of participating sites

Screening of eligible patients will be performed by :

- Emergency department of Saint Louis hospital, Paris
- Outpatient consult of the internal medicine department of Saint Louis Hospital, Paris
- Emergency department of Bichat hospital, Paris
- COVID-19 screening center at Bichat hospital
- Emergency department at Argenteuil hospital
- Emergency department at H.Mondor hospital, Créteil
- Outpatient consult of the infectious disease department – COVID-19 screening center at Henri Mondor hospital, Créteil
- Outpatient consult of the Sickle Cell Disease and inherited Red Blood Cell genetic disorders coordinating referral center, at H.Mondor hospital, Créteil
- Emergency department of Lariboisière hospital, Paris
- Centre de Santé Richerand (primary care outpatient clinic center), 75010 Paris
- Centre médical international (primary care outpatient clinic center), 75010 Paris
- Dr Karima Amazzough, 75011 Paris
- Dr Laurent Haas, 75017 Paris
- Occupational medicine departments in recruiting hospitals

Recruiting centers

Eligible patients will then be referred to one of the following participating centers for inclusion and treatement allocation:

- Emergency department of Saint Louis Hospital (PI : Dr Olivier Peyrony)
- COVID-19 screening center at Bichat hospital (PI : Dr Dorothée Vallois)
- Emergency department of Argenteuil hospital (PI : Dr Gaëtan Plantefève)
- Centre de Santé Richerand (primary care outpatient clinic center), 75010 Paris (PI : Dr Mariela Skendi)
- Emergency department of Henri Mondor hospital (PI : Dr C. Kassasseya)
- Outpatient consult of the Sickle Cell Disease and inherited Red Blood Cell genetic disorders coordinating referral center, at Henri Mondor hospital, Créteil (PI: Pr Pablo Bartolucci)
- Outpatient consult of the infectious disease department – COVID-19 screening center at Henri Mondor hospital, Créteil (PI: Dr Raphaël Lepeule)
- Post-emergency – Internal medicine department of H. Mondor hospital (PI : Dr C. Guillaud)

- Department of Infectious and Tropical Diseases / Public Health Unit, Groupe Hospitalier Sud Ile de France (GHSIF), Melun
- Emergency department of Lariboisière hospital, Paris

Follow-up visits will include a medical interview at one of the participating centers (recruiting and non-recruiting centres, detailed below), either via physical consultation or teleconsultation, and a paramedical (by a registered nurse) assessment, and biological sampling.

Non-recruiting centers (follow-up visits only):
- Internal medicine department of Argenteuil hospital (PI : Dr Claire Le Pendu)
- Office of Dr K. Amazzough, 75011 Paris (PI: Dr Karima Amazzough)
- Office of Dr J Marzouk, 75017 Paris (PI: Dr Jean Marzouk)

5.2.3 Identification of participants

The participants in this research will be identified as follows:
Site number (3 digits) - Sequential enrolment number for the site (4 digits) - surname initial - first name initial
This reference number is unique and will be used for the entire duration of the study.

A randomisation number will also be assigned when the participant is randomised. This number will have the following format: RXXXXX.

A treatment number will be also assigned when the participant is allocated to a treatment arm. This number will have the following format: TXXXXX.

5.2.4 Randomisation

Patients will be centrally randomized to one of investigational or the placebo arm, in a balanced allocation process (1:1), stratified on age (<50, 50-64 and ≥65 years), and randomization center.

Randomization will be performed by the Service de Biostatistique et Information Médicale (SBIM), Saint-Louis hospital, Paris (Pr S. Chevret). It will be centralized via a web-based server 24/7, following the pre-specified randomization lists that will be stratified on age (<50, 50-64 and ≥65 years) and center.

To promote periodic group balance (in the sense that sequential patients are distributed equally between groups), each list will use permutation blocks of various sizes, which will not be mentioned to the investigators to ensure allocation concealment.

5.2.5 Blinding methods and measures put in place to protect blinding

Patients allocated to the control arm will receive a placebo, with the same administration schedule. Due to the emergent need for therapeutic interventions in COVID19 and the prolonged delay to obtain a placebo that is indistinguishable from the experimental drug, a standard placebo (APHP formule 515) has been chosen. Therefore, only patients will be truly blinded to the treatment group.

Upon randomization, the patient will be allocated a trial identification number (see 4.2.3).

The entire course (14 days) of trial medication (placebo or camostat mesylate) will be supplied to the patient by the GP in charge of the patient at the COVID center, after randomization.
Investigational products will be repackaged in numbered boxes in order to ensure blinding of patients, by APHP pharmacy (AGEPS) based on the randomization number provided by SBIM (see 4.2.4). Boxes containing placebo and camostat mesylate will be identical. In the boxes, packaging will also be identical.

A numbered box of treatment will be allocated automatically via an electronic web system to each randomized patient. Treatment box will include the quantity for all 14 days of treatment.

5.2.6 Unblinding procedures, if applicable

Unblinding will be requested for any reason considered essential by the investigating physician by calling upon:

- **In emergency cases**: the poison control centre at Fernand Widal Hospital, Telephone: **+33 (0)1 40 05 48 48.**
- **Apart from an emergency situation** : the DRCI (Clinical Research and Innovation Department) to the DRCI project advisor whose contact information are listed on the protocol cover page

Unblinding will be applied, whenever possible, after advising with the sponsor, the coordinating investigator, who will assess the relevance of the request for unblinding in each case. All requests for unblinding made over the phone will be confirmed by a written unblinding request using the study's standardized form for unblinding requests.
.
Contact information :
- ***DRCI Tel : 01 44 84 17 23 Fax : 01 44 84 17 01***
- ***Coordinating investigator***: ***Dr BOUTBOUL Tel : 01 42 49 91 40***

6 IMPLEMENTATION OF THE STUDY

6.1 *Screening visit*

The screening visit takes place between 4 and 1 days before the baseline visit.

Consecutive potential eligible patients will be first informed about the study by either investigator, a collaborating GP, emergency or occupational medicine physician in the participating centers, as follows:

Whose consent must be obtained	**Who informs the individuals and collects their consent**	**At what point the individuals are informed**	**At what point the consent is obtained**
The patient participating in the study	Participating GP physicians (general practitioner family medicine or hospital occupational medicine or emergency medicine staff) will screen and pre-inform the	Screening visit (standard of care GP or ER visit or hospital occupational medicine) and baseline visit	After a reflection period of 30 min max., at the latest, at the time of the baseline visit (see below)

	patients. Physicians from the 10 recruiting centers, declared and trained in the study, will inform and collect their consent.		

In the case of participating emergency departments, potentially eligible patients will be pre-informed about the study via a specific flyer succinctly presenting the study (see addendum 5). Formal information will be further performed by a participating registered physician in case the patient is eligible.

In the case of healthcare workers (HCW) screened in the setting of occupational medicine, since results are usually sent to patients by email, a flyer about the study will be available to HCW at the time of their initial SARS-CoV2 test consult (nasal or saliva PCR, antigen test) (see addendum 5). The flyer will mainly mention the title of the study, local contact person (investigators), coordinating investigator, funding, sponsor and NCT registration number.

At the end of the screening visit, potentially eligible patients will be directed to one of the participating COVID centers for a SARS-CoV2 nasal or saliva PCR or antigen test, if not already available. This will ensure a proper time between sampling and result (<24h at these centers). Each positive result will be reported to the investigators of the concerned center.

Eligibility to participate to the trial will be assessed, notably belonging to a high-risk group, confirmed positive PCR for SARS-CoV2 (nasal or saliva) or antigen test, absence of initial severity COVID-19 criteria requiring hospitalization, known clinical or biological contraindications to investigational treatment, pregnancy if applicable.

6.2 Baseline visit and randomisation visit

Following informed written consent, initial clinical and biological assessments will formally verify inclusion and non-inclusion criteria, as follows:

Patients will be interviewed to collect:

- Age, sex, weight, height, smoking status
- Medical history: comorbidities, date of diagnosis (notably asthma, COPD, any chronic respiratory affections, diabetes, cardiovascular diseases)
- Concomitant medications
- COVID-19 history: symptoms, date of first symptoms, contact
- Known hypersensitivity to camostat mesylate
- Pregnancy

Clinical examination will notably include: respiratory rate measurement, and SpO2 in ambient air, lung auscultation, body temperature and blood pressure measurement.

Baseline laboratory results will also be required for inclusion:

- Laboratory-confirmed SARS-CoV-2 infection as determined by PCR (nasal or saliva), or other commercial or public health assay including antigen test in any specimen < 96 hours

- Plasma level of beta hCG in women with potential childbearing.

Randomization will be performed once patient has consented to participate (written informed consent).

Upon inclusion, baseline biological assessments will be performed: complete blood count, chemistry and liver enzymes measurement, and baseline biobanking (20 mL blood on heparinate lithium and 5 mL on EDTA). Cytokine measurement, droplet quantification of SARS-CoV2 RNAemia (as detailed in (18)) and SARS-CoV-2 serology will also be performed.

At the inclusion visit, patient's contact information will be collected, as well as a closed one contact (*personne de confiance*) and his/her usual GP contact. If the patient misses D21 visit, the investigating team will try and contact the patient, and if necessary then the closed one and the GP, to retrieve information on the study endpoints and reasons for missed study visit(s).

6.3 Follow-up visits

Follow-up visits will be conducting at any of the participating centers (recruiting or non recruiting)

Day 7, 14 and 21:

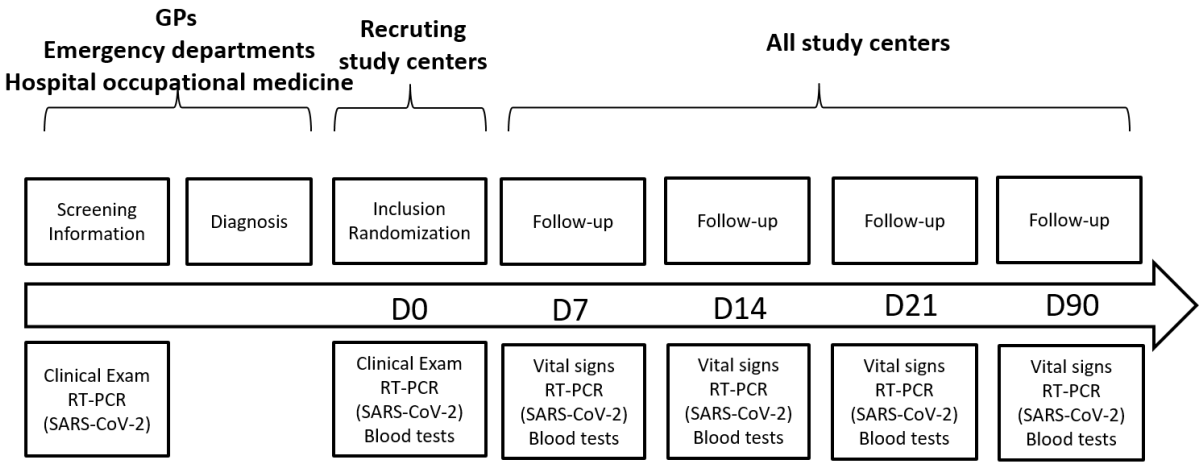
Medical interview and vital signs assessment by a registered nurse, including:

- Hospitalization status: hospitalization since last visit
- Symptoms: fever, cough, anorexia, fatigue, myalgias, dyspnea, anosmia, dysgeusia, gastrointestinal symptoms (diarrhea, nausea), headaches, sore throat, rhinorrhea, thoracic pain
- Vital signs : blood pressure, respiratory rate, SpO2, temperature, pulse rate
- Evaluation of adverse events
- Assessment of compliance to the trial medication

Laboratory sampling: SARS-CoV-2 virological assessment by RT-PCR on nasal swab and plasma (droplet technique); SARS-CoV-2 serological assessment; liver enzymes, clinical chemistry (including sodium, potassium, chloride, bicarbonate uricemia, BUN, creatininemia with estimation of glomerular filtration rate), AST, ALT, total bilirubin, alkaline phosphatase, , complete blood count with differential (including lymphocytes and neutrophils, platelets), plasma cytokine measurement and biobanking (20 mL blood on heparinate lithium and 5 mL on EDTA).

Hospitalization status will be primarily evaluated by interview with the patient. In case of hospitalization and discharge since last visit, hospitalization report will be collected by the GP investigator, to collect reason for hospitalization, days in intensive care, of oxygen therapy, of mechanical ventilation). In case the patient misses the study visit, the investigating team will try and contact the patient by phone and, if unsuccessful, the patient's contact person, to retrieve information on hospitalization status.

Figure 1. Summary of the study design



6.4 Day 90: Last study visit

A clinical examination will be performed and vital status will be collected at Day 90. In case of death, date and cause of death will be collected. A final SARS-CoV-2 serological assessment will be performed.

6.5 Expected length of participation and description of the chronology and duration of the study

Duration of enrolment period	12 months
The length of participation for participants, of which:	
• Maximum period between screening and enrolment • Treatment duration:	3 days 14 days
• Duration of follow-up period:	90 days
Total study duration:	15 months

6.6 Table or diagram summarising the chronology of the study

Actions	D-1 +/- 1 days (Screening visit)	D0 (Baseline)	D7 and D14 +/- 1 day	D21 +/- 1 day	D90 End of study
Information	X	X			
Informed consent		X			
Verification of inclusion and exclusion criteria	X	X			
History	X	X			
Clinical examination	X	X			
SpO2	X	X	X	X	X
Pregnancy test (urinary or blood)	X				
SARS-CoV-2 virological assessment	X	X	X	X	
SARS-CoV-2 serological assessment		X	X	X	X
Immunological assessment (plasma IL-6, IL-1b, TNFa, IL-8 levels)		X	X		

Chemistry and creatininemia		X	X	X	
Liver transaminases, gamma-GT, alkaline phosphatase		X	X	X	
Biobanking (20 mL blood on heparinate de lithium, 5 mL blood on EDTA)		X	X		
Hospitalization status			X	X	
Dispensation of treatments		X			
Compliance		X	X	X	X
Adverse events	+/-X (consistent with the section on Vigilance)	+/-X (consistent with the section on Vigilance)	X	X	X

6.7 Distinction between standard care and study

TABLE: "Standard care" vs. "additional interventions" required specifically for the study

Interventions, procedures and treatments carried out for research purposes	**Interventions, procedures and treatments associated with <u>standard care</u>**	**Interventions, procedures and treatments added for <u>research purposes</u>**
Treatments	Paracetamol Antibiotics Oxygenotherapy Any therapeutics related to COVID-19 management or comorbidities, other than investigational products, including hospital-based therapeutics	Camostat mesylate Placebo
Visits	Any visit related to standard of care COVID-19 management or comorbidities, including hospital-based management	Visit at D7, 14, 21, 90
Blood samples	Any blood test related to standard of care COVID-19 management or comorbidities	Pregnancy test when appropriate (inclusion) Clinical chemistry , Liver transaminases, gammaGT, alkaline phosphatase, complete blood count, (D1, 7, 14, D21) Biobanking (20 mL blood on lithium heparinate, 5 mL blood on EDTA taken at D1, D7, D14) SARS-CoV-2 serological assessment at D1, D7,D14 D21, D90

		Plasma SARS-CoV-2 virological assessment at D1, D7, D14 D21 Immunological assessment (IL-6, IL-1b, TNFa, IL-8 levels) at D1, D7, D14
SARS-CoV-2 virological assessment by RT-PCR on nasal or saliva swab	Diagnostic assessment within 96 hours of D1	D1, D7, D14, D21
SARS-CoV-2 virological assessment by antigen test	Diagnostic assessment within 96 hours of D1	
Imaging	Any imaging related to standard of care COVID-19 management or comorbidities	

6.8 Biological samples

The samples for SARS-CoV-2 biological assessment (virological RT-PCR, serological and immunological) retrieved during the trial (D1, D7, D14, D21, D90) will be performed in the 5 COVID centers then centralized at Saint Louis hospital (Department of Virology, Pr C Delaugerre, and deparment of Immunology, Pr S Caillat Zucman).

Kidney and liver functions biological assessments (D1, D7, D14, D21) will be performed in primary care ambulatory laboratories.

The blood samples that are taken during the trial (whole blood including serum, DNA and Peripheral Blood Mononuclear Cells storage) will be stored in a biological sample bank.

During the trial, these biobanking samples (collected at D1, D7, D14) will be stored at the Centre de Ressources Biologiques (CRB), Institut Imagine, Paris under the supervision of Marie-Alexandra ALYANAKIAN for peripheral blood lymphocyte phenotyping (Dr Sylvain LATOUR) and telomere length measurement (Dr Patrick REVY).

At the end of the trial, the samples will be kept without time limitation.

At the end of the trial, the samples may be used for further analysis not described in the initial protocol but which may be useful for our investigation of COVID19 pathophysiology in light of developments in scientific knowledge, provided the subject is informed and gives consent, as stated in the information sheet/consent form. In particular, biobanking samples could be used for evaluation of candidate surrogate marker in the future.

If the samples are kept at the end of the trial, the sample bank will be declared to the relevant minister (Article L. 1243-3 CSP).

Type of sample	**Quantity**	**Storage location**	**Manager of the sample bank**	**Purpose of the sample bank**	**Storage period**	**Outcome (destruction, etc.)**
Whole blood Lithium heparinate	20 mL D1, D7, D14,	CRB Institut Imagine, Paris	M-A ALYANAKIAN	Peripheral blood lymphocyte phenotyping Surrogate	Unlimited period	Conservation without time limitation (see information

				marker evaluation		notice)
Whole blood EDTA	5 mL D1, D7, D14,	CRB Institut Imagine, Paris	M-A ALYANAKIAN	Telomere length measurement Surrogate marker evaluation	Unlimited period	Conservation without time limitation (see information notice)

6.9 Ancillary study

Blood samples (20 mL blood on lithium heparinate and 5 mL blood on EDTA) taken at D1, D7, D14 of the trial and stored at the CRB (Institut Imagine, Paris) will allow to study the role of camostat mesylate in the modification of immune responses to COVID19 and to evaluate potential candidate surrogate markers in COVID-19 in ambulatory patients, in the future (unindentified at the time of this protocol version). This study will be conducted under the supervision of Drs Sylvain LATOUR (Institut Imagine, analysis of lymphocyte responses) and Patrick REVY (Institut Imagine, analysis of telomere length and lymphocyte exhaustion).

7 ELIGIBILITY CRITERIA

7.1 Inclusion criteria

1) Patients ≥ 18 years old
2) Patients with an increased risk of severe COVID-19 belonging to one or more of the following groups :
* Age ≥ 50 years
* Body Mass Index ≥ 30kg/m²
* Diabetes
* Hypertension
* Chronic renal failure (GFR<60 mL/min)
* Chronic heart disease
*Asthma/Chronic Obstructive Pumonary Disease/Cystic fibrosis
* Chronic liver disease
* Chronic neurological disease
* Solid organ transplant
* Bone marrow transplant
* Sickle cell anemia/ Major thalassemias
* Active *or* currently treated *or* <1 year diagnosed cancer
* Active *or* currently treated *or* <1 year diagnosed malignant blood disease
* Immunosuppressive treatment observed for more than 1 month
3) Laboratory confirmed SARS-CoV2 infection with mild COVID-19, fulfilling all the following criteria:
- Positive SARS-CoV-2 RT-PCR nasal or saliva swab samples or positive SARS-CoV-2 antigen test performed within 96h of inclusion visit
AND
- Clinical symptoms and signs consistent with SARS-CoV2 infection including but not limited to, fever, upper respiratory tract infection signs, digestive signs, muscle pain, anosmia, dysgueusia…(1)
4) Informed consent to participate to the trial
5) Patients must be able and willing to comply with study visits and procedures

7.2 Exclusion criteria

1) Initial need for hospitalization for COVID-19 management : defined as any of the following severity criteria : respiratory rate > 24 /min at rest, Sp02 < 95% on room air, blood pressure < 100 mmHg, lethargy or unconsciousness, brutal overall deterioration or lethargy in the elderly (recommendations HCSP) and all other reasons requiring immediate hospitalization left at the discretion of the physician

2)Pregnancy and breastfeeding

3) Participation to another interventional drug trial

4) Subject protected by law under guardianship or curatorship

5) Absence of health insurance

6) Known hypersensitivity to camostat mesylate

7) Known person sharing the same household already included in the study

8) Participation to another COVID-19 ambulatory interventional study

9) Patients having completed a full SARS-CoV2 vaccine immunization procedure less than 4 weeks prior to COVID-19 diagnosis (last vaccine injection performed less than 4 weeks prior to COVID-19 diagnosis).
Patients who have not received any SARS-CoV2 vaccine, patients with an incomplete SARS-CoV2 vaccine immunization (not all scheduled injections performed), patients with a completed vaccine procedure for more than 4 weeks will be eligible.

7.3 Recruitment procedure

This multicentre study relies on the screening of eligible patients at: Saint Louis hospital emergency department, Bichat hospital emergency department and COVID-19 screening center, emergency department at Argenteuil hospital, emergency department at Henri Mondor hospital (Créteil), ambulatory outpatient clinics: Centre de Santé Richerand and Centre médical international (75010 Paris), internal medicine outpatient consult at Saint Louis hospital, Red blood cell diseases center and Infectious disease outpatient consults at H.Mondor hospital, in the practices of Dr Amazzough and Dr Haas, and in departments of occupational medicine of the recruiting hospitals.

Recruiting centers

Eligible patients will then be referred to one of the 8 recruiting ambulatory centers (from 5 sites) for inclusion and randomization:

- Emergency department of Saint Louis Hospital
- COVID-19 screening center at Bichat hospital
- Emergency department of Argenteuil hospital
- Centre de Santé Richerand (primary care outpatient clinic center), 75010 Paris
- Emergency department of Henri Mondor hospital, Créteil
- Outpatient consult of the infectious disease department – COVID-19 screening center at Henri Mondor hospital, Créteil
- Post-emergency – Internal medicine department of H. Mondor hospital, Créteil
- Outpatient consult of the Sickle Cell Disease and inherited Red Blood Cell genetic disorders, coordinating referral center, at Henri Mondor hospital, Créteil
- Department of Infectious and Tropical Diseases / Public Health Unit, Groupe Hospitalier Sud Ile de France (GHSIF), Melun
- Emergency department of Lariboisière hospital, Paris

Non recruiting centers

The following centers will participate as non recruiting centers, and conduct follow-up visits only (D7, 14, 21, 90):

- Internal medicine department of Argenteuil hospital
- Office of Dr K. Amazzough, 75011 Paris
- Office of Dr J. Marzouk, 75017 Paris

Follow up visits will then be performed at one of the particpating centers (recruiting and non recruiting).

	Number of participants
Total number of participants to be included	596
Number of centers Recruiting Non recruiting	10 (7 sites) 3
Enrolment period (months)	12
Number of participants/recruiting centre (average)	60
Number of participants/recruiting centre/month	5

7.4 Termination rules

7.4.1 Criteria and procedures for prematurely terminating the study treatment

Several situations are possible:

- Temporary suspension of treatment: the investigator must document the reason for suspending and resuming the treatment in the participant's source file and the case report form (CRF)
- Premature discontinuation of treatment, but the participant remains enrolled in the study until the end of their participation
- Premature discontinuation of treatment and withdrawal from the study

The investigator must:

- Document the reason(s)
- Collect the assessment criteria at the time of ending participation in the study, if the participant agrees
- Schedule a follow-up for the participant, particularly in case of a serious adverse event.

In the case of severe adverse events, the investigator must notify the sponsor and follow up the participant for 3 months following the premature discontinuation of treatment camostat mesylate or placebo. Notification of a serious adverse event must be sent by email (eig-vigilance.drc@aphp.fr) to the sponsor. The serious adverse event will be monitored until it is resolved. If a Data Safety Monitoring Board has been created, the committee can specify and/or validate the follow-up methods.

7.4.2 Criteria and procedure for premature withdrawal of a participant from the study

- Participants may exit the study at any time and for any reason.
- If, during the course of his/her participation in the study, the participant presents one of the following exclusion criteria, then the study product must be discontinued but the participant will continue to be monitored for the study:
    - Negative SARS-CoV-2 PCR viral assessment at inclusion visit
    - Pregnancy, breastfeeding
    - Platelet count < 50 10^9/L
    - Absolute neutrophil count < 0.5 10^9/L
    - ASAT or ALAT > 5*ULN
    - K+>5 mmol/L

In case of COVID-19 deterioration with hospitalization, study medication should be maintained as planned as long as the patient' clinical status allows, at discretion of the physician in charge.

- The investigator can temporarily or permanently withdraw a participant from the study for any safety reason or if it is in the participant's best interests.
- Participant lost to follow-up: the participant cannot be located. The investigator must make every effort to reconnect with the participant (and document his attempts in the source file), at least to determine whether the participant is alive or dead

If a participant exits the study prematurely or withdraws consent, any data collected prior to the date of premature exit may still be used.
- If a participant exits the study prematurely, and if the participant agrees, state the procedure and schedule for collecting the data required by the protocol (primary endpoint, secondary endpoints, safety assessment) (NB: this must be stated in the information and consent form)
- State how premature exit from the study will affect the participant's ongoing care (state exactly what the participant will be offered).
- In case of serious adverse events, see the corresponding section on vigilance

The case report form must list the various reasons why the participant has discontinued the study:
- ☐ Lack of efficacy
- ☐ Adverse reaction
- ☐ Another medical issue
- ☐ Personal reasons of the participant
- ☐ Explicit withdrawal of consent
- ☐ Lost to follow-up

7.4.3 Follow-up of participants following premature withdrawal from the study

In case of early discontinuation, clinical examination at day 21 will be performed and he patient analysed in intent to treat. Cause of treatment discontinuation will be notified in the patient source file and, when notified to the sponsor when appropriate (SAE).
If a participant discontinues the study, this will in no way affect their usual care for their condition.
In the event of serious adverse events following premature discontinuation of treatment and participation of the patient in the study; see section 6.4.1

7.4.4 Procedures for replacing participants

Patients will not be replaced.

7.4.5 Full or partial discontinuation of the study

AP-HP as sponsor or the Competent Authority (ANSM) can prematurely discontinue all or part of the study, temporarily or permanently, further to the recommendations of the Data Safety Monitoring Board in the following situations:

- first of all, if suspected unexpected serious adverse reactions (SUSARs) are observed in one of the treatment arms or if there is a discrepancy in the serious adverse reactions between the treatment arms, requiring a reassessment of the benefit-risk ratio for the study
- if an interim analysis confirms the efficacy of one of the treatment arms or, alternatively, the lack of efficacy**.**

Similarly, AP-HP, as the sponsor, or the Competent Authority (ANSM) may decide to prematurely discontinue the study due to unforeseen issues or new information about the product, in light of which the objectives of the study or clinical programme are unlikely to be achieved**.**

AP-HP as sponsor reserves the right to permanently suspend enrolment at any time if it appears that the inclusion objectives are not met.

If the study is prematurely discontinued for safety reasons, the decision and justification will be provided by the sponsor (AP-HP) to the Competent Authority (ANSM) and to the CPP (Research Ethics Committee) without delay, and within a maximum period of 15 days, along with recommendations from the Data Safety Monitoring Board in the case of substantial modification.

8 TREATMENT ADMINISTERED TO STUDY PARTICIPANTS

8.1 *Description of the investigational medicinal products*

8.1.1 Camostat Mesylate

Camostat mesylate tablets for oral administration.
Content per tablet: 100 mg
Posology: 600 mg/day in three divided doses (2 tablets every 8 hours) from day 1 to day 14
Each therapeutic unit is a sealed and numbered box containing 90 tablets (9 press-through packages (blisters) of 10 tablets). This medication should be taken on empty stomach (i.e, 90 minutes before or after having a meal). The necessity of administration on empty stomach is justified by recent pharmalogic data obtained from Ono on healthy volunteers (enclosed to this protocol after authorization from Ono).
The information appearing on the labelling of blisters and boxes, in French, comply with Annex 13 of Good Manufacturing Practice.
The tablets have to be stored in the provided packaging at room temperature.

8.1.2 Placebo

Posology: 6 tablets/day in three divided doses (2 tablets every 8 hours) from day 1 to day 14
Each therapeutic unit is a sealed and numbered box containing 90 tablets (9 press-through packages (blisters) of 10 tablets). This medication should be taken on empty stomach (i.e, 90 minutes before or after having a meal).
The information appearing on the labelling of blisters and boxes, in French, comply with Annex 13 of Good Manufacturing Practice.
The tablets have to be stored in the provided packaging at room temperature.

8.1.3 Concomitant medications

Any other medication may be associated to the experimental drug tested in the present study, as indicated by the product safety data. Antiviral and immunosuppressive treatments prescribed as local standard of care are therefore authorized.
We excluded the possibility of participation to another concomitant interventional study in patients that are included in CAMOVID and are still ambulatory, in order to allow proper evaluation of the experimental drug efficacy.

In case of missed dose, patient can catch up on the missed dose at the next scheduled treatment administration (double-dosing, 4 tablets).
In case of one vomiting episode within 1 hour of investigational treatment intake, patient can catch up on the missed dose at the next scheduled treatment administration (double-dosing, 4 tablets).
In case of repeated vomiting and emesis, patient should contact the investigator in charge without delay.

8.2 *Description of traceability elements accompanying the investigational medicinal product(s)*

The identification number of the treatment box automatically allocated by the web randomization server Cleanweb® / CTMS will be printed on the prescription.

8.3 *Authorised and prohibited treatments (medicinal, additional medicinal, surgical), including rescue medications*

The medical staff is expected to monitor patients and administer any drug required for the treatment and/or prevention of all the usual complications that can develop in this setting. For all additional treatments, the summary of product characteristics must have been obtained

from the EMA website (http://www.ema.europa.eu/ema/), or from the ANSM website (http://agence-prd.ansm.sante.fr/php/ecodex/index.php), or http://base-donnees-publique.medicaments.gouv.fr
No treatment is prohibited.

8.4 *Methods for monitoring compliance with the treatment*

Participants will be given a treatment diary (log book) to be completed during the duration of treatment.

9 EFFICACY ASSESSMENT

9.1 *Description of efficacy endpoints assessment parameters*

The **primary endpoint** is the occurrence of hospitalization between day 1 and day 21, for COVID-19 deterioration, or death without hospitalization between day 1 and day 21. Investigators will collect information about patients' hospitalization at day 21 visit, and, in case of hospitalization, use the hospitalization report as data source.
At the inclusion visit, patient's contact information will be collected, as well as a closed one contact (*personne de confiance*) and his/her usual GP contact. If the patient misses D21 visit, the investigating team will try and contact the patient, and if necessary then the closed one and the GP, to retrieve information on the primary endpoint and reasons for missed study visit.

Secondary endpoints are:

- Occurrence of hospitalization between day 1 and day 21, as evaluated by the Endpoint Adjudication Comittee (Dr V Lemiale), blinded to the randomization group (hospitalization reports will be used as data source for this independent evaluation, in hospitalized patients). More specifically, hospitalization reports will be anonymized by the investigation teams on study sites, uploaded to the online electronic Case Report Form as attachment . Dr Lemiale will have access to the hospitalization report on the eCRF platform, for independent review,
- Admission to an ICU within 21 days from inclusion
- Number of days alive without hospitalization, up to 21 days
- Initiation of invasive mechanical ventilation for COVID19- severe within 21 days from inclusion
- Initiation of oxygen-therapy for COVID19 within 21 days from inclusion
- Overall survival up to day 90
- Number of days alive without symptoms, up to day 21
- SARS-CoV-2 virological assessment at day 1, day 7, day 14 and day 21 (nasal swab and droplet quantification of SarS-CoV2 RNAemia)
- SARS-CoV-2 serological assessment at day 1, day 7, day 14, day 21 and day 90
- Plasma IL-6, IL-1b, TNFa, IL-8 levels at day 1, 7, and 14, with biobanking for future surrogacy assessments
- Peripheral blood lymphocyte phenotyping and telomere length measurement at day 1, day 7 and day 14
- Acute kidney failure defined as at least serum creatinine increase of 0.3mg/dl or 1.5-1.9 times baseline and/or oliguria < 0.5ml/kg/h (KDIGO2012 scale), within 21 days
- Serum electrolytes and estimated Glomerular Filtration Rate at day 1,day 7, 14 and 21
- Liver transaminases , gamma-GT and alkaline phosphatase at day 1, day 7, 14 and 21
- Percentage of COVID-19 affected individuals sharing the same household at day 1, 7 and 14, in the population of patients living with at last one other person.

9.2 *Anticipated methods and timetable for measuring, collecting and analysing the efficacy data*

At the inclusion visit, patient's contact information will be collected, as well as a closed one contact.

If the patient misses a study visit, the investigating team will try and contact the patient, and if necessary then the closed one and the usual GP, to retrieve information on the study endpoints as appropriate, reasons for missed study visit(s), and to reschedule a visit following the study protocol.

The following table describes the timetable for efficacy assessments:

Actions	D-1 +/- 1 days (Screening visit)	D0 (Baseline)	D7 and D14 +/- 1 day	D21 +/- 1 day	D90 End of study
Clinical examination	X	X			
Vital signs (blood pressure, respiratory rate, SpO2, temperature, pulse rate)		X	X	X	X
SpO2	X	X	X	X	
SARS-CoV-2 virological assessment	X	X	X	X	
SARS-CoV-2 serological assessment		X	X	X	X
SARS-CoV-2 immunological assessment		X	X		
Biobanking (20 mL blood on heparinate de lithium, 5 mL blood on EDTA)		X	X		
Hospitalization status			X	X	
Vital status					X

10 SPECIFIC STUDY COMMITTEES

10.1 *Steering Committee*

- Committee members: David Boutboul, José Timsit, Lucie Biard, Lara Zafrani, Dorothée Vallois

10.2 *Scientific Committee*

- Committee members*:* David Boutboul, José Timsit, Lucie Biard, Lara Zafrani

10.3 *Endpoint Adjudication Committee*

- : Dr Virginie Lemiale

10.4 *Data Safety Monitoring Board*

- Committee members: Pr Nadia Aissaoui, Pr Muriel Fartoukh, Pr Corinne Alberti

10.5 *Data Monitoring Committee*

- Committee members: Pr Laurent Papazian, Pr Alexandre Demoule, Dr Audrey De Jong

11 SAFETY ASSESSMENT - RISKS AND BURDEN ADDED BY THE STUDY

11.1 *Description of Safety endpoints assessment parameters*

Safety assessment will include the following collection of adverse events (AE):

- Occurrence of adverse events will be evaluated at each study visit by patients' interview, and clinical examination, up to day 90
- **Gastrointestinal symptoms** : nausea, abdominal pain at D1, D7, D14 and D21
- **Blood electrolytes** at D1, D7, D14 and D21
- **Elevated liver enzymes (transaminases, gamma-GT, alkaline phosphatase)** at D1, D7, D14 and D21
- **Blood urea nitrogen (BUN), uricemia, creatininemia and kalaemia** at D1, D7, D14 and D21
- **Glycemia at** D1, D7, D14 and D21
- **Hypersensitivity reactions and anaphylactoid symptoms**: monitoring of occurrence of skin rashes and blood pressure at D1, D7, D14 and D21
- **Platelet count at** D1, D7, D14 and D21
- **Neutrophil count at** D1, D7, D14 and D21

Treatment with Camostat Mesylate has been associated with a decrease in neutrophil count and/or platelet count in less than 0.1% of the cases, hyperkalemia in <0.05%, mild asymptomatic uricemia (recent report from Ono, enclosed to this protocol) and liver abnormal function in <0.05%. Complete blood count, liver enzymes and blood chemistry should be monitored at D7, D14 and D21 after start of therapy and according to clinical judgment thereafter.

Camostat should be discontinued if one of the following biological events occur :

- Platelet count < 50 10^9/L
- Absolute neutrophil count < 0.5 10^9/L
- ASAT or ALAT > 5*ULN
- K+>5 mmol/L

Participating patients will be instructed to notify their GP (investigator) of any adverse events that should occur between study visits.

The safety assessment will be based on:
- number of AEs,
- number of serious AEs (SAEs),
- investigational medication discontinuation (for any reason).

11.2 *Anticipated methods and timetable for measuring, collecting and analysing the safety endpoints*

The following table describes the timetable for safety assessments:

Actions	D-1 +/- 1 days (Screening visit)	D1 (Baseline)	D7 and D14 +/- 1 day	D21 +/- 1 day	D90 End of study
Verification of inclusion and exclusion criteria	X	X			
History	X	X			
Clinical examination	X	X			
Vital signs (blood pressure, respiratory rate, SpO2, temperature, pulse rate)		X	X	X	X
Pregnancy test (urinary or blood)	X				
Liver transaminases, gamma-GT, alkaline phosphatase		X	X	X	
Platelet and neutrophil counts		X	X	X	
Blood electrolytes, BUN, creatininemia, kalaemia, uricemia,		X	X	X	
Compliance		X	X	X	X
Adverse events	+/-X (consistent with the section on Vigilance)	+/-X (consistent with the section on Vigilance)	X	X	X

11.3 *Recording and reporting adverse events*

11.3.1 Definitions

According to Article R.1123-46 of the *Code de la Santé Publique* (French Public Health Code):

- **Adverse event**

Any untoward medical occurrence in a study participant, which does not necessarily have a causal relationship with the study or with the product subject to the study.

- **Adverse reaction**

An adverse event occurring in a study involving human participants when this event is related to the study or to the product being studied.

- **Adverse reaction to an investigational medicinal product**

Any untoward and unwanted reaction to an investigational medication regardless of the dose administered.

- **Serious adverse event or reaction**

Any adverse event or reaction that results in death, threatens the life of the participant enrolled in the study, requires hospitalisation or prolongs existing hospitalisation, causes a severe or long-term disability or handicap, or results in a congenital abnormality or deformity, and in the case of a medication, regardless of the dose administered.

- **Unexpected adverse reaction to an investigational medicinal product**

Any adverse reaction to the product whose nature, severity, frequency or outcome is inconsistent with the standard safety information described in the summary of the product characteristics, or in the investigator's brochure if the product is not authorised.

<u>According to Article R.1123-46 of the Code de la Santé Publique and the guidelines for sponsors of clinical trials (ANSM)</u>:

- **Emerging safety issue**

Any new information that may lead to a reassessment of the risk/benefit ratio of the trial or of the product under investigation, modifications in the investigational medicinal product use, the conduct of the clinical trial or the clinical trial documents, or a suspension, interruption or modification of the clinical trial or of similar trials.
For studies involving the first administration of a health product in healthy volunteers: any serious adverse reaction.
Examples:
a) any clinically significant increase in the frequency of an expected serious adverse reaction;
b) suspected unexpected serious adverse reactions in patients who have terminated their participation in the clinical trial which have been notified to by the investigator to the sponsor , as well as potential follow-up reports;
c) any new fact relating to the conduct of the clinical trial or the development of the investigational medicinal product, if the new fact is likely to affect participant safety
Examples:

- a serious adverse event likely to be related to the trial's interventions and diagnostic procedures and which may impact the conduct of the clinical trial,
- a significant risk for the trial participants such as a lack of efficacy of the investigational medicinal product used in the treatment of a life-threatening disease,
- significant safety results from a recently completed study on animal subjects (such as a carcinogenicity study),
- the premature termination, or temporary suspension, of a trial conducted with the same investigational medicinal product in another country, for safety reasons
- an unexpected serious adverse reaction related to a non-investigational medicinal product required to conduct the trial, (e.g.: "challenge agents", rescue treatment)

d) recommendations from the Data Safety Monitoring Board (DSMB), if applicable, if they are relevant to the safety of the participants
e) any unexpected serious adverse reaction reported to the sponsor by another sponsor of a clinical trial carried out in a different country but relating to the same medication

11.3.2 The role of the investigator

The investigator must **assess the seriousness of each adverse event** and record all serious and non-serious adverse events in the case report form (eCRF*)*.

The investigator must **document** serious adverse events **as thoroughly as possible** and provide a definitive medical diagnosis, if possible.

The investigator must **assess the intensity** of the adverse events:
- by using general terms:
    - *Mild: tolerated by the patient, does not interfere with daily activities*
    - *Moderate: sufficiently uncomfortable to affect daily activities*
    - *Serious: prevents daily activities*

Note: the degree of severity should not be confused with seriousness.

The investigator must **assess the causal relationship** between serious adverse events and the investigational medicinal products (camostat mesylate), or interventions/procedures added by the study (placebo in the control group, trial procedures).

The method used by the investigator is based on the WHO Uppsala Monitoring Centre method and uses the following 4 causality terms:

- Certain
- Probable/likely
- Possible
- Unlikely (not excluded)

Their definition is presented in the following table (excerpt from WHO-UMC causality categories, version dated 17/04/2012).

Table: WHO-UMC causality categories (excerpt)

Causality term	Assessment criteria*
Certain to occur	· Event or laboratory test abnormality, with plausible time relationship to drug intake** · Cannot be explained by disease or other drugs · Response to withdrawal plausible (pharmacologically, pathologically) · Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) · Rechallenge satisfactory, if necessary
Probable/Likely	· Event or laboratory test abnormality, with reasonable time relationship to drug intake** · Unlikely to be attributed to disease or other drugs · Response to withdrawal clinically reasonable · Rechallenge not required
Possible	· Event or laboratory test abnormality, with reasonable time relationship to drug intake** · Could also be explained by disease or other drugs · Information on drug withdrawal may be lacking or unclear
Unlikely	· Event or laboratory test abnormality, with a time to drug intake** · that makes a relationship improbable (but not impossible) · Disease or other drugs provide plausible explanations

*All points should be reasonably complied with
**Or study procedures

In the present study, the investigator will also assess the relationhip between SARS-CoV2 infection (COVID-19 disease) and any adverse event.
From the current knowledge on COVID-19 disease, the following serious adverse events could be related to an evolution of the disease (not exhaustive):

- Thrombo-embolism (arterial and/or venous disease)
- Acute respiratory distress syndrome severe
- Neurological deterioration
- Diabetes or hypoglycaemia

This list is only for indicative purposes and should not be considered as definitive nor exhaustive. All adverse event will be assessed individually for causal relationship with COVID-19.

11.3.2.1 Serious adverse events that require the investigator to notify the sponsor without delay

As per article R.1123-49 of the *Code de la Santé Publique* (French Public Health Code), the investigator notifies the sponsor without delay on the day the investigator becomes aware of any serious adverse event which occurs during a study that meets the description in line 1° of Article L.1121-1 of the Code de la Santé Publique, with the exception of any event which is listed in the protocol and, if applicable, in the investigator's brochure as not requiring notification.

A serious adverse event is any untoward medical occurrence that:

1- results in death
2- is life-threatening to the participant enrolled in the study
3- requires hospitalisation or prolongation of existing hospitalisation
4- results in persistent or significant disability/incapacity
5- is a congenital anomaly/birth defect

11.3.2.2 Specific features of the protocol

11.3.2.2.1 Emergency contact for patients

For safety purposes and monitoring during their participation, all included patients patients will be able to contact a study investigator at any time during their participation and follow-up, notably in case of COVID-19 worsening, new symptoms or advserse events.
At the baseline visit, all patients will be given information these aspects, along with a personal patient card. This card will state the individual participates to the CAMOVID trial and it will include contact information for the investigator in charge of the patient (name, center, phone number). Patients will be asked to present this card at each encounter with any healthcare professional during their participation to the study. It will also include emergency indications and guidelines in case of COVID-19 worsening, new symptoms or advserse events, on how to reach a study physician.
Specifically, in case of any new symptoms, patients will be asked to:

- During business hours: contact their referent study center (recruitement center) and physician (exact contact information will be stated on the individual partient card]
- Out of Business hours: contact the Emergency Departments of Hôpital Saint Louis (referent physician for the study: Dr O Peyrony), Hôpital Bichat, Mondor or Argenteuil hospital
- In case of call to the SAMU: give their individual patient card to the physician of the mobile team, so that they can contact a study investigator as described above.

11.3.2.2.2 Other events that require the investigator to notify without delay the sponsor

- Adverse events deemed "medically significant", defined as events with CTCAE grade 3 or higher.

The investigator must notify the sponsor without delay on the day the investigator becomes aware of these adverse events, in the same manner and within the same deadline as for serious adverse events (see above).

- ***In utero* exposure**

The investigator must notify the sponsor without delay on the day the investigator becomes aware of any pregnancy that occurs during the study, even if it is not associated with an adverse event.

- Exposure **while breastfeeding**

Exposure while breastfeeding occurs if an infant or a child may have been exposed to a medicinal product *via* the breast milk of a mother being treated with an investigational medicinal product.
Even if it is not associated with an adverse event, the investigator must notify the sponsor without delay on the day the investigator becomes aware of the exposure while breastfeeding.

11.3.2.2.3 Serious adverse events that do not require the investigator to notify the sponsor without delay

These serious adverse events are only recorded in the case report forms.

- *Normal and natural course of the condition*:

- Worsening of the condition under investigation (In patient hospitalisation for routine treatment or monitoring the condition under investigation, ICU hospitalization)

11.3.2.3 Period during which SAEs must be notified without delay by the investigator to the sponsor

The investigator must notify the sponsor without delay of any serious adverse events as defined in the corresponding section:

- From the date on which the subject signs the consent form
- Throughout the whole follow-up period intended by the trial (90 days)

  After the end of the clinical trial, if the SAE is likely to be due to the investigational medicinal product (IMP) or to the study interventions (e.g. serious reactions that could appear long after exposure to the medication, such as cancers or congenital abnormalities).

-In that case, the investigator does not have to systematically and indefinitely collect all SAEs possibly related to the IMP, but must notify all possible SAEs related to the IMP of which he has knowledge.

11.3.2.4 Procedures and deadlines for notifying the sponsor

The initial notification of an SAE must be provided in a written report signed by the investigator using a SAE notification form specific to the study and intended for this purpose (in the case report form).

Each item in this form must be completed by the investigator so that the sponsor can carry out the appropriate analysis.

The initial notification to the sponsor of a serious adverse event must be quickly followed by an additional detailed written report (or reports) so that the case outcome may be monitored by the Safety Department or to provide further information.

Whenever possible, the investigator will provide the sponsor with any documents that may be useful (medical reports, laboratory test results, results from additional examinations, etc.). These documents must be non-identifying. In addition, the documents must include the following: study acronym, number and participant's initials.

Any adverse event will be monitored until fully resolved (stabilisation at a level considered acceptable by the investigator, or return to the previous state) even if the participant has left the study.

The initial notification, the SAE follow-up reports and all other documents must be sent to the sponsor's Safety Department by email (eig-vigilance.drc@aphp.fr). It should be noted that it is possible to send SAE reports to the Safety Department by fax to +33 (0)1 44 84 17 99 only in the event of a failed attempt to send the SAE report by email (in order to avoid duplication).

For studies which use e-CRFs **:**

- the investigator completes the SAE notification form in the e-CRF, then validates, prints, and signs the form before sending it by email;
- if it is not possible to connect to the e-CRF, the investigator should complete, sign, and send the SAE notification form to the Safety Department. As soon as the connection is restored, the SAE notification form in the e-CRF must be duly completed.

The investigator must respond to all requests from the sponsor for additional information.
For all questions relating to the notification of an adverse event, the Safety Department can be contacted via email: vigilance.drc@aphp.fr.

For cases of *in utero* exposure, the investigator will complete the Notification and Follow-up form for a pregnancy occurring during participation in a study".
The investigator must monitor the pregnant woman throughout her pregnancy or until the pregnancy is terminated, and must notify the sponsor of the outcome of the pregnancy using this form.
If the outcome of the pregnancy falls within the definition of a serious adverse event (miscarriage, pregnancy termination, foetal death, congenital abnormality, etc.), the investigator must follow the procedure for reporting SAEs.
The initial pregnancy notification, the SAE follow-up reports, and any other documents will be sent to the sponsor according to the same procedures specified herein.
If it was the father who was exposed, the investigator must obtain the pregnant woman's permission before collecting information about the pregnancy.

11.3.3 Role of the sponsor

The sponsor, represented by its Safety Department, shall continuously, throughout the trial, assess the safety of each investigational medicinal product throughout the study.

11.3.3.1 Analysis and declaration of serious adverse events

The sponsor assesses:

- the **seriousness** of all the adverse events reported
- the **causal relationship** between these events and each investigational medicinal product (camostat mesylate, placebo) and any other treatments,
  All serious adverse events which the investigator and/or the sponsor reasonably believe may have a causal relationship with the investigational medicinal product are classed as suspected serious adverse reactions.
- the **expected or unexpected nature** of the serious adverse reactions
  Any serious adverse reaction whose nature, severity, frequency or outcome is inconsistent with the safety information described in the summary of product characteristics, or in the investigator's brochure if the product is not authorised, is considered unexpected.
  The sponsor, represented by its Safety Department, assesses the expected/unexpected nature of a serious adverse reaction based on the information described below**.**

❖ For serious adverse events likely to be related to the investigational medicinal product: **camostat mesylate**:

- refer to the Summary of Product Characteristics enclosed in addenda.

The sponsor will report all suspected unexpected serious adverse reactions (SUSARs), within the regulatory time frame, to the ANSM:

- The sponsor must send the initial report without delay upon learning of the unexpected serious adverse reaction if is fatal or life-threatening, or otherwise within 15 days from learning of any other type of unexpected serious adverse reaction;
- All additional, relevant information must be declared by the sponsor in the form of follow-up reports within a period of 8 calendar days starting from when the sponsor had this information.
- **NB: according to the request of the ANSM, the sponsor will also report to ANSM all life threatening or fatal expected serious adverse reaction within the same regulatory time frame.**

Any suspected unexpected serious adverse reaction must also be declared electronically using the Eudravigilance European adverse drug reactions database managed by the European Medicines Agency (EMA).

The sponsor must notify all the investigators involved about any information that could adversely affect the safety of the research participants.

Specific case of double-blinded trials

After unblinding by the sponsor and if the patient is receiving the product under investigation: the case will be reported without delay as a suspected unexpected serious adverse reaction. If the patient is receiving the comparator product: the sponsor will reassess the unexpected nature of the adverse reaction based on the reference document for the comparator product identified in the protocol.

In exceptional situations, if the study involves a condition with a high mortality and/or morbidity rate, and if the ANSM grants permission at the request of the sponsor as part of the clinical trial authorisation application, the methods for unblinding and for reporting suspected unexpected serious adverse reactions can be modified. These methods will then be defined thoroughly in the study protocol.

11.3.3.2 Analysis and declaration of other safety data

This means any new information that prompts a reassessment of the risk/benefit ratio of the trial or of the product under investigation, or which could be sufficient to consider changes to the use of the product, the trial procedures or trial documentation, or the suspension, cancellation or amendment of the research trial or of other similar trials.

The sponsor will inform the competent authority and the Research Ethics Committee without delay upon knowledge of any emerging safety issue and, if applicable, describe what measures have been taken.

Following the initial declaration of any emerging safety issue, the sponsor will address to competent authorities any additional relevant information about the emerging safety issue in the form of a follow-up report, which must be sent no later than 8 days after learning of the information.

11.3.3.3 Annual safety report

Once a year for the duration of the clinical study, the sponsor must produce an annual safety report (Development Safety Update Report - DSUR) which includes, in particular:

- a safety analysis for the research participants,
- a description of the patients included in the study (demographic profile etc.)
- a list of all the suspected serious adverse reactions that occurred during the period covered by the report,
- summary tables of all the serious adverse events that have occurred since the start of the study,

The report must be delivered no later than 60 days after the anniversary of the date on which the ANSM authorised the trial.

11.3.4 Data Safety Monitoring Board (DSMB)

The Data Safety Monitoring Board (DSMB) may be established by the sponsor. Its primary mission is to monitor safety data. It can have other missions, such as monitoring efficacy data (especially if the protocol includes interim analyses).
The sponsor is responsible for justifying the creation or absence of such a committee to the Competent Authority (ANSM) and to the CPP (Research Ethics Committee).

A DSMB will be established for this trial. The DSMB must hold its first meeting before the first participant is enrolled and ideally before the protocol is submitted to the competent authority and the CPP (Research Ethics Committee).
All missions as well as the specific operating procedures of the DSMB are described in the study's DSMB charter.

The DSMB members are:

- Pr Nadia Aissaoui ,Pr Muriel Fartoukh, Pr Corinne Alberti

The DSMB will operate in accordance with the sponsor's procedures. The DSMB works in an advisory capacity only and the sponsor retains all decision-making authority.

12 DATA MANAGEMENT

12.1 Data access

In accordance with GCPs:
- the sponsor is responsible for ensuring all parties involved in the study agree to guarantee direct access to all locations where the study will be carried out, the source data, the source documents and the reports, for the purposes of the sponsor's quality control and audit procedures or inspections by the competent authority
- the investigators will ensure the persons in charge of monitoring, quality control and auditing or inspecting the interventional study involving human participants have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code)

12.2 Source documents

Source documents are defined as any original document or item that can prove the existence or accuracy of a data or a fact recorded during the study. These documents will be kept in accordance with the regulations in force by the investigator or by the hospital in the case of a hospital medical file.

- General Practitioner(investigator) medical file,
- Original biological examination results,
- Hospitalization report within study participation period
- Summary from imaging examinations

12.3 Data confidentiality

The persons responsible for the quality control of clinical studies (Article L.1121-3 of the *Code de la Santé Publique* [French Public Health Code]) will take all necessary precautions to ensure the confidentiality of information relating to the investigational medicinal products, the study, the study participants and in particular their identity and the results obtained.
These persons, as well as the investigators themselves, are bound by professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the *Code Pénal* [French Criminal Code]).
During and after the research involving human participants, all data collected concerning the participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be rendered non-identifying.
Under no circumstances shall the names and addresses of the participants involved be shown.
The sponsor will ensure that each participant has given written permission for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

12.4 Data processing and storage of research documents and data

12.4.1 Identification of the data processing manager and location(s)

Pr. Matthieu RESCHE-RIGON from Service Biostatistique et Information Médicale (SBIM) Hôpital Saint Louis, AP-HP, Paris will be responsible for data entry and the relevant procedures. The same goes for conducting the statistical analysis.

12.4.2 Data entry

Data entry for data made non-identifying will be carried out on electronic media via a web browser (Cleanweb) linked to a database stored on the sponsor server.

12.5 Data ownership

AP-HP is the owner of the data. The data cannot be used or disclosed to a third party without its prior permission.

13 STATISTICAL ASPECTS

13.1 Description of statistical methods to be used including the timetable for the planned interim analyses

The following analysis set will be considered:

- Intent-to-treat (ITT) defined as all randomized patients in the study and in their randomized group whatever the eligibility criteria and treatment received). This will refer to the primary analyses.

As a general strategy, categorical efficacy and safety endpoints will be summarized as counts (percent), and continuous efficacy and safety endpoints will be summarized using summary measures (median and interquartile range). Similarly, characteristics of patients will be presented using summary measures (median and interquartile range for quantitative characteristics and counts and percentages for categorical characteristics)

Analyses by treatment group will be presented according to the treatment to which subjects were randomized (ITT).

The endpoints (primary and secondary) will be mainly analysed without adjustment.
Exploratory analyses will include adjustment on potential prognostic factors and description of hospitalization motives and characteristics (primary endpoint) per hospital.
Planned subgroup analyses include: analyses stratified on age, on baseline use of macrolides, on vaccine immunization status (SARS-CoV2 vaccine yes/no, completed immunization (all required shots received) yes/no, type of vaccine).

The primary endpoint (probability of hospitalization or death within 21 days) will be compared between groups using a one-sided z-test (2.5% significance level, see section 12.2 below).
One interim analysis of the primary endpoint was initially planned to be conducted after one third of observations had been completed, with efficacy and futility decision rules, for early trial termination (see 12.2 for details). However, as of fall 2021, it was decided to resume enrolment and terminate the trial. Only one final analysis will be performed at the 2.5% one-sided significance level, on the available sample. Other endpoints will be analysed as planned.

Secondary endpoints will be compared across groups using Fisher's exact test when comparing probabilities between groups and Wilcoxon's rank sum test when comparing quantitative endpoints. A 5% two-sided significance-level will be used for comparisons of secondary endpoints.

Exploratory re-analyses on the endpoints will be conducted using Bayesian inference, incorporating external information, such as information on camostat efficacy from published trials and data across the world.

13.2 Calculation hypotheses for the number of participants required and the result

From the current knowledge on SARS-CoV2 infection, we expected roughly 20% of newly diagnosed patients being hospitalized within 21 days, in high-risk adults consulting for medical assessment in outpatient settings (8).
From this reference risk, we designed the study to show an absolute reduction of 10% of hospitalization related to camostat treatment, with a 90% statistical power (see calculation details below). An absolute 10% difference (corresponding to a 50% relative reduction) seems clinically relevant and reasonable, as it represents a number of 10 treated patients to avoid 1 hospitalization. This latter figure appeared adapted to multiple upcoming waves of infection with a necessity of inpatient regulation.

The design was planned to include aninterim analysis after one third of observations have been completed. A total sample size of 536 evaluable patients (268 per treatment group) would have allowed 90% power to detect an absolute difference of 10% in the probability of hospitalization or death at day 21 between groups (e.g. reduction from 20% to 10%), using a z-test, with one-sided 2.5%-significance level for efficacy, using Lan & DeMets risk-spending functions (O'Brien & Fleming boundaries approximation), for efficacy and futility stopping rules.
More precisely, the interim analysis was planned to be performed after 180 observations (90 per group) had been completed. At that point, interim futility boundary would be -0.726 on z-scale (control - intervention) corresponding to an observed increase in hospitalization rate of 4.51% or more in the camostat group compared to the control group, at the interim look.
Interim efficacy boundary would be 3.695 on z-statistic scale (p-value=0.00011), corresponding to an observed decrease in hospitalization rate of 17.5% or more in the camostat group compared to the control group, at the interim look.
Efficacy boundary for the final analysis would be 1.961 on the z-statistic scale (P-value 0.024962), corresponding to an observed decrease in hospitalization rate of 6.35% or more

in the camostat group compared to the control group, on the total sample planned sample size.
Overall, 596 patients (298 in each group) would be included to anticipate a potential 10% drop-out rate, given the ambulatory follow-up.

However, in the context of fall 2021 with the SARS-CoV2 epidemics status in France at that time and the widespread vaccination in France, it was decided to stop the trial: enrolment will be discontinued and already included patients followed-up as per the protocol.
The planned interim analysis sample size has not been reached. Only one final analysis will be performed on the primary endpoint on the available sample, with a one-sided 2.5% significance level for efficacy. Based on the obtained statistics, conditional power corresponding to the total sample size will be computed.

13.3 Anticipated level of statistical significance

The anticipated level of significance is 2.5% (one-sided), for the primary endpoint.
Other comparative analyses will be performed with a two-sided 5% significance level.

13.4 Method for taking into account missing, unused or invalid data

Missing data will be described on the overall population and by treatment group, and method of handling them according to their frequencies and nature will be used. Sensitivity analysis will confirm reliability of conclusions upon various hypotheses on missing values

13.5 Choice of individuals to be included in the analyses

No exclusion will be allowed. Any patient included by mistake or with departures from trials procedures will be accounted in their allocated group in the analysis (intent to treat).
All primary analyses will be performed in both Intention To Treat (ITT): patients will be analysed according to the treatment arm they were randomized, even if the participant did not accept or received the allocated intervention.

Subgroup exploratory analyses (descriptive and comparative) will be conducted according to vaccine immunization status: SARS-CoV2 vaccine yes/no, completed immunization (all required shots received) yes/no, type of vaccine.

14 QUALITY CONTROL AND ASSURANCE

Every research project involving human participants managed by AP-HP is ranked according to the projected risk incurred by study participants using the classification system specific to AP-HP sponsored interventional research involving human participants.

14.1 *General organisation*

The sponsor must ensure the safety and respect of individuals who have agreed to participate in the study. The sponsor must implement a quality assurance system to best monitor the implementation of the study in the investigation centres.

For this purpose, the sponsor shall assign Clinical Research Associates (CRA) whose primary role is to carry out regular follow-up visits at the study locations, after having carried out the initial visits.
The purpose of monitoring the study, as defined in Good Clinical Practices (GCP section 5.18.1), is to verify that:

- the rights, safety and protection of the research participants are met
- the data reported are exact, complete and consistent with the source documents

• the study is carried out in accordance with the protocol in force, the GCPs and the statutory and regulatory provisions in force

14.1.1 Strategy for centre opening

The strategy for opening the centres established for this study is determined using the appropriate monitoring plan.

14.1.2 Scope of centre monitoring

In the case of this risk study the appropriate monitoring level has been determined based on the complexity, the impact and the budget for the study. Therefore, in agreement with the coordinating investigator, the sponsor has determined the logistical score and impact, resulting in a study monitoring level to be implemented: level D.

14.2 Quality control

A CRA appointed by the sponsor will be responsible for the good completion of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the DRCI (Clinical Research and Innovation Department) and in accordance with Good Clinical Practices as well as the statutory and regulatory requirements.

The investigator and the members of the investigator's team agree to make themselves available during regular Quality Control visits carried out by the Clinical Research Associate. During these visits, the following elements will be reviewed depending on the monitoring level:

- written consent
- compliance with the study protocol and with the procedures defined therein
- quality of the data collected in the case report form: accuracy, missing data, consistency of the data with the "source" documents (medical files, appointment books, original copies of laboratory results, etc.)
- management of the treatments used

14.3 Case report forms

All information required by the protocol must be entered in the case report forms. The data must be collected as and when they are obtained, and clearly recorded in these case report forms. Any missing data must be coded.
Every site will have access to the electronic case report forms via a web-based data collection system. Investigators will be given a document offering guidance on using this tool.
When the investigators complete the case report form via the Internet, the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and relevance of all the data entered. In addition, the data are immediately verified as they are entered, thanks to consistency checks. To this end, the investigator must validate any changes to the values in the case report form. An audit trail will be kept of all changes. A justification can be added when applicable, as a comment.
A print-out, authenticated (signed and dated) by the investigator, will be requested at the end of the study. The investigator must archive a copy of the authenticated document that was issued to the sponsor.

14.4 Management of non-compliances

Any events that occur as a result of non-compliance – by the investigator or any other individual involved in running the study – with the protocol, standard operating procedures, good clinical practices or statutory and regulatory requirements must be recorded in a declaration of non-compliance and sent to the sponsor.

These non-compliances will be managed in accordance with the sponsor's procedures.

14.5 Audits/inspections

The investigators agree to consent to the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits and inspections. These audits and inspections cannot be refused on the grounds of medical secrecy.

An audit can be carried out at any time by individuals appointed by the sponsor and independent of those responsible for the research. The aim of the audits is to ensure the quality of the study, the validity of the results and compliance with the legislation and regulations in force.

The persons who manage and monitor the study agree to comply with the sponsor's requirements and with the competent authority regarding study audits or inspections.

The audit may encompass all stages of the study, from the development of the protocol to the publication of the results, including the storage of the data used or produced as part of the study.

14.6 Principal Investigator's commitment to assume responsibility

Before starting the study, each investigator will give the sponsor's representative a copy of his/her updated personal *curriculum vitæ*, signed and dated less than one year, with his/her RPPS number (*Répertoire Partagé des Professionnels de Santé*, Collective Database of Health Professionals). The CV must include any previous involvement in clinical research and related training.

Each investigator will commit to comply with legislation and to conduct the study in line with GCP, in accordance with the Declaration of Helsinki.

The Principal Investigator at each participating site will sign a commitment of responsibility (standard DRCI document) which will be sent to the sponsor's representative.
The investigators and their staff will sign a delegation of duties form specifying each person's role and will provide their CVs.

14.7 Pharmacist's commitment of responsibility

Production problems must be recorded according to the Manufacturing unit (LTCG) procedures.

15 ETHICAL AND LEGAL CONSIDERATIONS

15.1 Methods for informing research participants and obtaining their consent

In accordance with Article L1122-1-1 of the Code de la Santé Publique (French Public Health Code), no interventional research involving human participants can be carried out on a

person without his/her freely given and informed consent, obtained in writing after the person has been given the information specified in Article L.1122-1 of the aforementioned Code.

A reflection period of 24h is given to the individual between the time when he or she is informed and when he or she signs the consent form.

The person's freely-given, written, informed consent will be obtained by the principal investigator or a physician representing the investigator before the person is enrolled in the study, at the baseline visit.

A copy of the information note and consent form, signed and dated by the research participant and by the principal investigator or the physician representing the investigator will be given to the individual prior to their participation in the study. The principal investigator or the physician representing him/her will keep a copy.

At the end of the study, one copy will be placed in a tamper-proof sealed envelope containing all the consent forms. This envelope will be archived by the sponsor.

In addition, the investigator will specify in the person's medical file the person's participation in the research, the procedures for obtaining his/her consent as well as the methods used for providing information for the purpose of collecting it. The investigator will retain one copy of the signed and dated consent form.

15.2 Prohibition from participating in another clinical study or exclusion period set after the study

An exclusion period of participation after the participant has finished this study is defined in the context of this research. It will last for 21 days after inclusion.

The participant may not enrol in another interventional study protocol involving human participants for the duration of his or her participation without consulting with the physician monitoring him or her in the context of the study.

The participants can however participate in other non-interventional studies

15.3 Compensation for participants

There will be no compensation for participating to the study.

15.4 Authorisation for the research location

The study will be carried out in treatment units on individuals presenting a clinical condition for which the units are specialised and who require interventions that are routinely performed at those units. Therefore, the research location does not require specific authorisation.

Special circumstances:

Control subjects or patients will be included in the study. The interventions performed on these participants are acts usually conducted at the unit. We therefore consider that the research location does not require specific authorisation.

15.5 Legal obligations

15.5.1 Role of the sponsor

Assistance Publique - Hôpitaux de Paris (AP-HP) is the sponsor of this study and, by delegation, the DRCI (Clinical Research and Innovation Department) carries out the study's missions in accordance with Article L.1121-1 of the *Code de la Santé Publique (French Public Health Code)*. Assistance Publique - Hôpitaux de Paris reserves the right to halt the study at any time for medical or administrative reasons. In this case, notification will be sent to the investigator.

15.5.2 Request for approval from the CPP (Research Ethics Committee)

Prior to starting the study, AP-HP, as sponsor, must obtain for this interventional study involving human participants concerning a medicinal product for human use, approval from the appropriate CPP (Research Ethics Committee), within the scope of its authority and in accordance with in force legislation and regulatory requirements.

15.5.3 Request for authorisation from ANSM

Prior to starting the study, AP-HP, as sponsor, must obtains authorisation from the ANSM (French Health Products Safety Agency) for the interventional study involving human participants concerning a medicinal products for human use, within the scope of the ANSM's authority and in accordance with in force legislation and regulatory requirements.

15.5.4 Procedures relating to data protection regulations

The computer file used for this research is implemented in accordance with French (amended “Informatique et Libertés” law governing data protection) and European (General Data Protection Regulation – GDPR) regulations.

- Commitment to comply with “Reference Methodology” MR-001

This research is governed by the CNIL (French Data Protection Agency) “Reference Methodology for processing personal data used within the scope of health research” (amended MR-001). AP-HP, as sponsor of the research, has signed a declaration of compliance with this “Reference Methodology”

15.5.5 Amendments to the research

Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain, approval from the CPP (Research Ethics Committee) and authorisation from the ANSM within the scope of their respective authorities, before the amendment can be implemented.
The information note and the consent form can be revised if necessary, in particular in case of a substantial amendment to the study or if adverse reactions occur.

15.5.6 Final study report

The final report for the research involving human participants referred to in Article R1123-67 of the *Code de la Santé Publique* (French Public Health Code) is written and signed by the sponsor and the investigator. A report summary drafted according to the reference plan of the competent authority must be sent to the competent authority within a period of one year following the end of the study, i.e., the end of the participation of the last participant in the study.

15.5.7 Archiving

Specific documents for an interventional study involving human participants concerning a medicinal product for human use will be archived by the investigator and the sponsor for 10 years after the end of the research.

This indexed archiving includes, in particular:

- A sealed envelope for the investigator containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- A sealed envelope for the sponsor, containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- "Study" binders for the Investigator and the sponsor, including (non-exhaustive list) :
    - the successive versions of the protocol (identified by the version number and its date), and any appendices
    - the ANSM authorisations and CPP (Research Ethics Committee) decisions
    - any correspondence
    - the enrolment list or register
    - the appendices specific to the research
    - final study report
- The data collection documents

16 FUNDING AND INSURANCE

16.1 *Funding sources*

PHRC (Hospital Funding for Clinical Research), COVID-19-20-0095

16.2 *Insurance*

For the duration of the study, the Sponsor will take out an insurance policy covering the sponsor's own public liability, as well as the public liability for all the physicians involved in the study. The sponsor will also provide full compensation for any damages caused by the study to the participant enrolled and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any collaborator. Compensation cannot be refused on the grounds of a third-party act or the voluntary withdrawal of the person who initially consented to participate in the study.

Assistance Publique-Hôpitaux de Paris (AP-HP) has taken out insurance with HDI-GLOBAL SE through the insurance broker BIOMEDIC-INSURE for the full study period, which covers its own public liability and that of any collaborator (physician or research staff), in accordance with Article L.1121-10 of the *Code de la Santé Publique* (French Public Health Code).

17 PUBLICATION RULES

The author(s) of any publication relating to this study must include the AP-HP among their affiliations and must name the sponsor AP-HP (DRCI) and the source of funding, if funded by a call for tenders (e.g. national or regional PHRC); a copy of the publication must be sent to the sponsor (see below for rules governing affiliation, and naming of the sponsor and funders).

17.1 Mention of AP-HP affiliation for projects sponsored by AP-HP

- If an author has several affiliations, the order in which the institutions are mentioned (AP-HP, University, INSERM, etc.) is unimportant

- However, if the study is funded in the context of an internal AP-HP call for tender, the first affiliation must be “AP-HP”
- Each of these affiliations must be identified by an address and separated by a semicolon (;)
- The AP-HP institution must feature under the acronym “**AP-HP**” first in the address, specifically followed by: **AP-HP**, hospital, department, city, postcode, France

17.2 Mention of the sponsor AP-HP (DRCI) in the acknowledgements of the text

- “The sponsor was Assistance Publique – Hôpitaux de Paris (Délégation à la Recherche Clinique et à l’Innovation)”

17.3 Mention of the financial backer in the acknowledgements of the text

- “The study was funded by a grant from Programme Hospitalier de Recherche Clinique PHRC 2020 (French Ministry of Health)”

This study is registered on the website http://clinicaltrials.gov/ : NCT04608266.

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18 LIST OF ADDENDA

18.1 **List of investigators** (PI indicating principal investigator by center)

Address of the study location	Title	First name Surname	Telephone/E-mail/Fax
Service des Urgences, Hôpital Saint Louis, 1 avenue Claude Vellefaux 75010 Paris	Dr	Olivier Peyrony (PI)	olivier.peyrony@aphp.fr
Service des Urgences, Hôpital Saint Louis, 1 avenue Claude Vellefaux 75010 Paris	Dr	Marwa Chbihi	marwa.chbihi.e@gmail.com
Service des Urgences, Hôpital Saint Louis, 1 avenue Claude Vellefaux 75010 Paris	Dr	Dominique Vanjak	dominique.vanjak@curie.net
Centre de dépistage COVID-19 Hôpital Bichat, 46 rue Henri Huchard, 75018 Paris	Dr	Dorothée Vallois (PI)	dorothee.vallois@aphp.fr
Service des Urgences, Centre Hospitalier d'Argenteuil, 69, rue du Lt-col Prudhon, 95107 Argenteuil Cedex	Dr	Gaëtan Plantefève (PI)	gaetan.plantefeve@ch-argenteuil.fr
Service de médecine interne, Centre Hospitalier d'Argenteuil, 69, rue du Lt-col Prudhon, 95107 Argenteuil Cedex	Dr	Claire Le Pendu (PI)	claire.lependu@ch-argenteuil.fr
Service des Urgences, Hôpital Henri Mondor, 51 av. du Maréchal De Lattre de Tassigny, 94010 Créteil	Dr	Christian Kassasseya (PI)	christian.kassasseya@aphp.fr
Unité des Maladies Génétiques du Globule Rouge, Hôpital Henri Mondor, 51 av. du Maréchal De Lattre de Tassigny, 94010 Créteil	Pr	Pablo Bartolucci (PI)	pablo.bartolucci@aphp.fr
Service d'Aval des Urgences – Médecine Interne, Hôpital Henri Mondor, 51 av. du Maréchal De Lattre de Tassigny, 94010 Créteil	Dr	Constance Guillaud(PI)	constance.guilaud@aphp.fr
Service d'Aval des Urgences – Médecine Interne, Hôpital Henri Mondor, 51 av. du Maréchal De Lattre de Tassigny, 94010 Créteil	Dr	Noémie Saada	noemie.saada@aphp.fr
Unité Transversale de Traitement des Infections Département de Virologie, Bactériologie-Hygiène, Parasitologie-Mycologie, Hôpital Henri Mondor, 51 av. du Maréchal De Lattre de Tassigny, 94010 Créteil	Dr	Raphaël Lepeule (PI)	raphael.lepeule@aphp.fr
Centre de Santé Richerand, 4 Avenue Richerand, 75010 Paris	Dr	Mariela Skendi (PI)	marielaskendi@gmail.com
Cabinet médical, 21 rue Faidherbe, 75011 Paris	Dr	Karima Amazzough(PI)	karima.amazzough@aphp.fr
Cabinet médical, 13 rue de Tocqueville, 75017 Paris	Dr	Jean Marzouk (PI)	marzoukjean@yahoo.fr
Service de maladies Infectieuses et Tropicales / Unité de Santé Publique, Groupe Hospitalier Sud Ile de France (GHSIF), 270 Avenue Marc Jacquet, 77000 Melun	Dr	Pierre Leroy (PI)	pierre.leroy@ghsif.fr
Service d'Urgences, Hôpital Lariboisière, 2 rue Ambroise Paré, 75010 Paris	Dr	Anthony Chauvin (PI)	anthony.chauvin@aphp.fr

18.2 Serious Adverse Events notification form

Direction de l'Organisation Médicale et des relations avec les Universités (DOMU) Délégation à la Recherche Clinique et à l'Innovation (DRCI)	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS **Serious Adverse Event (SAE) form for a clinical trial conducted on an investigational medicinal product or a related product involving human subjects**	**SECTION FOR THE SPONSOR USE ONLY** **INTERNAL SAFETY REFERENCE:** GED Reference: REC-DTYP-0385

Dès la prise de connaissance de l'EIG par l'investigateur, ce formulaire doit être dûment complété (3 pages), signé et retourné sans délai au secteur Vigilance de la DRCI par mail (eig-vigilance.drc@aphp.fr)

Il est possible de transmettre les formulaires de notification d'EIG au secteur Vigilance par télécopie au +33 (0)1 44 84 17 99 uniquement en cas de tentative infructueuse d'envoi par mail afin d'éviter les doublons.

Initial report ☐ **Follow-up report** ☐ **Follow-up number** |__|__|

1. Clinical trial information

Acronym: CAMOVID

Sponsor study number: APHP200702

Risk:

Clinical trial concerning the 1st administration of the medicinal product (to be added or deleted depending to the trial)

Date of report: |__|__| |__|__| |_2_|_0_|__|__|
dd mm yyyy

Date the investigator became aware of the SAE: |__|__| |__|__| |_2_|_0_|__|__|
dd mm yyyy

Full title of the clinical trial: **CAMOVID: A multicenter randomized trial to evaluate the efficacy and safety of camostat mesylate for the treatment of SARS-CoV-2 infection- COVID-19 in ambulatory adult patients**

2. Clinical investigation center information

Center name: .....
City and address: .....
Department: .....

Investigator (last name/name): .....

Phone: ..... Fax: .....

3. Identification and medical history of the subject

Subject identification number: |__|__|__| - |__|__|__|__| - |__| -|__|
Center No. - Selection order No. - initial last name - initial name

Sex: ☐ M ☐ F

Weight: |__|__|__| kg
Height: |__|__|__| cm

Date of birth: |__|__||__|__||__|__|__|__|
dd mm yyyy

Age: |__|__|__|years

Informed consent signature date: |__|__| |__|__| |_2_|_0_|__|__|
dd mm yyyy

Randomization date: |__|__| |__|__| |_2_|_0_|__|__|
dd mm yyyy

Please provide any medical, surgical or family history which may impact the assessment of the case (medical anonymized documentation to be attached as appropriate):

.....
.....
.....
.....
.....
.....
.....

☐ Group Camostat Mesylate ☐ Group Placebo

4. Investigational Medicinal Product(s) (IMP) or related product(s) [to be specified] administered prior the occurring of the SAE

(cross out the box if the treatment has not started yet)

Brand name (preferably) or International Nonproprietary Name	Route (1)	Dosage (specify the dosing unit ex: mg/d)	Start date *(dd/mm/yyyy)*	Ongoing (2)	End date *(dd/mm/yyyy)*
Camostat Mesylate	oral	.....	|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|
Placebo Camostat Mesylate	oral	.....	|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|

5. Additional procedures or medical cares performed during the	Date	Chronology

clinical trial *(ex.: biopsies, MRI …)* ***(cross out the box if no additional procedure has been performed)***	*(dd/mm/yyyy)*	Before the SAE onset	After the SAE onset
.....	|__|__| |__|__| |_2_|_0_|__|__|	☐	☐
.....	|__|__| |__|__| |_2_|_0_|__|__|	☐	☐

6. Concomitant Medication(s) at the time of the SAE, excluding those used to treat the SAE ***(please fill the table below and the related annex on the concomitant medication(s) as appropriate. Cross out the box if not applicable.)***

⇨ **Annex attached to this form:** ☐ Yes ☐ No

Brand name (preferred) or International Nonproprietary Name	Route (1)	Dosage (specify the dosing unit ex: mg/d)	Administration of the medicinal product date *(from dd/mm/yy to dd/mm/yy)*	Ongoing (2)	Indication	***Action undertaken*** *0: dosage remained unchanged* *1: drug withdrawal* *2: dosage reduction* *3: dosage increasing* *4: unknown*	***Causality of the SAE*** *0: not related to the drug* *1: related to the drug* *2: unknown*
			from |__|__| |__|__| |__|__| to |__|__| |__|__| |__|__|	☐			
			from |__|__| |__|__| |__|__| to |__|__| |__|__| |__|__|	☐			

(1) Route of administration: PO=oral route; IM=intramuscular; IV=intravenous; SC=subcutaneous or other (specify) (2) Ongoing at the time of the SAE

7. Serious Adverse Event [SAE]

Diagnosis: ☐ Definitive ☐ Provisional

.....

.....

.....

Organ(s) affected:

.....

.....

.....

.....

.....

.....

Date first symptoms occurred: |__|__| |__|__| |_2_|_0_|__|__|

Describe the symptoms:

.....

Date of start of SAE:

|__|__| |__|__| |_2_|_0_|__|__|

dd mm yyyy

Onset time: |__||__| hh |__||__| min

☐ *missing data*

Time interval between the last treatment dose intake/absorption of the product or the date of the additional procedures or medical cares performed during the clinical trial and the start of the SAE:

|__||__| / |__||__| / |__||__|

dd hh min

Seriousness criteria:

☐ Hospitalization or prolongation of existing hospitalization:

from |__|__| |__|__| |_2_|_0_|__|__|

to |__|__| |__|__| |_2_|_0_|__|__| ☐ *ongoing*

☐ Death

☐ Life threatening

☐ Persistent or significant disability or incapacity

☐ Congenital anomaly/birth defect

☐ Other significant medical event, specify:

.....

.....

The occurrence of the SAE led to:

☐ no action undertaken regarding the IMP

☐ IMP dosage reduction ☐ IMP dosage increasing

☐ definitive withdrawal of the IMP

☐ temporary withdrawal of the IMP, resumption date: |__|__| |__|__| |_2_|_0_|__|__|

☐ unknown

Recurrence of the SAE after resumption: ○ No ○ Yes, Date: |__|__| |__|__| |_2_|_0_|__|__|

○ Not applicable

Has any symptomatic measure been taken?

☐ No ☐ Yes Date: |__|__| |__|__| |_2_|_0_|__|__| Specify: ……

Did the event require unblinding?

☐ No ☐ Yes Date: |__|__| |__|__| |_2_|_0_|__|__| ☐ Not applicable

Please specify if the SAE is the outcome of:

- A medication error? ☐ No ☐ Yes Date: |__|__| |__|__| |_2_|_0_|__|__|
- An overdose? ☐ No ☐ Yes Date: |__|__| |__|__| |_2_|_0_|__|__|
- A misuse? ☐ No ☐ Yes Date: |__|__| |__|__| |_2_|_0_|__|__|
- Other (specify): ……. ☐ No ☐ Yes Date: |__|__| |__|__| |_2_|_0_|__|__|

Severity ***(to be adapted to the typology of the clinical trial):***

☐ Mild ☐ Moderate ☐ Severe

Outcome of the SAE

☐ **Death** Date: |__|__| |__|__| |_2_|_0_|__|__|

dd mm yyyy

○ unrelated to the SAE

○ related to the SAE

☐ **Not yet recovered**, specify:

○ Stable condition ○ Improvement ○ Worsening

☐ **Resolved:** Date: |__|__| |__|__| |_2_|_0_|__|__|
○ without sequelae dd mm yyyy
○ with sequelae, specify the sequelae: |__|__| |__|__|
…… hh min

☐ **Unknown outcome**

8. Other etiology(ies) considered

☐ No ☐ Yes Specify: ……
……
……

9. Additional test(s) performed

☐ No ☐ Yes Please specify date, type and results: [please attach the anonymized reports where
……
……
……

10. According to the investigator, the SAE is (multiple choice allowed)

Related to the clinical trial:

☐ **Yes:** ☐ **to the investigational medicinal product(s): which one(s)?**
Specify: …… ☐ **Certain relationship** ☐ **Probable/Likely relationship** ☐ **Possible relationship** ☐**Unlikely relationship**
Specify: …… ☐ **Certain relationship** ☐ **Probable/Likely relationship** ☐ **Possible relationship** ☐**Unlikely relationship**
☐ **to the additional procedures/care: which one(s)?**
Specify: …… ☐ **Certain relationship** ☐ **Probable/Likely relationship** ☐ **Possible relationship** ☐**Unlikely relationship**
Specify: …… ☐ **Certain relationship** ☐ **Probable/Likely relationship** ☐ **Possible relationship** ☐**Unlikely relationship**

☐ **No:** ☐ **to the disease progression:** (to be filled)
☐ **to one (or more) concomitant medicinal product(s) administered, specify: ……**
☐ **to an intercurrent disease, specify: ……**
☐ **other, specify: ……**

Reporter:	**Investigator:**	Department stamp:
Name and function: Signature:	Name: Signature:	

18.3 Pregnancy notification form

Direction de l'Organisation Médicale et des relations avec les Universités (DOMU) Délégation à la Recherche Clinique et à l'Innovation (DRCI)	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS ***Notification et suivi d'une grossesse apparue au cours d'une recherche portant sur un Médicament ou produit assimilé***	**PARTIE RESERVEE AU PROMOTEUR** **REFERENCE INTERNE :** Référence GED : REC-DTYP-0185

Ce formulaire doit être dûment complété (2 pages), signé et retourné sans délai au secteur Vigilance de la DRCI par mail (eig-vigilance.drc@aphp.fr)

Il est possible de transmettre ce formulaire au secteur Vigilance par télécopie au +33 (0)1 44 84 17 99 uniquement en cas de tentative infructueuse d'envoi par mail afin d'éviter les doublons.

1. Identification de la recherche

Acronyme : **CAMOVID**
Code de la recherche APHP 200702
Recherche prioritaire sur COVID-19

Notification initiale ☐ **Suivi de notification** ☐ **N° du suivi** |__|__|

Date de notification : |__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa

Date de prise de connaissance de la grossesse par l'investigateur : |__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa

Titre complet de la Recherche : **CAMOVID: A multicenter randomized trial to evaluate the efficacy and safety of camostat mesylate for the treatment of SARS-CoV-2 infection– COVID-19 in ambulatory adult patients**

2. Identification du centre investigateur

Nom de l'établissement : ……

Investigateur (nom/prénom) : ……

Ville et code postal : ..... Service :	Tél :	Fax :

3. Identification de la personne présentant une grossesse

Référence de la personne : |__|__|__| - |__|__|__|__|__| - |__| - |__|
n°centre - n° ordre de sélection - initiale nom - initiale prénom

Date de naissance : |__|__| |___|___|__|__|

Date d'inclusion : |__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa

Date de randomisation : |__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa

Groupe de randomisation :

Numéro de randomisation :

☐ **Groupe Camostat Mesylate**

☐ **Groupe Placebo**

Date des dernières règles : |__|__| |__|__| |_2_|_0_|__|__|

Et/ou date début de grossesse : |__|__| |__|__| |_2_|_0_|__|__|

Expositions au cours de la grossesse :

Tabac :	☐ non	☐ oui (préciser nombre de paquets/année) :	☐ arrêt (préciser date) :	☐ poursuite
Alcool :	☐ non	☐ oui (préciser unités OH) :	☐ arrêt (préciser date) :	☐ poursuite
Drogue :	☐ non	☐ oui (préciser substance) :	☐ arrêt (préciser date) :	☐ poursuite

Autre (préciser) :

4. Antécédents maternels

Médicaux :	**Chirurgicaux :**

Obstétricaux : |__|__| geste |__|__| pare

Préciser si fausse couche, grossesse extra-utérine, interruption de grossesse (médicale ou volontaire), mort *in utero*, malformation congénitale, pathologie congénitale/néonatale non malformative, … (*nombre, date et nature/raison si applicable).*

5. Médicament(s) expérimental (aux) administré(s) ou non pendant la grossesse

Nom commercial (de préférence) ou Dénomination Commune Internationale	Date de première administration Ou non administré	Date de dernière administration Ou en cours	Voie d'administration(1)	Posologie / 24h
Camostat Mesylate ..... ☐ NA				
Placebo Camostat Mesylate ..... ☐ NA				

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser)

6. Procédures et actes ajoutés par la recherche ***(Barrez l'encadré si procédures et actes non réalisés)***	Date de réalisation *(jj/mm/aaaa)*	Chronologie	
		Avant la grossesse	Au cours de la grossesse
	|__|__| |__|__| |_2_|_0_|__|__|		

7. Médicament(s) concomitants administré(s) dans le cadre du soin

(Cf. annexe « Liste relative aux médicaments concomitants » complétée : ☐ ***Oui*** ☐ ***Non applicable)***

Nom commercial (de préférence) ou Dénomination Commune Internationale	Date de première administration	Date de dernière administration Ou en cours	Voie d'administration(1)	Posologie / 24h
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser)

8. Suivi de la grossesse

☐ Echographiques. Date(s) et résultats à préciser *(joindre les CR anonymisés)* :

☐ Autres examens. Date(s) et résultats à préciser *(joindre les CR anonymisés)* :

9. Grossesse en cours ☐ (envoyer par mail un nouveau formulaire complété à l'issue de la grossesse pour le suivi de la notification initiale)
ou issue de la grossesse ☐ (compléter ci-dessous)

Date : |__|__| |__|__| |_2_|_0_|__|__| Terme : |__|__| SA |__|__| J

☐ Fausse couche
→ Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :

☐ Grossesse extra-utérine
→ Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :

☐ Interruption de grossesse → Raison :
→ Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :

☐ Accouchement : ☐ Spontané ☐ Provoqué ☐ Voie basse ☐ Césarienne

Naissance multiple : ☐ Non ☐ Oui, précisez le nombre :
Souffrance fœtale : ☐ Non ☐ Oui, précisez :
Mort-né : ☐ Non ☐ Oui, précisez :
Placenta normal : ☐ Oui ☐ Non, précisez :
Liquide amniotique : ☐ Clair ☐ Autre, précisez :
Anesthésie : ☐ Générale ☐ Péridurale ☐ Rachianesthésie ☐ Aucune

10. Nouveau-né (Si naissance multiple, compléter les parties 1, 2, 3, 9 et 10 d'un nouveau formulaire et l'envoyer par mail)

Sexe : ☐ Masculin ☐ Féminin

Poids : |__|__|__|__| grammes Taille : |__|__|__| cm Périmètre crânien : |__|__|__| cm

APGAR : 1 minute : _____ 5 minutes : _____ 10 minutes : _____

Malformation(s) congénitale(s) : ☐ Non ☐ Oui, précisez :

Pathologie(s) congénitale(s)/néonatale(s) non malformative(s) : ☐ Non ☐ Oui, précisez :

Le nouveau-né a-t-il bénéficié d'un suivi particulier à la naissance : ☐ Non ☐ Oui, précisez : ☐ Non applicable

Notificateur	**Investigateur**	Tampon du service :
Nom et fonction : Signature :	Nom : Signature :	

18.4 Summary of product characteristics

The summary of product characteristics is attached to this protocol (publication date : 2019)

Attached file

18.5 Study flyers for emergency and occupational medicine departments in participating hospitals

See attached file