ClinicalTrials.gov Upload Document Cover Page

NCT Number	NCT04455815
EudraCT Number	2020-002110-41
Sponsor Protocol Number	CRUKD/20/002
Official Title	A Randomised Phase II trial in early COVID-19, assessing use of camostat by blocking SARS-CoV-2 Spike protein-initiated membrane fusion.
Document, Version & Date	Protocol Version 6.0 dated 20 September 2021

SPIKE-1 TRIAL: A Randomised Phase II trial in early COVID-19, assessing use of camostat by blocking SARS-CoV-2 Spike protein-initiated membrane fusion.

Date and Version No: 20 September 2021, Version 6.0
Protocol No.: CRUKD/20/002
EudraCT No.: 2020-002110-41

Chief Investigator: Professor Kevin Dhaliwal, University of Edinburgh

Sponsor: [redacted]

PARTICIPATING INVESTIGATORS AND CENTRES:

Details of Chief Investigator (CI), Principal Investigators (PIs) and investigational sites are recorded on the Participating Investigators and Centres list in the Sponsor's Trial Master File (TMF).

CONFIDENTIALITY STATEMENT:

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host NHS Trust/Boards(s), regulatory authorities, and members of the Research Ethics Committee (REC).

SPONSOR STATEMENT:

This project is supported by Cancer Research UK (CR UK) in support of the response to the coronavirus-19 (COVID-19) pandemic. CR UK researchers and collaborators across the globe turned their expertise and infrastructure towards COVID-19 research and this project is supported and sponsored by CR UK as part of that global effort. The full extent of the disruption COVID-19 will have on cancer services and people affected by cancer is unprecedented therefore CR UK supports COVID-19 research with the ambition of ensuring cancer prevention, screening and treatment services, are restored and available to those affected by cancer.

AMENDMENT HISTORY:

Protocol Version No. and Date	**Summary of changes**
1.0 dated 26MAY2020	Initial version for REC/HRA and MHRA submission
2.0 dated 04JUN2020	Post initial submission changes to include: Table1: Typo correction, pregnancy test added. Section 5.4.2.1: New section, 'Dose interruption/Withdrawal criteria.' [redacted] Section 6.2: Exclusion criteria #2 added related to Liver Function Test result.
3.0 dated 25SEP2020	**Substantial**

	Section 6.1: Inclusion criteria and reference to COVID-age for participant eligibility (associated Appendix 4 for COVID-age risk tool) Section 6.1: Reference to COVID-19 symptoms will be as per guidance issued by the UK health authorities. Section 7.2.5: Camostat administration to be taken in a fasted state (rationale provided in revised Section 3.0) **Non-substantial** • Amendment history table: Liver Function Test exclusion criteria added (omitted in error from v2.0 summary of changes). • Other minor updates/clarifications.
4.0 dated 25Jan2021	**Substantial** Section 6.1 Patients are now eligible if they have a 'symptomatic COVID-19 infection', and any patient that in the investigator's opinion would not make the patient a good candidate for the clinical trial should be excluded. Section 6.2 Any patient that, in the investigator's opinion would not make the patient a good candidate for the clinical trial should be excluded. [redacted] Section 8.3 Clarification of Day 28 and post-discharge visits. Section 12.5 SAEs relating to COVID will not need reporting post the Day 28 visit. Section 13.1 Definition of patient evaluability clarified. Trial dates expanded. Introduction of optional patient application ('app'). **Non-substantial** Clarification of processes (testing, recruitment, home visit, trial pack delivery, sampling) and administrative changes.
5.0 dated 15Apr2021	**Substantial** Trial changed from Phase II/III to Phase II only. Section 3.2 Text re-added relating to proposed dose and dosing schedule as per protocol version V3.0 as removed by error from V4.0.

	Section 4 Primary objective of efficacy removed and safety and tolerability of camostat added as primary objective. Pharmacokinetics added as secondary objective. Removal of secondary objective relating to overall mortality assessed one year following randomisation. Section 5 Trial design modified to eliminate continuation phase. Section 6 Inclusion Criteria removed requirement for moderate to severe COVID-19 age risk calculation Section 8 COVID-19 age risk to be collected at baseline Section 9 Recruitment expanded to include patients presenting to Emergency Departments, Acute Assessment Units and hospitalised patients who are admitted (for any reason) who subsequently test positive for COVID-19. Patients will also be identified through other methods such as NHS digital and Test and Trace Section 5&8 Text added in relation to the COVID-19 vaccine; permitted prior to entry but current NHS guidelines do not allow the vaccine to be given within 28 days following a positive text. Please refer to current NHS guidelines.
6.0 dated 20Sep2021	Changes include those relating to potential collaboration with several global study teams conducting camostat trials with similar study design to the CRUKD/20/002 trial with the aim of pooling all data and analysing the effect of camostat on viral load and clinical outcome. Changes include an update to the end of trial definition and end of trial date as well as the statistical section.

TABLE OF CONTENTS

1 ABBREVIATIONS

AAU	Acute Assessment Unit
ABPI	Association of British Pharmaceutical Industry
ACEI	Angiotensinogen-converting enzyme inhibitors
ACE-2	Angiotensin-converting enzyme 2
ADR	Adverse drug reaction
AE	Adverse event
ALAMA	Association of Local Authority Medical Advisors
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
AR	Adverse reaction
AST	Aspartate aminotransferase
CDD	Centre for Drug Development
CDM	Clinical Data Manager
CI	Chief Investigator
C_{max}	Maximum observed plasma concentration
CoA	Certificate of Analysis
COVID-19	Coronavirus disease 2019
[redacted]	[redacted]
CRA	Clinical Research Associate
CRUK	Cancer Research UK
CSM	Clinical Study Manager
CSR	Clinical Study Report
CT	Computerised tomography
CTA	Clinical Trials Authorisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTRG	Clinical Trials & Research Governance, University of Oxford
CXR	Chest X-ray
DMP	Data Management Plan
DPA	Data Protection Act
DSUR	Development Safety Update Report
EC50	Half maximal effective concentration
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic Case Report Form
ED	Emergency Department
EoT	End of Trial
FBC	Full blood count
[redacted]	[redacted]
GBPA	4-(4-guanidinobenzoyloxy) phenyl acetic acid
GGT	Gamma-glutamyl transferase
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMP	Good Manufacturing Practice
GP	General Practitioner
GTP	Gamma-glutamyl transpeptidase
Hb	Haemoglobin
HRA	Health Research Authority
IB	Investigator's Brochure
IC_{10}	10% of maximal inhibitory concentration
IC_{50}	Half maximal inhibitory concentration
ICD	Informed Consent Document
ICH	International Conference of Harmonisation
ID	Identification
iDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IV	Intravenous

IWRS	Interactive web response system
LFT	Liver function tests
MERS-CoV	Middle East Respiratory Syndrome coronavirus
MHRA	Medicines and Healthcare products Regulatory Agency
NLR	Neutrophil:lymphocyte ratio
NHS	National Health Service
NSAIDs	Non-steroidal anti-inflammatory drugs
NYHA	New York Heart Association
PI	Principal Investigator
PK	Pharmacokinetic
PSRB	Protocol and Safety Review Board
PT	Prothrombin time
qds	*quater die sumendum* (to be taken four times daily)
QP	Qualified Person
qPCR	Quantitative (real-time) polymerase chain reaction
REC	Research Ethics Committee
RNA	Ribonucleic acid
RRT	Renal replacement therapy
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SARS-CoV	Severe Acute Respiratory Syndrome coronavirus
SARS-CoV-2	Severe Acute Respiratory Syndrome coronavirus 2
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
tds	*ter die sumendum* (to be taken three times daily)
$T_{1/2}$	Terminal half-life
T_{max}	Time to maximum concentration
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom
U&E	Urea and electrolytes
USM	Urgent Safety Measure
Vd	Volume of distribution
WBC	White Blood Cells

PROTOCOL SIGNATURES

Sponsor Signature

The Sponsor has read and agrees to the protocol, as detailed in this document. I am aware of my responsibilities as the Sponsor under the UK Clinical Trials Regulations[1], the guidelines of Good Clinical Practice (GCP)[2], the Declaration of Helsinki[3], the applicable regulations of UK law and the trial protocol. The Sponsor agrees to conduct the trial according to these regulations and guidelines and to appropriately direct and assist sponsor's staff who will be involved in the trial and ensure that all staff members are aware of their clinical trial responsibilities.

Name: [redacted]

Title [redacted]

Signature: _____

Date: _____

[1] *The Medicines for Human Use (Clinical Trials) Regulations (S.I. 2004/1031) and any subsequent amendments to it.*

[2] *ICH Harmonised Guideline Integrated Addendum to ICH E6: Guideline for Good Clinical Practice E6(R2) Step 4 dated 09 November 2016*

[3] *WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and all subsequent amendments including Oct 2013.*

PROTOCOL SIGNATURES

Chief Investigator Signature

I have read and agree to the protocol, as detailed in this document. I am aware of my responsibilities as a Chief Investigator under the UK Clinical Trials Regulations[1], the guidelines of Good Clinical Practice (GCP)[2], the Declaration of Helsinki[3], the applicable regulations of the relevant NHS Trust/Boards and the trial protocol. I agree to conduct the trial according to these regulations and guidelines and to appropriately direct and assist the staff under my control, who will be involved in the trial, and ensure that all staff members are aware of their clinical trial responsibilities.

Chief Investigator's Name: [redacted]

Name of site: [redacted]

Signature: _____

Date: _____

[1] *The Medicines for Human Use (Clinical Trials) Regulations (S.I. 2004/1031) and any subsequent amendments to it.*

[2] *ICH Harmonised Guideline Integrated Addendum to ICH E6: Guideline for Good Clinical Practice E6(R2) Step 4 dated 09 November 2016*

[3] *WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and all subsequent amendments including Oct 2013.*

2 SYNOPSIS

Study Title	A Randomised Phase II trial in early COVID-19, assessing use of camostat by blocking SARS-CoV-2 Spike protein-initiated membrane fusion.
Short title	SPIKE-1
Sponsor	Cancer Research UK
Funder	LifeArc
Trial Design	A randomised, multicentre, prospective, open label, community-based clinical trial. There are two arms: **Treatment arm:** Patient to receive treatment with camostat tablets, 200mg four times daily (*qds*) for 14 days **Control arm (non-treatment):** Patient to receive best supportive care. Patients will be randomised 1:1 into each of these arms until both arms have recruited up to 50 patients. Early assessment of recruitment and trial feasibility will be critical therefore the Trial Management Group (TMG) will provide ongoing review of these aspects and propose modification for regulatory/ethical approval as appropriate.
Trial patients	▪ Adults, 18 years of age and above ▪ Symptomatic COVID-19 infection ▪ Evidence of current COVID-19 infection from a validated assay Patients will be recruited through various methods including but not limited to: • General Practitioner (GP) practices • Advertisement (e.g. on social media, at testing centres) • COVID hubs • Identification through other hospital departments (e.g. Emergency Departments, Acute Assessment Units, Oncology etc.) • NHS Digital • Hospital in-patients • Test and Trace, or equivalent
Sample size	Up to 100 patients (randomised 1:1 treatment and control arm).
Planned trial period	Start date August 2020. The anticipated end date for this trial is July 2021, however that may be amended based on emerging data and circumstances.
Planned recruitment period	Approximately 12 months
Primary Objective and Endpoint	
Objective	**Endpoint**
To further assess the safety and toxicity profile of camostat. to support integration into a Phase III trial.	Causality and severity of each adverse event (AE) to camostat.
Secondary Objectives and Endpoints	

To confirm that the PK profile aligns with the established PK profile for the active metabolite of camostat, 4-(4-guanidinobenzoyloxy) phenyl acetic acid (GBPA).	Confirm PK parameters of GBPA as assessed by population estimates from population PK analysis (popPK).
To assess the ability of camostat to reduce the requirement for COVID-19 related hospital admission in community patients with SARS-CoV-2 infection.	Rate of COVID-19 related hospital admission in community patients with SARS-CoV-2 infection.
To evaluate the requirement for supplementary oxygen (non-invasive or mechanical invasive) in patients who have received camostat as treatment for SARS-CoV-2 infection.	Supplementary oxygen-free days at 28 days (from randomisation).
To evaluate the requirement for ventilation in patients who have received camostat as treatment for SARS-CoV-2 infection.	Ventilator-free days at 28 days (from randomisation).
To evaluate efficacy of camostat by effect on COVID-19 related clinical improvement.	Time Frame: Days 1-28 Time to worst point on the scale or deterioration of two points or more (from randomisation) on a 9-point category ordinal scale. 9-point category ordinal scale: 0. Uninfected, no clinical or virological evidence of infection 1. Ambulatory, no limitation of activities 2. Ambulatory, limitation of activities 3. Hospitalised – mild disease, no oxygen therapy 4. Hospitalised – mild disease, oxygen by mask or nasal prongs 5. Hospitalised – severe disease, non-invasive ventilation or high-flow oxygen 6. Hospitalised – severe disease, intubation and mechanical ventilation 7. Hospitalised – severe disease, ventilation and additional organ support e.g. vasopressors, renal replacement therapy (RRT), extracorporeal membrane oxygenation (ECMO) 8. Death
Research Objectives and Endpoints	
[redacted]	[redacted]

Safety and tolerability

Camostat is a drug with 30 years of clinical experience in Japan and South Korea where it is in clinical use for treatment of an unrelated condition (chronic pancreatitis) and postoperative reflux oesophagitis, with a known, acceptable safety profile.

Daily self-assessment [redacted] with daily video call (or phone) consultation of all patients will support early reporting of study compliance.

Community patients will be given clear information regarding [redacted] thresholds, indications of progressive breathlessness, or other concerning symptoms that should trigger immediate self-referral to seek health advice from the appropriate channels as they normally would, according to urgency e.g. GP or dialling National Health Service (NHS) 111 or 999.

For community patients, daily video call (or phone) assessments will support reinforcement and safety netting of these features, allowing for self- or clinical trial team referral for appropriate primary care, 111 or 999 review, in accordance with local clinical pathways.

For patients in hospital, [redacted] by hospital team will support safety. If discharged, the patient management will be performed as for community-based patients.

Trial assessments

Screening (Home visit or in hospital):

- Demographics, medical history, height and weight, COVID-age risk (Appendix 4).
- Haematological and biochemical parameters measured in blood.
- Research blood samples taken for other markers and antibody testing (if available).
- [redacted]
- Collection of symptoms and functional score (where possible).

All patients (all arms): Days 1-14

- Daily monitoring for all patients (video or phone call for community patients).
- COVID-19 symptom collection using the Flu-iiQ questionnaire (see Appendix 2.0).
- Collection of symptoms.

- [redacted]
- [redacted]
- [redacted]
- Daily visit by hospital or research team for monitoring, collection of symptoms, [redacted] pulse rate [redacted]

Days 7 (+/- 1 day) and 14 (- 2 days)

For community patients home visit and consultation with clinical professional.

The intention is that home visits occur on Days 7 and 14 to take research bloods and [redacted] However, this requirement may change if patients are able to provide samples by visiting the site (e.g. 'red hub') but only in accordance with government and clinical advice. If the Sponsor and site decide that sampling is not required, this will be communicated to the patient. The Day 7 and 14 video (phone) calls will still go ahead as planned regardless of sampling. For patients recruited while in hospital sampling on Day 7 and 14 will be performed by hospital or research team.

- [redacted]
- Haematological and biochemical parameters measured in blood.
- Research blood samples taken for other markers and antibody testing (if available).
- PK blood samples (where possible).
- [redacted]

Days 21 and 28

- [redacted]
- Collection of symptoms.
- [redacted]
- [redacted]

Days 1-28

For any patient who is randomised and enrolled on the trial, if they require hospitalisation due to COVID-19 within the 28 days of Day 1, the research team will make every effort to maintain contact with the patient and if the patient has been randomised to camostat, that this continues unless it interferes with clinical care.

Review of hospital and primary care records if applicable to evaluate use of any form of supplementary oxygen, imaging (chest X-ray or computerised tomography [CXR/CT scanning]) CXR/CT reports or images to assess progression or evolution of pneumonia and evidence of pulmonary thromboembolic events plus documentation of death (COVID related mortality) during the trial period.

Patients who are hospitalised will be followed up following discharge. The Day 28 visit can be done up to 28 days post discharge if the patient was hospitalised at the time of Day 28.

3 BACKGROUND AND RATIONALE

There is currently a critical lack of approved therapies for COVID-19, caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus (Liu, 2020) and the main standard of care is supportive treatment only (Arabi, 2020) (Ruan, 2019). Recently, remdesivir received conditional marketing authorisation in the EU (03 July 2020) for the treatment of COVID 19 in adults and adolescents with pneumonia requiring supplemental oxygen. There is also an ongoing evaluation by the European Medicines Agency of a marketing authorisation for dexamethasone for the treatment of hospitalised adult patients with COVID 19. The clinical manifestations of COVID-19 range from asymptomatic infections or mild, transient symptoms to severe viral pneumonia with respiratory failure. Although many patients do not progress to severe disease, a significant number are hospitalised with pneumonia as the SARS-CoV-2 infection spreads.

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA β-coronavirus similar to the severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) coronaviruses. Cell entry of coronaviruses, such as SARS-CoV and MERS-CoV, depend on initial binding of the viral spike (S) proteins to the angiotensin-converting enzyme 2 (ACE-2) receptor, found on the cell surface of target cells and subsequent priming of the S protein by host cell proteases. The serine protease type II transmembrane serine protease (TMPRSS2), also expressed at the cell surface, 'primes' the S protein on the virus facilitating its activation and enabling the fusion of the virus and target cell membranes and transfer of viral RNA (Shulla, 2011) (Shirato, 2013); this process is shown schematically in Figure 1. Inhibition of TMPRSS2 in *in vitro* and *in vivo* models has been shown to play a significant role in reducing viral infection and viral spread (Matsuyama, 2010) (Shulla, 2011) (Iwata-Yoshikawa, 2019).

SARS-CoV-2 has been shown to also infect human cells via binding of its spike (S) protein to the ACE-2 receptor on the cell surface and priming of the S protein by the cellular serine protease, TMPRSS2, which facilitates its activation and enables the fusion of the virus with the host cell (Yan, 2020).

[redacted]

Camostat has been shown to inhibit the serine protease TMPRSS2 and block SARS-CoV (Kawase, 2012) and SARS-CoV-2 (Hoffmann, 2020) (Hoffmann, APR 2020) infection of human epithelial lung cells *in vitro* and improved survival outcomes in a mouse model of SARS-CoV (Zhou, 2015). Camostat significantly reduced SARS-CoV-2 viral entry in Calu-3 cells with an EC_{50} of 87 nM and no interference in cell viability reported (Hoffmann, APR 2020). This reported EC_{50} is consistent with IC_{50}'s determined in other cell-based assays investigating the inhibition of SARS-CoV and MERS-CoV viral entry by

camostat, which have been in the range of 1 to 0.1 µM (Hoffmann, SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and is Blocked by a Clinically Proven Protease Inhibitor, 2020) (Kawase, 2012) and (Yamamoto, 2016).

Camostat may therefore present a potential solution to treat COVID-19 infected patients.

For further information on the background and rationale for investigating camostat as a potential treatment for COVID-19 refer to the current version of the 'Camostat Investigator's Brochure'.

3.1 Investigational Medicinal Product – Camostat

Camostat is a non-peptide serine protease inhibitor and after oral administration, acts promptly on kinin formation, fibrinolytic, coagulation and complementary systems to inhibit enzyme activities and their abnormal increases. It has also been shown to inhibit TMPRSS2, a host cell factor involved in the cellular entry of coronaviruses (Kawase, 2012) (Hoffmann, SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and is Blocked by a Clinically Proven Protease Inhibitor, 2020) (Hoffmann, APR 2020).

Camostat is rapidly hydrolysed to its active metabolite 4-(4-guanidinobenzoyloxy) phenyl acetic acid (GBPA) *in vivo*; the inhibitory effects of both camostat and GBPA on serine proteases have been shown to be comparable *in vitro*.

Camostat (camostat mesilate, FOIPAN®) is licensed for clinical use in Japan and South Korea and was first approved for use in these countries in 1985 and 1989, respectively. It is marketed by Ono Pharmaceutical Co., Ltd. and has been in clinical use for over 30 years. Camostat is indicated for the treatment of acute symptoms of chronic pancreatitis (recommended dose 600 mg [200 mg *tds*]; guidance on administration in a fed or fasted state is not given) and for the treatment of postoperative reflux oesophagitis (recommended dose 300 mg [100 mg *tds*]; doses to be taken after food); it has a known, acceptable safety profile. Camostat is not approved for use in the EU for any indication and will be used outside of its licensed indication and investigated for the treatment of COVID-19 in the CRUKD/20/002 trial.

For further information on camostat, refer to the current version of the 'Camostat Investigator's Brochure'.

3.2 Proposed dose and dosing schedule for CRUKD/20/002

The concentration of camostat required to suppress viral entry and significantly affect SARS-CoV, MERS-CoV or SARS-CoV-2 infection [redacted] can be informed from the *in vitro* EC_{50} of 0.087 µM (Hoffmann, APR 2020) and estimated IC_{50}'s in the range 1 to 0.1 µM (Hoffmann, 2020) (Kawase, 2012) and (Yamamoto, 2016).

An important consideration in determining the recommended dose and schedule for this trial is whether the concentration of GBPA (active metabolite of camostat[5]) achieved after dosing in humans, is sufficient to achieve plasma concentrations in this range (target concentration considered to be 0.1 µM). The reported PK parameters for a 200 mg oral dose of camostat (2 x 100 mg tablets) administered in a fasted state are: [redacted] This is within the range of camostat concentrations that have been shown to inhibit viral entry *in vitro*.

[5] All PK and plasma concentrations relate to GBPA, the active metabolite of camostat and not to the parent molecule. This due to rapid metabolism of camostat *in vivo*, however, the potency of both are considered to be equivalent.

On the basis of this PK data, dosing camostat in a fasted state at 200 mg every 8 hours (the approved dosing schedule), and given a $T_{1/2}$ of 100 min, the plasma concentration of camostat would only be expected to remain above the IC_{50} of [redacted] for approximately [redacted] after each dose.

Options to increase exposure levels and the duration of exposure above the target level of [redacted] in the CRUKD/20/002 trial, were considered by the Sponsor and a dose of [redacted] was initially considered.

The effect of increasing the dose to [redacted] on Cmax can be estimated from dose proportionality. If dose proportionality is assumed to be linear, then [redacted] However, in a separate study the plasma concentration reported following a [redacted], resulted in a Cmax of [redacted]. Comparing this to a Cmax of [redacted] reported after an oral dose of [redacted] (administered in a fasted state), the dose proportionality for Cmax is closer to [redacted], therefore predicting a Cmax of [redacted] dose administered in a fasted state (refer to the current version of the 'Camostat Investigator's Brochure' for further details).

Recent unpublished data provided by Ono Pharmaceutical Co. Ltd from an ongoing Phase I trial in healthy male adult volunteers (NCT04451083), is also consistent with a dose proportionality in Cmax of approximately ×1.5 for doses of camostat administered in a fasted state [redacted] (Ono Pharmaceutical Co., Ltd., 2020). Preliminary PK parameters from this trial following administration of a single dose of camostat, 600 mg in a fasted state (Day 1), are: [redacted] This trial additionally compared PK parameters from two cohorts ([redacted], Japanese healthy males per cohort) after repeat dosing at [redacted] in both a fed and fasted state. Draft unpublished results have shown that there is a notable food effect on dosing, with plasma exposure (Cmax) significantly lower in subjects administered a single dose of camostat after food as compared to dosing in a fasted state. This is most clearly evidenced by comparing the Cmax and AUC values from subjects dosed in a fasted state [redacted] with values obtained when the subjects received doses after food [redacted] For further details of this study refer to the current version of the 'Camostat Investigator's Brochure'.

The target camostat plasma concentration for inhibition of viral entry based on preclinical data is estimated to be [redacted] Using the expected plasma Cmax for a 300 mg dose administered fasted, the plasma concentration over time was simulated to estimate how long a concentration [redacted] would be expected to be sustained; the higher dose of 300 mg is predicted to have only a minimal effect on the time that a plasma concentration of [redacted] will be maintained (Figure 2). Further PK modelling was performed to consider dosing [redacted] (Figure 2). With this dosage and dosing regimen, the camostat plasma concentration is maintained above the [redacted], for a longer period of time ([redacted] resulting in greater exposure to the drug. The effect of variation in dosing interval on plasma concentration with [redacted], was also modelled (Figure 3) and illustrates that a [redacted] target concentration of [redacted] As the half-life of camostat is [redacted], supported by the results from the recent Ono Pharmaceutical Co.Ltd Phase I trial (NCT04451083) referenced above (refer to the current version of the 'Camostat Investigator's Brochure' for further details). [redacted]

[redacted]

[redacted]

[redacted]

Camostat has been in clinical use for over 30 years and is indicated for the treatment of acute symptoms of chronic pancreatitis (recommended dose 600 mg [200 mg tds]) and for the treatment of postoperative reflux oesophagitis (recommended dose 300 mg [100 mg tds]). Dosing instructions in the approved Package Insert state doses should be taken after a meal for the treatment of postoperative reflux oesophagitis but no guidance on dosing in a fed or fasted state is given for the treatment of chronic pancreatitis. The recent unpublished data from the Ono Pharmaceutical Co. Ltd. Phase I trial (NCT04451083) has [redacted] (see Section 5.2), [redacted]

[redacted]. It is likely that the safety data for the use of camostat in the treatment of chronic pancreatitis (total daily dose 600 mg [200 mg tds]) will have been generated from a mixed population in terms of dosing in both a fed and fasted state, but with no obvious difference in adverse event (AE) profile noted and a known, acceptable safety profile for the agent at the recommended dose and schedule.

Additional safety data to support the 200 mg qds dosing schedule in a fasted state is provided from the ongoing NCT04451083 trial. As noted above, two cohorts of healthy Japanese male adults (n=7 per cohort) were administered a single dose of camostat [redacted] on Day 1 and then [redacted] dose proposed in the CRUKD/20/002 trial [200 mg qds]). In this trial, [redacted] (Ono Pharmaceutical Co., Ltd., 2020). Pharmacokinetic parameters reported in this trial for doses administered fasted, [redacted] (refer to the current version of the 'Camostat Investigator's Brochure' for further details).

The camostat dose proposed for the treatment arm in the CRUKD/20/002 trial is therefore a total daily dose of 800 mg (200 mg qds) for 14 days. Whilst the proposed 14-day dosing period is double that explored in the ongoing NCT04451083 trial, the total daily dose to be administered is three-fold less and considered acceptable based on the safety data available and lack of accumulation observed. Patients will be required to take their doses one hour before each meal and then before bed, with an interval of approximately three hours between eating and the next dose, so approximately four hours apart (except for the overnight interval between the last dose on one day and first dose of the next day which will be longer) and at the same time each day.

3.3 Safety considerations

For further information on the safety of camostat and specific safety considerations refer to the current version of the 'Camostat Investigator's Brochure'.

3.3.1 Adverse events

Camostat has been in clinical use for over 30 years in Japan and Korea and has a known, acceptable safety profile. Adverse reactions reported during the safety surveillance of camostat for its licensed indications include shock or anaphylactoid symptoms, thrombocytopenia, changes in liver enzymes. gastrointestinal disorders, rash and hyperkalaemia, all with low reported incidences (<1% patients).

3.3.2 Patient population

The majority of clinical studies supporting the original registration of FOIPAN® in Japan were conducted in a Japanese/Asian population.

Two Phase I PK studies have been performed in Caucasians, one by Forrest,1989 and one by Midgley, 1994. Camostat is rapidly metabolised in vivo by a carboxyesterase to its active metabolite GBPA and the inactive by product 4-guanidinobenzoic acid (GBA) (Midgley, 1994). The active metabolite GBPA is further metabolized by arylesterase, glucuronidated and excreted in the urine (Midgley, 1994). Genetic variations due to ethnicity have not been reported for any of these enzymes involved in the metabolism

of camostat. From the available data, it is concluded that the PK/PD differences between the Asian and Caucasian populations are predicted to be minimal and that the known safety of camostat in Asians and Caucasians is expected to be similar (Forrest, 1989) (Midgley, 1994).

3.3.3 Risk and benefit assessment

For the overall risk and benefit assessment for the investigation of camostat in protocol CRUKD/20/002, refer to Section 5.8 in the current version of the 'Camostat Investigator's Brochure'.

4 OBJECTIVES AND ENDPOINTS

Primary Objective and Endpoint	
Objective	**Endpoint**
To further assess the safety and toxicity profile of camostat. to support integration into a Phase III trial.	Causality and severity of each adverse event (AE) to camostat.
Secondary Objectives and Endpoints	
Objective	**Endpoint**
To confirm that the PK profile aligns with the established PK profile for the active metabolite of camostat, 4-(4-guanidinobenzoyloxy) phenyl acetic acid (GBPA).	Confirm PK parameters of GBPA as assessed by population estimates from population PK analysis (popPK).
To assess the ability of camostat to reduce the requirement for COVID-19 related hospital admission in community patients with SARS-CoV-2 infection.	Rate of COVID-19 related hospital admission in community patients with SARS-CoV-2 infection.
To evaluate the requirement for supplementary oxygen (non-invasive or mechanical invasive) in patients who have received camostat as treatment for SARS-CoV-2 infection.	Supplementary oxygen-free days at 28 days (from randomisation).
To evaluate the requirement for ventilation in patients who have received camostat as treatment for SARS-CoV-2 infection.	Ventilator-free days at 28 days (from randomisation).
To evaluate efficacy of camostat by effect on COVID-19 related clinical improvement.	Time Frame: Days 1-28 Time to worst point on the scale or deterioration of two points or more (from randomisation) on a 9-point category ordinal scale. 9-point category ordinal scale: 0. Uninfected, no clinical or virological evidence of infection 1. Ambulatory, no limitation of activities 2. Ambulatory, limitation of activities 3. Hospitalised – mild disease, no oxygen therapy 4. Hospitalised – mild disease, oxygen by mask or nasal prongs 5. Hospitalised – severe disease, non-invasive ventilation or high-flow oxygen 6. Hospitalised – severe disease, intubation and mechanical ventilation 7. Hospitalised – severe disease, ventilation and additional organ support – vasopressors, renal replacement therapy (RRT), extracorporeal membrane oxygenation (ECMO) 8. Death

Research Objectives and Endpoints	
Objective	**Endpoint**
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

5 TRIAL DESIGN

5.1 Summary of trial design

A randomised, multicentre, prospective, open label clinical trial.

The trial aims to recruit up to 100 patients.

The Trial Management Group (TMG) described in Section 5.2.1, will perform ongoing review of the emerging data to inform adaptive decision making during the trial. Please see Section 5.2.1. for further details.

During the trial, patient enrichment strategies may be implemented *e.g.* adapting the inclusion criteria to include emerging co-morbidities, neutrophil/lymphocyte ratio, other blood biomarkers, age, in order to support trial endpoints and feasibility. All clinical data will be reviewed on a regular basis by the Sponsor and TMG to inform this adaptive design, collaborating with the Trial Steering Committee (TSC) as per Section 5.2.2.

If review of the data (during any part of the trial) results in proposed substantial amendments, these will be submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) and Research Ethics Committee (REC) for an opinion.

Patients may be identified in/through various settings e.g. GP practices, primary care COVID hubs, community-based testing centre, drive through testing facilities, advertisement, secondary care or equivalent clinical settings. Further detail on how patients will be recruited is provided in Section 9.1. It is likely that testing availability and strategy will change in the UK and the trial will respond by engaging with testing sites as applicable, to support recruitment. Before any new sites are opened for this trial, risk assessments will be performed to ensure that the protocol and procedures can be performed safely for both patients and site staff.

If a patient consents to the trial and fulfils eligibility criteria, they will be randomised to either the treatment arm or the control arm. Patients in the treatment arm will be asked to take camostat for 14 consecutive days and patients in the control arm will be asked to continue with best supportive care. [redacted] A clinical research team member will call the patient daily during this period. On Days 7 and 14, patients will be visited at home by the clinical research team, for blood draws and COVID-19 swab (or equivalent) testing. Home visits may be replaced by patient site visits (e.g. to a ‘red hub’) but only in accordance with government and clinical advice. If the Sponsor and site decide that sampling is not required, this will be communicated to the patient. The video (phone) calls on Days 7 and 14 will still go ahead as planned regardless of sampling. Patients will also be called weekly (Days 21 and 28) before the follow up period ends.

Patients who are in hospital for non COVID-19 related reasons may be recruited if they tested positive while in hospital. In this situation daily phone calls may be substituted by face to face visits, if feasible, by the hospital team until the patient is discharged. At that point the patient will be managed as described above. Further detail on how patients will be recruited and managed in this situation is provided in Section 9.

Adverse events (AEs) or hospital admissions related to camostat or COVID-19 will be followed up as per Section 12.0.

During the trial period (Days 1-28), patients who are hospitalised will also be followed up, up to 28 days post discharge.

5.2 Safety oversight and committees

5.2.1 Trial Management Group

The TMG is responsible for the day to day running of the trial including but not limited to, the Sponsor, Chief Investigator (CI), Trial Statistician, Principal Investigators (PIs) and Co-Investigators who will have oversight of all clinical and safety data throughout both phases of the trial. A core study team will oversee management of the trial and make decisions at the operational level.

Early assessment of recruitment and trial feasibility will be critical therefore the TMG will provide ongoing review of emerging clinical and feasibility data during the trial and propose modification where required for regulatory/ethical approval as appropriate. The TSC will be asked for an opinion as appropriate when these modifications are proposed by the TMG.

5.2.2 Trial Steering Committee

A TSC will be convened to review safety and pharmacokinetic data from the trial on an ongoing basis. The TSC will include the CI, Sponsor representatives including the Medical Advisor, at least two independent experts with expertise in COVID infection and/or other relevant specialities, trial statistician and one member of the Sponsor's Protocol and Safety Review Board[6] (PSRB).

The TSC will provide expert advice in the event of any concerns around toxicity and will have the authority to suspend or terminate the trial and/or make recommendations to the Sponsor to modify the trial design.

Meetings of the TSC will be convened by the Clinical Study Manager (CSM) for the trial to review data generated at time points where key decisions are required. Additional ad hoc meetings may be convened should unforeseen events occur, and independent expert advice would be beneficial.

The responsibility for calling and organising TSC meetings lies with the CSM for the trial in association with the Chair of the TSC. Meetings will take place at least every six months if a review has not already taken place. The TSC, CI or Sponsor can request additional meetings at any time.

A TSC Charter will be made available to support the trial. The charter will include reference to the Statistical Analysis Plan (SAP) and how results from any analysis will be communicated to the TSC to inform decision making.

5.2.3 Safety oversight

Safety evaluations by the TMG will be conducted at regular intervals throughout patient recruitment. Data reviewed includes all clinical data, safety data listings and trial feasibility. Any concerns relating to safety can be escalated to the TSC for an opinion and recommendation.

5.3 Intervention

5.3.1 Randomisation

Patients will be randomised by the site staff using an interactive web response system (IWRS). Confirmation of the patient randomisation will be sent to the Investigator, site clinical trial team and Sponsor following enrolment and randomisation of the patient. The patient will be notified of their allocated group by the clinical research team.

Randomisation will be to one of two arms and a randomisation ratio of 1:1 will be applied:

- **Treatment arm:** patient to receive treatment with camostat 200 mg *qds* for 14 days.
- **Control arm:** patients will receive best supportive care.

---

[6] *The PSRB acts as an independent body across the portfolio of studies at the CR UK Centre for Drug Development (CDD). The PSRB charter mandates that the members are independent from CR UK, CDD and can act as an independent body.*

All patients randomised will receive a trial pack to include [redacted] instructions for use as well as a diary card to record these readings and, if randomised to camostat, to document their compliance with dosing. If patients wish to do so, they can use the Medidata patient application ('app') in addition to the diary card. The trial pack will include an app instruction and consent document. The research team or courier will deliver the appropriate trial pack.

For patients recruited while in hospital, all assessments will be performed and camostat will be given by the hospital staff (if the patient is randomised to camostat). Patients will receive a trial pack to include [redacted] instructions for use only on discharge. If patients wish to do so, they can use the Medidata patient application ('app') in addition to the diary card and app instructions and consent form can be provided.

Patients randomised to the treatment arm will also be offered best supportive care in managing the disease.

5.3.2 Dose modification

The planned dose for all patients who are randomised to the treatment arm is 800 mg per day (200 mg *qds*) for 14 days. Dose modifications may occur such as reducing the daily dose. Dose reductions for individual patients may be considered based on emerging clinical data and if agreed with the Sponsor, CI and PIs. These dose reductions could take the form of reduction of times that camostat is administered e.g. *qds* to *tds* or to a reduction at each of the daily administrations e.g. 200 mg *qds*, down to 100 mg *qds*.

The patient will be contacted daily during the treatment period by the clinical research team for assessment of any AEs and difficulties the patient may be experiencing with the administration schedule.

Escalation of patient management is further discussed in Section 8.5.

5.3.3 Dose interruptions/ Withdrawal criteria

- If a clinically significant abnormality is identified, camostat will be interrupted and blood samples will be taken for analysis.
- If abnormal results are identified, the patient will be referred to the GP for further assessment where local protocols will be followed.
- If required, patient hospital attendance with a suspected adverse event will trigger SAE reporting and the Investigator and Sponsor will make a causality assessment.
- Possible, Probably and Highly Probable causality assessment to camostat will result in treatment withdrawal.
- If the patient recovers symptomatically and biochemical analysis returns to the normal range, re-starting camostat can be considered by the Investigator and Sponsor to include an assessment whether the patient is likely to be past the initial stage of infection. For patients where it is deemed appropriate to re-start the patient, a maximum of 48 hrs treatment interruption will be allowable.

5.3.4 Day 7 visit

It is intended that the Day 7 interaction with the patient is made by a clinical professional who can assess whether the patient has recovered. Patients may be visited at home on Day 7 (to collect research bloods and [redacted] as well as receiving the daily video (phone) call. If at this visit/during the call, it is assessed that the patient (on the treatment arm) has recovered, the patient may be asked to discontinue with camostat administration, and the drug will be disposed of as per an approved process. Follow up calls and visits as per protocol will continue.

5.3.5 Patient hospital admission during Days 1-14

If during Days 1-14 the patient is admitted to hospital due to COVID-19, patients on the treatment arm will be asked to continue to take their camostat as per protocol following agreement from the treating

clinician. A patient identification (ID) card will be provided to all patients with relevant contact details. Patients requiring hospital admission will continue to take camostat unless contraindicated by their clinical condition or other clinical care.

For patients who are hospitalised, clinical research teams should still seek to perform the protocol mandated assessments as per Section 8.3, so long as they do not interfere with clinical care and management of the patient.

5.3.6 Pharmacokinetic sampling

The Sponsor may propose that for patients who are hospitalised, if they have consented, and so long as the sampling schedule does not interfere with their hospital care, pharmacokinetic (PK) blood samples may be taken at Sponsor defined timepoints for analysis as per laboratory manual.

The patient will be asked to consent to this when first recruited to the trial and then asked again for verbal affirmation of consent (recorded in the patient's medical record) before these blood samples are taken. If the patient is unable to give consent or incapacitated, these samples will not be taken.

A maximum of 4 mL of blood will be taken at each timepoint for this analysis.

During the course of the trial, patients who remain able to recover at home, may also be asked to consent to PK sampling. Patients will be asked to consent to this at the time of recruitment and verbal affirmation of consent will be confirmed with the patient (and documented in the patient's medical record) before these samples are taken.

The process for PK sampling for this trial will be included in the laboratory manual. PK samples will be analysed to confirm that the PK profile aligns with the established PK profile for the active metabolite of camostat, 4-(4-guanidinobenzoyloxy) phenyl acetic acid (GBPA) and will be assessed by population estimates from population PK analysis (popPK).

5.3.7 Concomitant medications

Routinely used medications for the alleviation/treatment of symptoms of COVID-19 are permitted. Only approved anti-viral therapies to treat SARS-CoV-2 will be permitted.

Any other medication (including over the counter or prescription medicines, vitamins, and/or herbal supplements) that the patient is receiving at the time of enrolment (including screening) or receives during the study must be recorded in the eCRF along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

The COVID-19 vaccine is currently not recommended for anyone who has had a positive test within 28 days or 28 days after symptoms started and not before symptoms have resolved. Please also refer to the current NHS guidelines for information.

5.3.8 Trial partners

Patients will be asked to nominate a Trial Partner that the clinical research team can contact if the patient cannot respond during the trial period e.g. if the patient is sick at home, or because they are in hospital or have died. This is not a requirement of trial participation but a proposed way of supporting the patient's participation on the trial.

5.3.9 Expenses and benefits

Reasonable travel expenses for any visits additional to normal care will be reimbursed, although no such additional visits are envisaged to be required.

6 PATIENT SELECTION

During the trial, there will be ongoing review of the emerging data to inform adaptive decision making if required. Patient enrichment strategies may be implemented e.g. revision to inclusion criteria regarding co-morbidities, neutrophil/lymphocyte ratios, age.

6.1 Inclusion Criteria

1. Patient willing and able to give informed consent.
2. Adults, 18 years of age and above
3. Symptomatic COVID-19 infection
4. Evidence of current COVID-19 infection from a validated assay.

6.2 Exclusion Criteria

The patient may not enter the trial if ANY of the following apply:

1. Significant electrolyte disturbance (e.g. hyperkalaemia, potassium > site specific upper limit of normal).
2. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) and/or alkaline phosphatase (ALP) $\geq$ 2.5 x ULN.
3. Any condition that, in the Investigator's opinion, would not make the patient a good candidate for the clinical trial or would prevent adequate compliance with trial therapy e.g. mild cognitive impairment (unable to follow instructions for self-assessment readings as assessed by the Investigator).
4. Patients on long term supplementary oxygen requirement (patients for whom hospital admission would not be considered e.g. care plan in the community is in place, are not excluded).
5. Known hypersensitivity to camostat.
6. Platelet count <100 x 10^9/L.
7. Co-enrolment with a Clinical Trial of an Investigational Medicinal Product (CTIMP) will not be permitted. Co-enrolment with a clinical investigation of a Medical Device or a non-interventional clinical study will be considered on a study-by-study basis and in discussion with the relevant Chief Investigators and Sponsors and industrial collaborators.
8. Co-enrolment involving non-interventional research (including questionnaire or tissue only studies) will be allowed provided this is not expected to affect the outcomes of both studies or place undue burden upon participants and their families.
9. Female patients who are able to become pregnant[7](or are already pregnant or lactating). However, those patients who are of child bearing potential and have a negative serum or urine pregnancy test before enrolment and agree to use two forms of contraception (one effective form plus a barrier method [oral, injected or implanted hormonal contraception

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

and condom; intra-uterine device and condom; diaphragm with spermicidal gel and condom]) or agree to sexual abstinence* [8], effective from the first administration of camostat, throughout the trial and for 28 days afterwards are considered eligible.

(*Abstinence is only considered to be an acceptable method of contraception when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.)

10. Male patients with partners of child-bearing potential[7](unless they agree to take measures not to father children by using a barrier method of contraception [condom plus spermicide] or to sexual abstinence*[8] effective from the first administration of camostat, throughout the trial and for 28 days afterwards. Men with partners of child-bearing potential must also be willing to ensure that their partner uses an effective method of contraception for the same duration for example, hormonal contraception, intrauterine device, diaphragm with spermicidal gel or sexual abstinence). Men with pregnant or lactating partners must be advised to use barrier method contraception (for example, condom plus spermicidal gel) to prevent exposure of the foetus or neonate.

    (*Abstinence is only considered to be an acceptable method of contraception when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.).

11. Significant cardiovascular disease (as assessed via the participant's medical record and history) as defined by:

    a. History of congestive heart failure requiring therapy (New York Heart Association [NYHA] III or IV – Appendix 3).

    b. History of unstable angina pectoris or myocardial infarction up to 6 months prior to trial entry.

    c. Presence of severe valvular heart disease.

    d. Presence of a ventricular arrhythmia requiring treatment.

Known allergic reactions to components of camostat e.g., lactose intolerance (see Section 7.2.1)

7 PHARMACEUTICAL INFORMATION

Please see IB supplement and SmPC for further information if required.

7.1 Supply of Investigational Medicinal Product

A complete Certificate of Analysis (CoA) and a Qualified Person (QP) certification must be provided with each delivery of camostat.

For information on camostat and re-ordering of supplies, contact the Clinical Research Associate (CRA)/Clinical Study Manager (CSM) responsible for the trial who will arrange further supplies.

Camostat will be supplied by:

Fisher Clinical Services U.K. Limited

[8] *Abstinence is only considered to be an acceptable method of contraception when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.*

[redacted]

The Manufacturing Organisation (Fisher Clinical Services U.K. Limited) must provide confirmation of the shipment to the CSM/CRA on despatch of the investigational medicinal product (IMP).

The primary and secondary packaging for the IMP will be labelled according to Eudralex Volume 4: Annex 13 'Manufacture of Investigational Medicinal Products' of the European Union guide to Good Manufacturing Practice (GMP).

Upon arrival at site, patient ID must be added to the applicable variable fields on the primary and secondary labels.

An example of the approved label can be found in the Trial Master File (TMF).

7.2 Pharmaceutical Data

7.2.1 Formulation of camostat

Camostat (camostat mesilate marketed as [FOIPAN®]) will be supplied as 100mg tablets.

Other ingredients as follows: Hydroxypropylcellulose, Carmellose calcium, Magnesium Stearate, Polyoxyethylene (105), polyoxypropylene (5) glycol, Lactose hydrate.

7.2.2 Storage conditions

All supplies must be stored in a secure, limited access storage area in its original packaging. Camostat must be stored at room temperature.

7.2.3 Stability and labelling of camostat

The tablets are supplied in boxes containing 5 blister packs. Patients should be instructed to store camostat at room temperature and out of sight and reach of children.

Labelling applied by pharmacy for camostat must include the following information:

Name of IMP; dose; expiry time/date; patient ID (and any other local requirements e.g. Pharmacy batch number).

NB: Any Pharmacy applied labels must not obscure the Annex 13 labels applied by the Manufacturing Organisation. Example labels should be filed in the TMF and approved by the Sponsor.

7.2.4 Dispensing of camostat

Sufficient tablets of camostat must be dispensed on each occasion to cover the prescribed dose for the full treatment period i.e. Days 1-14.

Patients should be supplied with the required quantity of camostat in the original boxes to cover the prescribed dose. Blister packs must not be cut to reduce tablet numbers at dispensing.

The tablets are supplied in blister packs and must not be removed from the primary packaging (provided to the patient) and placed in any other container. Tablets should be stored at room temperature and out of sight and reach of children.

7.2.5 Camostat administration

For patients randomised to the treatment arms:

Before dispensing the camostat tablets, the exact dosage must always be double-checked by a second suitably qualified person. All checks and double-checks must be documented (signed and dated) and the documentation must be available for the CRA/CSM to verify.

The camostat tablets must be swallowed whole (with water) and not chewed, crushed, dissolved or divided. Patients will be provided with instructions for when they should take their camostat.

Patients will be asked to take their camostat four times a day, one hour before each meal. After the patient has finished eating, they should wait approximately three hours before taking the next dose. Again, the patient should wait one hour after dosing before they can eat. The patient should aim to take their last dose of camostat before they go to bed.

Patients should be advised that there should be approximately a four-hour interval between doses, except between their last dose of the day and the next dose the following morning; this overnight interval will be longer.

Should a patient miss a scheduled dose in error, for example, forgetting to take the dose, then the patient can take that delayed dose within two hours of the scheduled dose (but will need to refrain from eating for an hour afterwards). Subsequent doses will be delayed accordingly.

The patient will be supplied with a diary card and asked to record each dose (time and dose) and timing of each meal.

For dose modification guidance, see Section 5.3.2.

7.2.6 Camostat accountability

Accurate records of all IMP shipments, tablets dispensed, and all IMP returned must be maintained. This inventory record must be available for inspection at any time by clinical research associates (CRAs) or CSMs of the Sponsor. Investigational Medicinal Product supplies are to be used only in accordance with this protocol and under the supervision of the Investigator.

The Investigator undertakes not to destroy any unused or returned IMP unless authorised to do so by the Sponsor. Any unused IMP must be destroyed according to hospital procedures and properly accounted for using the IMP Destruction Form and on the IMP Accountability Record. During the course of the trial the CRA will check the numbers of camostat tablets shipped to the centre, the number used, and the number destroyed or returned. The pharmacy will give an account of any discrepancy.

7.2.7 Camostat supply to primary and secondary care pharmacies

For trial sites affiliated to a hospital Trust/Board, camostat will be supplied to the hospital pharmacy and maintained by the clinical trial pharmacists.

If trial sites are opened where camostat is to be held in secondary pharmacies e.g. GP pharmacies, the Sponsor will perform a risk assessment to confirm the process by which camostat is managed and dispensed to patients and document this in the risk assessment and site management plan.

8 TRIAL PROCEDURES

8.1 Baseline assessments

All patients must have received a positive COVID-19 test result via oropharyngeal/nasopharyngeal swab (or other validated method) prior to baseline assessments being performed. [redacted] Other validated methodology may be used during the course of the trial e.g. saliva test, to improve the patient experience and assuming equal to or improved test validation and sensitivity.

When the patient has indicated their interest in the trial as per Section 6, the following information will be ascertained by the clinical research team member via an initial conversation (via video or phone call for community patients)*:

- Demographics – date of birth, gender.
- Height and weight.

- Symptoms of COVID-19, ancillary symptoms and length of symptoms – e.g. fever (≥ 37.8°C), persistent dry cough, muscle pain, shortness of breath, diarrhoea, headache, anosmia, other symptoms.
- COVID-age risk (Appendix 4)
- Other potential risk factors including smoking (pack year history), ethnicity, occupation, symptomatic household (or other) contact, other relevant medication history.
- Previous medical history – particularly chronic disease (specifically hypertension, cardiovascular disease, diabetes mellitus, hyperlipidaemia, cancer and existing respiratory conditions), history of influenza vaccination and COVID-19 vaccination (past two years).

*Alternatively, for patients recruited in a hospital setting, all baseline assessments would be performed during their attendance in the hospital, including a COVID-19 test if not previously performed.

If the above assessments are supportive of a home visit to conclude the below eligibility assessments, the patient will be asked to provide consent as per Section 9.2. The following will then be performed:

- Biochemical and haematological investigations to include:
  - Haematology – haemoglobin (Hb), white blood cells (WBC), neutrophils, lymphocytes, and platelets.
  - Biochemistry – sodium, potassium, magnesium, adjusted calcium, phosphate, urea, creatinine, total protein, albumin, bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), clotting- prothrombin time (PT), activated partial thromboplastin time (APTT), gamma-glutamyl transferase (GGT), troponin, D-dimer.
- [redacted]
- Pregnancy test for women of childbearing potential.
- [redacted]
- Ordinal scale status assessment (as per secondary endpoint).
- During this process the potential patient will be asked, if possible, to include a phone number and email address for a Trial Partner, who may be contacted by the clinical research team if the patient is unavailable

Radiological investigations over normal clinical care are not required as part of this trial, but if performed as part of clinical care, chest x-rays and chest CT scans will be assessed and included in analysis by accessing the secondary care patient records.

Additional laboratory investigations or procedures performed as part of clinical care during the trial period will be included in the analysis.

8.2 Confirmation of eligibility

Patients with a positive COVID-19 result and who are eligible according to the inclusion/exclusion criteria (post review of the assessments performed during baseline assessments), will be contacted by the clinical research team. They will be randomised by the clinical research team and informed of their allocated group.

8.3 On study assessments/procedures

All patients will be contacted as follows:

8.3.1 Days 1-14: Daily monitoring via video or phone call

Community patients will be monitored via video or phone call daily. If feasible for hospital patients daily monitoring will be performed face to face.

- [redacted]
- [redacted]

[redacted]

- [redacted]

  Number of patients asked to perform this test and days of testing may be adapted based on test availability.

- [redacted]
- Ordinal scale status assessment (as per secondary endpoint).

Those patients who have consented can enter their data [redacted] on the Medidata patient application 'app'.

The video (phone) calls made to the patient may be recorded for quality assurance purposes. Patients will be asked to consent to recording of their calls during the main consenting process and at the beginning of each call, the patient will be asked to verbally confirm their consent. These recordings will be emailed immediately afterwards to a secure NHS email address where they will be stored securely on the NHS server until the end of the trial. See Section 14.3.1. This is not a requirement of trial participation but a proposed way of supporting the patient's participation on the trial.

8.3.2 Days 7 and 14: Home visit consultation with clinical professional

The intention is that for community patients **home visits** occur on Days 7 and 14 to take research bloods [redacted]. However, this requirement may change if patients are able to provide samples by visiting the site but only in accordance with government and clinical advice. For those patients in hospital, Day 7 and 14 visits can occur in hospital face to face. If the Sponsor and site decide that sampling is not required, this will be communicated to the patient. The Days 7 and 14 video (phone) calls will still go ahead as planned regardless of sampling.

- [redacted]
- Biochemical and haematological investigations to include:
  - Haematology – Hb, WBC, neutrophils, lymphocytes, and platelets.
  - Biochemistry – sodium, potassium, magnesium, adjusted calcium, phosphate, urea, creatinine, total protein, albumin, bilirubin, ALP, ALT, AST, clotting-PT, APTT, GGT, troponin, D-dimer.

- Raised parameters will be managed as per usual Trust clinical management. If results indicate that the patient should be admitted, the clinical research team will contact the patient and arrange for them to come into hospital for further assessment. For dose interruption/withdrawal criteria, see Section 5.3.3

- [redacted]

- Blood sample for pharmacokinetics (PK) assessment (patient will be asked to consent to PK sampling within main study ICD and that this will also be document within the patient's medical notes)

- [redacted]

8.3.3 Days 21 and 28: Monitoring via video or phone call

Community patients will be monitored via video or phone call on Days 21 and 28. If feasible for hospital patients this monitoring will be performed face to face.

- [redacted]

- Ordinal scale status assessment – As per secondary endpoint.

- [redacted]

- [redacted]

Those patients who have consented can enter their data [redacted] on the Medidata patient application 'app'.

The video (phone) calls made to the patient may be recorded for quality assurance purposes. Patients will be asked to consent to recording of their calls during the main consenting process and at the beginning of each call, the patient will be asked to verbally confirm their consent. These recordings will be emailed immediately afterwards to a secure NHS email address where they will be stored securely on the NHS server until the end of the trial. See Section 14.3.1. This is not a requirement of trial participation but a proposed way of supporting the patient's participation on the trial.

8.3.4 Days 1-28

Review of hospital and primary care records to evaluate use of any form of supplementary oxygen, CXR/ CT reports or images to assess progression or evolution of pneumonia and evidence of pulmonary thromboembolic events plus documentation of death (COVID-19 related mortality) during trial period.

Patients who are hospitalised will be followed up following discharge. The Day 28 visit can be done up to 28 days post discharge if the patient was hospitalised at the time of day 28.

8.4 Sample collection and transport

Local arrangements for collection of samples taken at home may vary depending on the trial centre and feasibility but will include home visits by the clinical research team or patients attending site, if permitted (e.g. GP 'red hub').

8.5 Escalation of patient management

Patients will be informed of [redacted] indications of progressive breathlessness, or other concerning symptoms (safety rule set developed by the TMG) that should

trigger immediate self-referral to seek health advice from the appropriate channels as they normally would, according to urgency e.g. GP or dialling NHS 111 or 999. Hospital patients will be monitored by the hospital clinical team and any of these events will be managed accordingly.

- As well as the safety rules being provided to the patient, these rules will also be provided to the clinical research team making the call to the patient.
- Patients will be able to self-refer as per above however in the absence of patient action in response to a threshold being met, when the clinical researcher becomes aware during the call, this will trigger the clinical researcher to remind the patient of the safety rule set and their self-referral as needed.
- Data collected from each call will be entered on the same day by the clinical researcher and therefore be available to the PIs for review on a daily basis.

Daily video call (or phone) assessments will support reinforcement and safety netting of these safety rules, allowing for self or clinical research team referral for appropriate primary care, 111 or 999 review, in accordance with local clinical pathways. These calls to the patient will follow a set script to ensure consistent data collection and will take place at a consistent time for patient convenience but also at a time which will allow sufficient time for the Principal Investigator and/or Co-Investigator to review the data and to therefore contact the patient as needed.

Any escalation of patient management, triggered by safety signals experienced by a patient, the clinical research team will also notify the Sponsor.

Patients requiring hospital admission will have clinical investigations performed in line with clinical care. Patients requiring hospital admission will continue to take camostat unless contraindicated by clinical condition or other clinical care. Patients will be provided with a trial ID card.

For dose interruption/withdrawal criteria, see Section 5.3.3.

Table 1: Schedule of Assessments

		Screening (& randomisation if eligible)	Day 1	Days 1-7	Day 7 (+/- 1 day)	Days 8-14	Day 14 (- 2 days)	Day 21	Day 28
Assessment [G]	Testing site	Home (or at site if permitted)	Home visit	Daily video call (or phone)	Home visit (or at site if permitted)	Daily call	Home visit (or at site if permitted)	Video call (or phone)	Video call (or phone)
[redacted]	[redacted]	[redacted]			[redacted]		[redacted]		
Blood (FBC& U&Es & other markers)		X			X[A]		X[A]		
[redacted]		[redacted]			[redacted]		[redacted][A]		
Blood - PK					X[A]		X[A]		
Pregnancy test for women of childbearing potential		X							
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
▪ **Demographics** ▪ **Height, weight** ▪ **Medical history** ▪ **Risk factors** ▪ **COVID-19 symptoms check** ▪ **COVID-age risk**		X							
[redacted]		[redacted]							
Delivery of camostat [C]			X						
Camostat administration [E]			X (first dose)	X	X (if patient recovered, discontinue camostat)	X	X (last dose)		
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Documentation of supplementary oxygen administration/ high-flow oxygen device		X	X	X	X	X	X		
Assessment of: [redacted] ▪ **ordinal scale status assessment**		X	X	X	X	X	X	X	X
Call with clinical researcher				X	X	X	X	X	X

A. The intention is that home visits, by a clinical professional, occur on Days 7 and 14 to take research bloods, PK bloods and repeat swab. However, this requirement may change if patients are permitted to provide samples by visiting the site. If the Sponsor and site decide that sampling is not required, this will be communicated to the patient. The Day 7 and 14 video (phone) calls will still go ahead as planned regardless of sampling.

[redacted]

C. If randomised to the camostat arm, patients will also receive camostat tablets to last for 14 days.

D. Two readings a day.

E. Trial packs and, for those patients randomised to the treatment arm, camostat may be delivered by courier or site staff.

[redacted]

G. For community patients, home visits can be performed on site if permitted by government guidance. **For hospital based patients these assessments may be performed face to face, if feasible**.

9 RECRUITMENT

9.1 Identification of patients

The protocol is deliberately flexible so that it is suitable for several settings from which patients could be identified and recruited. These settings can include but are not limited to:

- GP practices (either as trial sites or patient identification centres texting/phoning potential patients)
- social media, traditional media, webpage, poster and leaflet advertisement
- advertisement at testing centres
- COVID hubs
- identification through other hospital departments (e.g. Emergency Department, Accident and Emergency, Oncology etc.)
- NHS Digital
- hospitalised patients who are admitted (for any reason) and subsequently test positive for COVID-19
- test and trace, or equivalent

At the time of initial regulatory submission, the approach for community/outpatient testing was, for those patients with mild symptoms, to stay at home and self-isolate, and only present to hospital/consult NHS 111 if symptoms got worse. Testing availability was also changing on a regular basis in the UK. However, testing is expected to expand rapidly and guidance for those with mild symptoms is also subject to change, especially if patients are in a high-risk group for more severe disease.

Sites with confirmed patient pathways for testing (and collection of results) and able to identify patients for out-patient support, will be selected in the first instance to support trial recruitment. In parallel, the Sponsor continues to liaise with primary care and hospital clinicians for regional variations in how patients are being tested and therefore will open further sites once there is clarity regarding the recruitment process. These sites will be submitted as a substantial amendment for appropriate regulatory approval. The Sponsor will document the patient recruitment process for each site in site management plans

Risk assessments will be performed for each site selected to ensure appropriate monitoring, training and consenting processes are in place to ensure protection of the patient's rights, safety and well-being.

As testing availability evolves across the UK, further sites will be confirmed in the primary care and hospital settings. These site management plans will be held in the TMF.

Prior to any involvement in the trial, patients who suspect they have COVID-19 should arrange COVID testing in line with government advice.

9.1.1 Testing at COVID hubs (GP practices or walk-in centres)

If the patient results confirm COVID-19 infection and they are aware of the trial, the patient can contact the clinical trial team to register their interest in participating. Alternatively, GP sites can contact patients that they know to have newly tested positive for COVID. At this point, the main patient Information Consent Document (ICD) can be emailed to the patient and the trial can be discussed with the patient with opportunity to ask questions via a video (phone) call. The patient may also undertake basic screening questions with the clinical research team.

If the patient wishes to consent to the trial, the patient will be asked to give verbal consent over the video (phone) call, with the researcher signing the consent form at that point with the patient on the call. To complete screening assessments, blood samples and assessments are required which require a face to face visit. The intention is that community research nurses or other suitably qualified medical professionals will attend to the patient in the home. Consent will be reaffirmed before any trial procedures take place and a paper version of the ICD will be signed at the earliest opportunity, by the patient which they will then keep (to avoid risk from paper copies handled by people with infection). See Section 9.2.

If eligibility is confirmed, the patient will be randomised by the clinical trial team and the patient informed of whether they are on the treatment or control arm. All randomised patients will receive a trial pack (to include diary card, Medidata patient app instructions and consent [redacted] and for those patients on the treatment arm, camostat tablets to cover 14 days of treatment. These packs will be delivered to the patient. The clinical trial team will speak to the patient to ensure the patient is clear with the instructions on how to use the contents of the pack.

9.1.2 Emergency Departments (EDs)

A positive COVID-19 result is required for enrolment in the CRUKD/20/002 trial.

In the absence of a known positive result, a Point of Care test (e.g. Lateral Flow test) will be performed. This is standard care in some departments, but not all. If not standard care, verbal consent for screening will be required prior to performing this test. Verbal consent should be recorded in the patient's medical notes.

In the event of a positive COVID-19 result:

If routine blood samples have already been analysed during the patient's attendance in the Emergency Department (ED), the results may be used for screening purposes (any trial-specific tests that are not performed as standard may be requested following written consent); an additional research blood draw will be taken where possible as per the patient information sheet.

Patients consented in the ED and confirmed eligible will be randomised in the department and provided with the trial pack +/- camostat. Home visits and the daily phone calls will be carried out according to the protocol. This may be by the local Primary Care Clinical Research Network Nurses or other community-based team.

9.1.3 Acute Assessment Units (AAUs)

Patients who present to AAUs are typically referrals from GP practices. In this setting, the process will follow that of the Emergency Department setting.

9.1.4 Hospitalised patients (admitted for any reason other than COVID-19) who subsequently test positive for COVID-19

Following admission to hospital, should a patient subsequently test positive for COVID-19, hospital teams will contact the research team (if different to the hospital team) to notify them of a possible patient. The hospital / research team will inform and consent the patient as well as coordinate the screening assessments. Patients consented in this setting and confirmed eligible will be randomised in the hospital and subsequent visits can either be performed face to face, if feasible, by the research / hospital team or via video / phone calls according to the protocol. For patients recruited while in hospital, all assessments will be performed and camostat will be given by the hospital staff (if the patient is randomised to camostat) and their routine hospital care will not be affected while participating in the trial. If patients wish to do so, they can use the Medidata patient application ('app') in addition to the diary card and app instructions and consent form can be provided. [redacted]

9.2 Informed Consent

Written and/or verbal versions of the ICD will be presented to the patients detailing the exact nature of the trial; what it will involve for the patient; the implications and constraints of the protocol; and any risks involved in taking part. It will be clearly stated that the patient is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

Given the acute nature of COVID-19 and the potential for rapid progression of symptoms, patients will be given sufficient time to consider their decision.

Wherever possible the patient will be provided with a copy of the ICD in a paper format. If paper is not permitted, an electronic version of the ICD will be provided that the clinical research team will go through with the patient either in person or over the telephone or video link.

In whatever way the information is presented, the patient must be given adequate time to think about their commitment to the trial and to allow them to ask any questions about the trial.

The patient may provide verbal consent under the current restrictions and be asked to sign a copy of the ICD (at the earliest opportunity) to be made available at a later date to the research team (this could take the form of a photograph which is sent to/taken by the clinical trial team). This consent in whichever form must be documented fully by the person taking consent and the person taking consent should sign a consent form also. Reconciling the two consent forms will take place later once restrictions are lifted, or if this is not possible, the documentation in the patient's records will serve to show that consent had been obtained and the way in which consent was obtained. The notation in the patient's record should also include a statement of why the ICD signed by the patient was not retained e.g. due to potential contamination of the document by infectious material).

It is acknowledged that usual research practice is for the researcher and the patient to both sign and date the same ICD, in person when together. However, given the nature of the COVID-19 outbreak and to minimise avoidable risks, the preceding process has been agreed and providing careful and thorough documentation, consent can be taken in this way. The patient's GP will be made aware of their participation in the trial via letter.

Patients who choose to use the Medidata patient app in addition to the diary card will be asked to sign a separate consent, covering data protection and instructions, for use of the app. Management of this consent will be the same as for the main trial consent.

10 DEFINITION OF END OF TRIAL

It is the responsibility of the Sponsor to inform the MHRA and the REC within 90 days of the End of Trial (EoT) that the trial has closed.

In cases of early termination of the trial (for example, due to toxicity) or a temporary halt by the CDD, the CDD will notify the MHRA and the REC within 15 days of the decision and a detailed, written explanation for the termination/halt will be given.

Recruitment will cease when:

- Camostat is considered too toxic to continue before the required number of patients have been recruited.
- The stated number of patients to be recruited has been reached.
- The stated objectives of the trial are achieved.
- The stated objectives of the trial are unlikely to be met based on emerging data from camostat trials worldwide, and it is confirmed the trial is to stop due to futility (end of trial will be the date of this decision).
- The stated objectives of the trial are likely to be met based on emerging data from camostat trials worldwide, and it is confirmed the trial is to stop due to efficacy proven elsewhere (end of trial will be the date of this decision).

Regardless of the reason for termination, all data available for patients at the time of discontinuation of follow-up must be recorded in the electronic/case report form (e/CRF). All reasons for discontinuation of treatment must be documented.

In terminating the trial, Investigators must ensure that provision is made to ensure appropriate ongoing care for the patient.

The End of Recruitment is defined as the date the last patient is recruited.

The End of Trial is defined as the date when the Day 28 data has been obtained for the last patient or the final follow-up visit or, if the trial is closed due to emerging data from camostat trials worldwide, the date of the Sponsor's decision to close the trial (whichever is the latter).

For analysis and reporting plans, please see Section 13.

To note: If camostat related SAEs are still ongoing at the EoT point, these will continue to be followed up as per protocol.

11 DISCONTINUATION/ WITHDRAWAL OF PATIENTS FROM STUDY TREATMENT

Each patient has the right to withdraw from the trial at any time. In addition, the investigator may discontinue a patient from the trial at any time if the investigator considers it necessary for any reason including:

- Ineligibility (identified retrospectively).
- Significant protocol deviation.
- Significant non-compliance with treatment regimen or trial requirements.
- Consent withdrawn*.

The reason for withdrawal will be recorded in the patient's records and e/CRF. In the case of a patient being withdrawn from the trial, attempts will be made to recruit a replacement.

*A decision by a patient that they no longer wish to continue receiving trial treatment should not be considered to be a withdrawal of consent for follow-up. However, patients are free to withdraw consent for some or all aspects of the trial at any time if they wish to do so. In accordance with regulatory guidance, de-identified data that have already been collected and incorporated in the trial database will continue to be used (and any identifiable data will be destroyed).

12 SAFETY REPORTING

12.1 Definitions

12.1.1 Adverse Event (AE)

An AE or adverse experience is:

An adverse event (AE) is any untoward, undesired or unplanned medical occurrence in a patient administered an investigational medicinal product (IMP), a comparator product or an approved drug.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the trial medication, whether or not considered related to the trial medication.

AEs should be reported for all patients regardless of which arm they were randomised to.

12.1.2 Adverse Drug Reaction (ADR)

All untoward and unintended responses to a medicinal product related to any dose.

The phrase "responses to a medicinal products" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.

12.1.3 Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening, NOTE: A "life-threatening" event is defined as an event when the patient was at substantial risk of dying at the time of the AE occurring; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires in-patient hospitalisation where they are admitted for more than 24 hours or prolongs existing in-patient hospitalisation (although some hospitalisations are exempt from SAE reporting, i.e. hospital admissions planned prior to the patient entering the trial; overnight stays for planned procedures). NOTE: if a patient is in hospital when they sign informed consent to participate in the trial, any event after consent that would have resulted in hospitalisation, or any event that prolongs the existing in-patient hospitalisation should be reported as serious.
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Other important medical events. NOTE: A medically important event is defined as any event that may jeopardise the patient or may require intervention to prevent one of the outcomes listed above. Examples include allergic bronchospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalisation. Development of drug dependency or drug abuse including overdose would also be examples of important medical events. Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning as defined in the bullet points above. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

12.1.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is a suspected, unexpected serious, adverse reaction that is deemed related to IMP, where the nature of the adverse event or severity of the event is not consistent with the applicable product information (e.g. reference safety information). All AEs and SAEs will be assessed by CDD for seriousness, causality and expectedness. The Pharmacovigilance Department will expedite all SUSARs to the relevant Competent Authority/Authorities and the relevant Ethics Committee(s) within the timelines specified in legislation (SI 2004/1031 as amended).

12.1.5 Urgent Safety Measures (USM)

The Sponsor or Investigator may take appropriate USMs in order to protect the patient of a clinical trial against any immediate hazard to their health or safety. This includes procedures taken to protect patients from pandemics or infections that pose serious risk to human health.

USMs may be taken without prior authorisation from the competent authority. However, The Medicines and Healthcare products Regulations Agency (MHRA) and the Research Ethics Committee (REC) must be notified within three days of such measures being taken.

Should the site initiate a USM, the Investigator must inform the Sponsor immediately either by:

[redacted]

The notification must include the minimum information:

- the date of the USM;
- who took the decision;
- what action has been taken and
- why the action was taken.

The Sponsor will then notify the MHRA and the REC within three days of USM initiation.

12.2 Causality

The relationship of each adverse event to the trial medication must be determined by a medically qualified individual according to the following definitions:

Highly probable	Starts within a time related to the IMP administration and No obvious alternative medical explanation.
Probable	Starts within a time related to the IMP administration and Cannot be reasonably explained by known characteristics of the patient's clinical state.
Possible	Starts within a time related to the IMP administration and A causal relationship between the IMP and the AE is at least a reasonable possibility.
Unlikely	The time association or the patient's clinical state is such that the trial drug is not likely to have had an association with the observed effect.

Not related	The AE is definitely not associated with the IMP administered.

Note: Drug-related refers to events assessed as possible, probable or highly probable.

The Investigator must endeavour to obtain sufficient information to determine the causality of the AE (i.e. IMP, other illness etc.) and must provide his/her opinion of the causal relationship between each AE and IMP. This may require instituting supplementary investigations of significant AEs based on their clinical judgement of the likely causative factors and/or include seeking a further opinion from a specialist in the field of the AE.

The following guidance should be taken into account when assessing the causality of an AE:

- Previous experience with the IMP and whether the AE is known to have occurred with the IMP.
- Alternative explanations for the AE such as concomitant medications, concurrent illness, non-medicinal therapies, diagnostic tests, procedures or other confounding effects.
- Timing of the events between administration of the IMP and the AE.
- IMP blood levels and evidence, if any, of overdose.
- De-challenge, that is, if the IMP was discontinued or the dosage reduced, what happened to the adverse reaction?
- Re-challenge, that is, what happened if the IMP was restarted after the AE had resolved?

12.3 Procedures for Recording Adverse Events

All AEs will be recorded in the eCRF.

The following information will be recorded: patient ID including the patient trial number, age and gender; verbatim term for the AE description, date of onset and end date as well as outcome, severity of the event, assessment of relatedness to trial medication, other suspect drug or device and action taken. Follow-up information should be provided as necessary. AEs should be recorded on the CRF from the date of written/verbal informed consent (whichever is the earlier) being given until they have completed the 28 days from Day 1 follow up period.

AEs considered related to the trial medication or COVID-19, as judged by a medically qualified investigator or the sponsor will be followed until resolution or the event is considered stable. All related AEs that result in a patient's withdrawal from the trial or are present at the end of the trial, should be followed up until a satisfactory resolution occurs.

It will be left to the investigator's clinical judgment whether or not an AE is of sufficient severity to require the patient's removal from treatment. Although the Sponsor will hold the final decision if there is a disagreement in the management of the patient's treatment. A patient may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the patient must undergo an end of study assessment and be given appropriate care under medical supervision until symptoms of the AEs cease or the condition becomes stable.

The severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe and as judged by a medically qualified investigator.

For hospitalised patients who are admitted (for any reason other than COVID-19) and subsequently test positive for COVID-19, medical occurrences or symptoms of deterioration that are expected as a consequence of the participant's admission hospital should be recorded in the patient's medical notes and only be reported as AEs in the eCRF if medically judged to have unexpectedly worsened during the study. AEs considered related to the trial medication or COVID-19, as judged by a medically qualified investigator or the sponsor will be reported in the eCRF.

12.4 Procedures for recording pregnancies

Any pregnancy occurring during the clinical trial (within 28 days after the last dose of camostat) and the outcome of the pregnancy (including the partner of a male patient), should be recorded using a pregnancy notification form and followed up until 6 months post a known outcome. If the outcome of the pregnancy results in an SAE such as congenital abnormality or birth defect, an SAE should be reported in accordance with Section 12.5.

The Investigator should document within the patient notes, the patient confirming consent for the Sponsor to collect pregnancy follow-up information. In the case that the partner of a patient becomes pregnant, a consent form should be provided to the patient's partner in order to obtain consent for collecting privacy data, in accordance with data protection regulation.

If a pregnancy is confirmed (for a female trial patient) whilst on the trial, the patient must be withdrawn from trial treatment.

12.5 Reporting Procedures for Serious Adverse Events

For eligible patients, SAE collection and monitoring (as per risk assessed monitoring plan) will commence at the time the patient gives their written/verbal consent (whichever is the earlier) to participate in the trial and will continue for 28 days from Day 1.

In addition to the SAE reporting criteria in Section 12.1.3,

During the trial period (Days 1-28):

- All hospitalisations as per the definition stated in Section 12.1.3 (regardless of causality) will be followed up until resolution, discharge or death.
- Patients who are hospitalised will also be followed up, up to 28 days after they are discharged.

Following the trial period, up to the Day 28 , only SAEs related to camostat are reportable. These will be followed up until resolution, discharge or death.

Should an Investigator become aware of any IMP-related SAEs after this period, these must also be reported to the CDD within the expedited timelines.

All SAEs regardless of causality must be reported to the Pharmacovigilance Department within 24 hours of becoming aware of the event. SAEs should be documented on an SAE report form, using the completion guidelines provided. SAE report forms should be emailed to the Pharmacovigilance Department mailbox: [redacted] The following information must be provided as a minimum:

- Patient identifiers including patient trial number and initials, age or date of birth and gender,
- SAE term, onset date and causality assessment
- A description of the SAEs
- Dose and duration of the treatment with the medicine
- The batch number of the medicine
- Any other medications being taken at the same time including non-prescriptive medicines, herbal remedies and contraceptives
- Any other health conditions the patient has or may have

Follow-up of SAEs by the Pharmacovigilance Department will continue until the events resolve or stabilise. The Pharmacovigilance Department will make requests for further information on SAEs to the Investigators at regular intervals. Requested follow-up information should be reported to the

Pharmacovigilance Department in a timely manner and as soon as possible after receipt of the follow-up request or within 24 hours of becoming aware of new/updated information.

12.6 Specific Events of Interest

The following events will be closely monitored as trial specific events of interest:

- Shock or anaphylactoid symptoms such as decreased blood pressure, dyspnoea and pruritis
- Rash, pruritis
- Gastrointestinal events (nausea, abdominal discomfort, abdominal distension)
- Changes in liver enzymes (AST, ALT, GGT) or jaundice
- Thrombocytopenia
- Hyperkalaemia

12.7 Annual Development Safety Update Reports (DSUR)

In addition to the expedited reporting above, CRUK will submit a DSUR in accordance with ICH E2F to the Competent Authority (MHRA in the UK) and the REC.

13 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

13.1 Description of statistical methods

All statistical aspects of the study will be fully documented in a comprehensive Statistical Analysis Plan authored by the study statistician and agreed by the independent Trial Steering Committee.

The primary outcome will be an exploration of camostat safety and toxicity, in terms of the number and severity of AEs and SAEs.

Descriptive statistics will be used to describe the demographics for each randomised group and overall. For categorical data, frequencies will be reported, and for continuous variables means and standard deviations, or for skewed data, medians and interquartile ranges will be reported.

Secondary outcomes will be reported in a similar way to the demographic data, with an estimate of the difference and standard error between the treatment groups for continuous or ordinal scale data. Medians and IQRs will be used where data are non-normally distributed. Absolute percentage difference and standard error will be reported for binary variables. Kaplan-Meier plots and life tables will be used to estimate median survival times

Subgroups will be explored where there are sufficient patients in each group. Data will be split by age *(< 65 years vs ≥65 years), fall in lymphocyte (<20% fall vs ≥20% fall), and neutrophil:lymphocyte ratio (<2.18 vs ≥2.18)* for key explanatory variables.

No significance testing will be performed. Differences between treatment groups will be reported solely to inform future trials.

All enrolled patients who receive at least one dose of camostat in the treatment arm and complete Day 1 in the control arm will be evaluable for safety.

In order to be evaluable for efficacy, treatment arm patients must receive camostat for a minimum of five days, and control arm patients must either complete up to Day 14 or come off trial at an earlier timepoint due to an endpoint (e.g. hospitalisation).

Safety data will be collected from the date of written, or verbal, consent. Safety variables will be summarised by descriptive statistics.

Adverse events will be reported as tables of frequency of AEs by MedDRA system organ class and by worst severity grade observed. Tables should indicate related and unrelated events

Adverse events will be reported for each arm and presented as tables of frequency of AEs by MedDRA system organ class and by worst severity grade observed. Tables should indicate related and unrelated events.

The clinical landscape of COVID-19 treatment continues to evolve, with a number of clinical trials of camostat ongoing globally. During the trial and prior to the final analysis, a data analysis and/or statistical review, may be performed. This review may include available information from other Camostat trials globally, to provide a recommendation to either continue or stop accrual for efficacy or for futility based on available clinical data. Prior to conducting such a review, criteria for decision making will be defined and agreed with the TSC.

13.2 Sample size determination

No formal hypothesis tests are required. However, in order to inform a future trial, the recruitment rate, that is, the proportion of patients who are randomised relative to those who are eligible and approached, will be calculated. One hundred recruited patients will allow us to estimate a recruitment rate of 50%, with a 95% CI of 43% to 57%, a standard error of 3.5%.

13.3 Clinical Study Report

At appropriate intervals, interim data listings will be prepared to give the Investigators the possibility to review the data and check the completeness of information collected. All clinical data will be presented at the end of the trial on final data listings. The Sponsor will prepare a Clinical Study Report (CSR) based on the final data listings. The report will be submitted to the Investigator(s) for review and confirmation it accurately represents the data collected during the course of the trial. Summary results of the trial will be provided by the Sponsor to the Regulatory Authority (MHRA) and to the Research Ethics Committee.

14 DATA MANAGEMENT

The plan for the data management of the trial are outlined below. Further details of the data management aspects of the study will be fully documented in a comprehensive Data Management Plan (DMP) authored by the trial Clinical Data Manager (CDM).

14.1 Source data

Source documents are where data are first recorded, and from which patients' eCRF data are obtained. These include but are not limited to: primary or secondary care records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. For some data, the data will be recorded directly into the eCRF and therefore acts as both source and CRF. All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the patient will be referred to by the trial patient number/code, initials, not by name.

Patients will be given the option of using the Medidata patient app in addition to a paper diary card, to record their vital signs and responses to the questionnaire. Separate consent, covering data protection, will be collected for all patients who choose to use the app. Data entered in the app will be considered source and uploaded directly into the database.

The DMP will clearly state which data is entered directly into the eCRF and which data is derived from other source documents for entering.

14.2 Access to data

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

14.3 Data recording and record keeping

The eCRF for this trial will be a RAVE clinical database. As per Section 14.1, source data may be separate documentation/diaries/records, however the eCRF itself may also act as a source for certain data items. As per the DMP, source documents will be clearly stated and the Sponsor may ask that certified copies are scanned/posted as appropriate for source data verification in a timely fashion, as it is anticipated that on-site monitoring visits may not be possible due to restrictions at sites.

The Investigator and/or Sponsor must retain copies of the essential documents for a minimum of 25 years following the end of the trial.

During the clinical trial and after trial closure the Investigator must maintain adequate and accurate records to enable both the conduct of a clinical trial and the quality of the data produced to be evaluated and verified. These essential documents (as detailed in Chapter V of Volume 10 (Clinical Trials) of The Rules Governing Medicinal Products in the European Union based upon Section 8 of the ICH GCP Guidelines), including source documents such as worksheets, scans, hospital records, diary cards, trial related documents and copies of the e/CRFs, associated audit trail and serious adverse event (SAE) report forms, shall show whether the Investigator has complied with the principles and guidelines of Good Clinical Practice (GCP).

All essential documents required to be held by the Investigator must be stored in such a way that ensures that they are readily available, upon request, to the Regulatory Agency or Sponsor, for the minimum period required by national legislation or for longer if needed by Sponsor. Records must not be destroyed without prior written approval from Sponsor.

The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

14.3.1 Recording of daily calls

During the trial, patients will be asked for permission and consent to record their daily video (phone) calls with the clinical trial team. Patients will be asked to consent during main trial consent and to also confirm consent verbally before each video/phone call begins. After each call is completed, the recording will immediately be emailed to a secure NHS email for storage on a secure NHS server. The recording will be deleted thereafter from the original recording device. Each NHS Trust/Board will be responsible for the security and confidentiality of these recordings. These recordings will not be shared with the Sponsor to protect the patient's confidentiality. The NHS Trust/Board will be solely responsible for the recording, transfer, storage and deletion of the recording. All recordings will be deleted from the NHS secure server at the end of the trial.

This is not a requirement of trial participation but a proposed way of supporting the patient's participation on the trial.

15 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

15.1 Risk assessment

A risk assessment and monitoring guidelines will be prepared before the trial opens and will be reviewed periodically throughout the trial to reflect significant changes to the protocol or monitoring activities.

15.2 Monitoring

In order to ensure that quality data is collected and that sites are adhering to the protocol, ICH GCP and other guidelines and local regulations, data will be monitored at regular intervals by the Sponsor.

The level of monitoring will be informed by the trial specific risk assessment and captured in the trial monitoring plan.

The Investigator and clinical trial teams will be responsible for entering trial data into the eCRF and providing certified copies of source data where applicable to facilitate source data verification. It is the Investigator's responsibility to ensure the accuracy of the data entered into any source document provided to the Sponsor, and to ensure that any patient data provided to the Sponsor is suitably anonymised.

Once source documents have been completed by site staff they will be scanned and emailed to the Sponsor. Any missing data or any data that requires querying with the site staff will be raised by the Sponsor.

Movement of people may be restricted, therefore, monitoring of patient medical records will be completed remotely where possible in accordance with the trial-specific monitoring plan.

Monitoring of the data will occur as the data is being entered into the database.

In order to verify that the trial is conducted in accordance with ICH GCP, regulatory requirements, and the trial protocol, and that the data is authentic, accurate and complete, source data will be verified.

Upon trial completion, a Closedown Visit will be conducted.

15.3 Quality assurance

The Sponsor will assess each trial site to verify the qualifications of each Investigator and the site staff and to ensure that the site has all of the required equipment. A Study Initiation meeting will occur where among other things the Investigator will be informed of their responsibilities and procedures for ensuring adequate and correct trial documentation. During this meeting, training will be provided to the investigator and the local study team, in accordance with the study-specific monitoring plan.

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the trial for each patient. Trial data for each enrolled patient will be entered into the Source Worksheets by study site personnel.

15.4 Protocol deviations and amendments

The protocol should be adhered to throughout the conduct of the trial, if a situation arises where the conduct of the trial may not be in line with the protocol, then site should contact the Sponsor to discuss this.

Amendments to the protocol may only be made with the approval of the Sponsor. A protocol amendment may be subject to review by the assigned REC, Health Research Authority (HRA) and the MHRA. Written documentation of the Ethics Committee and HRA (and if appropriate the MHRA) 'favourable opinion' (i.e. approval) must be received before the amendment can be implemented and incorporated into the protocol if necessary.

15.5 Serious Breach of GCP

A serious breach is a breach which is likely to effect to a significant degree: the safety or physical or mental integrity of the subjects of the trial, or the scientific value of the trial.

In order that the Sponsor can fulfil their obligations in terms of reporting serious breaches of GCP to the MHRA within seven calendar days of identification, site staff must inform the Sponsor of any unplanned deviations to the trial protocol (or GCP principles) as soon as possible after the deviation occurs to allow prompt evaluation by the Sponsor.

16 ETHICAL CONSIDERATIONS

Before starting the trial, the protocol and ICD must receive the favourable opinion of the REC.

It is the Chief/Principal Investigator's responsibility to update patients (or their authorised representatives, if applicable) whenever new information (in nature or severity) becomes available that might affect the patient's willingness to continue in the trial. The CI/PI must ensure this is documented in the patient's medical notes and the patient is re-consented.

The Sponsor and CI/PI must ensure that the trial is carried out in accordance with the GCP principles and requirements of the UK Clinical Trials regulations (SI 2004/1031 and SI 2006/1928 as amended), the ICH GCP guidelines and the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and all subsequent amendments including Oct 2013.

16.1 Approvals

The protocol, ICD and any proposed advertising material will be submitted as appropriate to the REC, regulatory authorities (MHRA in the UK), and host institution(s) for written approval.

The Sponsor will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

16.2 Patient confidentiality

The trial staff will ensure that the patients' anonymity is maintained. The patients will be identified only by initials and patient ID number on worksheets and any electronic database. Patient names and telephone numbers will be stored securely at each NHS Trust/Board by the clinical trial team and will only be accessible by the clinical trial team at site. All documents will be stored securely and only accessible by trial staff and authorised personnel.

The collection and processing of personal data from the patients enrolled in this clinical trial will be limited to those data that are necessary to investigate the efficacy, safety, quality and usefulness of the drug used in this trial. The data must be collected and processed with adequate precautions to ensure patient confidentiality and compliance with applicable data privacy protection according to the applicable data protection regulations. The data collected will comply with the EU General Data Protection Regulation (GDPR) 2016/679 on the protection of individuals with regard to the processing of personal data and the Data Protection Act (DPA), 2018.

Patients who agree to use the Medidata app will not be required to enter any personal data into the app other than their vital signs and responses to the questionnaire.

For long term follow up, patients will be asked to explicitly consent to this on the ICD.

16.3 Indemnity

This trial is sponsored by CR UK and therefore injury to a patient caused by the compounds under trial will not carry with it the right to seek compensation from the pharmaceutical industry. CR UK will provide patients with compensation for adverse side effects, in accordance with the principles set out in the Association of the British Pharmaceutical Industry (ABPI) guidelines on compensation for medicine-induced injury.

17 REFERENCES

.

Arabi, Y. M. (2020). COVID-19: A Novel Coronavirus and a Novel Challenge for Critical Care. *Intensive Care Medicine*, March. https://doi.org/10.1007/s00134-020-05955-1.

Corner, E. W. (2012). The Chelsea Critical Care Physical Assessment Tool (CPAx): validation of an innovative new tool to measure physical morbidity in the general adult critical care population; an observational proof-of-concept pilot study. *Physiotherapy Journal*, https://www.physiotherapyjournal.com/article/S0031-9406(12)00028-4/fulltext.

Forrest. (1989). Tolerance and Pharmacokinetics of Camostat Mesylate (FOY-305) in Normal Human Subjects after Single Rising i.v. Infusion Doses. *European Journal of Clinical Pharmacology*, PP14.68 no. 36 (Suppl.).

Hoffmann. (2020). SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and is Blocked by a Clinically Proven Protease Inhibitor. *Cell* , 181, 1-10.

Hoffmann. (APR 2020). Nafamostat mesylate blocks 1 activation of SARS-CoV-2: New treatment option for COVID-19. *Anitmicrob. Agents Chemother.*, doi:10.1128/AAC.00754-20.

Iwata-Yoshikawa. (2019). TMPRSS2 Contributes to Virus Spread and Immunopathology in the Airways of Murine Models after Coronavirus Infection. *Journal of Virology*, 93: 6.

Kawase. (2012). Simultaneous Treatment of Human Bronchial Epithelial Cells with Serine and Cysteine Protease Inhibitors Prevents Severe Acute Respiratory Syndrome Coronavirus Entry. *Journal of Virology*, 86: 12.

Liu, C. Q. (2020). Research and Development on Therapeutic Agents and Vaccines for COVID-19 and Related Human Coronavirus Diseases. *ACS Central Science*, 6 (3): 315–31.

Matsuyama. (2010). Efficient Activation of the Severe Acute Respiratory Syndrome Coronavirus Spike Protein by the Transmembrane Protease TMPRSS2. *Journal of Virology*, 12658–12664.

Midgley. (1994). Metabolic Fate of 14C-Camostat Mesylate in Man, Rat and Dog after Intravenous Administration. *Xenobiotica; the Fate of Foreign Compounds in Biological Systems* , 24 (1): 79–92.

Ono Pharmaceutical Co., Ltd. (2020). *FOY-305-02 Pharmacokinetic Analysis Results (Draft report dated 21 August 2020)*.

Osborne, R. H. (2011). Development and Validation of the Influenza Intensity and Impact Questionnaire (FluiiQTM). Value in Health: . *The Journal of the International Society for Pharmacoeconomics and Outcomes Research*, 14 (5): 687-99.

Rabi. (2020). SARS-CoV-2 and Coronavirus Disease 2019: What We Know So Far. *Pathogens*, 9, 231.

Ruan, S. (2019). Likelihood of Survival of Coronavirus Disease 2019. . *The Lancet. Infectious Diseases,* , March. https://doi.org/10.1016/S1473-3099(20)30257-7.

Sato. (1992). A Dose-Finding Study of FOY-305 in Postoperative Reflux Esophagitis – A Double-Blind Comparative Study. *J Clin Ther Med.*

Shirato, K. M. (2013). Middle East Respiratory Syndrome Coronavirus Infection Mediated by the Transmembrane Serine Protease TMPRSS2. *Journal of Virology*, 87 (23): 12552–61. https://doi.org/10.1128/JVI.01890-13.

Shulla. (2011). A Transmembrane Serine Protease Is Linked to the Severe Acute Respiratory Syndrome Coronavirus Receptor and Activates Virus Entry. *Journal of Virology,* , 873-882.

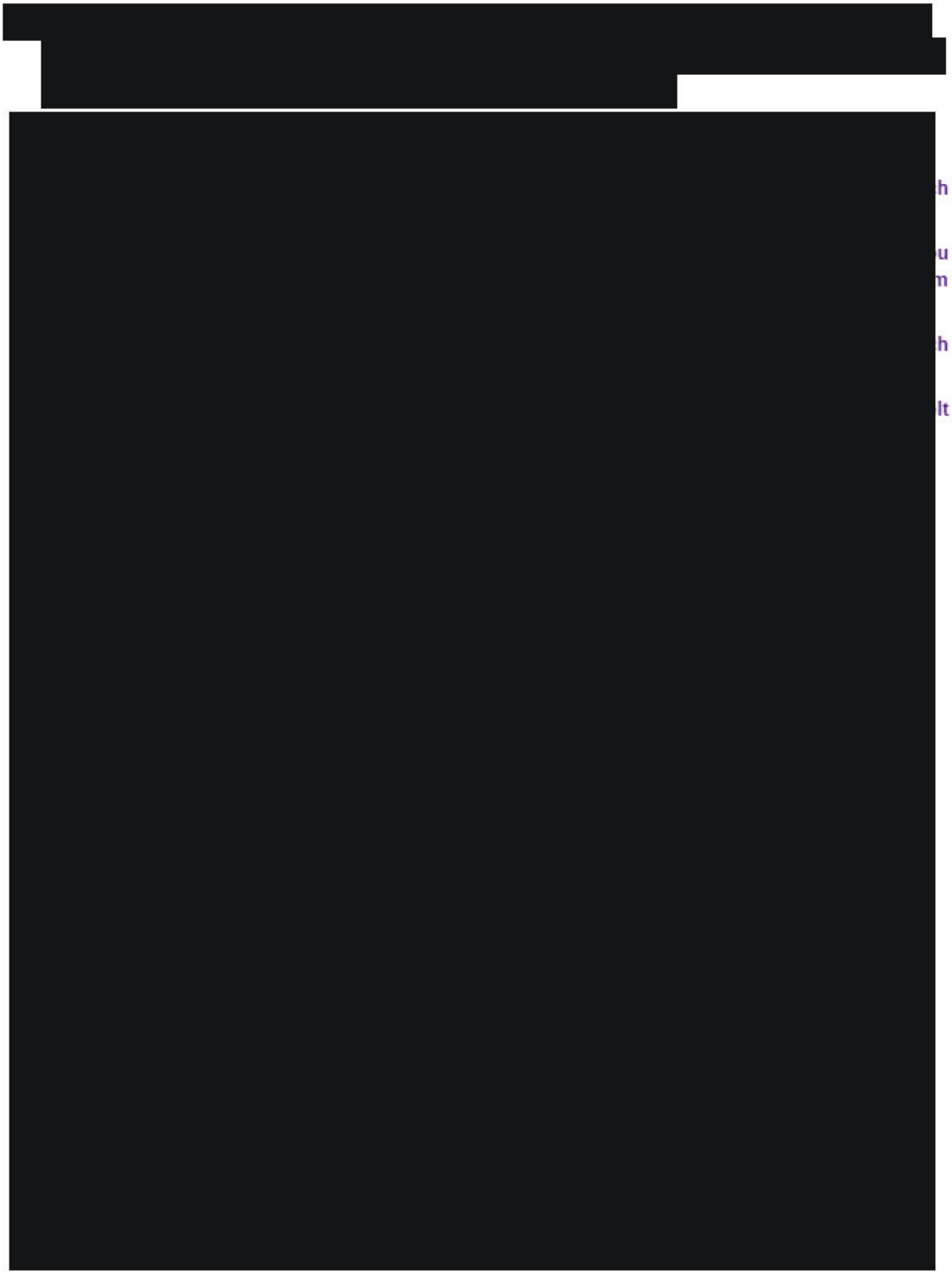
Yamamoto. (2016). Identification of Nafamostat as a Potent Inhibitor of Middle East Respiratory Syndrome Coronavirus S Protein-Mediated Membrane Fusion Using the Split-Protein-Based Cell-Cell Fusion Assay. *Antimicrobial Agents and Chmotherapy*, 6532-6539.

Yan. (2020). Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. *Science 367*, 1444-1448.

Zhou, Y. (2015). Protease inhibitors targeting coronavirus and filovirus entry. *Antiviral Res.*, http://dx.doi.org/10.1016/j.antiviral.2015.01.011.

18 APPENDICES

[redacted]



18.3 Appendix 3: New York Heart Association (NYHA) scale

Class I – Patients with cardiac disease but without resulting limitation of physical activity; ordinary physical activity does not cause undue dyspnoea (or fatigue, palpitation or anginal pain).

Class II – Patients with cardiac disease resulting in slight limitation of physical activity; they are comfortable at rest; ordinary physical activity results in dyspnoea (or fatigue, palpitation or anginal pain).

Class III – Patients with cardiac disease resulting in marked limitations of physical activity; they are comfortable at rest; less than ordinary physical activity causes dyspnoea (or fatigue, palpitation or anginal pain).

Class IV – Patients with cardiac disease resulting in inability to carry out physical activity without discomfort; symptoms of dyspnoea (or of angina) may be present even at rest; if any physical activity is undertaken, discomfort is increased.

18.4 Appendix 4: COVID-age calculation

https://alama.org.uk/covid-19-medical-risk-assessment/ (last accessed April 2021).

The COVID-age calculation tool authored by the Association of Local Authority Medical Advisors (ALAMA), will be collected for the SPIKE1 trial during on trial assessments.
The tool was originally created to help assess an individual's vulnerability to COVID-19 as part of an occupational health assessment of fitness for work. It is not intended for use in clinical treatment pathways. As new scientific evidence becomes available, its estimates of vulnerability may change.

COVID-age helps assess an individual's vulnerability to COVID-19. It is based on published evidence for the main identified risk factors.
COVID-age summarises vulnerability for combinations of risk factors including age, sex and ethnicity and various health problems. It works by "translating" the risk associated with each factor into years which are added to (or subtracted from) an individual's actual age. This then gives a single overall measure of vulnerability. It can be used in people with no underlying medical conditions or multiple medical conditions. One measure combines all of an individual's risk factors with their actual age.

COVID-age is translated into a risk level of low, moderate, high and very high. This score of moderate, high or very high, will be collected from participants in the SPIKE1 trial.

There are times when the internet is not available or the ALAMA website goes down for maintenance. The risk tables can be downloaded as an Excel spreadsheet calculator in the link above.