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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	Reporting Analysis Plan Version 2.0 dated 03 March 2022

CANCER RESEARCH UK

Reporting Analysis Plan

Protocol Number: CRUKD/20/002

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

EudraCT Number: 2020-002110-41

[redacted]

RAP Final Version:	Final V2.0
Date:	03Mar2022
Replaces Version:	1.0
Date:	27Sep2021

Name: [redacted] Date:

Title: Clinical Study Manager (Sponsor)

Signature:

Name: [redacted] Date:

Title: Medical Advisor (Sponsor)

Signature:

Name: [redacted] Date:

Title: Chief Investigator

Signature:

Name: [redacted] Date:

Title: Statistician

Signature:

Name: [redacted] Date:

Title: Statistician

Signature:

SUMMARY OF CHANGES TO PREVIOUS REPORTING ANALYSIS PLAN VERSION

This summary of changes is intended to highlight the important revisions that were made during the most recent update to the reporting analysis plan (RAP) to generate the current version.

This document has been written based on information contained in the study protocol and data management plan detailed in the table below.

Protocol version	DMP version	RAP version	Revised section of RAP	Summary of changes	Date updated
5.0	3.0	1.0	N/A	N/A – First Version	
Final review prior to database lock					
Protocol version	DMP version	RAP version	Revised section of RAP	Summary of changes	Date updated
5.0	3.0	2.0	6, 7 and SAP	• Ethnicity added to baseline characteristics table • Treatment compliance table added • Table replaced graphs for neutrophil V lymphocytes ratio • Population confirmation throughout • Updates to ct.gov section in line with current guidelines	03Mar2022

				• SAP clarification on secondary endpoints and outputs	

Protocol amendments may be applicable during the study. The RAP will be reviewed against the amendments and updated where necessary.

The summary of changes table above should record all changes to the RAP in light of protocol amendments however if no changes were required, this should be recorded also.

CONTRIBUTORS

Clinical Study Manager: [redacted]

Medical Writer: [redacted]

Clinical Data Manager: [redacted]

Clinical Database Programmer: [redacted]

Medical Advisor: [redacted]

Translational Scientist: [redacted]

Statistician: [redacted]

Statistician: [redacted]

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

	Abbreviation	Definition
A	AE	adverse event
C	CDD	Centre for Drug Development
	CDM	Clinical Data Manager
	CDP	Clinical Data Programmer
	CI	Chief Investigator
	C_{max}	maximum observed plasma concentration
	CRUK	Cancer Research UK
	CSM	Clinical Study Manager
	CSR	Clinical Study Report
E	EDC	electronic data capture
F	FAP	Full Analysis Population
G	GCP	Good Clinical Practice
H	Hb	haemoglobin
I	IB	Investigator's Brochure
	ICD	Informed Consent Document
	ICH GCP	International Conference on Harmonisation of Good Clinical Practice
	IMP	investigational medicinal product
	IMPD	investigational medicinal product dossier
M	MW	Medical Writer
P	PI	Principal Investigator
	PK	pharmacokinetic
R	RAP	Reporting Analysis Plan
S	SAE	serious adverse event
	SAP	Statistical Analysis plan
	SDV	source data verification
	SOP	Standard Operating Procedure
	SUSAR	suspected unexpected serious adverse (drug) reaction
T	$T_{1/2}$	terminal elimination half-life
	T_{max}	time to reach C_{max}
	TEAE	Treatment emergent adverse event
	TSC	trial steering committee
U	USM	urgent safety measure

1. TABLE OF CONTENTS

2. INTRODUCTION

This document explains in detail the reporting analyses that will be carried out for SPIKE-1.

The analyses described in this RAP are based upon and supplement those described in the current study protocol.

To support reproducibility of the research, a clear and comprehensive account of pre-planned reporting (or statistical) analyses must be available. This RAP will establish the essential items to be considered for interim and/or final reporting requirements within the CSR and for the results upload to clinicaltrials.gov.

3. TRIAL OBJECTIVES

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)phenylacetic 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]

[redacted]

4. TRIAL DESIGN

Table 1: Trial Design

A	Study design	This is a randomised, multi centre, Phase II, prospective open label 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.
B	Patient group	Patients with COVID-19 infection who are symptomatic
C	Sample size	Up to 100 patients will be entered into this trial. Up to 50 patients in each arm. Patients will be randomised 1:1 into each arm.
D	Study intervention	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. Both groups will be asked to take [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 [redacted] 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, who test positive for COVID-19, may also be recruited. Phone calls / home visits will be conducted where possible within hospital face to face.
E	Study analysis	Statistical Analysis Plan (Version 1.0, dated 27Sep2021)

For full details of the trial design, background and rationale for the study, please refer to the current study protocol.

5. PATIENT POPULATION AND ENDPOINTS

Patients must fulfil all the inclusion/exclusion criteria to be eligible for entry to the trial. Refer to the study protocol for the complete list of inclusion and exclusion criteria.

All enrolled patients who receive at least one dose of camostat 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)

5.1 Patient Populations

The analysis sets are defined as follows:

Full Analysis Population (FAP):	All enrolled patients. Patients who are enrolled in error onto the trial (due to ineligibility/administrative error), prior to receiving study treatment, will be excluded from the FAP.
Safety Population:	All enrolled patients who received at least one dose of camostat (or complete Day 1 of the control arm). Safety data will be collected from the date of written consent.
Efficacy Population:	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).
Pharmacokinetic Population:	All enrolled patients who received one dose of camostat (or complete Day 1 of the control arm) – PK sample required (optional).

All other populations will be the same definition as Efficacy Population as defined above.

6. DATA CONVENTIONS AND GENERAL ANALYSIS

6.1 Patient disposition

Patients excluded from any population (defined in Section 4.1) will be detailed.

The accrual and trial discontinuation details will be presented descriptively. This should include details of:

- Screening failure patients (screening failure information is available via the e-screening logs).
- Information on ineligible patients who were enrolled and/or received camosat (and control).
- Reasons for treatment discontinuation by number of doses received will be described by counts and percentages. Reasons for treatment discontinuation other than disease progression will be detailed and summarised separately (Section 5.1.2).

6.2 Baseline characteristics

Demographics and baseline characteristics will be summarised for all enrolled patients. Patients will be included to the randomised arm regardless of whether they received treatment or not.

Table 1: Baseline characteristics by treatment arm

Full Analysis Population.

	All	Treatment arm	Control arm
Patients			
Male Total			
Male ≥ 65 year old			
Male < 65 years old			
Female Total			
Female ≥ 65 year old			
Female< 65 years old			
Age (Years)			
Mean (SD)			
Median (IQR)			
Min			
Max			
BMI			
Mean (SD)			
Median (IQR)			
Min			
Max			
Ethnicity			
COVID-19 Vulnerability Level			
Low			
Moderate			
High			

Very High			
COVID-19 age			
Mean (SD)			
Median (IQR)			
Min			
Max			
Ethnicity			
Asian / Asian British - Indian			
Asian / Asian British - Pakistani			
White-English / Welsh / Scottish / Northern Irish / British			
Any other white background			

In case of pre-treatment characteristics with multiple measurements per patient before the start of treatment (laboratory assessments, vital signs), the baseline measurement will be considered the last value prior to or on the first day of treatment.

Other baseline assessments, including medical history, will be covered within the listings per patient..

6.3 Patient withdrawal / Completion

Reasons for patient withdrawal will be provided as the data is available and presented for each randomised treatment arm.

Table 2: Reasons for patient withdrawal / completion

Reason off study	No. of Patients (N=XX)	Patient Number (patients who withdrew only)	No. of patients in Treatment arm	No. of patients in Control arm
Completion of treatment / monitoring period	XX (%)		XX (%)	XX (%)
Recovered				
Adverse event/Serious adverse event				
Pregnancy				
Death				
Investigator withdrawal of subject				
Subject withdrawal of consent				
Subject withdrawal from treatment (treatment arm) / subject withdrawal (allows FU) (control arm)				
Protocol deviations				

Sponsor's decision to terminate the trial				
Other				
Lost to follow up				

Full Analysis Population

6.4 Protocol deviations

A protocol deviation is defined as any departure from what is described in the protocol of a clinical trial approved by an Independent Ethics Committee and Competent Authorities. Therefore, it applies to deviations related to patient inclusion and clinical procedures (e.g. assessments to be conducted or parameters to be determined), and also to other procedures described in the protocol that concern the Good Clinical Practice (GCP) guidelines or ethical issues (e.g. issues related to obtaining the patients' Informed Consent, data reporting, the responsibilities of the Investigator, etc.).

Protocol deviations are captured throughout the trial open phase on the Sponsor's central tracker and can be filtered by study and by deviation category or on the study specific PK/PD deviations tracker. Standard deviation categories have been defined by the Sponsor and are further defined by those which are deemed reportable (important deviations) in the Clinical Study Report (CSR). Those deviations which have been coded as CSR reportable will be summarised for all patients, according to the categories allocated at identification. Deviations are reviewed manually as per Sponsor SOPs.

A summary table with the number of patients with deviations will be presented per criterion. Deviations with no effects on the risk/benefit ratio of the clinical trial (such as minimal delays in assessments or visits) will be distinguished from those that might have an effect on this risk/benefit ratio.

The following are pre-defined protocol deviations with a direct bearing on the primary outcome and therefore will be reported in the CSR. A summary including but not necessarily restricted to the following categories will be presented:

- Ineligible patients as per protocol.
- Patient not withdrawn as per protocol.
- Excluded concomitant medication.
- Incorrect IMP dose or schedule

6.5 Treatment compliance

A list of all treatment compliance by patient will be produced for those patients on the treatment arm only.

Table 3: Treatment modifications and/or non-compliance (treatment arm only)

Patient number	Date of first dose	Date of treatment modification	Description of treatment modification/non-compliance	Comment

Full Analysis Population (Treatment arm only)

6.6 Safety

Descriptive statistics will be used for evaluation of safety. The incidence of AEs will be summarised and displayed in frequency tables using counts and percentages. Additional parameters including but not limited to [redacted], and laboratory results will also be considered when evaluating safety.

Deaths, serious adverse events (SAEs) and events resulting in trial discontinuation will be tabulated.

Additional safety analyses may be determined at any time, in order to most clearly enumerate rates of toxicities and to further define the safety profile of camostat.

- The safety population is composed by all patients that receive at least one dose of camostat / complete Day 1 of control arm. The safety patient population will be used for the general safety presentations.

6.7 Adverse Events

For patients on the treatment arm Pre-treatment AE's will be defined as those where "Did this AE start prior to first dose of IMP?" is ticked. Treatment Emergent AE's will be defined as those where "Did this AE start prior to first dose of IMP?" is not ticked. For patients on the control arm pre-treatment AE's will be defined as those where the AE started prior to Day 1. Treatment emergent AE's will be defined as those where the AE started after and inclusive of Day 1.

Treatment related AE's are those where causality to IMP is considered to be Possible, Probable or Highly Probable.

COVID-19 related AE's will be defined as those where "Is this AE related to COVID-19" is ticked yes.

The frequency of AEs will be summarised overall and by treatment arm. A patient can be counted multiple times per row for the No. of Episodes but will only be counted once per row for the No. of Patients.

Table 5: Frequency of All Adverse Events

Safety population

MedDRA System Organ Class (SOC) MedDRA Preferred Term	No. of Episodes Reported	No. of Patients N=XX	No. of Patients in Treatment Arm N=XX	No. of Patients in Control Arm N=XX
All AE's	N	N (%)	N (%)	N (%)
BLOOD AND LYMPHATIC…				
Anemia				
CARDIAC DISORDERS				
Sinus tachycardia				
Etc				

There will be additional versions of the above table based on pre-treatment AE's, treatment emergent AE's, treatment emergent SAE's (any AE that is considered Serious), related treatment emergent AE's. COVID-19 related AE's.

Overview of treatment emergent adverse events (by treatment arm). An AE is considered to have led to withdrawal if an adverse event with "Did the AE cause the subject to be discontinued from the study?" is recorded as yes.

Table 6: Overview of Treatment Emergent Adverse Events (Inclusive and post Day 1)

Safety population

Patients with TEAEs	Overall No. of Patients N=XX	No. of Patients in Treatment arm N=XX	No. of Patients in Control arm N=XX
Patients with >=1 TEAE	N (%)	N (%)	N (%)
Patients with >= 1 TE SAE			
Patients with >= 1 COVID-19 related			
Patients with >= 1 Treatment related			
Patients with >= 1 AE leading to withdrawal			
Patients who died			

Treatment emergent adverse events leading to withdrawal of treatment will be listed by patient. Patients will be included if an adverse event has "Action taken" recorded as "Drug Withdrawn" or "Did the AE cause the subject to be discontinued from the study?" is recorded as yes.

Table 7: Breakdown of TEAEs leading to Patient withdrawal.

Safety population

Patient number	MedDRA System Organ Class (SOC)	AE Term	Serious	Led to IMP withdrawal	Led to withdrawal from study

6.8 Laboratory results

Full set of Laboratory results will be presented in the listings per patient. Additional tables to represent Neutrophils:Lymphocytes ratio per patient will be presented as follows:

Table 8: Neutrophils:Lymphocytes ratio per patient (Treatment arm)
*Baseline to be included

	Neutrophils:Lymphocytes ratio (10^9/L)		
Patient Number	Screening	Day 7	Day 14

Table 9: Neutrophils:Lymphocytes ratio per patient (Control arm)
*Baseline to be included

	Neutrophils:Lymphocytes ratio (10^9/L)		
Patient Number	Screening	Day 7	Day 14

6.9 Efficacy

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

Table 10 Ordinal Scale.

Efficacy population

Patient Number	Randomised Arm (Treatment or Control Arm)	Day 1 Scale	Worst Point on Scale	Deteriorated by more than 2 points (yes/no)	Time to worst point (Days)

[redacted]

Table 11: Summary Table for Secondary Endpoint Data.

Efficacy population

	All	Treatment arm	Control arm

Number of community patients admitted to hospital due to COVID-19			
Total number of patients			
Proportion of patients per arm			
Supplementary oxygen-free days at 28 days			
Number of patients			
Proportion of patients per arm			
Ventilator-free days at 28 days			
Number of patients			
Proportion of patients per arm			

6.10 General data conventions

Data will be grouped according to the assigned treatment arm, as specified in the study protocol. Patients who deviate from the assigned treatment arm will be clearly described in the CSR with regards to their treatment modification and if applicable in the list of protocol deviations (Section 5.2).

Continuous variables will be summarised and presented with summary statistics.

Categorical variables will be summarised in frequency tables. Percentages in the summary tables will be rounded and may therefore not always add up to exactly 100%.

The convention in Rave is that an unknown day resolves to 1st of the month and an unknown month resolves to January. Dates may be ordered by this, however CRUK do not perform calculations on unknown dates.

Durations of AEs: the start date of an AE is considered as Day 1 of the event and should be included in all duration calculations (i.e. if an AE starts and stops on same day, the duration should be reported as one day).

- For unrelated AEs, those with missing or partially completed end dates will not be excluded from analysis and the duration of the AE will remain as unknown.
- For related AEs, prior to final data lock, an end date will be either i) confirmed AE end date or ii) stabilisation of AE. If lost to follow-up then the AE would stay as not recovered/not resolved. In both these cases duration would not be calculated.

Time to onset of AEs from IMP administration: the time to onset should be calculated from the date of the first administration of IMP in the trial (e.g. Day 1). Onset time will be calculated as 0 if the AE occurs on the same day as the dose.

6.11 Decimal places

When data is used in calculations it important that rounding is only conducted when the final test result is obtained (to avoid accumulation of errors).

All percentages should be presented to 1 decimal place. If a percentage value is less than 0.1% on rounding, then use '<0.1%'.

Days to be presented to 0 decimal places.

6.12 Statistical software

Medidata Rave will be used as the Electronic Data Capture (EDC) system for the trial.

Any statistical software should be defined.

SAS version 9.4 will be used to generate data listings and summary tables/graphs, as well as any statistical analysis as per the trial SAP.

6.13 Supplementary analysis (data collected outside of the clinical database)

6.13.1 Pharmacokinetics

Clinical study objectives	Description of clinical study endpoint	Sample used for this endpoint
Secondary Objective: To confirm that the PK profile aligns with the established PK profile for the active metabolite of camostat, 4-(4-Guanidinobenzoyloxy)phenylacetic acid (GBPA).	• Confirm PK parameters of GBPA camostat as assessed by population estimates from population PK analysis (popPK).	• PK plasma

Pharmacokinetics analysis will be described in analytical laboratory reports included in appendices. PK population only.

Interim reports will be received as agreed by CRUK with final reports at the end of the trial.

6.13.2 Tertiary/research endpoint/s

Clinical study objectives	Description of clinical study endpoint	Sample used for this endpoint
[redacted]	[redacted]	[redacted]

[redacted]	[redacted] negative swabs by qPCR.	
[redacted]	[redacted]	[redacted]

[redacted]

6.14 Other statistical analysis

Please see Appendix 1 for full Statistical Analysis Plan, Version 1.0 dated 27Sep2021

7 CLINICALTRIALS.GOV

The following tables illustrated for the Clinicaltrials.gov will not be part of the Clinical Study Report (CSR) and will be used for the upload of data to Clinicaltrials.gov only.

7.1 Arms and Interventions

The trial will be presented as a randomised trial.

Intervention Details: Patients will be randomised 1:1 into 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.

Drug: Camostat

7.2 Participant Flow

The participant flow section of the results upload will include the following details. Tables will be programmed for Randomised Phase and Treatment Phase for all patients.

Lines with text in blue are required rows from clinicaltrials.gov

Period Title	Overall Study		Programming notes
Arm/Group Title	Treatment arm	Control arm	
Arm/Group Description	Patient to receive treatment with camostat tablets, 200mg four times daily (*qds*) for 14 days	Patient to receive best supportive care	
	Number of Participants	Number of Participants	
Started			Day 1
<to add trial milestone>			
<to add trial milestone>			
<to add trial milestone>			
Completed			Complete up to and including Day 14

Not completed			Patients started Day 1 and did not complete up to and including Day 14
Adverse Event / Serious Adverse event			
Death			
Lack of Efficacy			
Lost to Follow-up			
Physician Decision			Investigator withdrawal of consent / Investigator withdrawal of subject
Pregnancy			
Protocol Deviation			
Withdrawal by Subject			Subject withdrawal from treatment (treatment arm) / subject withdrawal (allows FU) (control arm) as well as subject withdrawal of consent (all patients)
Recovered			
Other			

Number of patients started is defined as: Day 1

Number of patients Completed is defined as: Day 14

7.3 Reported Adverse Events (clinicaltrials.gov template sections)

AE Reporting Timeframe: Safety data will be collected from the time of informed consent until 28 days from Day 1. Patients who re hospitalised will be followed for up to 28 days after they are discharged.

All-Cause Mortality will be presented as per the clinicaltrials.gov template as follows:

	Treatment arm		Control arm	
	Affect/At Risk (%)	# Events	Affect/At Risk (%)	# Events
Total All Cause Mortality				

Serious Adverse events will be presented as per the clinicaltrials.gov template as follows:

	Treatment arm		Control arm	
	Affect/At Risk (%)	# Events	Affect/At Risk (%)	# Events
Total				
<AE term>				
<AE term>				
<AE term>				

Other (non-Serious) Adverse events will be presented as per the clinicaltrials.gov template as follows:

Frequency Threshold Above Which Other Adverse Events are Reported: 0%<TBC>

	Treatment arm		Control arm	
	Affect/At Risk (%)	# Events	Affect/At Risk (%)	# Events
Total				
<AE term>				
<AE term>				
<AE term>				

7.4 Endpoints/outcome measures to be reported

Primary and secondary endpoints will be reported on the clinicaltrials.gov website as outcome measures as follows. All secondary endpoint data will be taken from Table 9 and PK data relating to the PK secondary endpoint will be taken from the PK final report.

Primary Objective and Endpoint		
Objective	**Endpoint**	**Outcome Measures**
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.	Measure Title: Number of camostat related AEs and SAEs. Measure Description: Number of camostat related AEs and SAEs Measure Title: Number of AEs by severity grade Measure Description: Number of AEs by severity grade (mild, moderate, severe) Information to be presented: Refer to programmed table "Primary endpoint reporting for clinicaltrials.gov" Time frame: Days 1-28
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)phenylacetic acid (GBPA).	Confirm PK parameters of GBPA as assessed by population estimates from population PK analysis (popPK).	Measure Title: PK parameter Maximum concentration (Cmax) of 4-(4-Guanidinobenzoyloxy)phenylacetic acid (GBPA). Measure Description: Maximum concentration (Cmax) of GBPA as assessed by population estimates from population PK analysis Time frame: Days 7 and 14

		Information to be presented: Mean and standard deviation for each arm at each time point for each arm (to be provided in final PK report). Measure Title: PK parameter area under the curve (AUC) of GBPA Measure Description: Area under the curve (AUC) of GBPA, as assessed by population estimates from population PK analysis Time frame: Days 7 and 14 Information to be presented: Mean and standard deviation for each arm at each time point for each arm (to be provided in final PK report). Measure Title: PK parameter time to maximum concentration (Tmax) of GBPA, as assessed by population estimates from population PK analysis Measure Description: Time to maximum concentration (Tmax) of GBPA, as assessed by population estimates from population PK analysis Time frame: Days 7 and 14 Information to be presented: Median and range for each arm at each time point for each arm (to be provided in final PK report). Measure Title: PK parameter to confirm half-life (T1/2) of GBPA Measure Description: Half-life (T1/2) of GBPA as assessed by population estimates from population PK analysis

		Time frame: Days 7 and 14 Information to be presented: Mean and standard deviation for each arm at each time point for each arm (to be provided in final PK report).
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.	Measure Title: Number of community patients admitted to hospital due to COVID-19 Measure Description: Number of community patients admitted to hospital due to COVID-19 Time frame: Days 1-28 Population description: Patients who received camostat for a minimum of five days (treatment arm) or who either completed up to Day 14 or came off trial at an earlier timepoint due to an endpoint defined reason (e.g. hospitalisation). Information to be presented: Number of community patients admitted to hospital due to COVID-19 in each arm from programmed table.
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).	Measure Title: Number of oxygen free days Measure Description: Number of oxygen free days Time frame: Days 1-28 Population description: Patients who received camostat for a minimum of five days (treatment arm) or who either completed up to Day 14 or came off trial at an earlier timepoint due to an endpoint defined reason (e.g. hospitalisation).

		Information to be presented: Median and range of oxygen free days by treatment arm (provided in Stats report).
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).	Measure Title: Number of ventilator - free days Measure Description: Number of ventilator - free days Time frame: Days 1-28 Population description: Patients who received camostat for a minimum of five days (treatment arm) or who either completed up to Day 14 or came off trial at an earlier timepoint due to an endpoint defined reason (e.g. hospitalisation). Information to be presented: Median and range of ventilator free days by treatment arm (provided in Stats report).
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	Measure Title: Time to worst point on the scale or deterioration of two points or more (from randomisation) on 9 point category ordinal scale. Measure Description: Median time and range to worst point on the scale or deterioration of two points or more (from randomisation) on 9 point category ordinal scale Time frame: Days 1-28 Population description: Patients who received camostat for a minimum of five days (treatment arm) or who either completed up to Day 14 or came off trial at an earlier timepoint due to an endpoint defined reason (e.g. hospitalisation).

	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	Information to be presented: Median and range of times to worst point on the ordinal scale (provided in Stats report).

8 TABLES LISTINGS AND FIGURES

8.1 LISTINGS:

Completed or Discontinued patients

Treatment compliance End of monitoring period (Control arm)

End of study

Protocol deviations

Patients excluded from efficacy analysis

Screening failures

EnrolmentDemographic and Baseline Data

Demographics

Randomisation

Medical history

Risk factors

COVID-19 symptoms

Influenza or COVID-19 Vaccination

Concomitant medications

Medical procedures

Compliance and/or Drug Concentration Data

Treatment compliance Efficacy Response Data

[redacted]

[redacted]

9-point ordinal scale for clinical improvement

[redacted]

COVID-19/Camostat related hospitalisation details

Oxygen therapy and ventilation

Hospitalisation follow up

Safety Data

Adverse Events (by subject)

Adverse Events by SOCPregnancy test

Laboratory results

Imaging

8.2 TABLES

Demographic Data

Baseline characteristics by treatment arm

Reasons for patient withdrawal / completion

Compliance

Treatment modifications and/or non-compliance (treatment arm only)

Efficacy Data

Ordinal Scale

Summary of Secondary Endpoint Data

Safety Data

Overview of Treatment Emergent Adverse Events (Inclusive and post Day 1)

Frequency of All Adverse Events

Frequancy of pre-treatment AEs

Frequency of TEAEs

Frequency of All Camostat related treatment emergant AEs

Frequancyof all COVID-19 related treatment emergent AEs

Frequency of all treatment emergent SAEs

Breakdown of TEAEs leading to Patient withdrawal

Neutrophils:Lymphocytes ratio per patient (treatment and control arm respectively)

9 REFERENCES

- Guidelines for the Content of Statistical Analysis Alans in Clinical Trials, JAMA December 2017, Volume 318, Number 23. Gamble et al.

APPENDIX – STATISTICAL ANALYSIS PLAN

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.

Statistical Analysis Plan

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Author(s)	[redacted]
[redacted]	[redacted]l
CI Email address	[redacted]
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Version No	**Date**	**Summary of Revisions**
1.0	27Sep2021	Initial Creation
2.0	16Feb2022	Edits following changes to RAP

Contents

LIST OF ABBREVIATIONS

Abbreviation	Full name
AE	Adverse Event
CI	Confidence interval
IQR	interquartile range
ITT	Intention-to-treat
NLR	Neutrophil to lymphocyte ratio
PK	Pharmacokinetics
RT-PCR	Reverse transcription polymerase chain reaction
QC	Quality control
qPCR	Quantitative polymerase chain reaction

INTRODUCTION

This Statistical Analysis Plan is based on protocol version 6.0, dated 20 Sep 2021.

This is a Phase II randomised, multicentre, prospective, open label, clinical trial of camostat (200mg four times per day) vs best supportive care for adult patients (≥18 years) with validated COVID-19. Patients will be recruited from testing centres which may include primary care 'COVID-19 hub' clinics, COVID-19 community-based testing centres or equivalent clinical environments. Patients may be recruited in hospital if hospitalised for reasons other than COVID-19 and who have tested positive while in hospital. Patients will be randomised 1:1 into each arm. Patients will be stratified into four groups: Males 65 years or older; males below 65 years, females 65 years or older; females below 65 years. Up to 100 patients will be recruited, in a 1:1 ratio between treatment and control.

See section 13.2 of the protocol for the sample size calculation.

10 STATISTICAL METHODS SECTION FROM THE PROTOCOL

The primary outcome will be an exploration of camostat safety and toxicity, in terms of the number and severity of AEs and SAEs. Recruitment rate will be reported as numerator and denominator, with the percentage and exact binomial 95% confidence interval. The other feasibility measures will be reported in the same way.

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 will indicate related and unrelated events

11 OVERALL STATISTICAL PRINCIPLES

Analysis of the data will primarily be performed using the SAS statistical package (SAS software. Copyright © 2002-2012 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.). The statistical significance level will be p=0.05, although as a feasibility study, few hypothesis tests will be conducted.

11.1 Populations

The efficacy population will only include patients from the camostat arm where they have completed 5 days of treatment and in the control arm where they have completed 14 days of treatment or reached an endpoint (eg hospitalisation). All primary and secondary analyses will be conducted with this population. An intention-to-treat analysis of the main secondary outcomes (COVID-19 related hospital admissions, supplementary oxygen-free days, ventilator-free days, time to worst point on the 9-point ordinal scale) will also be conducted, should the data allow.

Patients who agree to the taking of blood samples will be included in the analysis of the PK data. The mean and SD will reported at each time point (Days 7 and 14), as will the mean changes. The data may be log (or other) transformed if not normally distributed. [redacted] Change will be change from previous blood test.

The safety population will include all patients with at least one dose of treatment (camostat or control). Safety data will be collected from the date of written consent. Safety variables will be summarised by descriptive statistics.

11.2 Missing data

Missing data is thought to be low (around 5%) but nonetheless the robustness of the findings to any patterns of missing data will be investigated using appropriate sensitivity type analyses, including multiple imputation under an assumption of missing at random.

11.3 Adjusting for centre

Due to the small sample size, adjustment by site is likely to be uninformative.

11.4 Subgroup analyses

Results will be reported by the strata created by the randomisation process (Males 65 years and older; males below 65 years; females 65 years and older; females below 65 years). Additional subgroup analysis by fall in lymphocyte (<20% fall vs ≥20% fall), and neutrophil:lymphocyte ratio (<2.18 vs ≥ 2.18) for key explanatory will be described should there be sufficient data. No formal comparisons of strata will be conducted.

12 LIST OF ANALYSES

Although the sample size has been calculated on recruitment rate, the primary outcome will be the comparison of adverse events and their severity between treatment arms. These will be listed overall and by strata.

12.1 Interim evaluation

At appropriate intervals, tables of results will be produced to give the Investigators the possibility to review the data and check the completeness of information collected.

This review will include:

- Feasibility of the trial to achieve the target recruitment. This will be informed by
    - Recruitment – what proportion of eligible patients consent to the trial
    - Retention – what proportion of the randomised trial patients complete the trial per protocol
    - Proportion of patients for whom the primary outcome is missing
    - Overall number of adverse events
    - Protocol deviations

No unblinded data will be made available to the investigators until the end of the trial or the DMEC decides to halt the trial.

12.2 Main study findings

The primary outcomes for this trial are safety and adverse events. These will be tabulated by treatment group and by strata/subgroups. Pregnancy, compliance, protocol deviations will also be tabulated in this way.

The majority of secondary outcomes will be reported in the main RAP. The secondary outcomes of number of oxygen-free days, ventilator-free days, and number of days to worst point on the 9-point ordinal scale (see secondary objectives in RAP for definitions) will be reported as median and range for the 28 days of follow up post-randomisation.

12.3 Transformations

[redacted]

12.4 Outputs

Tabular outputs have been described in the main RAP. The following analyses will be in addition to these tables.

Population: Efficacy population (at least 5 days of camostat/14 days of control)
Medians and range for the following variables will be produced by treatment group:

- Number of oxygen-free days,
- Number of ventilator-free days,
- Number of days to worst point on the 9-point ordinal scale

Kaplan-Meier plots of the following variables will be produced by treatment group:

- Time to worst point on ordinal scale

[redacted]

Plots of daily data will also be produced where this will aid interpretation.

13 VALIDATION AND QC

The statistical report will be read and sense-checked.